ENDOCRINE DISRUPTORS

Solutions to new challenges






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PREFACE

The prevention of occupational and environmental risks associated with the exposure to endocrine disruptors (EDC) represents a true challenge for experts worldwide.

Traditional risk assessment methods included in current legislation prove inadequate to protect human health and the environment from EDCs, given the specific characteristics of these compounds:

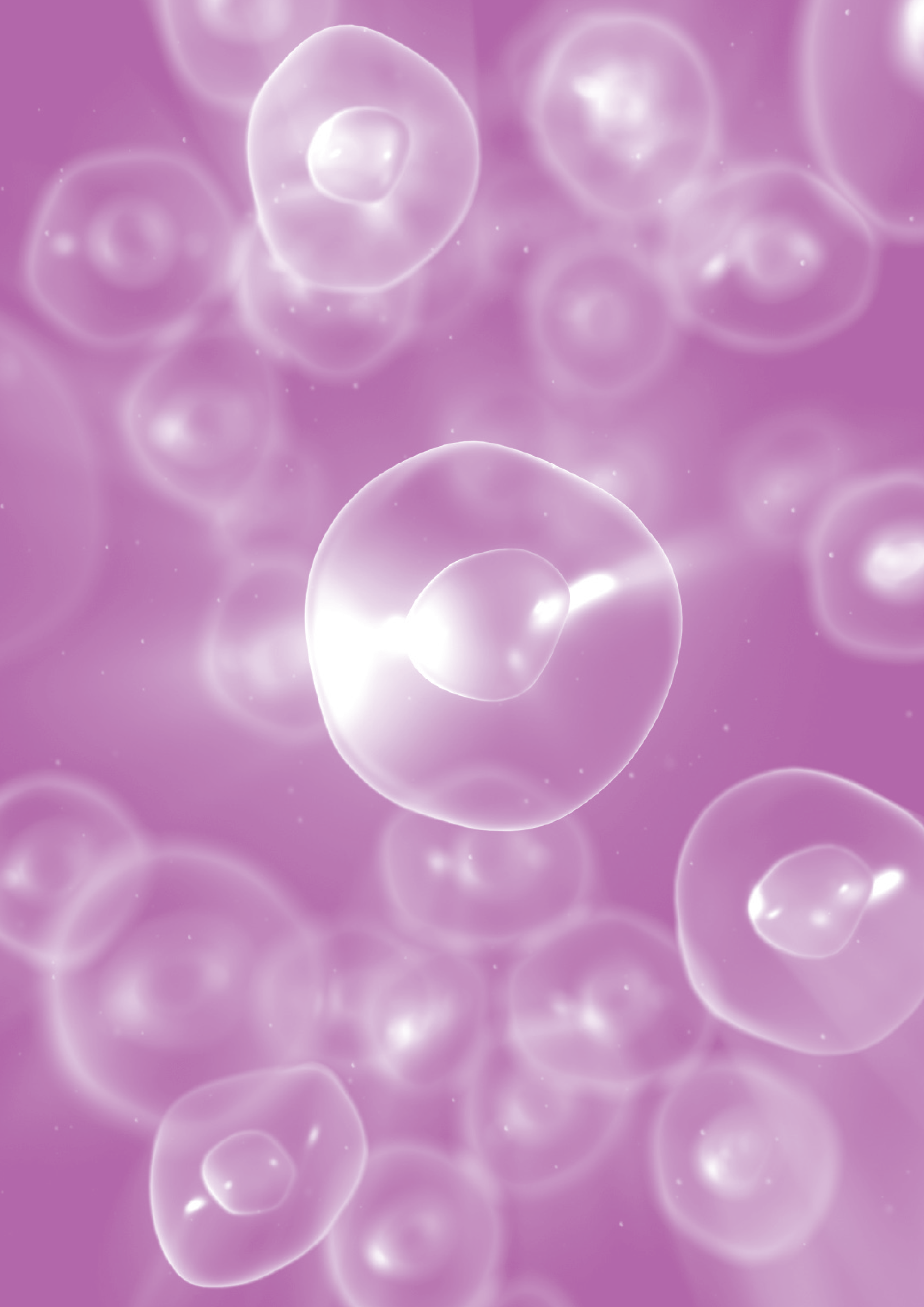
- EDC may have effect at very low doses
- Certain developmental periods are particularly vulnerable to endocrine disruption and exposure in such periods may have lifelong health effects
- EDCs do not have a linear dose-effect relation
- EDCs may have a combined effect
- Health effects may affect future generations
- Harmful effects of EDC may have long latency periods
- Ubiquity of exposure
- Impossibility to establish a safe threshold of exposure for EDCs

Protection from the effects of EDCs represents a new challenge that calls for a new paradigm based on the application of the precautionary principle* and the adoption of urgent measures.

Such measures include:

- Avoiding exposure to EDCs of children, pregnant women, breastfeeding mothers and women in reproductive age
- Eliminating or reducing exposure to EDCs as much as possible
- Implementing new methods of identification and statistical sampling that include all chemicals with potential to interfere with hormone systems

* *The* ***Wingspread Statement on the Precautionary Principle*** *summarizes the principle as follows:*
"When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically." The Wingspread Conference on the Precautionary Principle was convened by the Science and Environmental Health Network. (Science and Environmental Health Network. The Precautionary Principle: A Common Sense Way to Protect Public Health and the Environment: http://www.mindfully.org/Precaution/Precautionary-Principle-Common-Sense.htm)



1. ENDOCRINE DISRUPTORS

Endocrine disruptors are chemicals that interfere with human and animal hormone systems, and are capable of altering hormone balance and embryo development, with the risk of adverse effects on the health of organisms and their offspring. This section considers the following aspects of endocrine disruption:

1.1 The hormone or endocrine system.
1.2 What are endocrine disruptors and how do they act?
1.3 Effects on human health and wildlife.
1.4 Hazardous chemicals and activities.
1.5 Exposure to endocrine disruptors in Spain.

1.1. The hormone or endocrine system

In order to understand EDCs and how they affect us, we turn to a summary of the characteristics and functions of hormones and the endocrine system.

The hormone or endocrine system functions as a communication system. In many-celled organisms, communication between cells is essential for their coordinated function. Such communication is based on chemical signals.

Neighboring cells communicate via surface molecules and special junctions, whereas communication between distant cells is carried out through the release of chemical signals, hormones that activate target cells and interact with specific receptors.1 Chemical signals travel through the bloodstream (circulatory system) to reach target cells.

Anatomical structure of the endocrine system

Cells responsible for signal (hormone)[2] releases are called ENDOCRINE CELLS and are basically found in three locations:

- Endocrine cells that make up a specific organ, or ENDOCRINE GLAND (see Figure 1).

1 There are four types or categories of hormone secretion:
• **Autocrine signaling:** a cell secretes a hormone that binds to autocrine receptors on the same cell (e.g.: epidermal growth factor)
• **Paracrine signaling:** the target cell is near the signal releasing cell (e.g.: prostaglandins in the diffuse neuro-endocrine system).
• **Endocrine signaling:** target cells are located away from the signal releasing cells (hormones are secreted directly into the bloodstream).
• **Synapse:** direct communication between two nerve cells. The signal releasing cell, in this case a neuron, is in direct contact with the target cell (e.g.: another neuron, a myocyte, etc.) and passes an electrical or chemical signal to it (neurotransmitter) that might be shared with the endocrine system. Neurotransmission is a nearly instantaneous process.

2 Hormones are classified into four main type of cells:
- Hormones derived from amino acids (e.g.: adrenaline, noradrenaline, thyroxine)
- Peptides (enkephalin, vasopressin)
- Proteins (insulin, growth hormones)
- Steroids (cortisol, progesterone, estradiol, testosterone)
Most chemicals signals are hydrosoluble, they also diffuse easily and interact with surface molecules. However, steroids and thyroxine are hydrophobic and react with intracellular receptors through cell membranes.

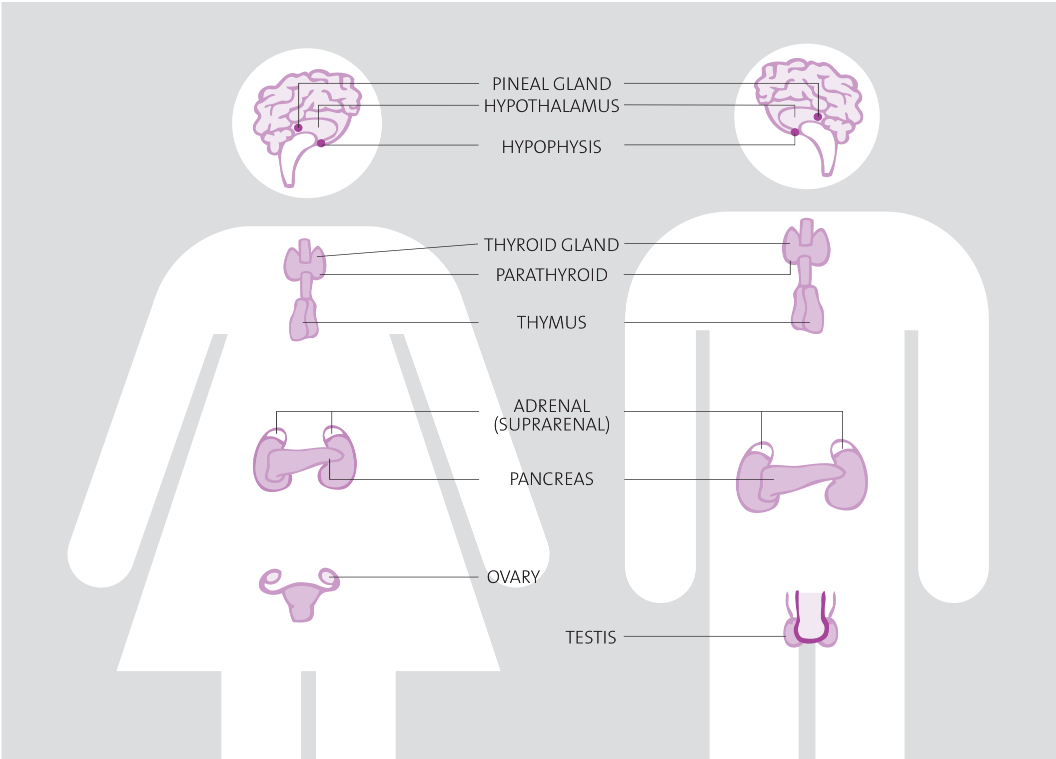


Figure 1. Endocrine glands

- Endocrine cells that form small groups in other specialized organs (ovary, testes, pancreas).
- Endocrine cells individually dispersed among epithelial tissue cells, especially in the digestive and respiratory systems, part of the DIFFUSE NEUROENDOCRINE SYSTEM.

Hormone action mechanisms

Hormones may act as enzymes through direct action on specific chemical reactions. They can also act on a target cell joining a specific receptor. Action mechanisms depend on the type of receptor:

- **Membrane receptors:** located in cell membranes, these are specialized integral membrane proteins that take part in communication between the cell and the outside world. The binding of the receptor with the membrane may alter the membrane's permeability (the basis of nervous impulse transmission in neurons; insulin and glucocorticoids act in the same way). It can also modify a second intracellular transmitter (AMPc or GMPc).[3]
- **Intracellular receptors:** located inside the cell, they are activated by hormones and are transported to the nucleus, where they stimulate synthesis of a new effector protein.

All vertebrates possess the same endocrine glands that control development, growth, and reproduction, among other functions.

Each endocrine gland secrets a specific amount of a hormone at a given time. That hormone circulates through the bloodstream in very small amounts.

Hormones are extremely effective chemicals. The amount of a given hormone needed to regulate a metabolic function is incredibly small. For example, estradiol, the most potent of the estrogens, acts in concentrations of parts per billion (pg/g, pg/ml).

Hormone concentrations in the blood vary from person to person, depending on age, sex, and reproductive cycle or health conditions. Each person has a specific hormonal balance. Table 1

3 Cyclic Adenosine Monophosphate (cAMP (cAMP) and Cyclic Guanosine Monophosphate (cGMP)

Table 1. Concentration of some endogenous hormone in humans

Hormone	Free concentrations (women)	Total concentration (women)	Free concentrations (men)	Total concentration (men)
Cortisol	20-300 ng/ml		20-300 ng/ml	
Estradiol	0,5-9 pg/ml (adult female)	<20 pg/ml (prepuberal)		10-60 pg/ml (adult)
		20-800 pg/ml (premenopausal)		
Progesteron		<30 pg/ml (postmenopausal)		
		0,2-0,55 ng/ml (prepuberal)		0,1-0,4 ng/ml (prepuberal)
		0,02-0,80 ng/ml (follicular phase)		
		0,90-4 ng/ml (luteal phase)		0,2-2 ng/ml (adult)
Insulin		<0,5 ng/ml (postmenopausal)		
GH		0-250 pmol/liter		
Prolactin		2-6 ng/ml		0-250 pmol/liter
Testosteron		0-15 ng/ml		2-6 ng/ml
Thyroid			0,3-250 ng/ml	0-10 ng/ml
	9-150 pg/ml (adult)		8-30 pg/ml (10-35 pM)	
TSH	8-30 pg/ml (10-35 pM)			
			0,5-5 µU/ml	
	0,5-5 µU/ml			

Source: Laura N. Vandenberg, Theo Colborn, Tyrone B. Hayes, Jerrold J. Heindel, David R. Jacobs, Jr., Duk-Hee Lee, Toshi Shioda, Ana M. Soto, Frederick S. vom Saal, Wade V. Welshons, R. Thomas Zoeller, and John Peterson Myers. Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses. *Endocrine Reviews*, March 14, 2012 er.2011-1050.

shows the range of endogenous concentrations of some hormones.[4]

Hormones regulate different functions with various degrees of complexity. Their functions include:

- Acting as simple information transmitters.
- Controlling maximum and minimum levels of metabolic function.
- Carrying out control functions by feedback.
- Controlling complex processes such as the menstrual cycle.
- Regulating the development of the mammary glands.
- Regulating metabolic levels.
- Regulating embryogenesis (embryo formation and development).

The hypothalamic-pituitary-gonadal axis (HHG) controls ovarian hormone synthesis via releasing factors (GnRH) and gonadotropic hormones (LH, FSH); ovarian steroids have a negative feedback effect on the hypothalamus and the hypophisis (pituitary gland), both located in the brain. The hypothalamic-pituitary-adrenal axis (HPA or HTPA axis) is an essential part of the neuroendocrine system that controls stress and regulates body processes such as digestion, the immune system, sexuality, and energy metabolism.

Hormones control the growth of the nervous and immune systems in the embryo and program the functions of tissues and organs such as the liver, blood, kidneys, and muscles, which work differently in men and women. In order that these systems develop normally, the embryo must receive correct and precisely timed hormonal signals. The disruption of signals during a critical developmental period can have serious consequences for the organism during the rest of its life.

The endocrine and nervous systems interact through the hypothalamus, the pituitary, and the network of neurotransmitters that connects them. Both systems interact with the immune system through cytokines, a category of signaling molecules (hormones). Given the close interaction between the three systems, some scientists refer to them as the neuro-immune-endocrine system.

4 Laura N. Vandenberg, Theo Colborn, Tyrone B. Hayes, Jerrold J. Heindel, David R. Jacobs, Jr., Duk-Hee Lee, Toshi Shioda, Ana M. Soto, Frederick S. vom Saal, Wade V. Welshons, R. Thomas Zoeller, and John Peterson Myers. Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses. *Endocrine Reviews*, March 14, 2012 er.2011-1050.

SUMMARY
THE HORMONE OR ENDOCRINE SYSTEM

- Is a complex signaling system that regulates vital bodily functions, including embryonic development.
- Is closely related to the nervous and immune systems.
- Is made up of glands, hormones, and hormonal receptors.
- Hormones are chemical substances that act as messengers.
- One hormone can regulate vastly different functions in different body organs.
- Hormones are highly effective and act at very low concentrations.
- Each human being has a different hormonal balance.
- The hormone system coordinates with the nervous and immune systems.

References

Center for Bioenvironmental Research. (2002) Environmental Estrogens and Other Hormones. Louisiana: Tulane and Xavier Universities. *http://www.som.tulane.edu/cbr/ecme/eehome/default.html*

Colburn, T., J.P. Myers, and D. Dumanoski. (2001) (Our Stolen Future). Nuestro futuro robado ¿Amenazan las sustancias químicas sintéticas nuestra fertilidad, inteligencia y supervivencia? Madrid: Ecoespaña Editorial.

Kortenkamp, Andreas, Olwenn Martin, Michael Faust, Richard Evans, Rebecca McKinlay, Frances Orton, and Erika Rosivatz. (2011) State of the Art Assessment of Endocrine Disrupters. Final Report. Project Contract Number 070307/2009/550687/SER/D3. 23.12.2011.

1.2. What are endocrine disruptors and how do they act?

Endocrine disruptors, environmental estrogens, xenoestrogens, endocrine modulators, environmental hormones, hormonally active compounds, philoestrogens

The terms listed above all refer to endocrine disruptors, that is, chemicals capable of altering hormonal balance and the development of embryos, and hence capable of causing adverse effects in living organisms and their offspring.

The ability of certain chemicals to interfere with the human hormone system was discovered 40 years ago when the pharmaceutical drug diethylstilbestrol (DES) was used to prevent miscarriage in pregnant women. However, the term endocrine disruptor chemical (EDC) was coined some 50 years later, in 1991, during the Wingspread Conference,[5] when a group of endocrinologists, toxicologists, epidemiologists, and other health experts met to assess harmful effects on humans and wildlife observed in epidemiological studies in the Northern Hemisphere. These included damage to the reproductive and immune systems and certain types of cancer in hormone-dependent organs, among other health problems. Participants hypothesized that the adverse effects were due to changes in embryonic and fetal development brought on by exposure

5 Bern, H et al. Statement from the work session on chemically-induced alterations in sexual development: the wildlife/human connection in Eds. T Colborn and C Clement. *Chemically-Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection*. NJ, U.S: Princeton Scientific Publishing Co., 1992.

Table 2. Action principles of some EDCs and examples of affected endpoints

Chemical	Use	EDC action	Affected endpoint
Atrazine	Herbicide	Increase of aromatase expression	Male sex differenciation /development
Bisphenol A (BPA)	Plastics, thermal papers, epoxy resins	Binds ER, mER, ERRγ, PPARγ, may weakly bind TH receptor and AR	Prostate, mammary gland, brain development and behavior, reproduction, immune system, metabolism
Chlorpyrifos	Insecticide	Antiandrogenic	Acetylcholine receptor binding (brain)
Dioxin (TCDD)	Industrial byproduct	Binds AhR	Spermatogenesis, immune function and oxidative stress, tooth and bone development, female reproduction, mammary gland, behavior
Hexachlorobenzene	Fungicide	Modulates binding of ligand to TRE, weakly binds AhR	Anxiety and aggressive behaviors
Methoxychlor	Insecticide	Binds ER	Immune system
4-Methylbenzylidine camphor	UV screen	Weakly estrogenic	Sexual behavior
Methyl paraben	Preservative	Estrogenic	Uterine tissue organization
Nonylphenol	Detergents	Weakly estrogenic	Testosterone metabolism
PCB180	Industrial lubricant, coolant	Impairs glutamate pathways, mimics estrogen	Diabetes (humans)
Perchlorate	Fuel, fireworks	Blocks iodide uptake, alters TH	TSH levels (humans)
Tributyltin oxide	Pesticide, wood preservation	Binds PPARγ	Obesity
Triclosan	Antibacterial agent	Antithyroid effects, androgenic and estrogenic activity	Altered uterine responses to ethinyl estradiol

ER, estrogen receptor; mER, membrane-associated ER;
AR, Androgen receptor; ERR, estrogen related receptor; PPAR, peroxisome proliferator-activated receptor; PRGR, progesterone receptor; RXR, retinoid X receptor; TH, thyroid hormone; TRE, thyroid response element.

Source: Adapted from Laura N. Vandenberg, Theo Colborn, Tyrone B. Hayes, Jerrold J. Heindel, David R. Jacobs, Jr., Duk- Hee Lee, Toshi Shioda, Ana M. Soto, Frederick S. vom Saal, Wade V. Welshons, R. Thomas Zoeller, and John Peterson Myers. Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses. *Endocrine Reviews*, March 14, 2012 er.2011-1050.

to chemical pollutants. Those pollutants were defined as endocrine disruptors. Experts expressed their concern about the public health and environmental implications of such findings.

The term endocrine disruptor is broadly defined as "an exogenous agent that interferes with the production, release, transport, metabolism, binding, action or elimination of natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes."[6]

The catalogue of endocrine disruptors is extensive and continues to grow. It includes synthesized chemical products, as well as substances found in the natural environment (see section 1.5).

6 Kavlock, R. J. et al. Research needs for the risk assessment of health and environmental effects of endocrine disruptors: a report of the U. S. EPA-sponsored workshop. *Environ. Health Perspect.*1996; 104 (Suppl. 4), 715–740.

Mechanisms and action principles

It is a priority for researchers in this field to understand the action principles and mechanisms of endocrine disruptors. Recent years have seen great advances in which researchers have managed to describe different ways in which endocrine disruptors can alter hormonal balance. Those processes include:

- **Mimicry of hormones:** for example, EDCs that act like estrogen are known as environmental estrogens; examples are DDT, some PCBs, and many philoestrogens, nonsteroidal chemical compounds found in vegetables that are similar to human estrogens.
- **Antagonizing hormone effects:** for example, the anti-estrogenic action of some PCBs or PCBS, such as vinclozolin (dicarboximide fungicide).
- **Altering hormonal binding and metabolism patterns**: for example, the effects of the flame retardant PBDE-99, which alters the synthesis of thyroid hormone (TH).
- **Modulating the levels of hormone receptors:** for example, bisphenol A (BPA), found in some plastics and epoxy resin, which interacts with estrogen receptors.

The most researched action mechanisms include:[7, 8]

- Estrogenicity/ anti-estrogenicity
- Androgenicity/ anti-androgenicity
- Thyroid alteration
- Alteration of hormone receptors: estrogenic receptor (ER), membrane-associated estrogen receptor (mER), androgenic receptor (AR), estrogen-related receptor (ERR), peroxisome proliferator-activated receptor (PPAR), progesterone receptor (PR), retinoid X receptor (RXRs); aryl hydrocarbon receptor (AHR)
- Alteration of retinoic acid, PPAR, and vitamin D routes
- Alteration of target tissues in the brain and in the reproductive and cardiovascular systems
- Pancreatic ß-cell (beta-cell) dysfunction
- Endogenous inhibition of hormone metabolism
- Multiple hormone-modifying effects

EDCs are considered "chemical chameleons," that is, a single EDC has different action mechanisms depending on its concentration (see Table 2).

Therefore, high doses of dioxins can be fatal, but very low concentrations (such as the ones to which the population is exposed through contaminated food products) may significantly increase the risk of reproductive anomalies in women.[9]

High levels (100–1,000,000 nanomolar) of hexachlorobenzene (HCB) suppress the androgenic activity of prostate cells, whereas low doses (1 nanomolar) increase this activity.[10]

For instance, in utero exposure of female mice to low doses (1ppb) of DES can cause obesity in adult offspring, while mice exposed in utero to higher doses exhibit weight loss at the same age.[11]

The same EDCs may also have different action mechanisms depending on the specific developmental stage of the affected tissue:

In order to obtain a uterotrophic response (affecting the uterus) in adult mice, it is necessary to administer 100 mg/kg/day of BPA. However, only 25 ng/kg/day of BPA (4,000,000 times less) during pregnancy may cause a response in mammary ductal tissue.

Adverse effects may vary depending on the time of exposure and the hormonal balance of the exposed individual, which is determined by age and sex, among other factors.[12]

7 Andreas Kortenkamp, Olwenn Martin, Michael Faust, Richard Evans, Rebecca McKinlay, Frances Orton and Erika Rosivatz. State of the Art Assessment of Endocrine Disrupters. Final Report. Project Contract Number 070307/2009/550687/SER/D3. 23.12.2011.

8 Miquel Porta and Duk-Hee Lee. Review of the science linking chemical exposures to the human risk of obesity and diabetes. CHEM Trust, 2012.

9 Laura Vandenberg. Opinion: 'There are no safe doses for endocrine disruptors'. *Environmental Health News*. March 15, 2012.

10 Myers P. & Hesler W. Does 'the dose make the poison? Extensive results challenge a core assumption in toxicology. *Environmental Health News*. April 30, 2007.

11 Miquel Porta and Duk-Hee Lee, Op. Cit.

12 Colborn T. Commentary: setting aside tradition when dealing with endocrine disruptors. *ILAR J.* 2004; 45(4): 394-400.

Periods of particular vulnerability/Time of exposure

Knowing the specific time of exposure in developing organisms is essential in assessing the nature, gravity, and subsequent evolution of EDC effects, as they are different in embryos, fetuses, newborns, and adults. If EDC exposure takes place during critical periods (like early developmental stages characterized by rapid cellular differentiation and organogenesis) damage is irreversible.[13]

There is substantial evidence about the particular sensitivity of developing organisms to chemicals that interfere with hormone activity during critical (in utero) phases of organogenesis. Effects are often irreversible and remain in affected organisms for the rest of their lives. Furthermore, the latency period (the time between exposure and manifestation of the first symptoms) can be lengthy.[14]

Exposure to biologically active chemicals in concentrations that affect hormones can lead to a series of effects that vary progressively through different developmental stages of the organism. Similarly, these effects might differ from the response observed during exposure to high doses of the same chemical, or from responses in fully developed individuals.[15]

While hormonal effects are mostly associated with signal activation and are reversible in adults, untimely exposure to hormones during fetal organ development primarily affects the structure and function of organs, causing irreversible damage.[16]

The effects of in utero exposure to EDCs are not necessarily evident at birth; they may remain latent for years or become apparent in the offspring of exposed individuals, so that the consequences of exposure occur more frequently in the offspring than in the exposed parents.

The genetic mechanisms by which the effects of exposure pass to future generations are known as epigenetic changes. Some examples are listed below:[17]

- Androgen antagonists such as pesticides and phthalates can interfere with androgenic action during the first stage of male fetal male development. The decrease of androgenic action, when seen in laboratory animals, only becomes evident in adulthood and its effects include malformation of reproductive organs. Most of these effects are irreversible.

- Epidemiological studies show that exposure to dioxins (TCDD) during the perinatal period has a negative impact on the quality of sperm, while exposure in adult life has no effect on sperm quality.

- Estradiol and estrogenic chemicals may interfere with the KiSS-1 peptide system in rodents during the neonatal period and affect the age of onset of puberty.

- The development of the female reproductive system is programmed during fetal development; this framework can be disrupted by chemicals such as DES, with multiple irreversible consequences.

- Some hormone-related cancers (breast, prostate, testicular, ovarian, and endometrial) may originate during either fetal development or puberty. During these periods, there is a high level of sensitivity to chemical exposure involving known carcinogens in these types of cancers.

- The action of thyroid hormones during in utero development is essential in multiple organs. Those include the brain and the neuroendocrine system. The interruption of thyroid action caused by chemical exposure during this period can have irreversible adverse effects.

- Many species have multiple periods of vulnerability, among them, grasshoppers, certain amphibians, and reptiles, which are extremely sensitive to EDCs.

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13 Marieta Fernández. FUNDAMENTOS DE TOXICOLOGIA. Seminario de actualización en Toxicología Laboral. ISTAS, Madrid, 21 de septiembre de 2011.
14 Bern, H et al. Op. Cit.
15 Laura Vandenberg. Op. Cit.
16 Ana M. Soto and Carlos Sonnenschein. Environmental causes of cancer: endocrine disruptors as carcinogens. *Nature Reviews Endocrinology* 6, 363-370 (July 2010) | doi:10.1038/nrendo.2010.87.
17 Bern, H et al. Op. Cit.

Low-dose effects

Many EDCs cause adverse effects at very low levels of exposure, equivalent to the amounts to which the population is generally exposed. As described previously, these low-dose effects may differ from effects associated with the same chemical at higher doses.

Table 3 shows the concentrations at which an estrogenic effect is observed in a selection of industrial chemicals, according to the E-SCREEN assay. Concentrations are expressed in the nano-micromolar range (pg/g to ng/g).[18]

A study on human exposure to persistent organic pollutants with estrogenic capability (PCBs, DDT, HCB) in Catalonia (Spain) detected concentrations of such chemicals in an average range of 20–300 ng/g in 90 percent of the population (Figure 2),[19] implying that the exposed population presented organic levels of EDC that might cause negative health effects.

Dose-response curve

Another significant characteristic of EDCs is that they do not have a linear dose-response pattern.

"Dose makes the poison" is the principle behind conventional chemical-risk assessment, which proves valid for most chemicals (see Figure 3). Safe exposure levels are calculated according to that principle. Toxicity testing for specific effects, for example, estrogenicity, is carried out by decreasing doses of a given chemical until the No Observable Adverse Effect Level (NOAEL) is reached.

NOAEL denotes the level of exposure at which there is no biologically or statistically significant increase in the frequency or severity of any adverse effects in the exposed population when compared to its appropriate control. Safe levels of exposure are determined by adding a safety factor to the NOAEL.

Table 3. Estrogenic effects of industrial chemicals measured by the E-Screen assay

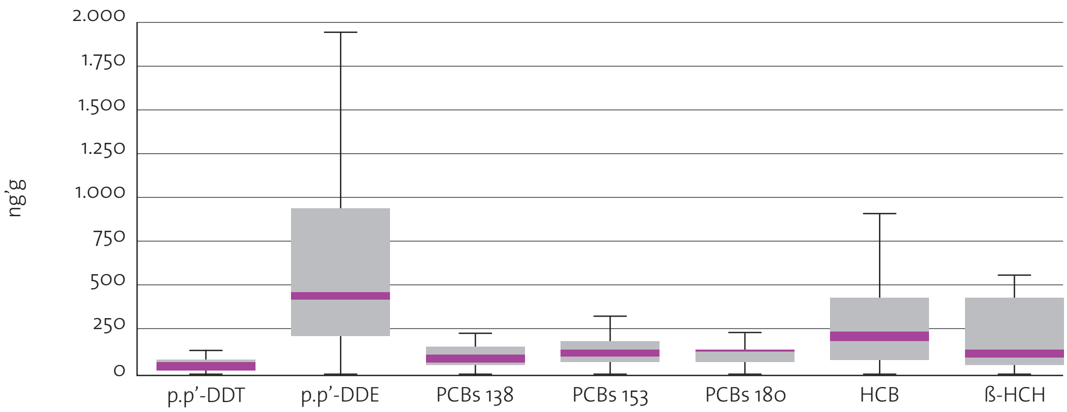
Chemical	Concentration[a]	APE, %[c]	APP, %
Estradiol	30 pM	100	100
Phenol	10 μM[b]	0	--
4-Ethylphenol	10 μM[b]	5	--
4-Propylphenol	10 μM	17	--
4-sec-Butylphenol	10 μM	76	0,0003
4-tert-Butylphenol	10 μM	71	0,0003
4-tert-Pentylphenol	10 μM	105	0,0003
4-Isopentylphenol	10 μM	93	0,0003
4-Butoxiphenol	10 μM[b]	0	--
4-Hexyloxyphenol	10 μM[b]	0	--
4-Hydroxibiphenyl	10 μM	87	0,0003
4,4-Dihydroxybiphenyl	10 μM	84	0,0003
1-Naphtol	10 μM[b]	0	--
2-Naphtol	10 μM[b]	0	--
5,6,7,8, -Tetrahydronaphtol-2	10 μM[b]	0	--
6-Bromonaphtol-2	10 μM	38	--
5-Octylphenol	100 nM	100	0,03
4-Nonylphenol	1 μM	100	0,003
Nonylphenol, technical grade	10 μM	102	0,0003
t- Butylated hydroxyanisole	50 μM	30	0,00006
Benzylbutylphthalate	10 μM	90	0,0003

Source: Ana M. Soto, Carlos Sonnenschein, Kerrie L. Chung, Mariana F. Fernández, Nicolás Olea, and Fátima Olea Serrano. The E-SCREEN Assay as a Tool to Identify Estrogens: An Update on Estrogenic Environmental Pollutants. *Environ Health Perspect* 1 03 (Suppl 7):113-122 (1995).

18 Ana M. Soto, Carlos Sonnenschein, Kerrie L. Chung, Mariana F. Fernández, Nicolás Olea, and Fátima Olea Serrano. The ES-CREEN Assay as a Tool to Identify Estrogens: An Update on Estrogenic Environmental Pollutants. *Environ Health Perspect* 1 03(Suppl 7):113-122 (1995).

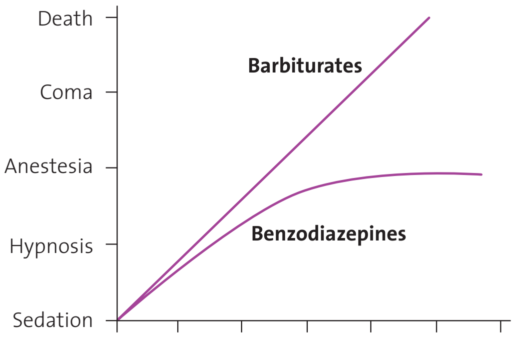
19 Miquel Porta, Elisa Puigdomènech, Magda Gasull y Magda Bosch de Basea. Distribución de las concentraciones séricas de compuestos orgánicos persistentes (COPs) en una muestra representativa de la población general de Cataluña. Barcelona: Departamento de Salud de la Generalitat de Cataluña, IMIM y Universidad Autónoma de Barcelona, 2009.

Figure 2: Concentrations of 7 Persistent organic Pollutants (POP) in more than 90% of monitored individuals in Catalonia



Source: Miquel Porta, Elisa Puigdomènech, Magda Gasull y Magda Bosch de Basea. Distribución de las concentraciones séricas de compuestos orgánicos persistentes (COPs) en una muestra representativa de la población general de Cataluña. Barcelona: Departamento de Salud de la Generalitat de Cataluña, IMIM y Universidad Autónoma de Barcelona, 2009.

Figure 3. Dose -response curve of barbiturates and benzodiazepines

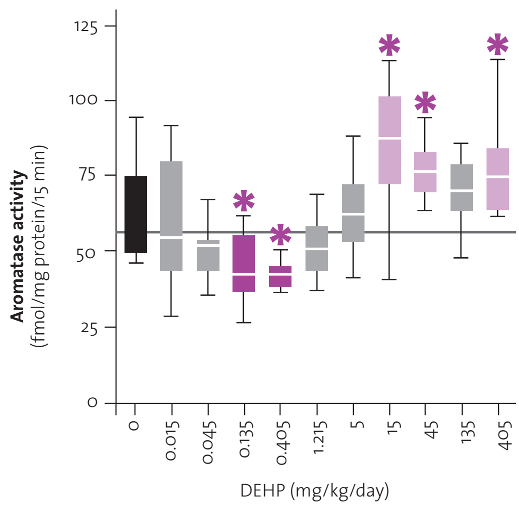


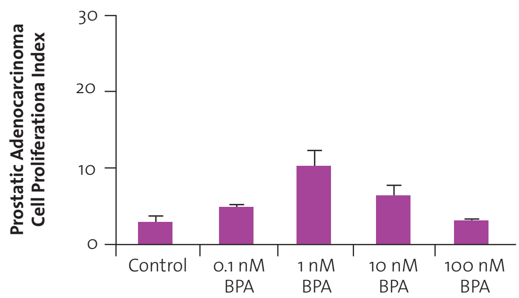
Fuente: Marieta Fernández. FUNDAMENTOS DE TOXICOLOGIA. Seminario de actualización en Toxicología Laboral. ISTAS, Madrid, 21 de septiembre de 2011.

However, many EDCs do not follow the dose-response pattern, and have a nonlinear (U or inverted U-shaped curves) pattern, which indicates that they may cause toxic effects at high doses, no effects at medium doses, and adverse effects at low doses (see Figures, 4, 5, and 6).[20]

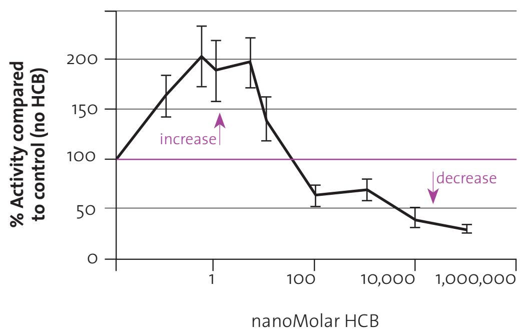
20 Myers P. & Hesler W. Op. Cit.10.

Figures 4, 5 and 6. Examples of non-monotonic dose-response curves





Adapted from Wetherill *et al.*

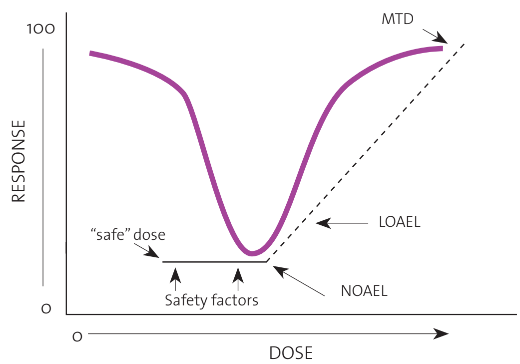


Adapted from Ralph *et al.* 2003

Source: Myers P. & Hesler W. Does 'the dose make the poison? Extensive results challenge a core assumption in toxicology. *Environmental Health News*. April 30, 2007.

Standard toxicity tests included in current EDC regulations do not detect adverse effects caused by exposure to low doses because no adverse effects are observed at higher doses and therefore no further testing is carried out at low doses (see Figure 7).

Figure 7. Calculation of exposure levels in standard toxicity tests



Source: Laura N. Vandenberg, Theo Colborn, Tyrone B. Hayes, Jerrold J. Heindel, David R. Jacobs, Jr., Duk-Hee Lee, Toshi Shioda, Ana M. Soto, Frederick S. vom Saal, Wade V. Welshons, R. Thomas Zoeller, and John Peterson Myers. Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses. *Endocrine Reviews*, March 14, 2012 er.2011-1050.

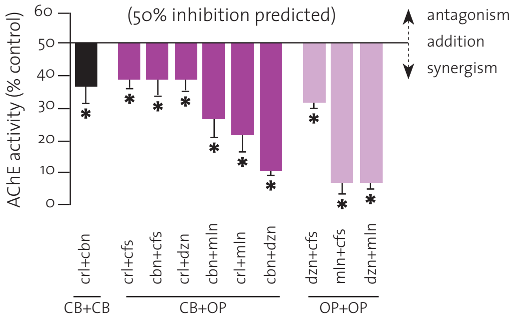
Therefore, **it is impossible to establish a safe level of exposure to EDCs that have nonlinear dose-response curves**. In addition, safe exposure levels to these chemicals that have been established for other toxic effects do not guarantee protection from endocrine disruption.

Mixes / combined effects

Another distinctive characteristic of EDCs that raises concern among researchers is that adverse effects might be the result of combined action by several chemicals that do not cause negative health effects separately, yet when mixed may cause a paradoxical reaction in the form of synergistic, antagonistic, or additive effects. This is particularly significant since in real life, the population is exposed to a low-concentration "cocktail" of multiple chemicals, yet risk-assessment procedures that are part of the existing regulatory framework only consider exposure to individual chemicals.

Figure 8 shows the potential of different pesticide combinations to inhibit the activity of acetylcholinesterase (an enzyme involved in neurotransmission).[21]

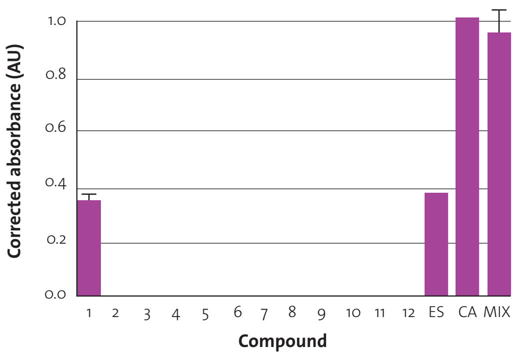
Figure 8. Combined effects of pesticides on on the inhibition of Acetylcholinesterase (AChE) activity



Source: Andreas Kortenkamp, Thomas Backhaus and Michael. Faust State of the Art Report on Mixture Toxicity. Final Report. Executive Summary. 22 December 2009. Study Contract Number 070307/2007/485103/ETU/D.1.

Figure 9 shows that substances which might have a low estrogenic effect separately increase their estrogenic effect in combined exposures (MIX).[22]

Figure 9. Combined estrogenic effects



Source: Rajapakse N, Silva E, Kortenkamp A 2002. Combining Xenoestrogens at Levels below Individual No-Observed-Effect Concentrations Dramatically Enhances Steroid Hormone Action. *Environ Health Perspect*. 110:917-921. http://dx.doi.org/10.1289/ehp.02110917

Several studies conducted by the University of Granada (Spain) on women in the Andalusia region showed an increased risk of breast cancer caused by combined exposure to estrogenic pollutants, measured as a total load of xenoestrogens (TEXB) in serum and fat tissue (Table 4).[23]

Table 4. Total xenoestrogens load (TEXTB) in serum and fat tissue of women with breast cancer and cases control

	Cases (n = 198)		Controls (n = 260)		
	GM	GSD[a]	GM	GSD	P[b]
DDE[c]	326,86	2,78	307,34	3,62	0,57
Aldrin[c]	2,84	4,12	2,37	4,21	0,33
Endosulfan-ether[c]	0,79	1,95	0,75	1,81	0,66
Lindan[c]	6,12	2,84	5,82	3,02	0,67
TEXB-alpha[d]	44,60	14,73	31,79	14,30	0,20
TEXB-beta[d]	76,48	13,74	72,70	14,44	0,86

a GM, Geometric Mean; GSD, Geometric Standard Deviation
b Assay Student's t.
c ng/g fat.
d Estradiol equivalent picomolar (Eeq)/gr. of fat.

Source: Jesus M. Ibarluzea, Mariana F. Fernandez, Loreto Santa-Marina, Maria F. Olea-Serrano, Ana M. Rivas, Juan J. Aurrekoetxea, Jose Exposito, Miguel Lorenzo, Pablo Torne, Mercedes Villalobos, Vicente Pedraza, Annie J. Sasco & Nicolas Olea. Breast cancer risk and the combined effect of environmental estrogens. *Cancer Causes and Control*. 15: 591-600, 2004.

Safe exposure limits

As previously described, either there is no exact threshold of concentration for the development of endocrine disruption, or that level is different from the known safety limit for other toxicological effects.

Although a theoretical safety threshold could be established for a substance in specific individuals, it is not possible to establish safety limits for a whole population given the different effects of EDCs on individuals, and the role in disease processes played by differences in exposure, whether endogenous or environmental.[24]

21 Andreas Kortenkamp, Thomas Backhaus and Michael. Faust State of the Art Report on Mixture Toxicity. Final Report. Executive Summary. 22 December 2009. Study Contract Number 070307/2007/485103/ETU/D.1.
22 Rajapakse N, Silva E, Kortenkamp A 2002. Combining Xenoestrogens at Levels below Individual No-Observed-Effect Concentrations Dramatically Enhances Steroid Hormone Action. *Environ Health Perspect*. 110:917-921. http://dx.doi.org/10.1289/ehp.02110917.
23 Jesus M. Ibarluzea, Mariana F. Fernandez, Loreto Santa-Marina, Maria F. Olea-Serrano, Ana M. Rivas, Juan J. Aurrekoetxea, Jose Exposito, Miguel Lorenzo, Pablo Torne, Mercedes Villalobos, Vicente Pedraza, Annie J. Sasco & Nicolas Olea. Breast cancer risk and the combined effect of environmental estrogens. *Cancer Causes and Control*. 15: 591-600, 2004.

For all of the above reasons, EDCs must be considered chemicals without safe levels of exposure.

SUMMARY

- Endocrine disruptors (EDCs) are chemicals capable of interfering with hormone balance.
- They act at very low doses, have multiple action mechanisms, and comprise an extensive group of substances with different chemical structures.
- A single EDC may have different action mechanisms depending on its concentration and on the specific developmental stage of the affected tissue. Adverse effects vary depending on the time of exposure and the hormonal balance of exposed individuals, determined by factors like sex and age.
- There are periods of particular vulnerability to EDC exposure. The most critical periods observed by researchers so far include the prenatal and perinatal. Effects of prenatal exposure might not develop until later in life. Adverse effects may also pass from one generation to another through genetic programming, e.g., epigenetic changes.
- Many EDCs cause adverse effects at very low doses, equivalent to current exposure levels in the population. Low-dose effects might differ from adverse effects caused by high-dose exposures.
- The general population is exposed to EDC levels that may have serious effects on health.
- The dose-poison rule does not apply to EDCs because many of these substances do not have a linear dose-response pattern, but have curve patterns (U or inverted U), which implies they may have toxic effects at high doses, no effect at medium doses, and adverse effects at low doses. Therefore, standard toxicity tests mandated by existing regulations do not detect the effects caused by EDCs at low concentrations.
- No safe exposure limit can be established for EDCs with nonlinear dose-response curves. Safe exposure levels established for other effects do not guarantee protection from endocrine disrupting effects.
- Adverse effects may be the result of combined action by different compounds that separately have no negative health impact, but when combined can cause a synergistic, antagonistic, or additive response.
- It is impossible to establish safe exposure thresholds for EDCs.

24 Bern, H et al. Op. Cit.

1.3. Effects on human health and wildlife

A significant body of scientific evidence shows that many EDCs studied to date have a wide range of effects on human health as well as on wildlife. This evidence is based on:

- Effects observed in wildlife species
- In vivo (animal) and in vitro (cell culture) tests
- Effects observed in humans
- Epidemiological studies

A report issued by the European Commission in February 2012[25] summarizes the following effects of EDCs on human health and wildlife.

1.3.1. Effects on human health

1.3.1.1. Damage to reproductive health

Damage to the male reproductive system

Exposure to EDCs is associated with three effects that are usually considered as a whole: (1) reduction of reproductive capability manifested by infertility and decrease of sperm quality; (2) changes in fetal development resulting in congenital deformity of the male genital tract such as chryptorchidism (failure of testicular descent) and hypospadias (abnormal placement of the male external urethral orifice); (3) the presence of testicular germ-cell tumors.

Reduced sperm quality

Joint studies carried out in several European countries show a continuous reduction of sperm quality by year of birth, with younger men showing the worst indicators. Approximately 20 percent of young men in Denmark and Germany show sperm concentrations below the 20 million per mililiter limit established by the WHO.

Chryptorchidism

Chryptorchidism (failure of testicular descent) is a male congenital deformity that is most common in newborn babies. The condition generally affects between 2 and 4 percent of children, but recent estimates show an increase of up to 9 percent in some countries. Researchers have observed an increased risk of chryptorchidism with prenatal exposure to DES, PCBs, polybrominated diphenyl ethers (PBDEs), heptachlor epoxide, hexachlorobenzene (HCB), and some pesticides, including DDT/DDE.

Hypospadias

Hypospadias affects between 0.2 and 4 percent of newborns. The action of androgenic hormones is essential to the proper development of the male external urethral orifice. A reduction of androgens causes the male urinary meatus to open anywhere along the urethral groove or even near scrotum.

Alterations in the female reproductive system

Exposure to EDCs, particularly during in utero developmental stages, is associated with precocious puberty, reduced fecundity, pregnancy complications, endometriosis, uterine fibroids (noncancerous tumors), as well as breast and ovarian cancer.

Precocious puberty

There is significant scientific evidence of the ability of certain synthetic chemicals to alter the programming of puberty during vulnerable developmental periods.

25 Andreas Kortenkamp et al. Op. Cit.

Precocious female puberty has increased over the last decades. The average age at menarche in Western Europe and in the United States in the 1990s was 14. This age had stabilized since the mid-20th century as a result of improved living conditions and nutritional habits in the population. However, since the 1990s to date, age at menarche has steadily fallen to 12 years, with signs of early breast development in 5-to-6-year-old girls.

Precocious puberty is associated with prenatal exposure to estrogenic EDCs.

Reduced female fecundity

Fecundity refers to the female ability to conceive, whereas fertility implies the potential to carry a pregnancy to term. Estimates show that at least one in ten European couples has difficulty conceiving, a significant cause of personal suffering and economic expense for families that seek assisted reproductive treatments.

Reduced fecundity is caused by damage to ova and alterations in the menstrual cycle. It is also associated with the alteration of neuroendocrine, endocrine, and paracrine processes that regulate ovogenesis, follicular development, and ovulation. Certain chemicals, such as organochlorine compounds, may alter these processes.

Polycystic ovary syndrome (PCOS)

Polycystic ovary syndrome (PCOS) is an endocrine disorder that affects several bodily systems and causes menstrual dysfunction, infertility, hirsutism, acne, obesity, and metabolic syndrome, among other medical conditions, with significant psychological, social, and economic impact. Polycystic ovary syndrome is the most common female endocrine disorder during the fertile period, with a prevalence of 18 percent in studied cases.

PCOS is associated with an excess of androgenic hormones. Androgenic EDCs include some flame retardants (hexabromocyclododecane, pentabromodiphenyl ether, and hexabromodiphenyl ether) and certain antibacterial agents such as triclosan, used in some cleaning products and soaps.

Reduced fertility and congenital damage

Fertility problems continue to grow among the European and Spanish populations, occasionally reaching epidemic levels.

Exposure to EDCs is related a series of disorders and medical conditions such as spontaneous abortion (miscarriage), ectopic pregnancy, fetal death, stillbirth, preterm birth, low birth weight, sex-ratio alterations (numbers of male and female babies), and congenital defects.

Miscarriages, preeclampsia, and intrauterine growth restriction (IUGR) are among the most common pregnancy complications caused by altered embryo implantation. Many researchers believe that these disorders are associated with the process of endocrine regulation (preparation of the uterus for pregnancy during the menstrual cycle).

Other endocrine disorders like diabetes, hypo/hyperthyroidism, oligomenorrhea, PCOS, hyperandrogenemia, and hyperprolactinaemia may be causes of miscarriage. Altered progesterone levels have also been associated with ectopic pregnancy and reduced fetal and placental growth, whereas altered estrogen levels are related to variation in sex ratios and certain kinds of congenital damage.

Some of the EDCs associated with fertility problems and congenital defects include DES, bisphenol A (BPA), organophosphorus compounds, organochloride compounds (DDT, pentachlorophenol, PCBs and PCDF), polybrominated biphenyls (PBB), and lead.

Endometriosis

Endometriosis is a common gynecological condition in which cells from the lining of the uterus (endometrium) appear and flourish outside the uterine cavity, most commonly in the abdominal cavity. It can cause chronic pelvic pain and infertility.

Endometriosis is believed to be caused by the combined effect of genetic predisposition, altered immune and hormonal response, and environmental factors. The prevalence of endometriosis varies between 6 and 15 percent of women of childbearing age, and is present in up to 50 percent of cases of pelvic pain and infertility. Endometriosis is associated with chemical exposure, namely to bisphenol A and B, phthalates, organochlorine pesticides, polybrominated biphenyls, polychlorinated biphenyls, and dioxins.

Uterine fibroids

Uterine fibroids (myomas) are noncancerous smooth muscle tissue tumors that originate in the smooth muscle layer (myometrium) of the uterus. Due to their location in the uterus and the pelvic cavity, they may cause menorrhagia (unusual and abnormally heavy menstrual periods), abdominal pain, pelvic organ prolapse, infertility, and complications during pregnancy. Uterine fibroids are the main reason for hysterectomy (surgical removal of the uterus). They affect 25 to 50 percent of women, and given their hormone-dependent nature, the role of EDC exposure in their development is a topic of medical interest. They have been associated with exposure to heavy metals, polycyclic aromatic hydrocarbons (PAHs), organochlorine pesticides, polychlorinated biphenyls, polybromated flame retardants (polybrominated diphenyl ethers or PBDEs), and bisphenol A.

1.3.1.2. Tumors in hormone-dependent organs

Breast cancer

The incidence of breast cancer has grown, causing great concern in industrialized countries.

Risk factors include reproductive determinants (age of menarche and menopause, number of children and age of first delivery, duration of the breastfeeding period), genetic predisposition, and exposure to environmental pollutants. The most critical periods are those in which breast tissue is more vulnerable, that is, during puberty and uterine development.

Although its development mechanism has not been accurately described, researchers have observed that breast cancer is hormone dependent and is associated with exposure to estrogenic EDCs such as polychlorinated biphenyls, polycyclic aromatic hydrocarbons (PAHs), dioxins, chlorinated furans, and organic solvents. Research conducted on Spanish women showed a relationship between breast cancer and the total load of estrogenic chemicals they are exposed to, proving that the combined effect of various pesticide compounds and chlorinated industrial chemicals affects breast cancer incidence, even though exposure to such chemicals separately does not (see the section on combined effects on page 13).

Prostate cancer

Prostate cancer is among the most frequent cancers in European men. There has been a dramatic increase of prostate cancer incidence in all European countries, reaching 24–114 cases per 100,000 inhabitants. Androgenic hormones play a key role in the etiology of prostate cancer. Research has shown that high levels of testosterone and its metabolite DHT increase prostate cancer risk. Prostate cancer incidence is related with exposure to EDCs, particularly organochlorine and organophospate pesticides during their manufacture and application, as well as to PCBs, cadmium, and arsenic.

Testicular cancer

Testicular cancer has reached epidemic proportions during the last three decades and has become the most frequent malignant neoplasms in men between ages 15 and 34, with a general incidence of 12 cases per 100,000 inhabitants in Europe. The reduction of androgenic action during the fetal period is among the risk factors.

Several organochlorine EDCs are associated with testicular cancer, among them p,p'-DDT, PCBs, and other organochlorine pesticides. As with breast cancer, the additive effect of exposure to a combination of estrogenic EDCs is considered a risk factor.

Thyroid cancer

Thyroid cancer is among the most prevalent diseases in young women. Its worldwide incidence is 1.18 per 100,000, lower than other tumors. Thyroid cancer is three times more frequent in women, affecting mostly those between ages 15 and 44. Genetics plays a key role as a risk factor but does not explain the sharp increase of this type of cancer in recent years.

Several EDCs act as thyroid antihormones, altering the availability of thyroid hormones. Exposure to chemicals that may alter the HPT (hypothalamus-pituitary-thyroid) axis contributes to the progression of the disease. Among the EDCs associated with thyroid cancer are several organochlorine compounds as dioxins, PCBs, pesticides, and solvents.

1.3.1.3. Alterations in the development of the neurological system

Disorders in the development of the neurological system include the following conditions:

- Cognitive, learning, and memory disabilities
- Autism, attention deficit-hyperactivity disorder (ADHD), mental retardation, and cerebral palsy
- Neurophysiological deficits: development milestones, cognitive functions, and behavioral problems
- Motor deterioration, memory loss, and subtle behavior changes
- Movement disorders (hypotonia, hyporeflexia, affected motor development), generalized slowing, and significant IQ deficit
- Sensory deficits including ototoxicity and vision defects
- Aggressive behavior
- Altered behavior during play
- Birth defects such as neural tube defects

U.S. data show an increase of neurological disorders during embryogenesis in recent years, of which some 25 percent are considered to be the result of a combination of genetic and environmental factors. Hundreds of thousands of children suffer from mental disabilities such as mental retardation, learning problems, autism, and ADHD.

Over 10 percent of children suffer from learning disabilities and 17 percent are affected by deafness (hearing impairment), blindness and vision problems, epilepsy, speech problems, and emotional disorders.

Endocrine mechanisms involved in neurotoxicity during embryogenesis include interference with neuroendocrine function (hypothalamus-pituitary), a key element in sexual and reproductive behavior, as well as interference with circulation hormones (thyroid hormones and the androgens/estrogens that regulate them).

The endocrine mechanism most commonly related with developmental neurotoxicity is thyroid disorder. A bibliographic search on 48 EDCs in 2004 showed that 50 percent of these chemicals had neurotoxic potential. Among them are organochlorine compounds (PCBs, dioxins, furans), brominated flame retardants (BFR), perchlorate, pesticides, bisphenol A, perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), phthalates, ultraviolet filters (4MBC, OMC, BP2 BP3), and heavy metals such as lead, mercury, and arsenic.

1.3.1.4. Metabolic disorders

Metabolic syndrome, diabetes, and obesity are three metabolic conditions associated with endocrine disruption whose global incidence has grown significantly. Obesity affects 150 million adults and 15 million children in Europe (20 percent of adults and 10 percent of infant population). Twenty-three percent of Spaniards over 18 are obese, a condition that affects 35 percent of the population over 65. In addition, 6 percent of Spanish adults suffer from diabetes, a disease whose treatment costs 6 percent of the Spanish healthcare budget.

Scientists have suggested several mechanisms by which chemical exposure contributes to obesity, such as the alteration of metabolic set-points, disorders of appetite control, and the alteration of lipid homeostasis during development. Although fetal development is a critical period (since the reprogramming of gene expression through epigenetic changes may favor future obesity problems), adult exposure to certain chemicals can also cause obesity.

The alteration mechanism associated with type 2 diabetes is the stimulation of estrogenic receptors ER-alpha from pancreatic ßeta cells, leading to excess insulin signaling. This can cause insulin resistance in the liver and muscles, as well as beta cell exhaustion.[26]

26 Angel Nadal, Paloma Alonso-Magdalenab, Sergi Sorianoa, Ivan Quesadaa, Ana B. Roperoa The pancreatic _-cell as a target of estrogens and xenoestrogens: Implications for blood glucose homeostasis and diabetes. Molecular and Cellular Endocrinology 304 (2009) 63–68 doi:10.1016/j.mce.2009.02.016.

EDCs that may influence the development of such conditions include pesticides and biocides (chlorpyrifos, diazinon, dichlorvos, and carbamates), phthalates, bisphenol A, polyphenols, metals and organometallic compounds (lead, arsenic, tributyltin), and other environmental and occupational pollutants such as diesel exhaust.

1.3.1.5. Neuro-immuno-endocrine disorders

A number of disabling disorders (myalgic encephalopathy, otherwise known as chronic fatigue syndrome or post-viral fatigue syndrome; fibromyalgia; and multiple sclerosis) have increased dramatically over the last few years, causing significant illness and suffering to the affected individuals and their families.

The global prevalence of myalgic encephalopathy (aka chronic fatigue syndrome and post-viral fatigue syndrome) is estimated at 0.004 percent—2.54 percent among the general population and 0.11–2.6 percent in primary care patients. Fibromyalgia, which predominantly affects women, has an incidence in the U.S. of 6.88 cases per 1,000 persons/year in men, and 11.28 cases per 1,000 persons/year in women. Multiple sclerosis mostly affects populations of European descent, its incidence increasing by 3.97 cases per 100,000 population as geographic latitude decreases.

The nervous, immune, and endocrine systems are closely related and regulate each other. Neuro-immuno-endocrine disorders can be attributed to adverse interactions between these systems, and associated with exposure to environmental pollutants, although they have not received the same level of attention as other medical conditions to date.

EDCs associated with neuro-immuno-endocrine disorders include polycyclic aromatic hydrocarbons (PAHs), organochlorine compounds (PCBs, dioxins, pesticides), metals, and organometallic compounds.

1.3.2. Effects on wildlife

Since the mid-twentieth century, scientists and naturalists have documented how different species (flora and fauna) in different regions of the planet suffer serious effects caused by endocrine disorders associated with exposure to EDCs.[27]

In 1952, American scientists observed a significant decline in the Florida bald eagle population, eventually concluding that 80 percent of bald eagles were sterile.

Otter populations in English rivers began to drop in the 1950s, with this decline continuing at least until the 1970s.

In the mid-1960s, female minks from mink farms on Lake Michigan suffered high mortality rates and reproductive failure as a result of being fed with fish from Lake Michigan tributaries contaminated with PCBs.

In 1970, scientists detected high pre-hatching mortality rates and deformities in 80 percent of herring gull chicks of Lake Ontario. Similar conditions were observed in lab chickens treated with dioxins.

In the early 1970s, female-female pairing was detected in western gulls of Southern California. This abnormal behavior was later observed in other species of birds in the Great Lakes, Massachusetts, and the Puget Sound.

In the late 1980s, researchers observed that only 18 percent of caiman eggs in Lake Apopka (Florida) were viable and that half of baby caimans died within ten days of birth. Sixty percent of males exhibited significantly reduced penis size, i.e., feminized features. Young females exhibited ovarian abnormalities and blood estrogen levels twice the normal for the species. An industrial accident at a Tower Chemical plant had caused a pesticide spill of dicofol and DDT into the lake in 1980.

In spring 1988, a sudden increase in seal mortality was noted in the North Sea region. The sudden death of thousands of seals was caused by a viral infection in 40 percent of the population. The epidemic was not as devastating in less polluted waters off the coast of Scotland.

Mediterranean striped dolphins were affected by a deadly viral epidemic in the early 1990s. Researchers observed elevated levels of PCBs in the dolphins' blood—two to three times higher than in healthy dolphins.

In the 1990s, British scientists observed widespread sexual disruption (feminization) of fish living near sewage treatment plants. The fish also exhibited abnormalities that were not observed in downstream fish. Scientists suspect that degraded detergents, plastics, alkylphenols, and other compounds routinely released into rivers are the cause of such abnormalities.

27 Colborn, Dianne Dumanoski, y John Peterson Myers. "Our Stolen Future" (New York: Penguin Books, 1996). Edición en castellano: Nuestro futuro robado, de Theo Colborn, Dianne Dumanoski y Pete Myers (1997); Ecoespaña y Gaia-Proyecto 2050, Madrid.

Effects on wildlife due to EDC exposure include:

Invertebrates

The most studied species regarding EDC exposure are arthropods and mollusks. Endocrine disorders observed in these species include imposex (development of male sex organs by female individuals eventually leading to sterility) and intersex (individuals with both male and female organs), larval mortality, inhibition of metamorphosis, and reduction of reproductive capability.

EDCs that cause endocrine disorders in arthropods include estrogenic EDCs such as BPA. EDCs with endocrine effects on mollusks include tributyltin and xenoestrogens (e.g., nonylphenol and octylphenol).

Fish

Induced intersex has been observed in fish exposed to effluents of wastewater discharges or sewage treatment plants. These fish also exhibit abnormally high concentrations of vitellogenin (VTG), a provider of egg yolk protein essential for their reproduction. Other effects of exposure to EDCs include altered sex ratios, thyroid disorders, and changes in sexual behavior in affected populations.

EDCs that may affect reproductive capability in fish include:

- Xenoestrogens (phenol derivatives with surfactant capacity such as nonyphenol, octylphenol, and propylphenol)
- Plastifying compounds (bisphenol A and phthalates)

- Mixed chemicals (natural and synthetic estrogens/alkynols/bisphenol A)
- Aromatase inhibitors such as TBT
- Anti-androgenic pesticides (vinclozolin, prochloraz, and fenarimol)

Exposure to UV filters (3-benzylidene camphor and 2-benzophenone) has recently been associated with endocrine disorders in fish.

EDCs that may alter fish growth and development include growth hormone disruptors such as PCBs and thyroid disruptors (perchlorate, PCBs, pesticides, and PFOS).

Amphibious species

Around 32 percent of known amphibious species are endangered. Environmental pollution is considered a major contributing factor.

Researchers have observed that EDC exposure in amphibious species (most commonly frogs, as the most studied species) leads to induced intersex and masculinization, changes in sexual behavior, and altered metamorphosis and development.

EDCs associated with endocrine disruption in amphibious species include:

- Antracine and organochlorine compounds
- The herbicide Roundup (glyphosate)
- Industrial pollutants (PCBs, PBDE, bisphenol A, phthalates, and effluents from waste treatment plants)

Reptiles

Endocrine disruption in reptiles due to EDC exposure is generally less explored. There exist some 8,225 known species of reptiles, of which 96 percent are snakes and lizards, 3.6 percent are tortoises, and 0.3 percent are alligators and caimans. EDC research on amphibious species focuses mainly on three of them: the American/Mississippi alligator (*Alligator mississippiensis*) and two species of freshwater turtles (the common snapping turtle, or *Chelydra serpentina*, and Reeve's turtle, or *Chinemys reevesii*).

EDC effects on alligators include altered sex ratios (feminization), altered steroid levels, and damage to the reproductive system such as reduced phallus size. EDCs like dicofol, DDD, DDE, and DDT are associated with these effects.

Known effects on turtles include altered sexual dimorphism due to exposure to organochlorine compounds.

Birds

The effects of DDT and its metabolites on birds were among the first types of environmental impact observed in wildlife, becoming widely known after the publication of Rachel Carson's book *Silent Spring* in 1962.

Exposure to EDCs causes reproductive disorders, altered egg development, and changes in the sexual behavior of birds.

Reproductive disorders caused by exposure to organochlorine-persistent organic pollutants, or POPs (DDT, PCBs, hexachlorobenzene [HCB], dioxins, and dieldrin) include abnormalities in sexual organs, altered sex ratio, and impaired fertility.

Thyroid disorders (associated with exposure to PCB, DDT, dioxins, and some PBDEs) are the cause of altered egg development.

Changes in sexual behavior of birds are associated with exposure to organochlorine pesticides, PCBs, and POPs.

Mammals

Mammalian exposure to EDCs has been explored mostly in sea mammals, polar bears, deer, and Mustelidae. In areas contaminated with POPs, the population of Cetaceans (whale family) and polar bears has diminished dramatically. These regions show a correlation between the loss of reproductive capability in Cetacea, Pinnipeds (e.g., seals), and Mustelidae, and POP concentrations in blood and tissues.

EDC exposure in mammals is associated with impaired fertility and abnormalities in the reproductive tract observed in deer and panthers in Florida. Thyroid disorders and lesions on the suprarenal glands have also been detected in these species.

Table 5. Relationship of chemicals of concern to human health/wildlife endpoints

Chemicals of concern	Investigated in connection with...																		
	Human Health Endpoints													Wildlife Endpoints					
	Male reproduct live health	Female precocious puberty	Female fecundity	Polycystic ovary syndrome	Female fertility	Endometriosis	Uterine fibroids	Breast cancer	Prostate cancer	Testis cancer	Thyroid cancer	Developmental Neurotoxicity	Metabolic syndrome	Invertebrates	Fish	Amphibians	Reptiles	Birds	Mammals
PCBs, PCDDs, PCDFs*	●	●	●		●	●	●	●	●	●	●	●	●		●	●	●	●	●
Polybrominated biphe-nylethers (PBDEs)	●	●					●			●		●	●			●		●	●
Perfluorinated com-puonds (PFCs)			●									●	●		●	●		●	
DDT/DDE	●	●	●		●	●	●	●	●	●		●	●		●	●	●	●	●
Other organochlorine pesticides	●		●		●	●		●		●	●	●	●		●	●	●	●	●
Organo-phosphate pesticides					●				●			●			●	●			
Carbamate pesticides					●				●		●			●	●				
Azole pesticides	●										●								
Phyrethroid pesticides									●										
Triazine herbicides															●	●	●	●	
Other pesticides	●		●		●				●		●	●		●	●	●		●	
Heavy metals	●	●	●		●			●	●			●						●	●
Alkylphenols, bisphe-nol A, parabens		●		●	●	●		●			●	●	●	●	●	●	●		
Phthalates	●	●			●	●	●			●		●	●		●	●			
Pharmaceutical estrogens	●				●	●	●	●	●	●	●	●	●	●	●			●	
Phytoestrogens		●	●			●	●	●	●		●	●						●	
Organotins													●	●	●				

*Polyclorinated biphenyls (PCBs), dioxins (PCDDs), furans (PCDFs)

Source: Andreas Kortenkamp A et al. STATE OF THE ART ASSESSMENT OF ENDOCRINE DISRUPTERS Final Report. Project Contract Number 070307/2009/550687/SER/D3. Annex 1. SUMMARY OF THE STATE OF THE SCIENCE. Revised version. Brussels: European Commission, DG Environment, 29 January 2012.

1.4. Hazardous chemicals and activities

Over 1,500 endocrine disrupting chemicals have been identified so far. These substances are found in common consumer products as well as in pesticides, biocides, industrial products, and environmental pollutants.
EDCs include:

- Traditional pollutants such as POPs (PCBs, dioxins, HCB, organochlorine pesticides, PFOS, PBDE)
- Solvents (styrene, perchloroethylene, trichlorobenzene)
- Metals (lead, cadmium, nickel, mercury, arsenic)
- Pesticides (organochlorine and organophosfate compounds, pyrethrins, pyrethroid)
- Plastics and their components (phthalates, bisphenol A)
- Ingredients in cosmetic and cleaning products (parabenes, triclosan)
- UV filters
- Components of detergents (alkylphenols)
- Environmental pollutants

Within the framework of the European Strategy on EDCs,[28] the European Commission ordered in 1999 the first scientific review of endocrine disrupting chemicals. The resulting list included 320 chemicals and groups identified as EDCs. The list can be consulted on the European Commission's website (http://ec.europa.eu/environment/endocrine/strategy/substances_en.htm#priority_list).[29] An update was published in April 2012.

The OECD adopted a work program to develop methods for the identification of EDCs and created a conceptual framework as well as several guidebooks.[30] The guidebooks do not include all of the health effects associated with EDCs (e.g., hormone-dependent cancers, diabetes) nor all fetal development effects.

Several NGOs and trade unions have published EDC lists based on reviews of scientific literature:

TEDX is an organization founded by Theo Colborn, a zoologist and co-author of Our Stolen Future (1997), that disseminates information about the grave effects of EDCs on human health and wildlife. TEDX's website includes a list of 1,517 endocrine disrupting substances supported by scientific evidence[31] (http://www.endocrinedisruption.com/endocrine.TEDXList. overview.php).

RISCTOX is a database developed by ISTAS that includes EDC lists published by the EU and various organizations, including Scorecard and Our Stolen Future. It is available in Spanish at http://www.istas.net/risctox/index.asp

Table 6 shows some of the most common EDC groups.

28 Community Strategy for Endocrine Disrupters. A range of substances suspected of interfering with the hormone systems of humans and wildlife COM (1999)706 final. COMMISSION OF THE EUROPEAN COMMUNITIES. Brussels. 17.12.1999
29 http://ec.europa.eu/environment/endocrine/strategy/short_en.htm
30 OECD. Conceptual Framework for Testing and Assessment of Endocrine Disrupters. http://www.oecd.org/env/chemicalsafetyandbiosafety/testingofchemicals/50067203.pdf
31 http://www.endocrinedisruption.com/endocrine.TEDXList.overview.php.

Table 6. **Uses of EDCs most commonly found in consumers' products and workplaces**

FAMILY	CHEMICAL	USE	CONSUMER PRODUCTS	OCCUPATIONAL ACTIVITIES
PERSISTENT ORGANIC POLLUTANTS (POP)	PCBs	Use is prohibited. Still found in some transformers and electric condensers that use dielectric oil, and in electric parts and construction material residues. PCBs are also residual byproducts resulting from industrial processes. Waste incineration is a significant source of PCBs.	Sealing and insulating compounds used in old electric equipment (buildings) Pollutant in fatty food products.	Storage, transport and management of equipment and material contaminated with PCBs: Electric maintenance Metal / machinery Waste management
	POLYCHLORINATED DIBENZODIOXINS (PCDDs)	Residual byproduct from waste and chlorine–based material incineration/ metal recycling and manufacture/ paper and paper pulp manufacture, chlorophenols, chlorinated herbicides/ chlorine production plants with graphite electrode systems.	Food pollutant	Chemistry Paper and paper pulp manufacture Waste management Metal
	PBBs PBDE	Brominated flame retardants used in plastic and textile products: - Electric and electronic circuits - Car wiring and upholstery /Upholstery in train seats - Panels, carpets and aircraft floor panels - Thermal insulators used in roofs, façades, floors and pipelines - Coating materials used in construction	Upholstery Electric and electronic equipment Construction materials (insulation) Car seat foams Pollutant in household dust	Manufacture of electric and electronic equipment Transport of wires and cables Construction Manufacture and maintenance of transport equipment
	ORGANOCHLORINE PESTICIDES (DDT, Hexachlorobenzene, Chlordane, Chlordecone, Mirex, Toxaphene, Lindane, Linuron, Acetochlor and Alachlor)	Most commercial applications are prohibited DDT is still used to control malaria Hexachlorobenzene is an industrial byproduct of chlorine	Pollutant in food	Chemical industry Waste management
	PERFLUORINATED COMPOUNDS (PFos, pfoa)	Multiple uses due to its waterproof and non-stick properties: Non-stick kitchen ware Fire fighting foam Waterproof and non-stick coatings in textile, paper and leather products; waxes, varnishes, paints, cleaning products; coating of metal surfaces and carpets Manufacture of semiconductors Photolithography Hydraulic fluids	Non-stick kitchen utensils Textiles, carpets Dental floss Car seats Food pollutants	Chemical industry Manufacture of plastic items Textile industry Metal industry Printing Electric sector Waste management Fire fighting Galvanization
UBICUOUS (SHORT-CYCLE) POLLUTANTS	PHTALATES (BBP, DBP, DEHP)	Mainly used in PVC plasticizers, cellulose, polyvinyl acetate and polyurethane Component in certain coatings; insecticides and insect repellents; perfumes, nail polish, hairspray and other cosmetics Lubricant agent in textiles	PVC products: toys, textile, carpets, curtains, floors, hoses, pipelines, windows, etc. Paints and cosmetics Soft plastic toys, putty Food pollutants Pollutant in household dust	Manufacture of plastic items Textile industry Metal industry Manufacture of cosmetics Cleaning services
	BISPHENOL-A	Used as a raw material in the manufacture of paints, epoxy resin plastics and polycarbonates Intermediate product in the manufacture of fungicides, anti-oxidants, dyeing compounds, phenoxy resins, polyester, and flame retardants	It may be released from plastic coatings in canned products, food containers and utensils made of polycarbonate Thermal paper printing (faxes and credit card machines) Dental sealing compounds Pollutant in food Pollutant in household dust	Chemical industry: manufacture, use, transport and packaging of Bisphenol A. Construction Metal industry Plastic industry

FAMILY	CHEMICAL	USE	CONSUMER PRODUCTS	OCCUPATIONAL ACTIVITIES
	ALKYLPHENOLS (nonylphenol ethoxylate, octylphenol ethoxylate and their metabolites (nonylphenol and octylphenol)	Raw material in the manufacture of detergents; emulsifiers, moisturizers and dispersing agents in paints and fungicides PVC anti-oxidants and stabilizers Additive in lubricant oils and contraceptive foams	Detergents Clothes Household pollutant	Chemical industry Cleaning services Agriculture Construction Manufacture and transformation of PVC
COSMETICS AND HYGIENE PRODUCTS	PARABENS ethylparaben, butylparaben, methylparaben and propylparaben	Preservatives used in cosmetic, pharmaceutical and personal hygiene products	Shampoos, hair conditioners, lotions, creams, gels and other beauty products	Chemical Industry Hairdressing Beauty products
	TRICLOSAN 5-chloro-(2,4-dichlorophenoxy) phenol	Antimicrobial agent	Soaps and detergents Deodorants Toothpaste Cosmetics Textiles and plastics	Chemical Industry Hairdressing Beauty products
	Musk Musk xylene (MX) Musk ketone (MK) galaxolide (HHCB) tonalide (AHTN)	Fragances	Perfumes Colognes Cosmetics Hygiene products Air fresheners Fragrances in consumers articles and toys	Chemical industry Retail business Hairdressing Beauty products
	UV SCREENS Benzophenone (BP2) Benzophenone -3 (BP-) 4 methylbenzyliden camphor (4MBC) octyl methoxicinnamate (OMC)	Sunscreens	Sun blocks	Agriculture Construction Gardening Maintenance Fishing
PESTICIDES, BIOCIDES AND HERBICIDES	ORGANOPHOSPHATE PESTICIDES (parathion, malathion, chlorpyrifos, diazinon, Dichlorvos, etc.) CARBAMATES PYRETHRINES AND PYRETHROIDS HERBICIDES GLYPHOSATE, ATRAZINE, etc. FUNGICIDES VINCLOCIN AND OTHERS	Fungicides, insecticides, molluscicides, herbicides, disinfectants	Pesticides Gardens and orchards Polluted food	Manufacture of agro-chemical products Agriculture Forestry Gardening Building fumigation Cleaning services Maintenance services
	Tributyltin	Molluscicides used as anti-fouling agent in ships hulls, buoys, docks. Biocide in bricklaying Disinfectants Biocide in cooling systems, refrigeration towers in power plants, paper and paper pulp plants, breweries, tanning and textile industries		Naval sector (shipyards) Fishing Construction Cleaning services Cleaning and maintenance of refrigeration towers
INDUSTRIAL PRODUCTS	SOLVENTS 1,2,4- Trichlorobenzene perchloroethylene octachlorostyrene	Solvents are used in industry as degreasing and cleansing agents and as diluting and carrying agents Solvents are contained in multiple products (paints, varnishes, glues, adhesives, paint strippers, lacquers, insecticides, herbicides, cleaning and dry cleaning products	Paints, varnishes, glues, adhesives, paint strippers, lacquers, insecticides, herbicides, cleaning and dry cleaning products	Chemical industry Metal sector Textile industry Leather industry Cleaning services Manufacture of electric and electronic parts
	RESORCINOL	Manufacture of special adhesives and adhesion improvers for tires and wood Manufacture of dyeing inks, pharmaceutical skin products	Adhesives	Wood industry Automobile industry Textile Pharmaceutical industry

FAMILY	CHEMICAL	USE	CONSUMER PRODUCTS	OCCUPATIONAL ACTIVITIES
	STYRENE	Main use in the manufacture of polystyrene and styrene copolymers Additional uses: manufacture of paints, lacquers and varnishes; paper industry; manufacture of birch panels and polymer industry	Paints, lacquers and varnishes Polystyrene foams	Production of styrene and polystyrene Manufacture, transformation and application of plastics Maintenance and cleaning of related industries
	CHLORINATED PARAFFINS	Cutting fluids in the metal industry Flame retardants and rubber additives, paints, coatings and sealing compounds Dielectric fluids	Construction materials	Metal sector Chemical industry Manufacture, transformation and application of plastics Construction Electric material
METALS	LEAD	In metal form is used in sound and radiation barriers, ammunition, wheel and fishing weights, roof coatings and electronic components Used in metal finishing and welding for metal alloys Used in chemical compounds as component of batteries and accumulators; PVC's rubber and resins; paints, varnishes, polishes and glass	Batteries Hard PVC products: blinds Paints Toy paints Costume jewelry Fish, seafood and other food products	Metal Foundries Chemical industry Waste management Glass manufacture Construction
	CADMIUM	Manufacture of nickel cadmium batteries Coatings in galvanoplasty Pigments (is used as yellow pigment) Low fusion alloys Welding Phosphorescent compounds in TV sets Semiconductors Stabilizers in plastics like PVC Pigments in paint manufacture (acrylic, oil)	Batteries PVC products Paints Toy paints Costume jewelry Fish, seafood and other food products	Metal Industry
	NICKEL	Stainless steel manufacture Alloys Rechargeable batteries Catalysis Coin minting Metal coatings and foundry	Batteries Consumption of fish, seafood and other food products	Chemistry Metal Industry Waste management
	MERCURY	Chlorine manufacture (chlorocaustic industry) Manufacture of vinyl chloride Batteries Dental amalgams Instruments of measure and control	Dental amalgam Consumption of fish, sea food and other food products	Chemistry Metal Industry Waste management
	ORGANOSTATIC COMPOUNDS Tributyltin (TBT)	Molluscicide used anti-fouling agent in ship hulls, buoys, shipyards, etc. Biocide in cooling systems, refrigeration towers in power plants, paper and paper pulp plants, breweries, tanning and textile industries	Consumption of fish, sea food and other food products	Naval sector Fisheries Construction Cleaning Cleaning and maintenance of refrigeration towers
METALLOIDS	ARSENIC	Wood preservative Semiconductor and LED Additives in lead and brass alloys Insecticide (arsenite in lead compounds) Herbicides (Sodium arsenite) Pigments and fireworks De-staining solution in glass manufacture	Consumption of fish, sea food and other food products	Chemistry Metal Foundry Waste management Electric maintenance Pyrotechnics

1.5. Exposure to endocrine disruptors in Spain

Population exposure

Several studies on the exposure of the Spanish population to endocrine disruptors have been published in recent years.32 Two of these studies, conducted in the Canary Islands33 and Catalonia,[34] determined the level of concentration of some EDCs in a representative population sample, offering a first glimpse of the social and health significance of population exposure.

The study of the Catalonian population, conducted by Dr. Miquel Porta, analyzed 19 organochlorine compounds (DDT and similar compounds, some PCBs, pentaCB, HCB derivatives, and certain HCH isomers) with endocrine disrupting capability in a sample of 919 persons. At least 3 EDCs were detected in all of the analyzed individuals. Eleven of the 19 analyzed compounds were detected in approximately 60 percent of the population, and all 19 compounds were found in 0.05 percent of the sample population. Over 85 percent of the Catalonian population studied exhibited detectable levels of p,p'-DDT, p,p'-DDE, PCBs 118, 138, 153, 180, HCB, and ß-HCH, whereas two chemicals were detected in the totality of samples. **These results matched those found in similar studies, and data suggest overall exposure of the population to a mix of EDCs.**

Detected concentrations vary depending on the chemical, the individual, and factors like sex, age, and educational level (e.g., the average highest concentration of PCBs was of 0.21 ng/g and for p,p'-DDE it was of 399ng/g). Chemicals with the highest concentrations detected were p'-DDE, HCB, and ß-HCH, with individuals exhibiting levels that were 7,700/6,000 and 2,000 times higher than the rest of the group. Women showed higher concentrations of these three compounds, whereas men showed the highest levels of PCBs.

Individuals with lower educational levels exhibited higher concentrations of these pollutants. Researchers noted a decline in the concentration of the all the eight POPs as the educational level of individuals increased.

The average concentrations detected (between 0.21 ng/g PCBs and 399 ng/g DDE) exceed the 10ng/g [35] level at which these chemicals have estrogenic effect.

Exposure during the most vulnerable periods

Fetal sensitivity to EDC exposure has been explored in previous sections. The Spanish Childhood and Environment Project (INMA) includes a significant number of researchers who study the role of environmental pollutants and their effects on children's growth and development. Some studies explore the presence of EDCs in the placenta and umbilical cord blood, which may provide a perspective on in utero exposure to endocrine disruptors.

A research team studying environmental pollutants and led by Dr. Nicolás Olea analyzed the presence of 16 pesticides with endocrine disrupting potential in 150 placenta samples from Andalusian women. At least one pollutant per sample was detected, with an average of eight pesticides per placenta. Concentrations fluctuated between 0.24 and 5.11ng/g (for aldrin and endosulfan diol), with maximum concentrations between 1.39 and 28.29 ng/g (endosulfan ether and p,p'-DDE).[36]

The same research team analyzed residues of endosulfan (a persistent organic pesticide with estrogenic effects) in umbilical cord blood from 200 women who gave birth in public hospitals of Granada and Almería (southern Spain). The pesticide was found in 81 percent of the samples, with an average concentration of 13.23 ng/ml and maximum concentrations of 83.22 ng /ml.[37]

Project INMA also analyzed infant exposure to mercury, an endocrine disrupting metal that alters thyroid hormone delivery, interferes with

32 M. Porta, E. Puigdomènech and F. Ballester (Eds.) Nuestra contaminación interna. Concentraciones de compuestos persistentes en la población española. Madrid: Los libros de la Catarata, 2009.
33 Ibid 32, Pp 71.
34 Porta M, Puigdomènech E, Gasull M y Bosch de Basea M. Op. Cit.
35 Ana M. Soto and Carlos Sonnenschein. Op. Cit.
36 López Espinosa MJ, Granada A, Carreno J, Salvatierra M, Olea-Serrano F, Olea N. Organochlorine pesticidas in placentas from Southern Spain and some related factors. *Placenta*. 2007:28:631-8.

sexual hormones, and causes neurodevelopmental disorders. A study led by doctor Ferrán Ballester analyzed mercury in hair samples of 218 newborns and pre-school-age children, and detected a total average of mercury (THg) in hair of 0.94 μg/g, which varied from 0.19 to 5.63 μg/g in pre-school-age children. The average detected in newborns was of 1.68 μg/g (0.13–8.43 μg/g).[38] In 42 percent of infants analyzed, mercury levels exceeded the reference dose (1 μg Hg/g of hair). Another study in the same project analyzed mercury in the umbilical cord blood of 1,683 newborns and detected an average level of 8.4 μg/L de THg.[39] Sixty-four percent of infants had in utero exposure to levels that exceeded 5.8 micrograms of methylmercury per liter of blood (the level considered admissible by the U.S. Environmental Protection Agency). The concentration of mercury in the blood of Spanish infants is among the highest in the world and is associated with increased fish consumption during pregnancy.

INMA's researchers assessed the effects of prenatal exposure and observed higher PCB levels in children with psychomotor disorders.[40,41]

SUMMARY

- The results of published studies on EDC exposure show that the general population is in fact exposed to a mixture of EDCs. EDCs are found at different levels in individuals, depending on factors like sex, age, educational level, and social status, but they exceed, both on an individual and collective scale, the concentration levels known to cause endocrine disruption. Pregnant women and infants are the most vulnerable population groups due to the high EDC concentrations they are exposed to. If the additive or combined effect is considered, the levels of EDCs in the Spanish population are of great concern.
- Differences in EDC concentration by sex, social status, and educational level show the potential of social and public health intervention to reduce exposure. The results of studies on exposure to EDCs should lead to public health measures to reduce the level of population exposure.

37 Ibid 32, Pp 81.
38 Díez S, Delgado S, Aguilera I, Astray J, Pérez-Gómez B, Torrent M, Sunyer J, Bayona JM. Prenatal and early childhood exposure to mercury and methylmercury in Spain, a high-fish-consumer country. *Arch Environ Contam Toxicol*. 2009 Apr; 56(3):615-22. Epub 2008 Oct 4.
39 Llop S, Guxens M, Murcia M, Lertxundi A, Ramon R, Riaño I, Rebagliato M, Ibarluzea J, Tardon A, Sunyer J, Ballester F; INMA Project. Prenatal exposure to mercury and infant neurodevelopment in a multicenter cohort in Spain: study of potential modifiers. *Am J Epidemiol*. 2012 Mar 1;175(5):451-65. Epub 2012 Jan 27.
40 Llop S, Guxens M, Murcia M, Lertxundi A, Ramon R, Riaño I, Rebagliato M, Ibarluzea J, Tardon A, Sunyer J, Ballester F; INMA Project.Prenatal exposure to mercury and infant neurodevelopment in a multicenter cohort in Spain: study of potential modifiers. *Am J Epidemiol*. 2012 Mar 1;175(5):451-65. Epub 2012 Jan 27.
41 Forns J, Lertxundi N, Aranbarri A, Murcia M, Gascon M, Martinez D, Grellier J, Lertxundi A, Julvez J, Fano E, Goñi F, Grimalt JO, Ballester F, Sunyer J, Ibarluzea J. Prenatal exposure to organochlorine compounds and neuropsychological development up to two years of life. Environ Int. 2012 Sep 15;45:72-7. Epub 2012 May 9.

Environmental exposure

There are no specific databases documenting environmental exposure to chemical pollutants in Spain. A comparative description of the current state of affairs in this field can be obtained from different emissions/waste registers and from research on pollutants conducted by various scientific teams.

Table 7. Emissions of selected EDCs in the Spanish Register of Emissions and Pollutant Sources (PRTR-España), 2010 (tonnes/year)

Pollutant	Air emissions	Water emissions
POP	33,75	0,53
NPE and NP		0,99
OPE and OP		0,2
Arsenic	4,77	3,23
Cadmium	1,5	0,6
Mercury	2,1	0,5
Lead	40,94	8,4

Source: Own research based on data from the Spanish PRTR register.

Table 8. EDC concentrations (ng/l) in surface waters (Spain, 2011)

	Barcelona	Mora la Nova (Tarragona)	Bertamirans (La Coruña)
2,4-D	44,21	27,39	27,17
PFOA	42,7	1,65	5,81
PFOS	253,97	3,84	6,17
Atrazine	Non-detectable (nd)	79,63	nd
Carbamate	127,84	9,66	157,49
Sulfamethoxazole	218,5	11,29	415,89
Simazine	54,56	34,58	nd
Diuron	278.43	14.32	166.65
NPE1C	654.18	864.28	988.47
Nonylphenol (NP)	305.29	nd	157.75
Bisphenol A	81.75	nd	nd
tert-OP	191.29	nd	nd

Source: http://fate.jrc.ec.europa.eu/monitoring/monitoring-overview

The Spanish Register of Emissions and Pollutant Sources (PRTR-España)[42] provides information on air, water, and soil emissions for 90 polluting substances and groups from a limited number of activities and industrial facilities that are compelled by law to notify and publish such information (Law 16/2002 on Integrated Pollution Prevention and Control). Table 7 shows data on total emissions of some EDCs included in the register in 2010.

The PRTR register does not include information on the use of pesticides. Estimates compiled by the AQUATERRA Project indicate that only atrazine and simazine (EDC pesticides commonly used in corn and vine crops) represent respective annual loads in the Ebro River of 800 and 500 kg.[43]

The Environment and Sustainability Institute of the European Commission's Joint Research Center controls the presence of water-borne pollutants to assess the impact of the EU environmental policies.[44] Table 8 shows data on EDC concentrations in Spanish surface waters.

Other EDC compounds detected in Spanish rivers by university and research center studies include:[45]

- Pesticides (atrazine, simazine, 2,4-D, MCPA, mecoprop and propanyl)
- Detergents (alkylphenols)
- Cleaning products (triclosan)
- Industrial pollutants (PDBE, short-chain chloroparaffins)

Researchers have linked the presence of EDCs (alkylphenol) in wastewater to the feminization of several fish species in Spanish rivers. Similarly, alkylphenols and TBT are associated with feminization observed in mollusks.[46]

Household exposure

Research published by Greenpeace on dust samples collected in 22 Spanish households detected phthalates, alkylphenols, organostatic compounds, brominated flame retardants, chloroparaffins, and other organic compounds in all samples. Samples were collected in Madrid, Granada, Valencia, Asturias, and León (see Table 9).[47]

42 Registro PRTR España http://www.prtr-es.es.
43 L Damià Barceló y María José López de Alda. Contaminación y calidad química del agua: el problema de los contaminantes emergentes. PANEL CIENTÍFICO-TÉCNICO DE SEGUIMIENTO DE LA POLÍTICA DE AGUAS. Universidad de Sevilla, 24 de enero de 2008.
44 http://fate.jrc.ec.europa.eu/monitoring/monitoring-overview
45 Laura Vandenberg. Op. Cit.
46 Marieta Fernández. Detergentes. Ponencia en el curso Plásticos, detergentes, cosméticos y otras hormonas. UNIVERSIDAD INTERNACIONAL DE ANDALUCÍA - CURSOS DE VERANO. Universidad de Granada-Hospital Universitario S. Cecilio. Sevilla, 14 a 18 Septiembre 2009.
47 Santillo D, Labunska I, Fairley M y Johnston P. Consumiendo química. Las sustancias peligrosas en el polvo doméstico como indicador de la exposición química en el hogar. Madrid: Greenpeace España. 2003.

Each granule of dust contained an average of 1 milligram of these pollutants, although concentration rates of individual chemicals varied depending on the sample.

Table 9. EDC (ng/g) in 22 samples of household dust (Spain)

	Median	Rank
Phthalates (total)	706.2	291-2.644
Alkylphenols (total)	<0,1	<0.1-4,5
Organostatic compounds (total)	1.495	1.125-1.958
Brominated flame retardant (HBCD)	225	190-850
Chlorinated paraffins	25	17-41

Source: Based on Santillo D, Labunska I, Fairley M y Johnston P. Consumiendo química. Las sustancias peligrosas en el polvo doméstico como indicador de la exposición química en el hogar. (Hazardous chemicals in household dust) Madrid: Greenpeace. Spain, 2003

Although comparatively fewer studies have been conducted on exposure through air and household dust than on exposure via food ingestion, results indicate that household concentrations might be primary sources of exposure to some pollutants (organostatic compounds, brominated flame retardants, chloroparaffins).

Results also show extensive EDC contamination of Spanish households. Contact with household dust can be a significant source of exposure, especially for infants, whose metabolism and social behavior imply direct contact, inhalation, and ingestion of pollutants contained in dust.

Exposure through food ingestion

Food is considered a primary source of exposure of the general population to POPs and certain metals. Research studies on the ingestion of pollutants conducted in Catalonia[48] and Andalusia[49] provide data on exposure to some EDCs through food ingestion in Spain.

The following tables show the results of a study on the population's diet carried out by the government of Catalonia in 2005.

Table 10. Concentration of EDC metals in food, Catalonia (µg/g fresh weight)

Food	Arsenic	Cadmium	Mercury	Lead
Meat and meat products	0,0200	0,0063	0,0123	0,0243
Fish and seafood	2,2100	0,0362	0,0970	0,0512
Vegetables	0,0015	0,0050	0,0005	0,0163
Tubers	0,0130	0,0198	0,0030	0,0259
Fruit	0,0015	0,0009	0,0005	0,0126
Eggs	0,0150	0,0080	0,0080	0,0150
Milk	0,0060	0,0015	0,0030	0,0060
Dairy products	0,0225	0,0060	0,0115	0,0225
Bread and cereals	0,0424	0,0329	0,0300	0,0242
Legumes	0,0015	0,0005	0,0005	0,0077
Fats	0,0917	0,0080	0, 0300	0, 0300

Source: Contaminants químics, estudi de la dieta total a Catalunya. Generalitat de Catalunya, 2005. (Food pollutants in Catalonia)

Table 11. Concentrations of organic EDCs in food, Catalonia (µg/g fresh weight)

Food	Dioxins (WHO-TEQ)	PAH (µg/kg)	HCB (µg/kg)	PBDE (µg/kg)	Polychlorinated naphthalenes (µg/kg)
Meat and meat products	0,08	13,434	173,2	102,4/116,1	17,59
Fish and seafood	0,321	7,894	256,4	325,3/342,5	39,49
Vegetables	0,01	0,887	5,8	5,2/10,5	3,38
Tubers	0,021	3,606	1,3	0/14,8	2,87
Fruit	0,016	0,946	0,7	0/11,5	0,71
Eggs	0,071	2,423	182,2	58,3/70,00	23,42
Milk	0,014	1,532	12,9	13,2/20,6	0,37
Dairy products	0,235	6,636	869,3	34,1/61,8	36
Bread and cereals	0,106	14,454	10,6	0/71,4	71,06
Legumes	0,023	2,742	0,6	2,0/19,4	3,33
Fats	0,303	8,683	136,9	569,3/606,0	447,1

Source: Contaminants químics, estudi de la dieta total a Catalunya. Generalitat de Catalunya, 2005.

48 Contaminants químics, estudi de la dieta total a Catalunya. Generalitata de Catalunya, 2005. http://www.gencat.cat/salut/acsa/html/ca/dir1538/doc10834.html

49 Carmen Cabrera Vique y Miguel Navarro Alarcón. Presencia de metales pesados en la dieta: un control necesario en Alimentación, medio ambiente y salud. Observatorio DKV de Salud y Medio Ambiente y ECODES, 2008.

The results of pollution prevention program studies of Spanish food products show a marked presence of EDCs in all food categories, particularly fish, seafood, and fats. They also show an increase in the number of contaminated samples, as well as the number of pollutants found in different food products.

All of the food analyzed contained EDC residues, but the most contaminated category was by far fish and seafood. Oils, fats, dairy products, and meat showed high EDC concentrations due to the lipophilicity of many organic EDCs, which favors their accumulation in fat.

Studies show that the ingestion of pollutants falls within safe levels established for each chemical in adults. However, in the case of children, the levels of ingestion of dioxins and polychlorinated biphenyls exceed those considered safe.

When assessing the ingestion of such pollutants, however, it must be noted that safety levels were established for effects other than endocrine disruption. As described previously, EDCs can have effects at very low doses. Nor does the assessment of ingestion take into account the combined effects of different EDCs. Table 12 shows different pesticides detected in food in Barcelona (2010) during a research program on health and food quality carried out by the Municipal Healthcare Agency (ASPB).[50]

The results of this study show an increase in the number of food samples that failed to comply with acceptable levels of residues and pesticides (see Table 13).

Table 12. Pesticides and metabolites detected in food, Barcelona, 2010

Pesticides and metabolites detected in food, Barcelona, 2010	
Children's foods containing vegetables	Heptachlor epoxide
Cereales y derivados	Ethyl chlorpyrifos, deltamethrin, diphenylamine, pyrimiphos methyl, tebuconazole
Vegetables	Azoxistrobín, boscalid, carbendazim (carbendazim + benomil), cipermetrín, etil-clorpirifòs, clortalonil, dimetomorf, fenhexamida, imidacloprid, iprodiona, miclobutanil, oxamil, piriproxifèn, tebuconazole, tiabendazole, triadimenol
Fruit	Azoxystrobin, boscalid, buprofezin, carbendazim (carbendazim + benomyl), cyporoconazole, difenylamine, dimethoate, fenhexamid, fludioxonil, imazalil, imidacloprid, iprodione, omethoate, procymidone, propargite, tiabendazole, triadimenol
Dried fruit	Bifenthrin, carbendazim (carbendazim + benomyl), cyprodinil, fenhexamid, fludioxonil, iprodione, myclobutanil, penconazole, pyrimethanil, pyrimiphos methyl, procimidone
Spices	Pyrimiphos methyl
Fresh fish	DDE p-p'

Source: La Vigilància i el control de plaguicides en productes alimentaris i pinsos d'origen vegetal i animal a Catalunya. Periodo 2009-2010. Generalitat de Catalunya. (Surveillance and control of pesticides in food products, catalonia 2009-2010).

50 La Vigilància i el control de plaguicides en productes alimentaris i pinsos d'origen vegetal i animal a Catalunya. Periodo 2009-2010. Generalitat de Catalunya. http://www.gencat.cat/salut/acsa/html/ca/dir2911/svc_plaguicides2009-2010.pdf

Table 13. Pesticides detected in food, Catalonia 2004–2010

Year	Analyzed samples	No. of analyzed pesticides and metabolites	No. of different pesticides and metabolites detected	Samples without detectable residues	Samples with residues ≤ MRL	Samples with residues ≥ MRL
2004	285	23-85	6	273 (96%)	8 (3%)	**4 (1%)**
2005	169	40-104	17	135 (80%)	31 (18%)	**3 (2%)**
2006	243	23-106	22	183 (75%)	50 (21%)	**10 (4%)**
2007	178	23-106	25	140 (79%)	31 (17%)	**7 (4%)**
2008	251	24-110	25	208 (83%)	40 (16%)	**3 (1 %)**
2009	335	42-192(1)	32	273 (82%)	48 (14%)	**14 (4%)**
2010	225	42-199(1)	36	161 (72%)	166 (26%)	**5 (2%)**

Source: La Vigilància i el control de plaguicides en productes alimentaris i pinsos d'origen vegetal i animal a Catalunya. Periodo 2009-2010. Generalitat de Catalunya.

Research suggests that food is an important source of EDC exposure in the human population. This type of exposure affects children in particular, whose ingestion of some pollutants (PCBs and dioxins) might exceed the recommended levels of exposure established for other categories.

Occupational exposure

There are few studies on occupational exposure to EDCs in Spain. Epidemiological studies relate some infant health disorders with parental occupation. Additionally, studies on male fertility in industrial sectors (pharmaceutical, plastics, and particularly agriculture) associate reproductive disorders and prostate cancer with pesticide exposure.

There are no available data with which to estimate occupational exposure to EDCs, however the existing information, although fragmented, could help outline significant traits in this field.

Despite a lack of specific data, it is reasonable to assert that endocrine disruptors affect a vast array of occupations. A recent job exposure matrix developed by British researchers estimates that exposure to EDCs is possible or probable in 102 different occupations.[51] According to such estimates, workers in at least 46 occupations would be exposed to EDCs, with exposure to metals in 45, and exposure to PAH, ethylene glycol, and others in 32 (see Table 14).

51 M. M. Brouwers, M. van Tongeren, A. A. Hirst, et al. Occupational exposure to potential endocrine disruptors: further development of a job exposure matrix. *Occup Environ Med* 2009 66: 607-614.

Table 14. Occupational exposure to EDC groups

EDC group	Uses/exposure
PAH	Produced by incomplete carbon combustion in diesel fuel Tar industry
Chlorinated organic compounds	By-product in waste incineration, industrial processes (metal, solvent, and pesticide production)
Pesticides	Agriculture Wood treatment Disinfection
Phthalates	Plastic industry Production and use of solvents, cosmetics, adhesives, and inks
Organic solvents	Production and use of paints, adhesives, and lacquers Production and use of resins Production and use of polystyrene plastics Metal degreasing Cleaning products
Bisphenol A	Polycarbonate plastics Production and use of epoxy resins
Alkylphenols	Production and use of pesticides, detergents, and cosmetics
PBDE	Production of PCBs, polyester, and rubbers
Metals	Electric and electronic industry Construction Manufacture of batteries Ink production and use Dental amalgam Pesticides

Source: M. M. Brouwers, M. van Tongeren, A. A. Hirst, et al. Occupational exposure to potential endocrine disruptors: further development of a job exposure matrix. *Occup Environ Med* 2009 66: 607-614.

Other examples come from a Spanish job exposure matrix (MATEMESP) that is currently being developed.[52] The matrix estimates that up to 50 percent of employees classified under the categories "painters, varnishers, wallpaper fitters and similar" and "floor layers, welders and similar" might be exposed to aromatic hydrocarbons like toluene and xylene. Furthermore, 30 percent of employees in the category "upholsterers, mattress manufacturers and similar" or 43 percent of "machinery operators in shoe manufacture" would be exposed to aliphatic hydrocarbons such as turpentine, naphtha, and hexane.

No exact data on economic activity is available to researchers, but some studies conducted by the Federation of Healthcare and Social Workers (CC. OO.) trade union provide information of interest. A study in the textile sector detected 17 endocrine disrupting chemicals, such as ethyl benzene, dichloromethane, and vinyl acetate (see Table 15).[53] These chemicals were used in a number of activities and workstations, including the manufacture of fibers and tissues, washing stations, textile dyeing, and finishing.

In a project on the prevention of exposure to solvents, researchers visited 156 companies in Madrid, Valencia, Aragón, and Cantabria, analyzing 656 different products; 22 different EDCs were detected.[54] Separate research was conducted in the cleaning sector, which employs some 250,000 workers, mostly women. The project allowed researchers to identify EDCs contained in cleaning products, such as tetrachloroethynene, dibutylphatalate, and styrene, and substances found in detergents, like nonoxynol, polyethylene glycol and octylphenyl.[55]

52 García AM, González-Galarzo MC, Benavides FG, Delclòs J, Gadea R, Jiménez R. Proyecto MatEmESp: construccion de una matriz empleo-exposición española. *Gac Sanit*. 2010; 24 (Especial Congreso 2): 35.
53 Gadea R, Mudemurra L, Jiménez R, Santos T, García AM. Disruptores endocrinos utilizados en la industria textil-confección en España. *Med Segur Trab* 2009; 55 (214): 111-118.
54 Romano D, Gadea R, Santos T, García AM. Utilización de compuestos orgánicos volátiles (COV) como disolventes en empresas españolas. *Arch Prev Riesgos Labor*. 2011; 14 (1): 28-37.
55 Losilla JM (coord.) Identificación del riesgo químico en el sector de la limpieza en la Comunidad Valenciana. CCOO País Valenciá, 2005.

Table 15. EDCs identified in the textile industry (Spain)

Chemical	CAS	Industrial process
Ethylbenzene	100-41-4	Dyeing
4,4' Diisocyanate methylendiphenyl	101-68-8	Pre-treatment
Acrylonitrile	107-13-1	Finishing
Vynil acetate	108-05-4	Finishing
Maleic anhydride	108-31-6	Finishing
2-Butoxyethanol	111-76-2	Maintenance, finishing
Bis (2-ethylhexyl) phthalate	117-81-7	Finishing
Tetrachloroethylene	127-18-4	Washing, finishing, quality control, maintenance, preparation of textiles
Polymer of diglycidyl ether of bisphenol A (epoxy resins)	25068-38-6	Gluing (bonding)
Nonoxynol-9	26027-38-3	Finishing
Diisononyl phthalate	28553-12-0	Finishing
Poly(oxy-1,2-ethanediyl), alpha-(isononylphenyl)-omega-hydroxy- (nonylphenol etoxilate)	37205-87-1	Finishing
Permethrin	52645-53-1	Finishing
Ethanol (anhydrous)	64-17-5	Finishing
Dichloromethane	75-09-2	Maintenance, weaving, quality control
Trichloroethylene	79-01-6	Washing, finishing, quality control, maintenance, preparation of textiles, weaving
Nonylphenol etoxylate	9016-45-9	Finishing

Source: Gadea R, Mudemurra L, Jiménez R, Santos T, García AM. Disruptores endocrinos utilizados en la industria textil-confección en España. *Med. Segur. Trab.* 2009; 55 (214): 111-118.

The most reliable source for assessing occupational exposure to EDCs is probably the database on exposure to carcinogens (CAREX), which identifies chemicals that are both endocrine disruptors and carcinogens.[56]

CAREX-ESP allows scientists to estimate the number of persons exposed to EDCs. For instance, 138,000 workers were exposed to PAHs, 34,000 to tetrachloroethylene, and 68,000 to lead (see Table 16).

Table 16. Workers' exposure to some EDCs (Spain 2004), according to CAREX-ESP

EDC	No. of exposed workers
Benzene	128.589
Carbon tetrachloride	6.067
Epichlorohydrin	2.072
PAH	138.181
PCBs	11.302
Tetrachloroethylene	33.911
Styrene	34.919
Trichloroethylene	21.799

Source: Own research based on data from CAREX-ESP.

These estimates, though partial, show that hundreds of thousands of workers are exposed to EDCs in the workplace.

56 IMIM, Midat Mutua, FIOH. Carex-Esp: Sistema de Información sobre Exposición Ocupacional a Cancerígenos en España en el año 2004.

2. CASE STUDIES

2.1. Alkylphenols (APEs)

Feminization of fish in Spanish rivers

Feminization of fish due to exposure to estrogenic pollutants was first detected in Spain in 2000 in the Llobregat River basin. The finding took place during the development of a surveillance program on water quality in two of the river's tributaries, the Anoia and the Cardener. Levels of APEs (detergent components) measured in the water and sediments correlated with estrogenic effects in some fish species, including abnormally high concentrations of plasma vitellogenin in carps (vitellogenin is an egg yolk precursor protein used as an indicator of exposure to estrogenic compounds), and the existence of intersex fish (fish that developed both male and female reproductive organs).

Fish feminization was observed later in other Spanish rivers, among them the Ebro, Guadarrama, Henares, and Jarama.[57]

Alkylphenol ethoxylates (APEs) are a group of nonionic surfactants. Commercial formulation usually includes a mixture of several APEs, mostly nonylphenol etoxylate (80 percent of APEs on the world market) and octylphenol etoxylate (20 percent).

Nonylphenol etoxylate (9EO); NPE9 (CAS 127087-87-0)
Octylphenol etoxylate (10EO); OPE10 (CAS 9036-19-5)

APEs degrade easily in water and sediments and break down into nonylphenol (NP) and octylphenol (OP), chemicals that are far more toxic and persistent, with more estrogenic potential than APEs.

Nonylphenol (CAS 25154-52-3)
Octylphenol (CAS 67554-50-1)

Use of APEs

Surfactants reduce water's surface tension, modifying the properties of liquids and facilitating their mixing. APEs are commonly used as:

- Surfactants
- Emulsifiers
- Wetting compounds
- Moisturizers
- Inerts (pesticides)
- Industrial detergents
- Drying agents
- Textile and tanning products
- Wood distillers
- Spermicide, e.g., nonoxynol

The use of APEs in detergents, industrial, and household products is restricted in the EU. However, some imported textiles and leather products contain APEs, which makes washing a primary source of surface water pollution with these chemicals in Europe.

Exposure

Nonylphenol, or NP, has been detected in household air. APEs are common pollutants in wastewater, rivers, and aquifers in relatively high concentrations. According to the Spanish Register of Emissions and Pollutant Sources (PRTR), 1.19 tonnes of NPEs, NO, OPE, and OP were discharged

57 Marieta Fernández. Detergentes. Ponencia en el curso Plásticos, detergentes, cosméticos y otras hormonas. Universidad Internacional de Andalucía- Cursos de Verano. Universidad de Granada-Hospital Universitario S. Cecilio. Sevilla, 14 a 18 Septiembre 2009.

into Spanish rivers by 12 major water treatment plants in 2010. NPEs have also been detected in fatty foods and consumer products such as food containers, cosmetics, and clothing.

Research conducted by Greenpeace detected NPE residues (in concentrations of 11–1.100 mg/kg) in 52 of 78 textile and footwear products manufactured by international firms in 18 different countries. After washing, the analyzed clothes contained NPE concentrations of 1.2–350mg/kg.[58] NP was also detected in air and dust present in Spanish households (0.1–4.5 APE).[59]

Effects

Human health

APEs and their metabolites (NP and OP) are toxic chemicals that mimic estrogenic and androgenic hormones and thus affect the reproductive system.

Wildlife

APEs and their metabolites are very toxic to the aquatic environment. Their EDC effects include:

- Feminization of aquatic organisms
- Masculinization of aquatic organisms
- Reduction of male fertility
- Reduction of juvenile survival rates
- Altered levels of natural hormones

In male fish, exposure to APEs is associated with the following conditions:

- Intersex
- Low testosterone levels
- Production of vitellogenin
- Changes in gonadal tissue
- Reduced fertility

In invertebrates (mollusks, insects), OP affects egg production and sexual maturity. It is also associated with imposex/intersex.

Alternatives

Regulatory restrictions promoted the use of several alternatives to APEs in detergents and cleaning products (see Table 17).

Table 17. Alternatives to the use of alkylphenols as surfactants

Chemical	CAS Number
C9-11 Alcohol etoxylates (6 EO)	68439-46-3
C12-15 Alcohol etoxylates (9EO)	68131-39-5
Oxirane, methyl-, polymer with oxirane, mono (2-ethylhexyl) ether	64366-70-7
D-Glucopyranose, oligomeric, decyl octyl glycosides	68515-73-1
Benzenesulfonic acid, C10-13-alkyl derivs., sodium salts	68411-30-3
Sodium dodecyl sulfate	151-21-3
Sodium lauryl ether sulfate	9004-82-4
Sorbitan stearate	1338-41-6

Source: DfE. Alternatives Assessment for Nonylphenol Ethoxylates. USEPA May 2012.

Case studies on elimination

CleanGredients® Database: www.cleangredients.org/home

The CleanGredients® database provides information on alternative chemicals to formulators who seek safer ingredients for cleaning products. The database also showcases surfactants and raw material suppliers that want to promote safer alternatives certified by the Design for the Environment program of the U.S. Environmental Protection Agency (USEPA). This database includes information and technical specifications on more than 300 surfactants. It also includes information on other chemicals (solvents, chelating agents, fragrances used in cleaning products, etc.).

58 Greenpeace. Dirty Laundry: Reloaded. How big brands are making consumers unwitting accomplices in the toxic water cycle. Greenpeace International, Amsterdam: March 2012.
http://www.greenpeace.org/eastasia/Global/eastasia/publications/reports/toxics/2012/Dirty%20Laundry%203%20D11.pdf

59 Santillo D, Labunska I, Fairley M y Johnston P. Consumiendo Química. Las sustancias peligrosas en el polvo doméstico como indicador de exposición química en el hogar. Madrid: Greenpeace, 2003.

2.2. Biocides

Fumigation of enclosed buildings

Employees and neighbors often suffer adverse health effects caused by toxic chemicals released during the fumigation of enclosed buildings.

The first fumigation accident registered in Spain occurred in Catalonia in August 1994 at the microbiology laboratory of the Vall d'Hebron Hospital. Eight workers were sickened by exposure to biocides (carbamates and pyrethrins) used to fight an ant infestation.

In the period between 1994 and 2001 alone, fumigation caused disabilities in 22 persons and serious conditions in more than 60 female employees in cleaning and management services. The first group was stricken with progressive muscular dystrophy, extreme fatigue, and serious cognitive disorders.

Patients affected by multiple chemical sensitivity syndrome (MCS) cannot tolerate aerosol sprays or be in contact with synthetic chemical products. They suffer lasting effects such as breathing difficulties in crowded spaces and areas of heavy traffic.

Other symptoms found in less-affected patients included headaches, respiratory conditions, diarrhea, smell disorders, and muscle contractions. Some patients also presented with increase of growth hormone, which in one case led to the removal of the pituitary.

A study conducted by Catalonia's regional trade union, CONC, showed that 83.4 percent of the affected individuals were women and only 16.6 percent were men, with an average age of 34. Patients presented with multiple symptoms that especially affected the nervous system.

In 2002, the Supreme Court of Justice of Catalonia ordered the Catalan Institute of Health (ICS, the regional health agency) to compensate two hospital employees from the Vall d'Hebron Hospital who had sustained irreversible damage (the amount of compensation was of 180,303 euros). The court considered the agency to be responsible for the fumigation accident since the agency managers were responsible for ensuring that the chemicals used "did not constitute any hazard to the employees."

ABC 28/03/2002, El Mundo 1/02/2001 y PEX 9/06/200

Traces of products used may remain in buildings and facilities after fumigation, especially when safety requirements are not met, or when the products themselves remain active for long periods of time. These residues might remain on surfaces and in air conditioning and heating pipelines, affecting employees and visitors.

The presence of at least one organophosphate pesticide was detected in most exposure accidents analyzed (and in those that led to permanent damage). The most frequently detected organophosphate pesticides in these cases were diazinon and chlorpyrifos.

Compounds like pyrethrines and pyrethroids are also frequently detected, with tetramethrine being the most frequently identified product of the latter group. A total of 13 active ingredients have been detected in the pesticides used in different combinations (see Table 18).

Table 18. Chemicals used as biocides involved in building fumigation accidents in Catalonia and their health effects

Chemical	Use	Health effects
Diazinon[1] (CAS 333-41-5)	Organophosphate insecticide used in agricultural, industrial, and household fumigation	Toxic to the nervous system. Increased risk of brain cancer in infants and non-Hodgkins lymphoma in agricultural workers. Reproductive damage in offspring of lab animals. Endocrine disruptor.
Chlorpyrifos[2] (CAS 2921-88-2)	Organophosphate insecticide used in agricultural and industrial fumigation	Damage to the central nervous system and the immune system. Birth defects. Genetic damage. Development of sensitivity to multiple substances. Possible endocrine disruptor.
Cypermethrin[2] (CAS 52315-07-8)	Insecticide used in agricultural and indoor fumigation against roaches, mosquitoes, and termites	Damage to the central nervous system. Possible endocrine disruptor. Weakening of the immune system. Birth defects. Chromosome abnormalities. Possible human carcinogen. Persistent in the air and on walls for months after application. Toxic to bees, caterpillars, fish, and shrimp.
Fenitrothion[2] (CAS 122-14-5)	Industry	Damage to the central nervous system. Possible endocrine disruptor.
Pyrethrins[2] (CAS 005)	Industry	Possible endocrine disruptor.
Alethrin[2] (CAS 584-79-2)	Industry	Contact may cause dermatitis, irritation, allergies. Inhalation may cause irritation of respiratory tract, coughing, suffocation, chest pain, runny nose, watery eyes, asthma, and allergic reactions. Probable endocrine disruptor.
Phenothrin[2] (CAS 26002-80-2)	Household	Contact may cause dermatitis, irritation, allergies. Inhalation may cause irritation of respiratory tract, coughing, suffocation, chest pain, runny nose, watery eyes, asthma, and allergic reactions. Probable endocrine disruptor.
Nonylphenols and nonylphenol etoxylates(CAS 9016-45-9) (CAS 9036-19-5) (CAS 26027-38-3)	Inert ingredients in multiple formulations to improve contact with treated surfaces	Persistent in the environment. May damage animal hormone system at very low doses. Estrogenic EDC. Highly toxic to a wide variety of species, causing loss of fertility and motion problems.

Source: Own research based on information from the trade union health and safety quarterly *Por Experiencia* 9, June 2000.

Exposure

The detected cases in Catalonia are estimated to be 31 percent of real cases with an estimated under-detection rate of 69 percent. Under-detection for the rest of Spain would practically be 100 percent.

According to these data, the estimated prevalence of exposures per year might affect 4.33 percent of the employed population in Catalonia (124,900). The annual incidence rate would be 19.61 accidents per 10,000 applications and 19.71 affected per 10,000 exposed individuals.[60]

Effects

Different chemical families are classified according to their effects on the organism. Generally, all insecticides are considered neurotoxic and affect the nervous systems of both insects and humans. The endocrine disrupting effects of a great number of biocides have been observed in recent years. Based on a rough estimate, the most dangerous biocides belong to the organochlorine family, followed by organophosphates, carbamates, pyrethroids, and pyrethrins.[61]

60 Jordi Obiols y Francisca López. Plaguicidas de uso ambiental: un riesgo poco conocido pero de efectos graves. Por Experiencia 9, junio 2000.
61 Dossier. Por Experiencia 9, junio 2000.

Organophosphate pesticides block cholinesterase, a necessary enzyme in brain and nervous system function. The blocking causes excessive and continuous muscle stimulation that leads to abdominal spasms and excessive sweating. Other symptoms of acute exposure include nausea, headache, fatigue, vertigo, blurry vision, and pupillary constriction.

Chronic exposure to small doses may affect the nervous system, causing chronic fatigue, headache, reduced libido, memory loss, dementia, and muscular dystrophy, symptoms that could persist for up to 10 years after exposure.

Pyrethrins may cause altered skin sensitivity in exposed workers. Symptoms of overexposure include skin numbness, itching, pins-and-needles sensation, and burning. Long-term effects include brain and motion disorders, sensorimotor polyneuropathy, and immunosuppression. Pyrethroids are highly toxic to the aquatic environment, including fish.

Exposure to organochlorine biocides is associated with disabling neuroimmune disorders such as myalgic encephalopathy/chronic fatigue syndrome/post-viral fatigue syndrome, fibromyalgia, and multiple sclerosis.[62]

It is hypothesized that repeated exposure to these chemicals causes damage to the hypothalamus-hypophysis axis through physical or chemical microtraumas that eventually cause endocrine disruption and immune disorders.[63]

Alternatives

The most effective way to eliminate the risks caused by biocide use is the implementation of an integrated pest control program.

These programs aim to achieve long-term pest control results through prevention—by acting on factors that contribute to pest proliferation before outbreaks, and by choosing control strategies that reduce exposure risks. Particularly vulnerable sites and facilities such as schools, health centers, restaurants, and bars may find such alternatives suitable.

An integrated pest control program includes the following activities:

1. Use of control and prevention systems
2. Use of chemical treatment only when absolutely necessary
3. Choosing less toxic pest control strategies
4. Choosing chemical application methods that carry the lowest possible health risks

Case studies on elimination

Recommendations for pest control by the Catalonian Regional Health Agency are found at: http://www.gencat.cat/salut/ctrlplagues/Du13/html/ca/Du13/index.html

The website of the Catalonian Health Agency includes recommendations on implementing integrated pest control programs for both building owners/managers and for agencies and people who request pest control measures. A special section includes tips and recommendations for household pest control.

http://www20.gencat.cat/portal/site/salut/menuitem.f33aa5d2647ce0dbe23ffed3b0c0e1a0/?vgnextoid=aa4ce327b80cf210VgnVCM2000009b0c1e0aRCRD&vgnextchannel=aa4ce327b80cf210VgnVCM2000009b0c1e0aRCRD&vgnextfmt=default

62 Ibid 7.
63 Carme Valls. Riesgo químico: un enfoque de género. Documentos del VI Foro ISTAS de Salud Laboral Retos de la Prevención del Riesgo Químico. Madrid: ISTAS, 2010.

2.3. EPOXY RESINS – Bisphenol A (BPA) and Epichlorohydrin

Worker exposure to epoxy resins on wind farms

The Spanish company Guascor (contracted by Gamesa) set up a temporary facility for the maintenance and repair of wind turbine blades. The activity was organized in tents located within the perimeter of a wind farm. Forty-five employees (mostly women) were involved.

Turbine blade repair tasks included drilling, injection of sealing compounds, and painting. Bisphenol A, epichlorohydrin, bisphenol A diglycidyl ether, resin-hardening compounds, additives, and solvents were used in the operation.

Sometime after the job began, at least seven female workers experienced menstrual disorders, lactation, headaches, nosebleeds, dizziness, and throat and eye irritation. All of the women experienced these symptoms, and some of the men experienced symptoms as well. Two of the affected workers required permanent portable respirators.

Employees were fully equipped with safety gloves, safety suits, and goggles, however, when the product splashed on protected parts of their bodies, it went through the protective equipment and caused skin burns similar to cigarette burns. When workers complained of dizziness, company managers advised them to stay home on sick leave. Some of the women were strongly advised by doctors to avoid pregnancy due to the risk of deformities.

Physicians from the mutual insurance agency (Spanish benefit society) diagnosed work-related allergies but the factor that caused the condition was never determined. Given the serious pathology and the number of affected workers, the Spanish CCOO trade union filed a claim with the Labor Inspector. All affected workers were dismissed.

Berta Chulvi. Trabajadoras desprotegidas ante el riesgo químico. Y por casualidad se descubrió el pastel. Por Experiencia 40, abril de 2008. (Workers unprotected before chemical risk).

Wind turbine blades are manufactured with epoxy resins, which are polymers obtained from a mix of resins and catalyzing (hardening) agents. The most frequently used epoxy resins in this process (95 percent) are based on bisphenol A diglycidyl ether, with epichlorhydrin and BPA as basic ingredients.

The most commonly used hardening compounds include amines, polyamides, phthalic anhydride, and formaldehyde resins. A wide variety of additives are introduced to improve versatility. They include diluents (epichlorhydin), plastifiers, and pigments.

Epoxy resins (several CAS numbers)
Ingredients:
Bisphenol A (CAS 80-05-7)
Epichlorhydin (CAS 106-89-8)
Bisphenol A diglycidyl ether (CAS 1675-54-3)

Use

Epoxy resins are currently the most widely used polymers in industry, and their use has increased continuously over the past decades. Global demand for epoxy resins in 2009 reached 1.8 million tonnes, mainly for industrial applications that included:

- Electric and electronic equipment (36 percent)
- Maritime industries (15 percent)
- Powder paint coatings (13 percent)
- Civil engineering (10 percent)
- Can coatings (9 percent)
- Automobile coatings (8 percent)
- Composites (5 percent)
- Adhesive compounds (4 percent)[64]

64 http://www.bisphenol-a-europe.org/index.php?page=epoxy-resins

Exposure

The population segments most exposed to epoxy resins include construction workers, electric and electronic manufacturers, composite manufacturers and painters. A report from the European Agency for Health and Safety at Work (EA OSHA) includes resins as one of the main emerging risks for workers' health.[65]

Health Effects

Epoxy resins

The best-known occupational health effects of epoxy resins are skin sensitivity and photosensitivity, as well as irritation of the eyes and the airways. Increased use of epoxy resins in the workplace has led to an increase in the number of cases of occupational dermatitis, the most frequent cause of allergic contact dermatitis. The incidence of allergic dermatitis in Europe is estimated at some 80,000 cases per year (EU-25).[66] France included in its national list of occupational diseases the "eczema caused by exposure to epoxy resins and their components."

Epichlorohydrin

Epichlorohydrin is classified as a probable human carcinogen. It is toxic via inhalation, ingestion, or skin contact, and is a neurotoxin that causes reproductive damage and may cause allergic skin reactions. Poisoning symptoms include fatigue, headache, and respiratory symptoms. The substance is included on several lists as a possible endocrine disruptor that may cause reduction of sperm quality, fertility problems, and adverse reproductive effects.

Bisphenol A (BPA)

European regulation classifies BPA as a chemical that may impair fertility, irritate airways, and cause serious ocular damage and allergic skin reactions.

BPA is also an endocrine disruptor and a known estrogenic chemical since the 1930s. Recent studies have shown that it binds selectively to endocrine receptors. BPA may stimulate estrogenic receptors in cell membranes at very low concentrations (parts per billion). It may also alter the capability to synthesize and metabolize hormones and modify hormone concentrations in blood. BPA modifies tissue enzymes and interacts with several hormone response systems.[67]

The effects of exposure to BPA include changes in gene expression, hormone functions, hormone receptors, lymphocytes, enzymes, and proteins. These changes are expressed in modifications of organ and system function in humans and animals. Effects may vary depending on the organ and the system, and they occur at environmental exposure levels, leading to the conclusion that there are no safe levels of exposure to BPA.[68]

65 Brun E et al. Expert forecast on emerging chemical risks related to occupational safety and health. European Agency for Safety and Health at Work, 2009.
66 Simon Pickvance, Jon Karnon, Jean Peters and Karen El-Arifi. The Impact of REACH on occupational health. School of Health and Related Research, University of Sheffield, 2005.
67 Rye Senjen & David Azoulay. Blissfully unaware of Bisphenol A. Reasons why regulators should live up to their responsibilities. A comprehensive review of the scientific knowledge available regarding controversial Bisphenol A., Friends of the Earth Europe, June 2008. http://www.foeeurope.org/safer_chemicals/Blissfully_unaware_of_BPA_report.pdf
68 TEDX The endocrine disruption exchange. SUMMARY AND COMMENTS ON THE LOW DOSE BPA SPREADSHEET. September, 2009 http://www.endocrinedisruption.com/endocrine.bisphenol.summary.php

Pathologies and health conditions associated with BPA exposure include damage to the reproductive system, certain types of cancer (breast, prostate), brain and behavior disorders, diabetes, and obesity.

Alternatives

Other materials used in the manufacture of turbine blades include:[69]

- Glass-fiber reinforced plastic (GFRP)
- Polyester resins and fiberglass
- Polyurethane resins

Case studies on elimination[70]

LM Wind Power
http://www.lmwindpower.com/

The Danish company LM Wind Power, with 12 manufacturing plants across three continents, is the world's largest manufacturer of wind turbine blades. The company holds a record for the largest turbine blades ever made: 73.5 meters for an offshore wind farm belonging to the French company Alstom.

LM Wind Power has used glass fiber and polyester instead of epoxy resins in the manufacture of turbine blades since 1978. The company maintains close collaboration with suppliers during the production process to ensure the highest quality. Resins and reinforcing materials have been optimized to achieve stronger, uniform, and bubble-free layers.

According to the company, both the raw materials and the manufacturing process are considerably more expensive when epoxy resins are used rather than polyester and fiberglass.

2.4. Mercury

Spanish newborns contaminated with mercury

In early 2011, Spanish authorities were alerted about alarming levels of mercury in newborn babies. The information was based on data from scientific research conducted within the scope of the Childhood and Environment Project (INMA).[71] According to studies, 64 percent of newborn babies in Spain were exposed to more than 5.8 micrograms of methylmercury per liter of blood (the limit established by the USEPA). Seventy-five percent of babies in the region of Asturias, 68.4 percent in Valencia, 64.7 percent in Guipuzkoa, and 49 percent in the municipality of Sabadell exceeded the limit. Furthermore, 10 percent of babies were exposed to 22 micrograms per liter, that is, their exposure exceeded the limit by four times.

Children are particularly sensitive to neurotoxic chemicals such as mercury, and exposure is associated with serious neurological damage. Mercury levels in babies' blood is linked to their mothers' ingestion of fish (especially tuna and swordfish) during pregnancy.

El 64 percent de los bebés nace con más mercurio en sangre del deseable (64 percent of Spanish babies overexposed to mercury), El País, 2 julio de 2011. Carlos de Prada. Niños españoles nacen sobreexpuestos a mercurio del pescado (Envir. International, 2011). Fondo Salud Ambiental 31 de enero de 2011. http:// www.fondosaludambiental.org/?q=node/493

69 Richard Stewart. Wind turbine blade production – new products keep pace as scale increases. Renewable Energy Focus.com: 24 January 2012. http://www.renewableenergyfocus.com
70 Ibid. 6.
71 Proyecto Infancia y Medio Ambiente (INMA) http://www.proyectoinma.org/presentacion-inma/resultados/#

Uses

Table 19 summarizes the main uses of mercury.

Table 19. Main uses of mercury

Source Category	Estimated Global Mercury Consumption in Metric Tons	Estimated Global Mercury atmospheric Emissions in Metric Tons
ASGM	806	350
Vinyl chloride monomer manufacture	770	-
Chlor-alkali plants	492	60
Batteries	370	20
Dental amalgam	362	26
Measuring and control devices	350	33
Lighting	135	13
Electrical devices	200	26
Other	313	29
Total	3.798	557

Source: Weinberg, Jack. An NGO introduction to mercury pollution, IPEN, 2010

Exposure[72]

The first representative analysis of heavy metals in the Spanish population, commissioned by the Ministry of the Environment, show levels of mercury that exceed by up to 10 times the levels found in the populations of Germany or the United States (6.3 mg/l in blood and 1.75 micrograms/grams in hair), implying a serious risk to the health of pregnant women and babies. The highest concentrations are found among populations of Spanish coastal areas (Andalusia, Murcia, Valencia, and the Balearic Islands). The study corroborates the high levels of mercury detected in the infant population by project INMA.

Mercury accumulates in fish tissues due to pollution from wastewaters, especially in urban areas (mercury is used in consumer products, medical equipment, and dental materials, etc.), and from chlorine manufacturing plants that continue to use obsolete technology based on mercury cells. In addition, a significant portion of air emissions, mostly from carbon combustion, is eventually discharged into the sea.

Polluting activities included in the Spanish Register of Emissions and Pollutant Sources (PRTR) discharged 2.18 Tm of mercury and mercury compounds into the atmosphere and 0.97 Tm into the sea, half of which came from urban wastewaters.

The use of mercury cells for the manufacture of chlorine in Spanish plants should have been replaced with diaphragm or membrane cells during the Integrated Environmental Authorizations grant process. However, the Ministry of the Environment signed a voluntary agreement with the sector that allowed companies to continue using dated technology and therefore continue discharging mercury until the year 2020, provided that discharges did not exceed 0.9 grams of mercury per tonne of chlorine. Even if the industry complies with the agreement, 681 kg of mercury will be discharged into the sea every year.

Carbon is estimated to contain traces of mercury (between 0.01 and 1.5 mg of mercury per kg of carbon).[73] Considering that 14,709 tonnes of carbon were consumed in Spain in 2009, carbon combustion may have discharged between 0.1 and 22 tonnes of mercury into the atmosphere during that year.

Effects

Mercury is a neurotoxic metal that causes serious intellectual development delays, and damages coordination capability and motor skills in affected individuals. Mercury is also toxic to the reproductive organs; affects the immune system; and causes damage to the kidneys, liver, and circulatory system. In addition, mercury is an endocrine disruptor associated with altered glucose metabolism and diabetes. A persistent and bioaccumulative chemical, it degrades in the environment into methylmercury, an even more toxic compound.

72 Dolores Romano. Niveles alarmantes de mercurio en la población española. Daphnia 55 (2011).
73 Jack Weinberg. Introducción a la contaminación por mercurio para las ONG. IPEN, 2010. http://www.ipen.org/hgfree

Alternatives

Table 20 summarizes the alternatives to the main uses of mercury.

Table 20. Alternatives to the use of mercury

Uses	Alternatives
Mercury cells (chlorocaustics)	Diaphragm cells
Mercury thermometers	Aneroid, electronic alternatives
Mercury sphygmomanometer	Aneroides, electrónicos
Gastric tubes	Tungsten gastric tubes
Batteries	Rechargeable batteries, mercury-free batteries
Fluorescent lamps	LED lamps
Dental amalgam	Ceramic

Source: Own research based on Weinberg, Jack. An NGO introduction to mercury pollution, IPEN, 2010

Case studies on elimination

Elimination of mercury from health centers in Aragón[74]

The Regional Healthcare Department decided to eliminate the use of mercury in all health centers in Aragón (Spain). The decision was made based upon demands for elimination submitted by the Federation of Healthcare and Social Workers (CCOO) of the Sectoral Commission on Workplace Safety, the major representative body for regional healthcare workers.

Trade union representatives prepared the necessary documents for the substitution of mercury and asked the department's main technical adviser to develop a substitution program for the total elimination of mercury in all health centers before the date set by law. The trade union (CCOO) sent a copy of the documents to the head of the regional healthcare agency and managed to bring up the topic for discussion before the agency's Health and Safety Committee.

The technical section of the regional health department drafted a report (*For Application to Certain Medical Equipment Containing Mercury*) that assessed the situation and became the starting point for the elimination of medical devices that contained mercury in all regional health facilities.

74 Rubén Eito y Luis Clarimón. Un elemento de cuidado. El mercurio se retirará de los centros sanitarios de Aragón. *Daphnia* 55 (2011).

2.5. Pesticides

Genital deformities in children of field laborers (Almería)

An increase in genital deformities has been observed in newborns over the last few years. These disorders include undescended testis (chryptorchidism) and abnormal placement of the male urinary meatus (hypospadias).

A study conducted by the University of Granada on a population of 702 mother-and-newborn pairs detected more frequent deformities in children of field laborers. Placentas were analyzed for exposure to estrogenic pesticides, and it was found that the total xenoestrogenic load in newborn babies with genital deformities exceeded the load of unaffected children.

Parental exposure to xenoestrogens was also related to higher incidence of deformities.

Use

Over 350 different pesticides are currently used in the European Union, of which at least 43 have potential to affect the endocrine system.[75] In 2003, with a pesticide consumption rate of 30,000 tonnes, Spain ranked as the second largest pesticide consumer in the EU after France. Pesticides are more frequently used on vegetables (some 15 kg of active substance per hectare), vines (12 kg/ha), and citrus fruits (10 kg/ha).[76]

The most frequently used active substances in 2003 included:

- Fungicides: sulphur, mancozeb, and folpet
- Soil fumigants: 1,3-dichloropropene
- Insecticides: methomyl, chlorpyrifos, dicofol, and organosphosphate pesticides
- Herbicides: glisophate

Pesticide sales amounted to 680 million euros in 2010.[77]

Exposure

Data on exposure to endocrine disrupting pesticides in section 1 show the ubiquity of exposure to such chemicals. One hundred percent of the Spanish population shows considerably high blood levels of EDC pesticides. Analysis of umbilical cord blood and of placentas, indicating the exposure of pregnant women and unborn children, raises concern among researchers.

Effects

Both acute and chronic exposure to pesticides cause serious damage to human health. Although research focuses more on acute exposure, multiple studies published over the last two decades reveal the chronic effects of low-dose exposure, such as cancers including leukemia, and endocrine, immune, and nervous system disorders.

Earlier, section 1.3 described the main endocrine-disrupting effects of exposure to pesticides (damage to the male reproductive system, precocious female puberty, impaired female fecundity and fertility, endometriosis, breast cancer, prostate cancer, thyroid cancer, neurotoxicity during development, metabolic syndrome, and obesity, among other health conditions).

Other disorders associated with pesticide exposure include Parkinson's disease, Alzheimer's disease, and attention deficit-hyperactivity disorder (ADHD).[78]

Alternatives

Organic farming[79]

Organic farming is an agricultural production system that produces fresh products relying on techniques that respect natural life cycles.

75 PAN Europe. Disrupting food. Endocrine disrupting chemicals in European Union Food. PAN Europe, 2012.
76 Eurostat. The use of plant protection products in the European Union. Data 1992-2003. Luxembourg: Office for Official Publications of the European Communities, 2007
77 http://servicios2.marm.es/sia/indicadores/ind/ficha.jsp?cod_indicador=23&factor=presion
78 PAN Europe. Health effects of pesticides. An impression of recent scientific literature August 2010. http://www.pan-europe.info/Campaigns/pesticides.html
79 http://ec.europa.eu/agriculture/organic/organic-farming/what-organic_es

Organic farming includes a series of goals, principles, and common practices aimed at minimizing the environmental impact of human activity and supporting the most natural farming methods possible.

Organic farming techniques include:

- Crop rotation
- Strict limitations on the use of pesticides and synthetic fertilizers
- Limited use of genetically modified organisms
- Natural fertilization methods such as green manure
- Selection of vegetable species

Case study on elimination

Organic farming cooperative (AGRIECO): http://www.agrieco.es

AGRIECO is an association of organic fruit and vegetable farmers located in the municipality of Pechina, Almería, in southern Spain. The association consists of 10 founding and 30 collaborating farmers who practice intensive organic farming on 120 hectares. They also own a 4,000-square-meter (43,056-square-feet area for the handling and packaging of products and a 1,100-square-meter (11,840-square-foot) storage facility for the sale and distribution of organic produce.

Farmers use several alternatives to chemical pesticides such as biological pesticides and herbicides, soil management, increased biodiversity, and the deployment of repellent and reservoir plants (lantana, rosemary, thyme, peppermint).

During the 2005–2006 crop season, AGRIECO's sales volume reached 3 million kilograms net with a staff of 90 workers.

Eighty-five percent of the farm's production is exported to foreign supermarket chains in Holland, Denmark, Sweden, Austria, Ireland, France, Germany, Eastern Europe, and Canada.

3. REGULATORY FRAMEWORK

3.1. EU regulations

EU legislation and environmental regulations control the marketing of chemicals and consumer products containing EDCs.

3.1.1. Community Strategy for Endocrine Disruptors

In 1999, the European Commission published the Community Strategy for Endocrine Disruptors—COM (1999) 706—which established the EU guidelines for medium- and long-term action to address the health and environmental risks of EDCs.[80] The European Commission published a series of reports in 2001, 2004, and 2007 on the implementation of the strategy.[81]

The strategy includes the following:

Short-term actions

- Establishment of a priority list of substances to further evaluate their role in endocrine disruption. This list has been published in the EDC section of the Commission's web page of the Commission and is currently being revised.[82]
- Measurement of EDC levels in food and the environment.
- Identification of vulnerable groups in the population, e.g., children, for whom special consideration is necessary from a consumer policy point of view.
- Creation of an international network to coordinate exchange of information as well as research and monitoring.
- Collect, exchange, assess, and provide information on EDs to the public in consultation with stakeholders.

Medium-term actions

Actions focus on EDC identification, coordination, and funding. They have been funded through EU framework research and development programs and include:

- Identification and assessment of endocrine disruptors
- Research and development
- Identification of substitutes and voluntary initiatives

Long-term actions

These actions address the need to update, amend, or adapt existing regulatory instruments in order to protect human health and the environment. They include:

- Testing and assessment methods
- Classification and labeling
- Review of existing regulation on pesticides, biocides, and consumer products
- Review of existing environmental regulations (Framework Water Directive, UNECE protocol on POPs)

The Community Strategy for Endocrine Disruptors is currently under review.

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80 COMMUNICATION FROM THE COMMISSION TO THE COUNCIL AND THE EUROPEAN PARLIAMENT. Community Strategy for Endocrine Disrupters. A range of substances suspected of interfering with the hormone systems of humans and wildlife COM (1999)706 final. COMMISSION OF THE EUROPEAN COMMUNITIES. Brussels. 17.12.1999

81 COMMISSION STAFF WORKING DOCUMENT on the implementation of the "Community Strategy for Endocrine Disrupters" - a range of substances suspected of interfering with the hormone systems of humans and wildlife (COM (1999) 706), (COM (2001) 262) (SEC (2004) 1372) and SEC(2007) 1635).

82 http://ec.europa.eu/environment/endocrine/strategy/short_en.htm

3.1.2. REACH Regulation

The use of endocrine disrupting chemicals is subject to authorization under article 57.f of the REACH regulation (1907/2006).[83]

So far, there are no specific guidelines for the identification and assessment of endocrine activity by EDCs. The deadline for the drafting of guidelines expires on December 9, 2013. However, the European Chemical Agency (ECHA) has already included one EDC, 4-tert-nonylphenol, in the list of Substances of Very High Concern (SVHC), which are candidates for authorization.

3.1.3. Regulation on the Marketing of Pesticides

The new Regulation on the Marketing of Pesticides (1107/2009)[84] prohibits the of use of endocrine disruptors (Annex II 3.6.5). According to this law: “an active substance, safener or synergist shall only be approved if, on the basis of the assessment of Community or internationally agreed test guidelines or other available data and information, including a review of the scientific literature, reviewed by the Authority, it is not considered to have endocrine disrupting properties that may cause adverse effect in humans, unless the exposure of humans to that active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with point (b) of Article 18(1) of Regulation (EC) No 396/2005.”

Such authorizations shall be granted once, for a period not exceeding five years.

The regulation also states that by 14 December 2013, *the Commission shall present to the Standing Committee on the Food Chain and Animal Health a draft of the measures concerning specific scientific criteria for the determination of endocrine disrupting properties to be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 79(4)*. The European Commission has appointed a group of experts to oversee this task. The same criteria will be applied with regard to REACH regulation, the Regulation on Biocides, and any other European regulation on EDCs (e.g., the Framework Directive on Water).

3.1.4. Regulation on Biocides

The new regulation on biocides (528/2012)[85] prohibits “active substances which … are considered as having endocrine-disrupting properties that may cause adverse effects in humans” (Art. 5.1.d). Criteria for EDC identification will be established by the afore-mentioned group of experts.

3.1.5. EU action regarding bisphenol A in baby bottles

Following a citizen-supported European campaign to ban BPA and the implementation of measures by several countries, on November 26, 2010, the Directorate General for Health and Consumers announced the total ban in the EU of baby bottles containing BPA. Manufacture was banned beginning in March 2011 and marketing since June 2011.

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83 REGULATION (EC) No 1907/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 18 December 2006b concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC Brussels: Official Journal of the European Union, 30.12.2006.

84 REGULATION (EC) No 1107/2009 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. Brussels: Official Journal of the European Union, 24.11.2009. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:309:0001:0050:EN:PDF

85 REGULATION (EU) No 528/2012 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 22 May 2012 concerning the making available on the market and use of biocidal products. Brussels: Official Journal of the European Union: 27.6.2012.

3.2. National regulations

Several EU countries have banned certain uses of EDCs:[86]

3.2.1. Regulation on BPA

Denmark
In March 2010, Denmark appealed to the precautionary principles to introduce a temporary ban on BPA for products that come in contact with food for children under age three.

France
In June 2010, the French government temporarily suspended the use of BPA in baby bottles. In October 2011, the French National Assembly adopted the ban on BPA for all food containers. This decision must be ratified by the Senate and will take effect in 2013 for any food container for children under 13, and will apply to all food containers in 2014.

Sweden
In July 2010, following the Danish initiative, the Swedish government published a press release on the future ban on BPA in baby bottles.

Austria
In September 2010, the Austrian Ministry of Healthcare announced its intention to ban BPA in children's products if the EU did not adopt measures to protect infants.

Germany
In June 2010, the German Ministry of the Environment published a press release recommending that manufacturers and consumers follow the precautionary principle and use alternative chemicals and products.

Belgium
In January 2012, the Belgian parliament banned the use of BPA in food containers for children under three. The measure takes effect September 2013.

3.2.2. Regulation on parabens and other EDCs

Denmark
Denmark was the first EU country to ban parabens in lotions and cosmetics for children under three.

France
In May 2011, the French National Assembly supported a proposal for the ban of parabens, phthalates, and alkylphenols. The measure is pending approval by the Senate.

3.2.3. Spanish regulations

The Spanish government has not introduced any initiatives regarding the ban of EDCs. So far it has only adopted EU directives (such as the ban on the marketing of baby bottles containing BPA).

The only significant improvement in this sense was the introduction of an explanatory note (titled "ED") on endocrine disruptors in the list of limit values for occupational exposure to chemical agents published every year by National Institute of Occupational Safety and Health[87] The ED note specifies that "no limit values have been assigned to these agents in terms of health effects and endocrine disruption to justify adequate health surveillance." To date, the Task Force on Limit Values of the National Health and Safety Commission has only considered the first list of endocrine disruptors published in the first report on the implementation of the Community Strategy (2001).

86 A CHEM Trust and HEAL briefing: Regulating chemicals with endocrine disrupting properties. May, 2012. http://www.env-health.org/IMG/pdf/36-_heal_ct_edc_criteria_briefing_paper.pdf
87 INSHT. Límites de exposición profesional para agentes químicos en España. Madrid: Instituto Nacional de Seguridad e Higiene en el Trabajo, 2012.

4. PROPOSALS

Scientific research shows that endocrine disruptors have special characteristics that call for new policies to protect human health and the natural environment (see section 1.2).

The characteristics of endocrine disrupting compounds may be summarized as follows:

- **May cause harm at very low doses:** Exposure levels that may damage human health are extremely low (on the level of parts per trillion). The population is currently exposed to such levels as a result of air pollution in households, food, or pollutants contained in consumer products.
- **Timing of exposure may be even more significant than level:** Unborn children and infants are particularly vulnerable to EDCs as these stages of development are especially sensitive to endocrine disruption. The damage caused in these periods can have lifetime health effects.
- **There is a nonlinear dose-effect relationship:** Damage can occur at very low doses whereas high or intermediate doses might have no effect at all.
- **"Cocktail" effect:** EDCs can have additive or synergistic effects whereby exposure to low-dose mixtures may imply adverse health effects at exposure levels considered safe for separate components of the mixture. ***EDCs must therefore be approached as groups of substances rather than as separate substances.***
- **Effects may pass to future generations** as they affect gene expression.
- **Latency:** Adverse effects may occur many years after exposure. Effects of prenatal exposure become evident mostly during adulthood. Therefore, ***exposure prevention measures adopted now will improve health indicators in the future***.
- **Ubiquity of exposure:** Studies that monitor the effects of EDC exposure show effects on all age groups in the population. EDCs have been detected in umbilical cord blood, hair, and urine of infants and children, as well as in adult blood and fat tissue. Analysis of food, consumer products, air, water, and household dust shows the ubiquity of exposure. This circumstance calls for the elimination of sources of exposure to EDCs.
- **No safe threshold can be established for EDC exposure.**

Such characteristics render inadequate the traditional risk-assessment methods implicit in current legislation designed to protect the population and the environment from EDCs. This new health and environmental challenge calls for a new paradigm. It also requires the application of precautionary principle and the adoption of urgent measures aimed at:

- **Eliminating or reducing exposure to EDCs when possible**
- **Avoiding the exposure of children, pregnant, breastfeeding women, and women of reproductive age**
- **Establishing new identification and testing methods that include chemicals that may interfere with the hormone system**

A series of opportunities will emerge in the upcoming period. They include:

Review of the Community Strategy for Endocrine Disruptors

The Community Strategy for Endocrine Disruptors, initially published in 1999, is currently being reviewed, the main objective being to include in the document the goal of reducing population and environmental exposure to EDCs through the application of the precautionary principle and the setting of specific deadlines for the elimination and restricted use of/exposure to EDCs. The measures reviewed include:

Short-term measures

- Publication of a EU database on EDCs, including an updated list of chemicals, toxicity information, and references on scientific publications. The list would be a reference for the implementation of EU regulation.
- Development of a specific labeling and classification system for EDCs.
- Development of a more efficient and proactive system for the identification of substances and uses by consumers and workers who wish to take urgent action.

Medium-term measures

The EU must adopt identification and monitoring systems for EDCs that take into account the complexity of the endocrine system. Traditional animal testing on mice has proven insufficient; new, improved toxicity tests are required to identify substances associated with increasing disease in the EU such as obesity, diabetes, breast and prostate cancer.

Identification and promotion of safer alternatives: In 2012, trade unions and NGOs put forth initiatives to disseminate information on safer alternatives, such as the substitution site SUBSPORT (www.subsport.eu), funded by the LIFE+ program. The EU and Member State authorities must address the limitations of the identification and promotion of safe alternatives, which include:

- Lack of transparency on substances contained in products
- Lack of information and training of users and consumers on alternatives
- Lack of incentives for the use of alternatives

Long-term measures

A review is necessary of regulations on chemicals, health and environmental protection, and occupational health (for instance Directive 92/85/CEE of October 19, 1992, on measures to encourage improvements in workplace safety and health of pregnant, post-partum, and breastfeeding workers) to guarantee that regulations include EDC risks.

Reviewing REACH Regulation

REACH Regulation addresses the registration, evaluation, authorization, and restriction of industrial chemicals. REACH could expedite the elimination of EDCs through restriction and authorization processes.

The European Commission is expected to review the conditions for the authorization of EDCs for certain uses before June 2013. In order to eliminate exposure to EDCs, the review must include the following:

- Authorization must only be granted if the use of the substance is proven absolutely necessary and there are no safer alternatives available. In such cases, authorization must be granted for a limited period only.
- Article 57, on the definition of Substances of Very High Concern, must include specific criteria for endocrine disrupting properties, aside from the current criteria for equivalent level of concern (57f).
- CMRs (carcinogens, mutagens, and reprotoxic substances) or PBTs (persistent bio-accumulative and toxic substances) must be included in the candidate list for authorization (in order to grant the reviewing of those authorizations when new conditions to authorize EDCs come into force).

Establishing criteria for EDC identification

Criteria adopted by law must allow identification of the highest possible number of EDCs to which the population is exposed. These criteria must be based on the hazardous characteristics of substances, as in the EU CLP Regulation in the case of CMR substances. In addition, independent scientific publications funded by the European R&D Framework Program must be taken into account. This would grant the use of current scientific knowledge on EDCs' effects and up-to-date identification methods.

National regulation

List of occupational limit values for exposure to chemical agents

The list of chemicals under the explanatory note ED (endocrine disruptors) must be extended to include all substances currently included in the European Commission's list. This will allow companies to identify EDCs at workplaces and adopt necessary protections and preventive measures.

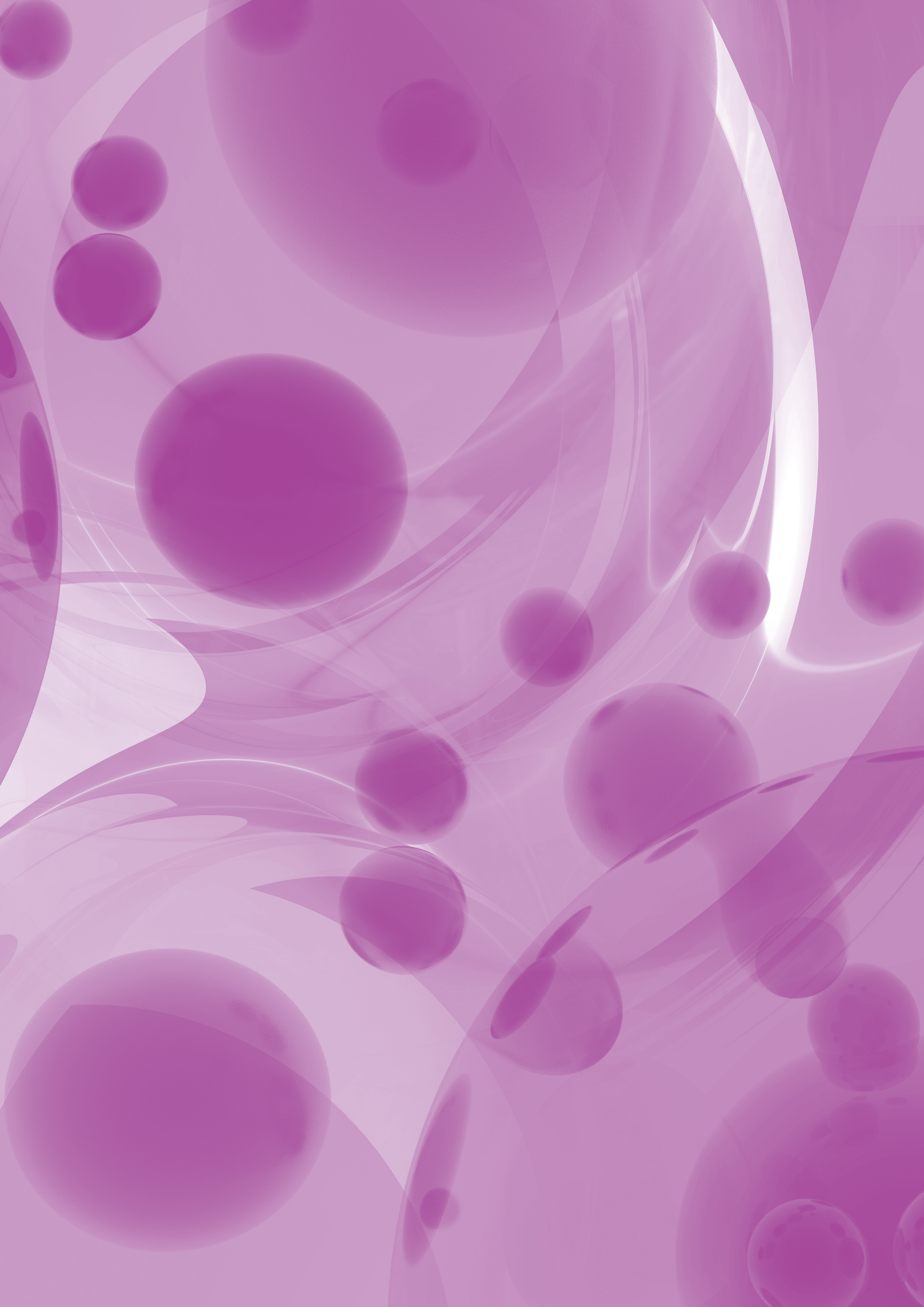
Prohibition of EDC exposure for pregnant and breastfeeding workers

Endocrine disruptors must be included in the list of chemical agents to be avoided, according to Royal Decree 298/2009 on the Adoption of Measures to Promote Occupational Health and Safety for Pregnant and Breastfeeding Workers.

RD 298/2009 introduces to Spanish legislation the list of agents that imply health risks for pregnant and breastfeeding workers and that must be assessed (Annex VII) or avoided (Annex VIII). The list of agents included in this regulation is based on the list published by Directive 92/85/EEC,[88] therefore it does not include new scientific knowledge on endocrine disruptors generated in the last two decades.

Banning the production and use of chemicals following the experience of the EU countries with the most advanced healthcare and environmental protection policies

88 Council Directive 92/85/EEC of 19 October 1992 on the introduction of measures to encourage improvements in the safety and health at work of pregnant workers and workers who have recently given birth or are breastfeeding (tenth individual Directive within the meaning of Article 16 (1) of Directive 89/391/EEC).



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