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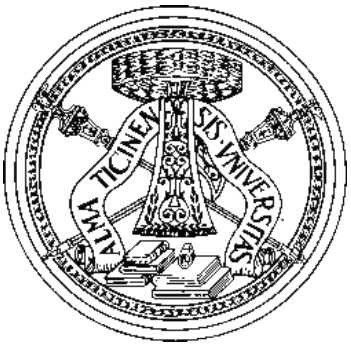

Doctoral Course in Psychology, Neuroscience and Data Science

CURRICULUM IN DATA SCIENCE IN BIOMEDICINE

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Endocrine Disruptors in Industry and Tertiary Sector: Hypothesis of a Risk Assessment Strategy in Lyon, France

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INTRODUCTION

GENERAL CONTEXT RELATING TO ENDOCRINE DISRUPTORS

Overview on endocrine-disrupting chemicals

The scientific evidence about some chemicals being possibly able to alter human and wildlife health and to cause environmental changes has become a relevant concern worldwide.(WHO/UNEP, 2013) These substances or mixtures, called endocrine-disruptors (EDs), can be found in many consumers' products, industrial as well as intermediate compounds, agricultural and farming commodities, medicine and health care chemicals, pharmaceuticals.(Karthikeyan et al., 2019) Some compounds of natural origin, heavy metals and pollutants are also comprised.(Karthikeyan et al., 2019) They act through a common mechanism: the interference on the functioning of the endocrine system. The endocrine system, in all vertebrates, presides over several essential biological operations that respond to external or internal stimuli by means of hormonal signals secreted by glands and adapted cells. The fulcrum of the system is the hypothalamus-pituitary axis. Hormones are natural chemical messengers transported by blood circulation and interacting with specific receptors in certain distant cellular targets.(Lauretta et al., 2019) The essential operations comprehend the regulation of metabolism, energy balance, sleep/wake cycles, temperature and homeostasis, the control of behaviour, stress response and immune system, the adjustment and setting of growth, development, fertility, aging and reproduction. These different functions, which are expressed cyclically or in defined periods during the lifetime, rely always on the same set of hormones, their conjugate receptors and a set of hormonally responsive tissues. A disruptive action on this system can lead to disease and can contribute to the aetiology of both malignant and non-malignant diseases, especially in vulnerable subjects or if the exposure occurs in specific periods in life. Moreover, the effects derived from the exposure, even at low doses, can involve the progeny's wellbeing and can entail long lasting alterations in the offspring. Recently, the role of EDCs has been even evaluated in its contribution to the course of COVID-19. Several signalling pathways of common proteins resulted significantly dysregulated after exposure to these chemicals and may also be involved in COVID-19 severity.(Q. Wu et al., 2020)

To find a way to detect modifications in the functioning of the endocrine system, to prevent such occurrences, and to create a sustainable economic and living system is a matter of debate and a widespread recognized priority. Many disciplines converge to consolidate findings and to provide adapted methodologies, including toxicology, endocrinology, pharmacology,

neuroscience, biology, ecology, epidemiology, occupational and environmental medicine, data science in biomedicine. Common regulations, strategies, guidelines, meetings, communications to various interlocutors, decision-making processes, questionings, and areas of research have been and are still implemented to coordinate actions and to find solutions. The public, politicians, regulators, scientists and industries are all active parts in this context.

Historical background

As mentioned in a recent mini-review (Darbre, 2019), the effects of hormones were presumed in ancient times, and they were exploited, for example when performing castration to change behaviour, attitudes, and physical characteristics of men. Anyway, it was only in 1902, with the identification of secretin's regulation role in the digestive system, that hormones began to be conceived as chemical messengers.(Darbre, 2019)

Only later, in the 1920s, pig farmers in the USA noticed a lack of fertility in swine herds fed on mouldy grain, leading to studies that made it possible to identify the role of mycooestrogens.(Darbre, 2019) In the 1930s, the oestrogenic properties of bisphenol A (BPA) were firstly recognized.(Schug et al., 2016) Observations in the 1940s from Australian sheep farmers highlighted raise in infertility after grazing on certain fields of clover, and scientific studies proved that phytoestrogens were responsible.(Darbre, 2019) In the 1950s, some chemicals used in livestock feedlots were suspected of entering the human body and mimicking hormonal activity.(Schug et al., 2016)

In 1958, the endocrinologist Roy Hertz was the first dissecting the nefarious potential of some hormones used in the cattle feed lots, reaching the human body through the food chain, and engendering consequences in development, growth and reproductive function. He introduced the concepts of "steroid cycle" and "bio-accumulation".(Pivonello & De Angelis, 2020)

These first findings remained almost confined within the scientific forum, until the publication, in 1962, of the book *Silent Spring* from Rachel Carson which addressed to the public.(Carson, 1962) The book stressed some chemicals, as dichlorodiphenyltrichloroethane (DDT), being a possible cause of harm, and long-term harm, to ecosystems and human health.(Schug et al., 2016) The public and scientific concern about environmental hazards some years later pushed the United States government to create the National Institute of Environmental Health Sciences (NIEHS) and the Environmental Protection Agency (EPA).(Schug et al., 2016)

In the 1970s, some studies addressed the links between exposure to chemicals and the development of rare cancers or reproductive effects in wildlife, as well as in humans. Effects of diethylstilboestrol (DES) on the progeny were reported.(Schug et al., 2016)
In this period, the NIEHS held the first Estrogens in the Environment Meeting, focusing mostly on the environmental contamination from oral contraceptives, and human effects from exposure to xenoestrogens.(Schug et al., 2016) The mechanisms permitting bioaccumulation and biodegradation in living organisms from environmental exposures were demonstrated. A second meeting in 1985 focused on the effects of environmental oestrogens on puberty in young children.(Schug et al., 2016) A third meeting in the 1990s addressed the raising concerns about non-monotonic doses-responses (NMDRs). Links were found between oestrogens exposures and human adverse effects and diseases, as falling sperms counts.(Schug et al., 2016)

The term “endocrine disruptor” (ED) was first used at the Wingspread meeting in 1991, a key conference regrouping scientists from different fields. The evidence on hormone-disrupting effects of man-made chemicals or natural chemicals on animals, including humans, was confirmed.(Lee, 2018) In the Wingspread Consensus Statement some important features of these chemicals are set; “the critical window of exposure of susceptibility”, the potential of bio-accumulation and the long latency between exposure and the appearance of the effects are mentioned.(Pivonello & De Angelis, 2020)
In 1996 the US EPA defined ED 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”.(Kavlock et al., 1996) According to this definition, the United States Congress included in the Food Quality Protection Act the obligation to evaluate EDCs in pesticide products and amendment the Safe Water Drinking Act to assess oestrogenic EDCs.(Schug et al., 2016) The final committee report detailed a two-tiered panel of assays to assess for oestrogenic, androgenic and thyroid-mediated effects.(Kassotis et al., 2020)
The same year, the first European Union (EU) Workshop on the Impact of Endocrine Disrupters on Human Health and Wildlife was held in England. The aim was to alert about the potential impact of endocrine disruption on the health of humans and wildlife and to launch an agreed integrated plan for guiding research and activities in this field. It ended with the publication of “The Weybridge Report”.
After accidents following contamination of batches or rice oil with PCBs in Japan in 1968 and in Taiwan in 1979, in the 1990s Japan started a dedicated task force, and the Japan’s

Environment Agency began a Strategic Program on Environmental Endocrine Disruptors, initially particularly oriented to aquatic toxicity tests.(Schug et al., 2016; Kassotis et al., 2020) In subsequent years, ten International EDC Symposia were sponsored, dealing with evaluation methods, animal models' experimentation and risk assessment.(Schug et al., 2016)

In particular, the Rotterdam Convention on the Prior Informed Consent Procedures for Certain Hazardous Chemicals and Pesticides ratified at an international level a list of chemicals that comprise also known EDCs. The list was updated in 2001, during the Stockholm Convention (Pivonello & De Angelis, 2020), which permitted international ban of Lindane, some organohalogen flame retardants and some polyfluoroalkyl substances (PFAS) from users' products (USA not signatory).(Kassotis et al., 2020) Other conventions from then on tried to monitor adherence to international agreements and to limit subsets of persistent organic pollutants (POPs).(Pivonello & De Angelis, 2020)

The first reference to EDs by the European Parliament dates back to October 1998, with the adoption of a resolution calling upon the European Commission (EC) to take coordinated action, to develop a legislative framework, to strengthen research efforts and to make information available to the public.(European Commission, 2016a)

Following the indications, in 1999, the Commission's Scientific Committee for Toxicity and Ecotoxicity and the Environment (SCTEE) published a report "Human and wildlife health effects of endocrine disrupting chemicals with emphasis on wildlife and ecotoxicology test methods".(European Commission, 2016a)

In response to its contents, after consultation with stakeholders, the EC adopted the "Community strategy for endocrine disruptors – a range of substances suspected of interfering with the hormone systems of humans and wildlife" (COM(1999)706), fixing the importance of the precautionary principle in order to protect the human health and the environment within the European Union. Some actions were prioritized. Consequently, short-term, medium-term and long-term interventions were outlined.(European Commission, 2016a)

The short-term actions (1-2 years) involved the organisation of information collection to provide a shared background to identify strategies and knowledge gaps to be addressed to. They comprised identification of substances for priority evaluation, establishment of exposure-effects monitoring programs, definition of vulnerable subjects, development of a common network for information exchange, coordination between countries for research and testing, organisation of meetings with stakeholders and communication to the public.(Kassotis et al., 2020)

They resulted in the publication of three studies: "Towards the establishment of a priority list of substances for further evaluation of their role in endocrine disruption - preparation of a candidate list of substances as a basis for priority setting", "Study on gathering information on 435 substances with insufficient data", "Study on enhancing the endocrine disruptor priority with a focus on low production volume chemicals".(European Commission, 2016a)

The medium-term actions (2-4 years), under the direction of the Organization for Economic Co-operation and Development (OECD) and with the contribution of the Commission, turned around the procedures to test suspected chemicals rapidly and accurately. They comprehended the validation of internationally agreed test methods of assessment for humans and wildlife, the definition of a European strategy consistent with the international context, the coordination and funding of research projects about causality, underlying mechanisms, exposure or risk assessment, environmental monitoring tools, methods identifying and ensuring the safety of substitute chemicals. The international cooperation with the World Health Organisation (WHO) was assured by the International Programme for Chemical Safety (IPCS). Research has been funded through the years under the Fourth, Fifth, Sixth and Seventh Framework Programmes for Research and Technological Development for R&D and Horizon 2020.(European Commission, 2016a)

The long-term actions (4 years or more) dealt with updating, amending or adapting the legislative instruments by considering the ED effects. They included more stress around the methods for hazard identification and risk assessment, and around testing disposal rules to ensure a proper risk management. Regarding EDs not addressed by specific legislation (e.g. natural substances and some by-products), the Commission declared the attempt to provide for more environmental legislative instruments, or to apply existing international legislation, such as the UNECE POPs Protocol.(European Commission, 2016a)

The following year, a conference series started, the Copenhagen Workshops on Endocrine Disruptors, while continued the Gordon Research Conferences on Environmental Endocrine Disruptors, and the Weybridge +10 workshop as well as the Environmental and Hormones meetings were held, the latter lasting till 2010.(Schug et al., 2016)

In 2000, the Environment Council adopted the Conclusions on the Commission Communication while the European Parliament adopted a Resolution on the overall chemical policy, stressing the necessity to identify chemical hazards requiring immediate action and to develop quick and effective risk management strategies.(European Commission, 2016a) The Resolution emphasised the adoption in the European Union of the precautionary principle, which consists in limiting or restricting the use of potentially harmful compounds whenever a

reasonable concern emerges from a preliminary scientific evaluation, until conclusive evidence is available.(European Commission, 2016a)

In 2001, the Commission presented a first update on the implementation of the strategy, COM(2001)262, which covers the time period 1999 to 2001. It established the priority list of substances for further evaluation of their role in endocrine disruption. Legislative actions directly or indirectly took into account EDCs in different proposals in the field of water policy, in the White Paper on a strategy for a future chemicals policy and in the proposed revision of the General Product Safety Directive.(European Commission, 2016a) A report appeared on low dose effects.(National Toxicology Program, 2001)

A move towards banning the use in stock farming of certain substances having hormonal activity began.

In 2002, the IPCS and WHO summarized the state of art on the subject defining an EDC as "an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse effects in an intact organism, or its progeny, or (sub)populations. A potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub)populations".(Damstra et al., 2002) Following this definition, the evidence of an adverse effect is required to recognize a hazardous compound as ED, as well as the proofs of an endocrine-disrupting activity and of a plausible link of causality or association between the two.

In 2004, the Commission published a Staff Working Document on the implementation of the strategy, SEC(2004) 1372, which covers the time period 2001 to 2003.

Two years later, the American Chemical Society was the first professional society to release a policy statement on EDCs.(Schug et al., 2016)

In parallel, in December 2006 the regulation concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) was formally adopted and two proposals passed for a directive setting environmental quality standards for priority substances under the water framework directive and for a regulation revising directive 91/414/EC on plant protection products.(European Commission, 2016a)

In 2007, the Commission presented the third update on the implementation of the strategy, SEC (2007) 1635, for the period 2004-2006.

In 2011, the Commission published a Staff Working Document on the implementation of the Community Strategy for Endocrine Disruptors-a range of substances suspected of interfering with the hormone systems of humans and wildlife SEC (2011) 1001.

In 2012, a UN Environment Programme (UNEP) and WHO report identified again EDCs as a top area of concern and underlined their pervasiveness globally. This report was received at the Fourth International Conference on Chemicals Management (ICCM4), and raised agreement about the possible adverse effects for humans and wildlife, the existence of vulnerable periods for exposure during lifetime, the possibility of the occurrence of adult-onset diseases following exposure during development. Agreed and validated test methods, as well as guideline endpoints capturing a wider range of the known spectrum of endocrine disrupting effects, were internationally required, also to avoid further underestimation of the risk. The European Environmental Agency established areas for further research and invoked the precautionary principle to try to limit EDCs' exposure, even before obtaining full scientific knowledge. In parallel, the Endocrine Society defined EDs as "an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action".(Thomas Zoeller et al., 2012) The same year an important summary of the weight of evidence on the occurring of non-monotonic dose-response curves was published, alerting on the need to change in testing methods and safety determinations to protect human health.(Laura N Vandenberg et al., 2012) Soon after, a statement of the European Food Safety Authority strengthened the same concepts.(Schug et al., 2016)

In 2014, the European Commission published a roadmap presenting several options to identify EDs; two years later draft criteria were selected according to the Joint Research Centre (JRC) and a screening exercise with about 700 example substances was performed.(Schuhmacher-Wolz et al., 2017)

In 2017, a report commissioned by UNEP and authored by the International Panel on Chemical Pollution identified 28 policy actions to address and limit hazardous EDCs, especially in industrial contexts.(Kassotis et al., 2020)

In 2018, the EC published a "Communication toward a comprehensive EU framework on EDs". The EU reaffirmed the application of precautionary principle and the need for minimising the overall exposure, in particular during critical windows in development, and mentioned the efforts as well to promote an active dialogue and decision-making policies. The need for a horizontal and coherent approach to the identification of EDs across sectors is acknowledged to homogenise, simplify and implement legal framework. This communication also tried to support scientific research, announced the organization of yearly forums, launched a web portal, called for definitions' uniformity with the international systems of classification, and proposed "fitness check" (evidence-based critical analysis of whether actions are proportionate to objectives and their delivery as expected).

A definition for EDCs, criteria and a guidance document relative to PPP and biocides were adopted the same year in the EU.(Leemans et al., 2019)

EFSA presented a document for public consultation on the establishment of cumulative assessment groups of pesticides for their effects on thyroid signalling, underlining the progresses in the identification of effects after exposure to mixtures.(Leemans et al., 2019)

The EU was in parallel reaching consensus on the move toward a circular economy, and the management of EDs in this context was addressed by a recent resolution of the EU Parliament (2018/2589(RSP)), raising concerns about EDs in recycled products and the need to consider these chemicals in the design stage of a product.

In 2019, the 8th Environment Action Program addressed the policies for the 2021-2030 period, stressing the aspects related to climate-neutrality, green economy, protection of biodiversity, fairness. It also urged the EC to present a strategy for a non-toxic environment, mentioning in particular endocrine disruptors and nanomaterial issues. A new circular economy action plan is evoked, as well as a long-term strategy.

European Parliament then adopted the resolutions 2019/2683(RSP) to ask for the creation of a global framework in relation to EDs.

A few months ago, the European Food Safety Authority stated that no safe exposure level could be set for chlorpyrifos, and approval for this compound has not been renewed.

A recent consensus on key characteristics of EDCs established 10 mechanisms of action of EDCs, and evaluated the available assays, proposing an approach following a similar framework with respect to carcinogens.(La Merrill et al., 2020)

Nowadays, we can still distinguish a hazard-based approach in Europe, less considering effective exposure, and a risk-based approach in the USA, considering exposure levels. According to a recent publication, the latter approach does not account for chronic disease burden, and could fail in evaluating long latency effects.(Kassotis et al., 2020)

In June 2020, 209 substances were placed in the candidate list for authorisation according to REACH Regulation: only few of these substances are listed because they own endocrine-disrupting properties.(European Chemicals Agency, 2020a) In September 2020, the ECHA's endocrine disruptors assessment list (the list of substances undergoing an ED assessment under REACH or the Biocidal Products Regulation that have been brought for discussion to the ED Expert Group) accounts for 94 substances that are under investigation or that have been investigated.(European Chemicals Agency, 2020b)

Economic burden and costs

Estimates of burden and costs of environmentally attributable diseases are powerful indications to lead policy making.(Kassotis et al., 2020) The economic burden from ED exposure-related diseases in EU and USA have been estimated to be huge in a subset of substances and outcomes.(Attina et al., 2016; Bellanger et al., 2015; Hauser et al., 2015; Hunt et al., 2016; Legler et al., 2015; Leonardo Trasande et al., 2015; L. Trasande et al., 2016) However, these estimations have been strongly criticized, mainly due to the employed methodology and the assumptions on causality in humans.(Lee, 2018; Bond & Dietrich, 2017) Other estimates were presented in a report dated 2016.(Rijk et al., 2016)

Recently, it has been suggested that, in a societal perspective, it could be more useful to weigh the costs of developing safer alternatives against the economic benefits of reduced disease and disability. In this perspective, the real costs of replacing EDCs are supposed to be often lower.(Kassotis et al., 2020)

Routes of exposure, pharmacokinetics

Ways of exposure comprehend typical routes including ingestion, inhalation, skin absorption, intravenous injection or subcutaneous administration.(O. Yang et al., 2015) EDCs can pass the placenta barrier, inducing *in utero* exposure. Moreover, breastmilk can be a further source of exposure.(Gingrich et al., 2020)

The distribution throughout the body is different for lipophilic and hydrophilic chemicals, the former being transported in blood lipids and bio-accumulating in adipose tissue, the latter being scarcely distributed or accumulated. Biotransformation include liver metabolization as happens for other xenobiotics, following hydroxylation by cytochrome P450-dependent oxidase system (phase I) and conjugation (phase II). The consequent modifications make these substances more hydrophilic, allowing for transport to excretory organs. A peculiarity of EDCs is the possible interaction with the xenobiotic biosensors of the human body, for example nuclear hormone receptors, resulting in an additional stimulus or antagonization of receptor activation capable of altering the metabolism process.(L. Vandenberg & Blumberg, 2018)

The excretion of lipophilic substances exploits the integration into micelles and the subsequent incorporation into bile to be eliminated into faeces, while hydrophilic chemicals are more typically discarded with urine.(L. Vandenberg & Blumberg, 2018)

Pharmacodynamics

The interaction of a chemical with a specific molecular component of the endocrine system can on the one hand alter homeostasis, on the other initiate processes at abnormal times in the life cycle.(Lee, 2018) Any aspect of endogenous hormones, including production, release, transport, metabolism, binding, action, or elimination, can be affected. Moreover, the underlying mechanisms can be activated simultaneously and/or multiple times, as EDCs can hit several targets, and multiple exposures can have effects on the same target. The consequent effects depend on both the level and the timing of exposure, as well as its reiteration.(Combarnous & Diep Nguyen, 2019) In particular, early developmental steps, as embryonic, foetal, neonatal, childhood, and puberty periods, have been called sensitive windows. It is also important to consider that bioaccumulation phenomena can lead to persistent internal exposure. Furthermore, different targets in the body can develop different types of responses following the stimulation of the same hormonal pathway.

The targets most commonly addressed by EDs are nuclear receptors, serving as hormone-dependent transcription factors controlling cells' phenotype.(Combarnous & Diep Nguyen, 2019) At present, 48 human nuclear receptors are known. Furthermore, these chemicals can act also via non-nuclear steroid hormone receptors, non-steroid receptors or orphan receptors.(Lee, 2018) These substances or mixtures can even alter membrane receptor signalling, most commonly leading to short-term effects (e.g. oestradiol, BPA).(Combarnous & Diep Nguyen, 2019)

ED can bind to a hormone receptor interacting with or activating its signal pathway, but it can also freeze the receptors conformation in an inactive state (e.g. polychlorinated biphenyls PCBs).(Combarnous & Diep Nguyen, 2019)

Another mechanism include modifications in the enzymatic hormone signalling pathway components downstream of receptor activation, including coregulatory factors as activators and repressors (e.g. bisphenols, phthalates, atrazine, tolylfluanid, neonicotinoid pesticides, DES, octylphenol).(Combarnous & Diep Nguyen, 2019; La Merrill et al., 2020)

An additional mode of action is the alteration of the concentration of the endogenous hormones by stimulating or suppressing biosynthesis, metabolism or degradation (e.g. BPA, 4-nonyphenol 4-NP, triclosan, flame retardants, parabens).(Combarnous & Diep Nguyen, 2019)

Changes in hormonal transport across cell membranes by selective and passive processes (e.g. BPA, imidazoline) are possible as well.(La Merrill et al., 2020)

EDs can also affect the endogenous free active hormone concentration indirectly, by binding circulating proteins and competing with small hydrophobic hormones in relation to transport. In these cases, both interference in blood stream (e.g. phthalates) and modification in biosynthesis or degradation of these proteins (e.g. flame retardants) are responsible for the effects.(Combarnous & Diep Nguyen, 2019)

ED can even modify hormone receptors turn-over or availability by stimulating or inhibiting expression (e.g. BPA, cadmium) or internalization (e.g. DDT).(Combarnous & Diep Nguyen, 2019; La Merrill et al., 2020)

Moreover, alteration of hormone metabolism or clearance (e.g. PCB, some wood preservatives) can be documented.(La Merrill et al., 2020)

A further mechanism is the induction, during development or adulthood, of epigenetic modifications in hormone producing or responsive cells, including DNA or histone alterations or non-coding RNA expression (e.g. PCBs, phthalates, BPA, DES, triclosan). Tissue structure and cellular organisation can thus change because of reprogramming of proliferation, migration, differentiation, apoptosis or necrosis in the concerned targets. Skinner et al. reported that when the epigenome of a somatic cell is involved, disease may arise in the exposed subject, while when the germ line is affected, transgenerational transmission to offspring can occur.(Karoutsou et al., 2017; Skinner et al., 2011)

Besides having endocrine disrupting properties, these chemicals can also generate additional adverse effects into the body through other toxicological mechanisms, as cytotoxicity, reprotoxicity, teratogenicity or genotoxicity.(Combarnous & Diep Nguyen, 2019) Non-endocrine-mediated adverse effects comprise mechanisms different than the direct interaction of a chemical with a specific component of the endocrine system.(Marty et al., 2018) These mechanisms can relate to a gland, a tissue or to some physiological processes that either control or are controlled by the endocrine system.(Marty et al., 2018) A paper examines endocrine endpoints possibly involved in these processes.(Marty et al., 2018) Therefore, some important distinctions must be made when characterizing toxicity, as legal framework can apply differently to non-endocrine and endocrine-mediated effects.(Marty et al., 2018)

Further toxicological characteristics

In general toxicology, to assess the dose-response relationship of a chemical is fundamental to set toxicity ranges and indications. For the purpose, several and specific doses are tested to assess specific effects and to obtain a dose-response curve, which can be resumed by

mathematical formulas. The number of the tested doses influence the level and detail of the characterisation and the confidence in the shape of the obtained curve.(Kohn & Melnick, 2002; L. Vandenberg & Blumberg, 2018) In particular, it is crucial to define the no observed adverse effect level (NOAEL) and/or the lowest observed adverse effect level (LOAEL) for the same endpoint.(Lagarde et al., 2015) A linear dose–response model applies when responses vary at a constant rate, proportionally or constantly, to the tested doses. Log-linear dose-responses and sigmoidal dose-responses can someway be considered analogous. In these cases, some fundamental assumptions can be made permitting to predict from high-dose testing low dose safety indications, for example for human exposures.(Beronius & Vandenberg, 2016; Hill et al., 2018) In these cases, the NOAEL indicates a conservative threshold below which, irrespective of the dose, the chemical is not expected to induce adverse effects.(Lagarde et al., 2015) Linear and sigmoidal responses are considered as monotonic: mathematically the sign of the slope does not change over the tested doses.(L. Vandenberg & Blumberg, 2018) When linear dose-responses curves are plotted with the toxicant effect in ordinate and the logarithm (log10) of dose in abscissa a sigmoidal-shaped curve is found.(Lagarde et al., 2015) In contrast, Non-Monotonic Dose–Response Curves (NMDRCs) are mathematically defined as having at least one change in the sign of the slope of a dose–response relationship over the range of doses tested.(Kohn & Melnick, 2002) They can appear as biphasic or multiphasic curves. Plotting the biphasic relationships, a bell-shaped profile is found: an inverted-U shape is characterized by responses at intermediate dose; a U-shape curve shows highest responses at low and high exposure levels. In this case, the standard notion of threshold is not inclusive of all potential harmful effects and reference doses or acceptable daily intake doses cannot be extrapolated.(Lagarde et al., 2015) These characteristics allowed the use in literature of the definition of "low dose effects", referring to biological responses in the dose range of a typical human exposure.(L. Vandenberg & Blumberg, 2018; Beausoleil et al., 2017; Kohn & Melnick, 2002; Laura N. Vandenberg, 2019) NMDRCs can arise from opposing monotonic dose-responses acting on a single endpoint or from effects mediated by multiple receptors differing in their expression or hormonal affinity. Other explications include the availability and expression of different co-factors and/or receptor proteins binding the same hormone, the different binding activities of a single hormone for several specific receptor proteins. Furthermore cellular responses, such as receptor desensitization, degradation or downregulation, negative or positive feedbacks or modulation while changing doses, can contribute.(Lee, 2018; L. Vandenberg & Blumberg, 2018) Numerous studies have recognized the occurrence of NMDRCs in the responses *in vitro* and *in vivo*, even in humans, to essential

nutrients, vitamins, pharmacological compounds, and natural hormones.(L. Vandenberg & Blumberg, 2018) In general toxicology literature, some estimates show that non-monotonicity occurs in 12-24% of all dose-response studies.(L. Vandenberg & Blumberg, 2018)

The existence of dose-thresholds considering EDCs is still debated(Beausoleil et al., 2017), while hundreds of examples of NMDRC have been reported in vitro and in animal models, with several concordant results in epidemiological studies.(Combarnous & Diep Nguyen, 2019)

There is evidence of this kind of dose-response curves for some chemicals as resveratrol, permethrin, chlorothalonil, and phthalates.(Hill et al., 2018)

In 2013, an analysis on bisphenol A (BPA) dose-response data reported that 34% of the publications included some results consistent with nonmonotonicity.(L. N. Vandenberg, 2013)

To try to control for the limitations of the concept of NOAEL, which is dependent on the analysed endpoint and the experimental conditions, a benchmark dose has been proposed (BMD), that has been defined as the dose corresponding to a specific change in an adverse response compared to the response in untreated animals.(Crump, 1995)

Considerations on mixtures

As EDCs are globally widespread, exposure to several components at a time is largely possible and must be taken into account when developing studies and risk assessment. It is often difficult to precisely distinguish the single components in these mixtures, stimulating the need of new evaluating approaches in definitions and testing assessments. Growing evidence on the role of mixtures is accumulating. Results of a study recently demonstrated associations between exposure to EDCs mixtures and alterations in the inflammasome analysing either maternal and cord blood cytokines.(Kelley et al., 2019)

The effects of several substances binding to the same receptor can vary with respect to the effects from a single substance, as phenomena of additivity, synergism, antagonism or modulation can occur.

This consideration is of the outmost importance when considering exposure to mixtures, as the combined exposure can be more harmful than those of the single constituents taken separately. For example, a recent study on a predictive risk assessment approach for anti-androgenic exposures during foetal life concluded that mixtures suppressed testosterone synthesis in human foetal testicular explants to a greater extent than single chemicals. A shift towards lower doses in the dose–response curves appeared with an increasing number of components.(Gaudriault et al., 2017)

Scientific efforts have been made in the last few years to try to develop a specific validated methodology to assess, or at least estimate, the risks associated to the exposure to mixtures, and to try to reproduce "real-life" conditions.(A. Bergman et al., 2019; Bornehag et al., 2019; Lazarevic et al., 2019; Nagel et al., 2020; Beronius & Vandenberg, 2016; Bopp et al., 2018; Gennings et al., 2018; Laura N. Vandenberg et al., 2016; Marshall et al., 2013) These methods often combine epidemiological data and statistical models and take into account results from *in vitro* and *in vivo* testing, for example when addressing associations between exposures and the development of metabolic syndrome.(Kassotis & Stapleton, 2019)

Recently, EDC-MixRisk, an EU Horizon 2020 research project, addressed the effects of prenatal exposure to mixtures of suspected EDCs on the development and health in children. The analysis supports assessment factors also with health-based guideline values from epidemiology data. The results indicated a higher risk compared to estimates by single-compound assessment and showed that when adding add up components the risk quotients exceed more and more acceptable risk level. Moreover, genetic background diversity has been shown to alter the sensitivity to chemical exposure.(A. Bergman et al., 2019)

Windows of sensitivity (WOS), long-term effects and susceptibility

According to a WHO/UNEP report, each tissue has a specific period during development, called WOS; when it is forming, and it is more susceptible to the effects of EDCs. As some tissues continue developing after birth, longer WOS are possible.(WHO/UNEP, 2013)

Changes in epigenetic plasticity and programming constitute the base of this phenomenon, that, once started, can be fixed, maintained through cell divisions, and persist in mature tissues long after the exposure occurred. It is speculated that it could reflect an evolutionary drive for later generations(Walker, 2016), meaning a person's health could be affected by exposures experienced by previous generations.(*Endocrine Disrupting Chemicals - OSHWiki*, n.d.)

According to a review, studies about toxicologically relevant chemicals and genetic variants or windows of breast susceptibility evidenced links between environmental exposures and breast cancer, however it concluded that many biologically relevant chemicals, have not been adequately studied in humans.(Rodgers et al., 2018)

Another paper analysing epidemiologic data and aiming to address long latency effects evidenced links between the human exposure of chemicals and metals during relevant WOS and breast cancer; intermediate breast outcomes, including specific breast tissue characteristics

and breast density in adolescence and adulthood, are proposed to address the study of long-term alterations.(Terry et al., 2019)

Other factors of vulnerability for the development of effective and efficient disruption comprehend sex, age, comorbidities, diet, socio-economic conditions, smoke, living environment, ethnicity, genetic background and the exposure characteristics (route of exposure, dose, timing and frequency).

Effects on human health

Hormones play their role through ubiquitous regulation of fundamental body's processes; thus, their disruption can potentially have a huge health impact concerning many systems.(Lee, 2018) Despite the evidence from *in vitro* and *in vivo* studies, there is still a lack of clear evidence of the health effects on humans and results are sometimes contradictory.(Lee, 2018) In this context, prenatal and children's exposures are issues of great concern, as they can irreversibly affect the development of neurological and reproductive system, as well as induce predisposition to chronic diseases, or bring to initiating-events leading to epigenetic alterations.(Alavian-Ghavanini & Rüegg, 2018) Epigenetic alterations can in turn cause transgenerational effects.

Some limited evidence of endocrine-mediated effects in humans raised from high levels exposures, such as after the accident of Seveso, Italy (dioxin) in 1976, and after treatment with diethylstilboestrol (DES) in the 1950s and 1960s.

Nowadays, recent reviews focus for example on female reproductive effects.

A critical analysis on the development of primary ovarian insufficiency, considering also occupational exposures, ended up highlighting the need for more studies to evaluate the effects of exposure, dose-response effects, and the effects of longer-term exposure, mostly due to the lack in biological endpoints and to possible measurement errors derived from deficient assessment methodologies.(Monteiro et al., 2020)

Another review evaluating the impact of environmental exposure to EDCs on the reproductive potential among women showed a decrease in oestradiol levels (BPA), in anti-Müllerian hormone concentrations (PCBs), in antral follicle count (BPA, parabens, phthalates), in oocyte quality (BPA, triclosan, phthalates, PCBs), in fertilization rate (PFCs, PCBs), in implantation (BPA, phthalates, PCBs), in embryo quality (triclosan, PCBs, BPA) and in the rate of pregnancy

or live births (parabens, phthalates). However, more epidemiological data are urged to confirm the findings.(Karwacka et al., 2019)

Moreover, a paper on the suspected causal relationships between exposure to non-persistent EDCs and representative female reproductive issues (menstrual cycle, endometriosis, uterine fibroids, polycystic ovarian syndrome), changes of ovary and/or uterus development and alterations in hormonal signalling underlined controversial results in humans, although the majority of publications confirmed the reproductive related effects.(Cho et al., 2020)

A further study targeting the effects of EDCs' exposure on female puberty concluded for the existence of somewhat controversial results in literature, while leaning towards a role in the acceleration and anticipation of the maturation of secondary sexual characteristics and in the predisposition to breast cancer. The role of oestrogen-mimicking actions in the proliferation of the breast stromal cells, obesogenic actions on the adrenal androgen levels, and additional epigenetic mechanisms is highlighted.(Predieri et al., 2020)

A mini-review of the evidence regarding transgenerational effects of EDCs in humans stated that more studies are needed to understand if effects on health could be confirmed, as well as that literature is lacking in the explanation of the underlying mechanisms, stressing the importance of testing relevant dose ranges and of considering the role of mixtures.(Brehm & Flaws, 2019)

Changes in the menstrual cycle, fibroids, endometriosis and endometrial cancer have also been analysed and pending confirmation.(Hall & Greco, 2019; Wen et al., 2020)

Other studies address male reproductive effects raising preoccupation regarding some EDCs, comprising pesticides, PCBs, dioxins, PBDE, phthalates.(*Endocrine Disrupting Chemicals - OSHWiki*, n.d.)

A paper on the effects of EDCs in male reproductive system and in the decline of male fertility argued that in humans the majority of the evidence positively associated exposure and infertility, testicular cancer, poor sperm quality and/or function, increased sperm DNA damage, alterations in testis morphology and hormonal imbalance. However, inconsistent results on semen quality, reproductive hormones and male fertility exist, according to the authors, probably due to small-sized study samples and lack of control for potential confounding variables.(Costa-Amaral et al., 2019)

According to another study, the epidemiological evidence was compatible with a small increased risk of male reproductive disorders following prenatal and postnatal exposure to EDs, but the evidence was limited. No evidence of distortion due to publication bias was found, but

exposure–response relationships were not evident. There were also insufficient data on rapidly metabolized endocrine disruptors and on specific exposure–outcome relations. A particular data gap was evident with respect to delayed effects on semen quality and testicular cancer.(Hougaard et al., 2009)
EDCs may be related to prostate cancer.(Hall & Greco, 2019)

Epidemiological studies focusing on the effects of anti-androgenic or pro-oestrogenic EDCs on testicular steroidogenesis were lacking according to some authors, and the main evidences on such an effect derive from several studies performed on animal models.(Pivonello & De Angelis, 2020) In animals, when developmental plasticity is high (*in utero*, during peri- and postnatal periods), the reproductive function can be altered in the offspring, at adulthood, and the effects of exposure may persist through generations.(Pivonello & De Angelis, 2020) According to the same authors, scarce epidemiological studies investigated the effects on the human testis and semen quality, by making it difficult to draw definitive conclusions(Adoamnei et al., 2018); in particular a study pointed out that chronic exposure, in a pre-existing condition of obesity, might exacerbate the deleterious effect of BPA on semen quality.(Pivonello & De Angelis, 2020)
Epidemiological evidences in humans, as well as studies in humans and animal models, link exposure to some lipophilic EDCs showing anti-androgenic or pro-oestrogenic activity (such as TBT, triphenyltin, phthalates, parabens and BPA) with obesity and metabolic syndrome-associated disorders.(Papalou et al., 2019) The promotion of adipogenesis, lipid accumulation and differentiation of adipose stromal mesenchymal stem cells or fibroblasts in adipocytes is the reason why they are defined “obesogens”.(Pivonello & De Angelis, 2020)
A recent study about the role of EDC exposure in the development of metabolic alterations, as obesity, diabetes, and fatty liver disease, drawn the conclusion that, while epidemiological and experimental data were mounting, predictive methods and models to evaluate mechanisms and pathways behind these observed effects were lacking.(Küblbeck et al., 2020)
According to another paper, analysis evaluating the potential role of exposure to EDCs on the pathogenesis of type I diabetes in humans were few and demonstrated contradictory results; more evidence was thus needed to better understand the causal mechanisms and to implement prevention strategies.(Predieri et al., 2020)
A further review regarding EDCs and the risk of diabetes pointed out moderate evidence for a relationship with exposure to dichlorodiphenyldichloroethylene, poor evidence for polychlorinated biphenyls (PCBs) and scarce evidence for BPA, phthalates and perfluorinated

chemicals, while brominated flame retardants did not show significant associations.(Lind & Lind, 2018)
Moreover, a review concerning the diabetogenic effect of the exposure to EDCs in the workplaces found some positive findings for certain pesticides and dioxins, nevertheless variable conditions of exposure, bias in environmental or biological monitoring and differences in the evaluated outcomes did not allow to define a specific causality.(Leso et al., 2017)

In adults, reduced levels of thyroid hormones have been related to higher cholesterol and blood pressure, and decreased bone density.(WHO/UNEP, 2013) EDCs with some evidence for thyroid effects are PCBs, PBDEs, phthalates, BPA, and perfluorinated compounds.(*Endocrine Disrupting Chemicals - OSHWiki*, n.d.)
Thyroid-hormone disruption is involved too in cognitive and behavioural performance alteration. Examples of chemicals provoking imbalance are lead, methylmercury, PCBs (*Endocrine Disrupting Chemicals - OSHWiki*, n.d.). Recent data showed that prenatal exposure to mixtures of thyroid hormone– disrupting chemicals constituted a plausible mechanism contributing to current increase in the incidence of neurodevelopmental diseases and intelligent quotient (IQ) loss.(Mughal et al., 2018)
Deficiencies in thyroid hormones in pregnant women have been associated with brain damage, and even limited decreased hormonal levels have been linked to lower IQ and attention deficit hyperactive disorder (ADHD).(*Endocrine Disrupting Chemicals - OSHWiki*, n.d.)

A recent review on EDCs' human exposure and autism spectrum disorder (ASD) argued that generally a positive association is found, but after accounting for limitations the overall strength of evidence remains "limited" and inconclusive.(Marí-Bauset et al., 2018)
Another review concluded that convergent studies reported an association between exposure to EDCs and ASD, ADHD, global developmental delay, intellectual disability, communication disorders and unspecified neurodevelopmental disorders, and that sufficient data support the hypothesis that EDCs are a risk factor for the emergence of neurodevelopmental disorders (Rivollier et al., 2019).
An epidemiological data revision revealed that older pesticides (organochlorine, organophosphate, carbamates) were more often associated with thyroid axis disruption than modern compounds (pyrethroids, neonicotinoids, and phenylpyrazoles), however the authors stressed the need for a better systematization of measurements, for determination of more sensitive brain endpoints and for more longitudinal studies.(Leemans et al., 2019)

A study about the development of complex chronic human brain disorders suggest a role of estrogenic endocrine disrupting chemicals in modifying genes of both oestrogen and NRF1 signalling pathways through genomic and epigenomic multiple mechanisms.(Preciados et al., 2016)
Exposure to EDCs may contribute to immune deficiency and altered immunity.(Nowak et al., 2019) Kidney and respiratory diseases could be favoured.(Hall & Greco, 2019)

Other hormone-related cancers may be promoted, but the role of EDCs in cancer development is still to be defined.(Hall & Greco, 2019)

Controversies

Many debates surround the scientific evidence regarding EDCs.
As the same set of hormones and their respective receptors operate in the same set of hormonally responsive tissues to regulate different functions, it is a recognized difficulty to design sensitive, hormone-specific assays that clearly distinguish permanent changes from transient fluctuations, or adverse alterations from adaptive responses.(Keller et al., 2012)·(Marty et al., 2018) Furthermore, the efficacy of a hormone or an EDC on different endpoints can vary by several orders of magnitude, so the choice of endpoints in regulation is crucial, but again there is a lack in indication regarding robust endpoints and assays.(Demeneix et al., 2020) The same observation can be made considering that events controlled by hormones can be both temporally and spatially specific, with some events in development, changing as development proceeds and different in adulthood.(Demeneix et al., 2020)
Moreover, all organs and tissues can be affected by physiological stimuli, xenobiotics or natural substances, which may lead to toxicological processes affecting or not the endocrine system, and which in turn can indirectly trigger endocrine responses.(Marty et al., 2018)
The possibility to establish a clear set of methods for analysing the evidence for non-monotonicity is also discussed. Moreover, mathematically at least three data points are required to define a linear dose-response curve and at least five to determine a non-monotonic response, and in literature it is no common to find a proper number of dose groups, as it is also rare for the slope to be calculated.(Lee, 2018) As reported in a recent study, significant biological plausibility of NMDR does not systematically imply a causality link with the observed effects, determining whether an effect is adverse can be difficult for small-magnitude effects and should consider windows of sensitivity, vulnerability periods could be the only ones showing a non-monotonic curve.(Lagarde et al., 2015) Furthermore, the identification of dose-response curves

is difficult when non exposure groups do not exists or the exposure range is limited.(Lee, 2018) The quality of exposure assessment is often limited and suffering from large within-subject and day-to-day variability.(Lee, 2018)

A recent review argues that thresholds of adversity exist for EDCs, even for directly acting genotoxic agents.(Brescia, 2020)

Statistical methods have been suggested for analysing exposome and epigenetic programming, but they presume unrealistic simple conditions, such as linearity.(Lee, 2018) To account for the observed health effects, other mechanisms have been suggested, as mitochondrial impairment or chronic glutathione depletion.(Lee, 2018)

Several inconsistencies concern the evaluation of mixtures, comprising the difficulty of exposure assessment, the difficulty to develop models better approximating "real life" conditions and the evaluation of multiple interactions in which the observed modulation or antagonization could be predicted.(Lee, 2018)

Understanding is still partial about how and when translation of animal research to humans is feasible. Studies are needed to properly take into account exposures that occurred decades before diagnosis or access biological samples stored that long.(Rodgers et al., 2018) For some years now, test techniques combining epidemiological data, genomics and exposome analysis, in order to create "precision" preventive medicine.(Alofe et al., 2019)

About definitions, what should be considered an "adverse" outcome has not yet reach international agreement, especially regarding the possibility of reversible effects, the occurrence of a continuum of effects from initiating to apical effects, and that disruption can include all hormonal cycle from synthesis to metabolism. The IPCS defined in 2004 an adverse effect as "a change in morphology, physiology, growth, development or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to the harmful effects of other environmental influences". The US EPA's definition is "a biological change, functional impairment, or pathologic lesion that affects the performance of the whole organism, or reduces an organism's ability to respond to an additional environmental challenge". Us Food and Drug Administration and the European Food Safety Authority have not ratified a definition, opening up to uncontrolled variability in decision making.(L. Vandenberg & Blumberg, 2018)

Some authors reported that stress responses should not be interpreted as primary endocrine-mediated effects, but rather as non-endocrine-mediated effects. These responses reflect activation of the sympathetic nervous system or the hypothalamic pituitary-adrenal axis to restore physiological conditions, and their magnitude and endpoints are altered by many factors

as type, duration and magnitude of stress, gender, age, physio-pathological state and individual variability. Thus, discerning specific endocrine-mediated effects from secondary, stress-induced changes in endocrine-sensitive endpoints appears challenging.(Everds et al., 2013;ˏMarty et al., 2018)

Different regulatory frameworks worldwide using alternative definitions resulted in that the scientific evidence can support or not in different countries the classification of one given substance or mixture as EDCs.(Lee, 2018;ˏKassotis et al., 2020)

Most frequently encountered EDCs and their targets

Exposure to EDCs may occur in everyday life and in many occupations. Some substances have been banned in most countries; however, exposure is possible through remediation, disposal, or renovation activities.

Table 1 lists different classes of suspected and confirmed EDCs, adapted from Van Tongeren et al. (Van Tongeren et al., 2002), Brouwers et al. (Brouwers et al., 2009), https://oshwiki.eu/wiki/Endocrine_Disrupting_Chemicals and http://auvergne-rhone-alpes.direccte.gouv.fr/Retrouvez-les-plaquettes-d-information-Perturbateurs-endocriniens, with particular attention to occupational settings.

Table 1. Examples of EDCs and their potential employment

Classes of potential EDCs	Chemical subgroups	Application
Polycyclic aromatic hydrocarbons (PAHs)		Occupations and activities exposing to incomplete combustion products of carbon-containing fuels, tar.
Polychlorinated organic compounds	▪ Polychlorinated biphenyls (PCBs) ▪ Dioxins, furans, polychlorinated naphthalene ▪ Octachlorostyrene	PCBs were used until the 1970s as insulating and cooling fluids, including in capacitors and electronic items. Exposure may still occur from disposal, removal, or repair/renovation of old equipment or buildings. Dioxins are by-products of waste incineration and industrial processes involving carbon and chlorine. Octachlorostyrene is a by-product of industrial processes, including PVC recycling, aluminium refining, metal degreasing, etc.
Pesticides	▪ Organochlorines ▪ Carbamates ▪ Organophosphates ▪ Tributyltin ▪ Pyrethroids ▪ Other	Agricultural applications Pest treatment/removal Wood preservation, anti-fouling applications

Phthalates	▪ Di-2-ethylhexyl phthalate (DEHP), di-isononyl phthalate (DINP), di-n-hexyl phthalate (DnHP) ▪ Benzyl butyl phthalate (BBP) ▪ Dibutyl phthalate (DBP) ▪ Diethyl phthalate (DEP)	High molecular weight compounds (DEHP, DINP, DnHP) primarily used as plasticizers in polyvinyl chloride Low molecular weight compounds (BBP, DBP, DEP) used in cosmetics, adhesives, ink, dyes, plastic packaging.
Organic solvents	▪ Ethylene glycol ethers (EGEs) ▪ Styrene ▪ Toluene ▪ Xylene ▪ Trichloroethylene (TCE) ▪ Perchloroethylene (PCE)	EGEs, toluene, xylene used in products such as paints, adhesives, thinners, lacquers, resins Styrene used in polystyrene plastics and resin production TCE and PCE used in metal degreasing and other industrial cleaning processes.
Phenols	▪ Bisphenol A (BPA) ▪ Halogen phenols and alkyl-derivatives ▪ Benzophenone ▪ Parabens	Polycarbonate plastic and epoxy resin production. Food plastics, cosmetics, receipts, cans, disinfectants,...
Alkylphenolic compounds	▪ Alkylphenolic ethoxylates (APEs) ▪ Alkylphenols (APs)	APEs are non-ionic surfactants used as detergents, emulsifiers, wetting and dispersing agents, used in agricultural, industrial, and consumer applications. APs are precursors to APEs and used in the production process.
Brominated flame retardants	▪ Polybrominated diphenyl ethers (PBDEs) ▪ Tetrabromobisphenol A (TBBPA) ▪ Hexabromocyclodecane (HBCD)	Polymer and textile manufacturing, electronics.
Metals and metalloids	▪ Arsenic ▪ Cadmium ▪ Copper ▪ Lead ▪ Mercury	Mining, refining, smelting, pesticides, electronics manufacture, construction, medical industry.
Parabens	▪ Parabens	Parabens are used as preservatives in cosmetics and pharmaceuticals.
Benzophenones		Benzophenones are a UV filter used in cosmetics and plastics. Also used in printing industry, paints, furniture and wood coatings.
Cyclic methyl siloxanes		Siloxanes used in cosmetics, personal care products, and cleaning.
Perfluoroalkyls	▪ Perfluorooctanoic acid ▪ Perfluorooctane sulfonate	Used in non-stick coatings, stain repellents, insulators, textiles.
Hormones	▪ Water-soluble: amino-, peptide-hormones ▪ Fat-soluble: retinoid, steroids, thyroid	Drugs production, contraception, hormone replacement therapies, surgery, urgency, anabolic substances,..
Dioxins and furans	▪ Polychlorinated dibenzo-p-dioxins ▪ Polychlorinated dibenzofurans	Waste incineration fumes
Perfluorinated compounds (PFC)	▪ Perfluorinated alkyl halides ▪ Fluorochloroalkenes ▪ Perfluoroethers and epoxides ▪ Perfluoroalcohols ▪ Perfluoroamines ▪ Perfluoroketones ▪ Perfluorocarboxylic acids	Breathable textiles, non-stick coatings for frying pans and kitchen utensils,..

LEGISLATIVE FRAMEWORK

General principles about EDCs Regulation in Europe

The existing legislation within the EU about chemicals follows a hazard-approach with toxic potential classified according to the use of a chemical itself.(European Commission, 2016b) Separate legislations direct testing and assessment, but the general rule is that, prior to marketing, testing should ensure the absence of dangers to humans and wildlife during utilisation, after or when released into the environment.(European Commission, 2016b)

The specific steps required for chemical risk evaluation until the regulation of hazardous sources of exposure start with the identification through validated tests. Therefore, agreement on tests and endpoints, on tests requirements, as well as on guidelines to apply definitions based on tests' results, is needed and it must ensue from the conclusions obtained from scientific evidence, as well as updated accordingly.(Risk & Policy Analysts Ltd & wca Environment, 2018;ˑChoi et al., 2017;ˑThe International Panel on Chemical Pollution (IPCP), 2017;ˑBrunel University London & National Food InstituteTechnical University of Denmark, 2017;ˑOECD GD 150, 2018;ˑAxelstad et al., 2019)
Secondly, these results would constitute the milestone for risk assessment. Risk management complete the process through the determination of the proper restrictions in chemicals' utilisation.(European Commission, 2016b)

For hazards' identification, specific batteries of tests are validated at the international level by the Organisation for Economic Co-operation and Development (OECD), and then adopted by the European Commission (EU) by the means of Directives.(European Commission, 2016b)
Under the existing EU legislation,

- Regulation (EC) N° 1907/2006 – Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Regulation addresses the production and employment of chemicals and their impact on human health and the environment, amending Dangerous Preparation Directive (Directive 1999/45/EC). It established the European Chemical Agency (ECHA), which has published and regularly updated the REACH Authorisation List addressing to the employment of Substances of Very High Concern (SVHCs) reported in annex XIV, including EDs, carcinogens, mutagens, substances toxic for reproduction substances with persistent, bio-accumulative and toxic (PBT) or very persistent and very bio-accumulative properties(vPvB). Moreover, articles meeting the criteria for CMR substances and possibly used by consumers, are listed in annex XVII. ECHA supervise manufacturers, importers and

retailers of SVHCs by delivering or not authorisation. The applicant has to submit a chemical safety report, as well as an analysis of possible alternative substances or technologies and development processes. ECHA publishes guidance documents on the compilation of safety data sheets. In June 2020 Commission Regulation (EU) 2020/878 amended annex II to comprise also specific requirements for EDCs;

- Regulation (EC) N° 1272/2008 – Classification, Labelling and Packaging (CLP) Regulation aligns European Union legislative framework on chemical substances and mixtures to the Globally Harmonised System (GHS), replacing Dangerous Substances Directive (Directive 67/548/EEC) and Dangerous Preparations Directive and complementing REACH Regulation. This regulation defines the main classes of hazards, including physical hazards, health hazards, hazards to the environment, so that they can be properly identified and communicated, for example with hazard symbols as pictograms and risk and safety statements.

The obtained data, together with the calculated or measured environmental levels, are used to assess if the proposed utilisation of a chemical could be threatful for human health or the environment.(European Commission, 2016b)

Several regulations and Directives settle the risk assessment of specific types of chemicals and provide a framework to refer to similar standards.(European Commission, 2016b)

- REACH Regulation supersedes the risk assessment replacing pre-existing regulatory acts, such as Regulation (EEC) No. 793/93 on the assessment of existing substances and Directive 76/769/EEC on the restriction of marketing and use of certain dangerous substances and preparations;
- Placing of plant protection products on the market (Directive 91/414/EEC), amended by Regulation (EC) N° 1107/2009 and Commission Regulation (EU) 2018/605 amending annex II, addresses pesticides;
- Directive 98/8/EC – Biocidal Products Directive (BPD), superseded by the Biocidal Products Regulation (EU) 2017/2100 pursuant to Regulation (EU) 528/2012, regulate biocides;
- Food contact materials are concerned by Directives 80/590/CEE and 89/109/EEC, repealed by Regulation (EC) N° 1935/2004 and Regulation EU N° 10/2011, while contaminants in food are addressed by Regulation (EEC) N° 315/93 and feed Directive 2002/32/EC.

If potential for harm is likely, restriction or reviewing of the employment are imposed to allow for risk management.(European Commission, 2016b)

Risk management within the EU is established by:

- Placing and Prohibition of placing on the market and use of Plant Protection Products (Regulation (EC) N° 1107/2009 and Commission Regulation (EU) 2018/605 amending annex II, replacing Directive 89/365/EEC that amended Directives 91/414/EEC and Directive 79/117/EEC);
- Maximum residue limits in agricultural products and foodstuffs (Directives 86/362/EEC, 86/363/EEC and 90/642/EEC, amended by Directive 2006/30/EC, repealed implicitly by Regulation (EC) N° 396/2005 and Directive on the sustainable use of pesticides 2009/128/EC);
- Fertilising Products Regulation (EU) 2019/1009;
- Regulation (EC) N° 1223/2009, replacing Directive 76/768/EC, on placing on the EU market of finished cosmetics products;
- Detergent Regulation (EC) N° 648/2004;
- Materials and articles intended to come into contact with food stuffs (Directive 89/109/EEC and its specific directives, repealed by Regulation (EC) N° 1935/2004, Directive 2011/8/EU on Bisphenol A, repealed by Regulation EU N° 10/2011);
- Food additives regulation (1333/2008/EC);
- Restrictions on marketing and use of certain dangerous substances and preparations (Directive 76/769/EEC), replaced by REACH Regulation;
- General Product Safety Directive 2001/95/EC, last amended by Regulation (EC) N° 596/2009;
- Prohibition on the use in stockfarming of certain substances having a hormonal or thyrostatic action and of beta agonists (Directive 96/22/EC);
- Measures to monitor certain substances and residues thereof in live animals and animal products, application of measures on food and feed law (Directive 96/23/EC, repealed and replaced by Regulation (EU) 2017/625);
- Integrated pollution prevention and control of industrial emissions (Directives 96/61/EC and 2008/1/EC, repealed by Directive 2010/75/EU);
- Water Framework Directive (Directive 2000/60/EC), until Directive 2013/39/EU and European Parliament resolution P8-TA(2019)0320;
- Drinking Water Directive 98/83/EC and Groundwater Directive 2006/118/EC;
- Regulation (EU) 2017/745 on medical devices, amending Directive 2001/83/EC, Regulation (EC) N° 178/2002 and Regulation (EC) N° 1223/2009;
- Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices;

- Directive 2009/48/EC on the safety of toys;
- Regulation (EC) N ° 1223/2009 on cosmetic products and review following COM/2018/739 report.

Examples of compound- and sector-specific regulation addressing to specific chemicals follow.

- Restriction of Hazardous Substances (ROHS) Directive (2011/65/EU) limit concentrations of some phthalates, lead, mercury, cadmium, hexavalent chromium, polybrominated biphenyls (PBB), PBDEs;
- International Stockholm Convention on Persistent Organic Pollutants (POPs), ratified by the European Community in 2004, allowed a ban of the production and use of DDT, PCBs, chlordecone, penta- and octa-BDE, and a restriction of a polybrominated flame retardant (PBDE);
- POPs Regulation (EU) 2019/1021 and Regulation (EU) 2020/784 amending annex I as regard the listing of PFOAs, as well as the amendments introduced by Commission Delegated Regulation (EU) 2020/1203 and 2020/1204;
- Bisphenol A was firstly restricted from baby bottles (EU (regulation 321/2011)), and then from food containers for infants and young children. Regarding the general population, a migration limit of bisphenol A from varnishes or coatings (Commission Regulation 2018/213) and toys is established, as well as a maximal concentration in thermal papers. In 2017, bisphenol A has been recognized as a substance of very high concern (SVHC) for its endocrine disrupting properties by ECHA;
- Triclosan use cannot be used in the manufacture of plastics intended to come into contact with food. In cosmetics, it is authorized with some restriction in concentration;
- Some phthalates (BBP, DEHP, DIBP, DBP) have been added in REACH annex XIV. The use of BBP, DEHP and DBP is limited in plasticized materials used in toys and childcare articles;
- Some pesticides and other chemicals are restricted by Regulation (EU) N° 649/2012, amended by Commission Delegated Regulation (EU) 2020/1068 concerning export and import of hazardous substances.

Complete this background some directives and strategy-indications aiming at reviewing and taking more into account hormonal disruption as:

- the proposal for a Regulation on transparency and sustainability of risk assessment under EU food law (COM(2018) 179), which aims at implementing the regulatory process, including for the assessment of substances suspected to be endocrine disruptors;
- the European Plastics Strategy (COM(2018) 28 and COM(2018) 32), following up from the Circular Economy Action Plan COM(2015) 614, which aims to promote recycling and to accelerate the substitution of substances of concern, including endocrine disruptors;
- the proposal to revise the Drinking Water Directive, which adds more endocrine disruptors to the list of parameters for determining the safety of drinking water;
- the New Deal for Consumers (COM(2018) 183) and the Goods package (COM(2017) 795), addressing product safety requirements and the illegal presence of endocrine disruptors in a variety of products;
- the update of the existing legal framework on Occupational Safety and Health to protect workers exposed to hazardous chemicals, some of which have endocrine disrupting properties.(European Commission, 2018a);
- the Chemical Strategy for Sustainability Towards a Toxic-Free Environment (COM(2020) 667) addressing also endocrine disruptors and safety in the workplaces;
- the Commission Staff Working Document Fitness Check on endocrine disruptors accompanying the Chemical Strategy for Sustainability (SWD(2020) 251).

It is important to remark that the definition of endocrine disruptors for substances in plant protection and biocidal products adopted in 2017 (EU Regulations 2017/2100 and 2018/605) represents at the European level the only legal criteria for the determination of endocrine-disrupting properties. This definition does not apply in other key sectors *per se*. In these areas some endocrine related effects, such as reproduction alteration or development of chronic pathologies including cancers, are accounted for indirectly but not as a separate endpoint and generally no specific management logic exists. Moreover, it is significant to consider that even for biocides and plant protection products, the regulation introduces some illogicality, as tests actually do not cover all the main disrupting modalities and endpoints are compulsory in application dossiers for product authorization, in particular for biocides, making identification very difficult in practice.(Coady et al., 2017)

It is also noteworthy that the CLP Regulation provides definitions for carcinogenic, mutagenic substances and substances toxic for reproduction, but not for EDs. Furthermore, it does not apply to sectors such as cosmetics, animal nutrition, drugs, medical devices, food or feeding stuffs. The responsibility for the identification of hazards and their classification is in the hands of manufacturers and stakeholders.

Regarding REACH Regulation, currently, only few chemicals have been classified as EDs and even less have been added to the REACH Authorisation List because of their disrupting properties, partly because of limited information in the application dossiers. The applicant for authorisation shall demonstrate in the application file that a threshold for the health or environmental effect exists. Otherwise, or if this demonstration is not accepted by ECHA, the candidate substance will be subject to authorization. Still poor incentive is given to applicants to demonstrate effects.
EDs are kept on the same level of concern as carcinogenic or mutagenic substances, but ED testing is still compulsory in application dossiers, restricted to available information and both test requirements and the related regulations appear limited. This also happens because the regulation does not rely on any definition of EDs; it does not recognize criteria about EDs nor is there any guidance document explicating how to identify them.

About compound- and sector-specific regulations, multiple sources and other sectors can be concerned, living space to an overall exposure in presence of some sparse limitations.

Safety data sheets (SDSs), introduced by REACH Regulation and adapted to take into account the rules of Global Harmonised System (GHS) and other elements of the GHS into CLP Regulation via amendments to Annex II of REACH, provide information to recipients of substances and mixtures in the EU (European Chemical Agency, 2020). Article 31 in REACH Regulation defines the criteria to draft the document and to list components of products or mixtures in section 3 of the SDSs. It is evident that on numerous occasions EDCs may not be included.

French context

In the 2010s, public concern pushed the French Parliament adopting a law to suspend the manufacture, import, export and marketing of all food packaging containing BPA. Subsequently, France was one of the first countries, after Canada, to ban BPA, firstly in babies' bottles and food contact materials, and then irrespective of the user's age. The regulation is

meant to reduce dietary exposure and to assure protection of the more vulnerable population. Then, based on a request by France assessed by the Agency, the European Commission adopted a proposal in 2016 to classify BPA as a category 1B reproductive toxicant.(*Endocrine disruptors | Anses - Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail*, n.d.)

ANSES contributed to define the criteria for the identification of endocrine disruptors at a European level in 2016 and it is responsible for assessment of several substances for their endocrine-disrupting nature in collaboration with other EU Member States. The purpose is to identify Substances of Very High Concern (SVHC) under the REACH Regulation.
Between 2009 and 2015, many studies turned around effects, uses, and sources of exposure, as well as the contamination of different environments.
These studies constituted a starting point for ranking substances to be assessed to in the National Endocrine Disruptor Strategy (SNPE 2014-2016).(*Endocrine disruptors | Anses - Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail*, n.d.)

France is the first country to launch a national strategy on endocrine disruptors (SNPE 2014-2016). It aims to reduce the exposure of the population and the environment to endocrine disruptors. In this context, ANSES has been tasked with the assessment of at least five substances per year over three years, which can also include potential substitutes for substances of concern.
When certain substances submitted to the Agency for appraisal are suspected of having endocrine-disrupting effects and/or posing a risk to health or the environment, ANSES is asked to propose appropriate risk management measures in the framework of the European regulations.(*Endocrine disruptors | Anses - Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail*, n.d.)

The 2019 project of French national strategy on EDs (SNPE247) highlights several actions to be enacted over the next four years with a view to protecting the population and the environment by reducing exposure to EDs. Targets include publishing a list of potential EDs by 2021 (classified by level of proof and/or need for further investigation), better informing the population, in particular through the labelling of consumer goods, improving knowledge on PE effects on wildlife and reducing environmental contamination by EDs.(*Endocrine disruptors | Anses - Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail*, n.d.)

Other studies concerned dietary and water exposures.(*Endocrine disruptors | Anses - Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail*, n.d.)
Research projects on endocrine disruption have been financed by the Ministry of the Environment in recent years.(*Endocrine disruptors | Anses - Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail*, n.d.)

ANSES's Scientific Conferences events and the publication of research papers, organised in partnership with the Research National Agency (ANR), focused on the scientific advances concerning exposure, the effects on human health and the mechanisms of action.(*Endocrine disruptors | Anses - Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail*, n.d.)

Italian context

In Italy since the 2000s efforts have been done to develop a research area addressing EDCs. A national coordination effort tried to create a virtuous circle starting from scientific evidence and addressing health and environmental actions, as well as legislative initiatives. The National Committee for Biosafety and Biotechnology created for this purpose a working group for the surveillance of exposure to EDs, and a first report appeared in 2007.(Gruppo di lavoro per la sorveglianza dell'esposizione agli interferenti endocrini, 2007)

In 2008, the Ministry of the Environment and Land and Sea Protection promoted a three-year study on the risk assessment of emerging contaminants in ecosystems and in the human population (PREVIENI Project – "Study in pilot areas on the environmental and health effects of some emerging chemical contaminants (endocrine disruptors): living environment, reproductive outcomes and repercussions in the developmental age").

In 2011, Italy participated to the LIFE-EDESIA Project on alternative methods to animal testing and strategies for substituting endocrine-disrupting products.
Italy has contributed to the evaluation of chemicals suspected for hormonal disruption and is engaged in communication projects and the proposal of shared platforms (Calamandrei et al., 2018). Several projects address maternal-foetus exposure.

In 2018 LIFE PERSUADED Project aimed to estimate the exposures of mother-child pairs to phthalates and bisphenol A, the results contributing to the implementation of the HBM4EU database, available in Europe for regulatory and risk assessment purposes.

European regulation concerning workers

Council Directive 98/24/EC refers to the protection of the health and safety of workers from the risks related to chemical agents at work. The lack of consideration concerning EDs has been documented in the 2018 Commission ED framework. A specific directive on the protection of workers from carcinogens and mutagens (2004/37/EC) is in vigour, and Directive (EU) 2017/2398 amended and introduced some articles and modified annexes. Directive (EU) 2019/130 addresses the protection of workers from the risks related to exposure to carcinogens and mutagens at work. Council Directive 92/85/EEC, last amended by Regulation (EU) 2019/1243, introduced measures to protect pregnant workers, workers who have recently given birth or breastfeeding. Young people at work are concerned by Directive 94/33/EC, last amended by Regulation (EU) 2019/1243.

French regulation concerning workers

In France, the employer is submitted to the obligations reported in the French labour law. Some general principles, applying also to the EDCs, are stated in the *Code du Travail*. Articles R. 4412-1-> R. 4412-93 outline the general approach in dealing with the chemical risk in the workplace. The employer must evaluate and regularly re-evaluate the chemical hazards, realize the chemical risk assessment and then take collective and individual actions in order to avoid, or, when it is not possible, to minimise the exposition and the risks to the health of workers. In particular, article R. 4222-10 defines the maximal concentrations of the inhaled total and alveolar dusts in the workplace, and the articles R. 4412-27 and R. 4412-76 regard the measurement of the concentrations of harmful chemical agents and the control of the threshold limit values (TLVs) fixed at the articles R. 4412-149 and -150. Furthermore, articles R. 4412-59->93 address the risks related to carcinogens, mutagens, and toxic for reproduction. The article R. 4412-3 defines what is meant for dangerous chemical agent. The definition includes any chemical agent, as such or part of mixtures, presenting a risk to the health and safety of workers due to its physicochemical, chemical or toxicological properties, to the modalities of presence or use in the workplace, and any chemical agent presenting occupational exposure limit values provided for by a decree. Articles D4152-9, -10 and -11 in the *Code du Travail* establish a framework for chemical exposures of pregnant or nursing women, including effects on reproduction, and reinforce the employer's obligation to inform women about the effects of exposures in the workplace on fertility, the embryo and foetus.

Italian regulation concerning workers

As in France, in Italy a labour law is in effect. In particular, the chemical risk evaluation and assessment are regulated under *Titolo IX* of the D.Lgs 81/2008. The employer is submitted to obligation of results and if the risk is not low for safeness and irrelevant for the health of worker, Artt. 225, 226, 229, 230 apply. The *Capo II* refers to the protection from carcinogens and mutagens. The employer has to evaluate risks even in specific groups of workers exposed to particular risks, including pregnant women, and relative to gender, age, origin. D.Lgs 151/2001, *Capo II*, guarantees pregnant women health protection, concerning also chemical risk.
Workers may also be impacted by the reorganisation of the regulatory framework of the establishments producing emissions into the atmosphere. The management of emissions into the atmosphere of substances classified as carcinogenic, mutagenic or reprotoxic is regulated by Art. 271 of the D.Lgs 102/2020, a decree that supplements and corrects D.Lgs 183/2017 concerning medium combustion plants. Moreover, certain restrictions are in force with respect to some hazardous substances and may apply to exposures in the workplace, for example, *DM Ambiente 19 maggio 2020* and *DM 5 agosto 2020* implemented European directives concerning electrical and electronic equipment.

ENDOCRINE DISRUPTORS IN INDUSTRY AND TERTIARY SECTOR

INTRODUCTION

The role of numerous lifestyle, genetic, physiological, pharmaceutical, environmental factors, as well as occupational exposures, in the development of disease or adverse effects such as hormonal imbalance, has been supported by the scientific literature. (X. Wang & Ji, 2020)

Workplaces are settings in which particular conditions of exposure may more easily reveal the adverse effects derived from exposure to chemicals, including EDCs, as chronic, possibly prolonged and repeated contacts may happen. Both high- and low-dose exposures may occur and be responsible for large effects.(Welshons et al., 2003; Reichard et al., 2007; A. M. Tsatsakis et al., 2016) Moreover, workers are often people of childbearing age, and exposures to reprotoxicants or mutagens, including EDCs, can result in transgenerational or chronic effects more easily, as they can affect the gametes or the foetus.

Some conditions should theoretically facilitate data collection on groups of workers exposed to chemicals. Indeed, in specific exposure situations, they undergo to periodic health surveillance. Thus, environmental and biological samples to monitor exposure could be collected at given time points. Furthermore, the first exposures to a new chemical often happen in the workplaces while manufacturing chemical products. Hence, an analysis of the evidence could be even more interesting in this field, as it can potentially reveal resulting adverse effects sooner. Prospective, case-control or cohort study design should be more easily applied in this context, but some challenging issue emerged in literature. For example, it is sometimes difficult to evaluate the contribution of each component when multiple contemporaneous exposures occur, as well as to consider the effects of comorbidities or para-physiologic status. It could be equally complex to evaluate the contextual exposure contribution to health effects from everyday life products.(A. Tsatsakis et al., 2019; A. M. Tsatsakis et al., 2016)

The evidence of alterations in the physiological levels of hormones and the occurrence of adverse effects following EDCs' occupational exposure in some workplaces are increasing.

Maybe the evidence in the occupational context can be less contradictory than regarding the general population, as exposure conditions and doses can be somewhat more controllable.

This review aims at evaluating the literature of the last decade on the effects of the exposure to EDCs on production, industry and tertiary workers. It is a generally less investigated field than the agricultural sector, for which the studies are numerous. However, the results can be more easily applied to urban backgrounds. Contextually, this study tries to make a survey of the methodologies in use to evaluate both exposure and health effects in the same period. Results could be useful, for example, from a preventive and risk management perspective to compare and propose already-in-use suitable biological surveillance methods and proper clinical endpoints. Furthermore, this search can help guide and prioritize actions for risk assessment involving certain activities. Some limitations in the studies in the workplaces are already known.(Papaleo et al., 2004) This analysis can underline if, in the last decade, some different conclusions or observations can be drawn.

MATERIALS AND METHODS

Literature was investigated by using several search engines and databases (Google Scholar, Scopus, Pubmed-Medline using Mesh options, ResearchGate). For this enquiry, we used as search items various combinations between: exposure identifiers ("ED", "EDCs", "endocrine disrupt*", "chemical", "exposure"), effect identifiers ("hormon*", "adverse effects", "disease") and context identifiers ("occupational exposure", "workers", "workplace", "job", "occupational setting").

The preliminary phase recalled, after removal of duplicates, 1030 articles. References of the selected articles were also evaluated to identify relevant publications, allowing the inclusion of additional articles.

Inclusion criteria comprised publication between 2010 and September 2020 of human peer-reviewed research articles (i.e.: cross-sectional, cohort, case-control, retrospective studies), published in English, addressing groups of workers or people evaluated for their occupational history and exposed to suspected or proven EDCs.

Exclusion criteria regarded *in vitro* and *in vivo* experimental studies, animal studies, posters, abstracts, case-reports, research letters, reviews, articles published in other languages than English, articles not focusing on settings or outcomes relating to workplaces or occupational exposure, articles lacking statistical results indications for associations (e.g. : not reporting nor p values or OR or RR or IC%).

Overall, a total of 254 publications were suitable for review after restriction for the period of publication, language, availability of the full-text, and type of study.

We further restricted our selection to 99 studies, after exclusion of analysis addressing exposure in agriculture-farming-logging-hunting-fishing. After a revision of contents (aims of the study, sample, methodologies, statistical results indication), we included 76 studies.

RESULTS

The studies summarized in Table 2 addressed the link between occupational exposure to EDCs and the possible effects on metabolic function or cardiovascular diseases.

The age of the analysed subjects varied between 18 and 86 years. The occupational exposures that have been considered varied from phthalates, pesticides, solvents, BPA, to PAHs, dioxins, metals or PFOA. Three studies examined the effects of BPA exposure. Two of them, on female marketing sellers (cross-sectional) (Vahedi et al., 2016) and nurses (longitudinal) (Sun et al., 2014), concluded for an association with type 2 diabetes in middle-aged subjects and polycystic ovary syndrome. The third one (S. Wu et al., 2019), on male subjects, concluded that the combination of the exposure and smoking lead to a weak augmentation in the risk of metabolic syndrome. Four other studies related the effects of metals. The first one highlighted higher odds ratios of type 2 diabetes in exposed workers. (A. M. Yang et al., 2015) A second study, on male subjects, concluded that the combination with smoking habits was associated with a greater prevalence and possibly higher risk of type 2 diabetes. (A. Yang et al., 2017) Another study found higher prevalence of atrial fibrillation (Bulka et al., 2019). The fourth one found that gender, different type of exposure and forms of mercury were associated to type 2 diabetes, but not to pre-diabetic status. (Goodrich et al., 2013) Two studies (Karnes et al., 2014; Winquist & Steenland, 2015) on PFOA based on the same cohort found no associations with development of type 2 diabetes, while one (Winquist & Steenland, 2015) stressed a possible association of higher exposure levels and higher prevalence of medically treated hypercholesterolemia. Three research groups took into account exposure to PCBs. A cross-sectional study found no associations with HbA1c levels (Eftekhari et al., 2018). Another study found a positive association with type 2 diabetes and age, and an inverse association with thyroid function parameters. No mechanisms of action involving endogenous hormones could be highlighted (Persky et al., 2012). A further study found an association with type 2 diabetes, which did not

involve the development of auto-antibodies.(Esser et al., 2016) Some studies involved larger samples. Two of them concerned exposure to PFOA and evaluated the clinical outcome mainly on the base of self-reported and medical records information.(Karnes et al., 2014; Winquist & Steenland, 2015) One study evaluated exposure on the base of exposure models and historical biomonitoring data.(Bulka et al., 2019) Other authors (A. M. Yang et al., 2015) evaluated the exposure on the base of estimates, but a subgroup of workers had undergone urine collection. About the cited scientific articles using larger samples, some limitations were reported, including possible misclassification in exposure and outcome assessment (e.g.: recall bias, lack in accounting for non-occupational or early-life exposures, lack in evaluation of actual exposure levels), non-systematic-realisation of dose-response analysis or reference to underlying biological mechanisms, non-evaluation of specific agents in some cases. Possible truncating bias due to employment of cohorts of survivors or reduction in hazard ratio with increasing follow-up due to possible decrease in susceptibility of the remaining population were also described. In some cases, sensitivity analyses accounting for strong risk factors and confounders were performed to reduce the weight of bias.

Other studies focused on the possible alteration of hormonal levels, as represented in Table 3.

These studies comprised samples that are more limited; thus, the statistical analysis could not include and adjust for possible confounders.(Fahim et al., 2020; Atasoy & Kanat, 2011; Saad-Hussein et al., 2011; Makey et al., 2016; Persky et al., 2012; Fong et al., 2015) The subjects were mostly aged 23-64 years. Two studies analysed the effects from phthalate exposure on men. The first study concluded for a relationship between exposure and reproductive hormones levels, possibly involving stimulation of aromatase activity.(Fong et al., 2015) The second study aimed at evaluate dose-effect responses. Exposed subjects developed inverted long-tailed J-shaped curves for free testosterone and follicular stimulating hormone. Hormonal production and hypothalamus-pituitary-testis axis were impaired, possibly through the stimulation of a positive feedback limiting decreasing circulating levels of free testosterone.(Pan et al., 2011) Several studies concerned metals. Two of them, from the same research group, concluded that low levels of cadmium could be associated to FSH levels in males (Ciarrocca et al., 2013), and could be negatively associated to fT3 and fT4 while positively associated to TSH in a cohort of both sexes.(Rosati et al., 2016) A study on lead and cadmium exposure on males concluded for an association of higher levels of testosterone with higher exposure and smoking.(Atasoy & Kanat, 2011) Two studies on the effects of lead exposure on male cohorts gave discordant results regarding a possible disruption of the thyroid function.(Fahim et al., 2020; Soltani et al.,

2012) Two studies focused on organic solvents. On the one hand, females showed an augmentation of menstrual disorders, which seemed mediated by a reduction of sexual hormones levels proportionally to the duration of exposure.(Ekpenyong et al., 2013) On the other hand, males developed an augmentation of hyperthyroidism, with a role played by an alteration in the oxidative-antioxidative balance.(Saad-Hussein et al., 2011) The largest samples were used in two studies.(Rosati et al., 2016; Ekpenyong et al., 2013) Both studies combined evaluation of self-reported and biomonitoring data, at least in a subgroup of subjects, outcome evaluation through hormonal dosing, and comprised adjustment for possible confounders in the statistical analysis.

A large group of articles analysed possible effects on sexual function, reproduction, pregnancy and offspring (Table 4).

Several studies evaluated the role of occupational exposures on cohorts extracted from research programs on the general population or case registries, as indicated in Table 4. Regarding exposure to solvents, two studies concerned workers. One showed a duration-dependent association with alterations in spermatic DNA integrity.(Katukam et al., 2012) The other indicated a level-dependent effect on spontaneous abortion, in synergy with shift work, and prolonged time to pregnancy.(Attarchi et al., 2012) Other authors concluded for a relationship between exposure to solvents and congenital malformations.(Desrosiers et al., 2012; Gilboa et al., 2012; Aguilar-Garduño et al., 2010) Literature on workers regarded also BPA exposure. Dose-response relationships with male sexual dysfunction, evaluated by validated questionnaires, emerged (Li et al., 2010), as well as reduced anogenital distances (Miao, Yuan, He, et al., 2011) in infants when exposure of mothers occurred. A reduced birth weight was shown in children when parental exposure had happened, especially if it concerned the mothers. (Miao, Yuan, Zhu, et al., 2011) Another study on general population found some relationship between exposure to bisphenols and hypospadias in offspring.(Giordano et al., 2010) Studies on mercury exposure in the workplace gave contradictory results.(El-Badry et al., 2018; Heggland et al., 2011) One of these studies found associations between air levels and several clinical results, as pregnancy outcomes, development of pre-eclampsia, augmentation of oxidative stress and increase in small-for-gestational age new-borns.(El-Badry et al., 2018) In studies on the general population, exposure to metals was associated with hypospadias or cryptorchidism when paternal exposure had occurred.(Morales-Suarez-Varela et al., 2011) On the other hand, maternal exposure was associated to cardiac congenital malformations.(C. Wang et al., 2015) A study concerned workers exposed to phthalates finding reduction in sperm

motility and DNA denaturation in semen of exposed subjects.(Huang et al., 2011) Some other authors found augmented length of the time to pregnancy and alterations in placental weight in exposed workers, and higher prevalence of congenital malformations in the offspring of exposed parents.(Snijder et al., 2012; Burdorf et al., 2011; Estors Sastre et al., 2019; Kalfa et al., 2015; Aguilar-Garduño et al., 2010) Some further evidence emerged on alkyl phenolic compounds and pesticide exposures. (Shirangi et al., 2020)

Some literature dealt with carcinogenesis, as shown in Table 5.

As indicated, most of the studies reported in Table 5 followed a case-control or a longitudinal design, the sample was drawn from the general population, and exposure, or outcome, data were often driven from self-reported information or medical registries. Solvent exposure was generally associated to breast cancer for exposures before first full-term birth (Ekenga et al., 2014), with different possible links to receptor expression in females depending on the authors.(Brophy et al., 2012; Ekenga et al., 2015) Solvent exposure was also associated to the development of male breast cancer after long-term exposure.(Laouali et al., 2018) Exposure to solvents was weakly associated with haematological cancers (Cocco et al., 2010), testicular and testicular germ cell tumours.(Olsson et al., 2018; Paoli et al., 2015; Le Cornet et al., 2017) Breast cancers seemed associated to exposure to acrylic- or nylon-fibres, soldering fumes, dyes and inks.(Labrèche et al., 2010; Ekenga et al., 2015) Exposure to biocides was dose-dependently associated to thyroid cancer (Zeng et al., 2017), while PCBs to testicular cancer and alterations in semen quality.(Paoli et al., 2015)

A group of studies referred to possible effects on immunity, DNA structure or antioxidant systems (Table 6).

Genetic damage was associated with benzene exposure and occurred transiently after recent exposure to perchloroethylene.(Costa-Amaral et al., 2019; Tucker et al., 2011) Exposure to phthalates seemed to have effects on pulmonary function as happens in allergic asthma.(Kolena et al., 2020) Some authors associated oxidative state with exposure to solvents and metals. (Kuras et al., 2018; Fahim et al., 2020; Saad-Hussein et al., 2011; Aisha Mohamed Samir & Wael Mohamed Aref, 2011)

Some other studies published in the last decade referred to the association between neuropsychiatric effects or neurobiological modifications and EDCs exposure. Four of them employed data from the Health Effects in high Level exposure to PCB (HELPcB) surveillance

program in Germany, a longitudinal program on workers in a recycling company (number of included subjects in between 116 and 178, of both sexes, aged 16-85 years).(Petra M. Gaum et al., 2014; Petra Maria Gaum et al., 2017, 2019; Putschögl et al., 2015) In the first one (Petra M. Gaum et al., 2014), exposure was assessed by means of the serum levels of 18 PCBs. Standardized psychological screening scales were used for the diagnostic of depressive, anxiety, panic and somatoform syndromes. A significant relationship was found between PCB burden and depression. Within the higher exposed group, prevalence rates were descriptively higher, except for anxiety syndrome. The second study used the serum levels of 14 PCBs congeners, and the urinary concentrations of the metabolites homovanillic acid and vanillylmandelic acid to evaluate effects of exposure on neurotransmitters of the dopamine and norepinephrine systems, respectively.(Putschögl et al., 2015) A cross-sectional analysis indicated a significant negative effect of PCB exposure on both metabolites. Longitudinally, an initially higher exposure to higher chlorinated PCBs was followed by constant reduced homovallinic acid level over three consecutive years. Exploratory analyses showed different long-term effects, according to the chlorination degree of the analysed PCBs. A third study assessed longitudinally serum levels of PCBs and both a validated questionnaire for depressive symptoms and urinary metabolites were collected. The association between PCB exposure and an increase of depressive symptoms after one year was mediated by the homovallinic acid levels.(Petra Maria Gaum et al., 2017) The fourth study assessed exposure using the serum levels of 37 PCBs, and depressive syndrome by the means of a serum thyroid function marker, urinary homovallinic acid levels, and a standardized questionnaire for depressive symptoms. The results suggested that a process involving the thyroid function and the dopamine system was responsible for depressive symptoms after PCB exposure.(Petra Maria Gaum et al., 2019) Another study in the United States on 89 capacitor workers (of both sexes, aged 51-85 years) investigated the dopamine system function after exposure to PCBs and pesticides.(Seegal et al., 2010) Serum levels of 27 PCBs and 9 organochlorine pesticides were collected and specific SPECT imaging was performed to evaluate the specific non-displaceable putamen uptake. Women, but not men, showed an inverse relationship between lipid-adjusted total serum PCB concentrations and dopamine transporter densities in the absence of differences in serum PCB concentrations. These sex differences may reflect age-related reductions in the levels of gonadal hormones. For the putamen and the caudate, densities were significantly and inversely related to log total serum PCB concentrations (on a lipid basis) only for women.(Seegal et al., 2010)

Table 2. Occupational exposure to EDCs and effects on metabolic function and cardiovascular diseases

Ref.	Design	Activity	Clinical Outcome	EDCs	Sex	n	Exposure Assessment	Outcome Assessment	Results
(S. Wu et al., 2019)	L	nuclear power plant	metabolic disorder	BPA	m	1227, 1038 at follow up	U BPA	Height, body weight, waist circumference, blood pressure. B glucose, lipids, liver function and renal function.	Compared with the lowest U BPA group, an increased risk of disease among subjects with middle (aHR=1.19, 95% CI 0.87 to 1.63) and high level of U BPA (aHR=1.16, 95% CI 0.84 to 1.59). The association was restricted primarily to the smokers, with a positive gradient with U BPA level (middle level: aHR=2.40, 95% CI 1.13 to 5.08; high level: aHR=2.87, 95% CI 1.38 to 5.98; p trend= 0.010).
(Vahedi et al., 2016)	C	marketing	glucose metabolism impairment, dyslipidaemia	BPA	f	124: 62 cases, 62 matched controls	B BPA	B FPG, triglycerides, cholesterol, HDL, LDL, TSH, LH:FSH ratio	Significant higher B BPA, triglycerides, cholesterol levels and LH:FSH ratio, and significant lower TSH concentration, in cases against controls (p< 0.05). In BPA-exposed PCOS women, BPA level was higher.
(Sun et al., 2014)	L	nurses	glucose metabolism impairment	BPA, phthalates	f	1941: 971 cases, 970 matched controls	U BPA and phthalate metabolites(9)	Self-reported information	BPA and phthalate exposures may be associated with the risk of T2D among middle-aged (p-trends=0.02), but not older, women.
(Goodrich et al., 2013)	X	dental staff	hypertension	Hg	b	284	Self-reported information, U Hg, hair methylHg	Blood pressure and pulse	Associations with blood pressure were found at exposure levels relevant to the general population, associations varied according to type of Hg exposure and gender. Linear regression models revealed significant associations between diastolic blood pressure (adjusted for medication use) and hair Hg (p = 0.02). Elemental Hg exposure was associated with a significant systolic blood pressure decrease (p = 0.04) driven by the male population.
(A. Yang et al., 2017)	X	mining and metallurgy	glucose metabolism impairment, dyslipidaemia	metals	m	26008	U nickel, copper and cobalt.	B FPG, total cholesterol, triglycerides, HDL and LDL.	Both exposure to metals and heavy smoking were associated with an increased prevalence of T2D. The adjusted prevalence ratio for T2D was 1.8 [95% confidence interval (CI) 1.3-2.4] for heavy smokers of >40 pack-years, 1.2 (95% CI 1.1-1.4) among mining/production workers and 2.7 (95% CI 2.4- 3.0) among smelting/refining workers, compared with non-exposed workers. A significant effect modification between smoking and metal exposure on the prevalence of T2D ($p_{interaction}$ = 0.001).
(A. M. Yang et al., 2015)	X	mining and metallurgy	glucose metabolism impairment	metals	b, m>f	42122	Estimation of likely metal exposure levels based on task, U nickel, copper, and cobalt	Blood pressure, BMI, B FPG, total cholesterol, triglycerides, HDL, and LDL.	The adjusted odds ratios for T2D among mining/production workers and smelting/refining workers compared to non-exposed workers were 1.5 (95% CI: 1.3, 1.7) and 3.8 (95% CI: 3.4, 4.3), respectively.
(Bulka et al., 2019)	X		cardiovascular disease	organic solvents, metals, pesticides	b	7404	Self-reported information	Self-reported information or ECG performed at baseline.	For individuals working with pesticides, the prevalence ratios for any cardiovascular disease was 2.18 (95% CI 1.34 to 3.55) after adjustment for confounders. Metal exposures were associated to atrial fibrillation with greater prevalence ratios (3.78, 95% CI 1.24 to 11.46).
(L. Yang et al., 2017)	X	mining and metallurgy	glucose metabolism impairment	PAHs	b, m>f	1472	U OH-PAHs(12)	Self-reported information	Elevated U 4-OHPh was significantly associated, in a dose-dependent manner, with increased risk of T2D (p_{trend} = 0.003). In stratified analysis, the association was more prominent in smokers, overweight, with longer working years and working at coke oven settings (all p_{trend}<0.05). High 4-OHPh combined with longer working years or overweight had a joint effect on the risk of diabetes.

(Eftekhari et al., 2018)	X	energy distribution; chemical industry, turning and casting; professional driving; office work	glucose metabolism impairment	PCBs	b, m>f	140(70 exposed)	B PCBs(21)	B HbA1c	Participants with an increased HbA1c had higher plasma PCBs, although this association was statistically not significant. In the logistic regression, adjusted for confounders, none of the pairwise differences between the exposure quartiles reached statistical significance.
(Esser et al., 2016)	X/L	recycling company	glucose metabolism impairment	PCBs	b, m>f	263/119	B PCBs(19)	B HbA1c, auto antibodies for glutamate acid decarboxylase (GAD), islet cell (ICA), Insulin (IAA) and Tyrosine-phosphatase (IA-2).	A detectable association was shown between internal PCB burden and glucose metabolism. An elevated odds ratio was found for the third quartile of PCB 52 (7.6; 95% CI: 1.4–41.0). An analysis of the autoantibodies GAD, IAA, IA-2 and ICA showed no association to PCB burden.
(Persky et al., 2012)	X	Capacitor manufacture	glucose metabolism impairment	PCBs	m	63	B PCBs(46), total of worked quarters from social security records, a job score.	Self-reported information. B glucose, triglycerides, cholesterol, GGT, CRP, T4, FTI, T3, TSH, DHEAS, cortisol, LH, insulin, SHBG, oestradiol, testosterone, SHBG-bound testosterone. U estrone metabolites, 2-hydroxyestrone and 16α – hydroxyestrone. Calculated insulin resistance and β-cell function.	PCB exposure was positively associated with T2D and age and inversely associated with TSH and triiodothyronine uptake. After controlling for confounders, some congeners were negatively and significantly related to TSH, while other relationships were of only borderline significance (p-value ≥ .05 but less than .10) History of T2D was related to total PCBs and all PCB functional groupings, but not to quarters worked and job score, after control for potential confounders. None of the exposures were related to insulin resistance in non-diabetic men.
(Winquist & Steenland, 2015)	X	explosive plant	cardiovascular disease, dyslipidaemia; hypertension	PFOA	b	32254(3713 exposed)	Estimates of exposure through an environmental fate and transport model, a residential exposure model, an occupational model based (historical B PFOA levels, work history, plant processes).	Self-reported information	Incidence of hypercholesterolemia increased with increasing cumulative PFOA exposure, most notably among males 40–60 years of age. Compared with the lowest exposure quintile, hazard ratios for subsequent quintiles were 1.24, 1.17, 1.19, and 1.19 overall and 1.38, 1.32, 1.31, and 1.44 among men 40–60 years of age. No association between PFOA exposure and hypertension or coronary artery disease incidence.
(Karnes et al., 2014)	L	explosive plant workers	glucose metabolism impairment	PFOA	b	30454(3713 exposed)	Estimates of exposure through an environmental fate and transport model, a residential exposure model, an occupational model based (historical B PFOA levels, work history, plant processes).	Self-reported information, medical records.	No association between PFOA exposure and incidence of type II diabetes.
(Kolena et al., 2020)	L	firefighters	metabolic disorder	Phthalates	m	32	U phthalate metabolites(11)	Body composition, BMI, waist-to-height ratio (WHtR), waist-to-hip ratio (WHR), fat mass index (FMI), fat-free mass index (FFMI), body shape index (ABSI).	A positive association between some phthalate metabolites and waist-to-hip ratio (p=0.003−0.09) and body shape index (p=0.039−0.09), and a negative association between other metabolites and hip circumference (p=0.005−0.02). A significantly higher concentration of phthalates if ingested food was heated in plastic containers or wrapper during the previous 24 h or after eating margarines and vegetable fat packed in plastic containers.

(Pelcl et al., 2018)	L	Herbicides plant workers;	metabolic disorder	TCDD	m	16(8 exposed)	B TCDD	Self-reported information, blood pressure, B cholesterol and triglycerides, FPG, HbA1c, duplex sonography of carotid arteries, eye fundus, skin microvascular reactivity, total body fat mass.	Several metabolic parameters were higher (for T2D 3.5-fold) in the group of severely TCDD-intoxicated subjects than in a general population of comparable age.

Case-control (C), cross-sectional (X), longitudinal (L), blood (B), urinary (U), hydroxy- (OH-), bisphenol A (BPA), polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), perfluorooctanoid acid (PFOA), tetrachlorodibenzo para dioxin (TCDD), fasting blood glucose (FPG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), follicle-stimulating hormone (FSH), body mass index (BMI), glycated haemoglobin (HbA1c), gamma-glutamyl transferase (GGT), C-reactive protein (CRP), thyroxine (T4), free thyroxine index (FTI), triiodothyronine (T3), thyroid-stimulating hormone (TSH), dehydroepiandrosterone (DHEAS), luteinizing hormone (LH), sex hormone binding globulin (SHBG), adjusted hazard ratio (aHR), polycystic ovary syndrome (PCOS), confidence interval (CI), type 2 diabetes (T2D), mercury (Hg)

Table 3. Occupational exposure to EDCs and effects on hormonal levels

Ref.	Design	Activity	EDCs	Sex	n	Exposure Assessment	Outcome Assessment	Results
(Ciarrocca et al., 2012)	X	Traffic policemen	As	m	185(108 exposed)	As air (TWA), personal air samples, U As.	B TSH, fT3, fT4 and Tg	In the total sample, U As was significantly correlated to TSH (p = 0.001) and Tg values (p = 0.006) and inversely correlated to fT3 (p = 0.03) and fT4 (p = 0.02).In traffic policemen, U As and As in the air were correlated to the airborne As and TSH values, respectively. U As was correlated to TSH, Tg, fT3, and fT4 values. The multiple linear regression models showed the following associations: i) among U As, As in the air and job title; ii) among TSH, fT3, Tg and U arsenic (p = 0.000, respectively); and iii) between fT4 and both U As and alcohol intake.
(Vahedi et al., 2016)	C	Marketing sellers	BPA	f	124: 62 cases, 62 matched controls	B BPA.	B FPG, triglycerides, cholesterol, HDL, LDL, TSH, and LH:FSH ratio	Significant higher B BPA, triglycerides, cholesterol and LH:FSH ratio and significant lower TSH were detected in cases against controls (P < 0.05). No significant associations between TSH and BPA.
(Rosati et al., 2016)	X	Traffic policemen	Cd	b, m>f	277	Cd air samples, U Cd.	B fT3, fT4, and TSH	A negative correlation between U Cd and fT3 and fT4 (p 0.023; p <0.001, respectively) and a positive correlation between U Cd and TSH (p 0.002).
(Ciarrocca et al., 2013)	X	Traffic policemen	Cd	m	172(86 exposed)	Cd air (TWA), personal air samples, B and U Cd.	B LH, FSH and testosterone	Multiple linear regression models showed associations between (a) U Cd, airborne Cd, working life, job category and consumption of water from water supply (b) B Cd, airborne Cd and job category (c) FSH and age, working life, job category, U and B Cd (p = 0.000, respectively) (d) LH and both the age and working life. Testosterone values were lower in the traffic policemen (p = 0.01).
(Ekpenyong et al., 2013)	X	petrol pump workers	gasoline	f	235(117 exposed)	BTEX compounds personal air samples.	Self-reported information. B oestradiol, FSH, LH, progesterone and prolactin.	Exposure to gasoline was significantly associated with disorders in both menstrual cycle length (p = 0.009) and quantity of flow (p = 0.002). Longer duration of exposure was significantly associated with higher likelihood of menstrual disorders (OR 4.15, CI 2.224-14.004). Persistent low serum levels of oestradiol, and fluctuating levels of other reproductive hormones were shown.
(Fahim et al., 2020)	X	foundry workers	Pb	m	87	B Pb	B fT3, fT4, TSH, malondialdehyde (MDA), glutathione (GSH)	The exposed group had significantly increased fT3, fT4 and significantly decreased TSH (p <0.0001). A state of oxidative stress was indicated by the significant increase in mean levels of MDA and significant decrease in GSH (p <0.0001). There was a significant positive correlation (p <0.05) between B Pb and duration of employment, while B Pb showed a significant negative correlation with TSH (p <0.001), and GSH (p <0.05). A significant positive relationship was found between GSH and TSH (p < 0.05), MDA with FT3 (p < 0.05) and FT4 (p < 0.0001) among exposed workers. Workers exposed to Pb were at risk of hyperthyroidism and showed a state of oxidative stress.

(Soltani et al., 2012)	X	Battery recycling	Pb	m	195	B Pb, chelatable Pb was calculated	B T3, T4, TSH, T3 resin uptake	No thyroid dysfunction from exposure to different B Pb levels.
(Atasoy & Kanat, 2011)	X	asphalt workers	Pb, Cd	m	61(30 exposed)	B Pb and Cd	B GOT, GPT and testosterone.	B Pb and Cd were significantly higher in asphalt workers than non-exposed group ($p<0.01$, respectively), with significant differences in smoking and non-smoking subjects ($p<0.01$). The amount of testosterone was significantly higher in non-smoking asphalt workers than in smoking workers ($p<0.01$) and in smoking asphalt workers ($p<0.01$).
(Saad-Hussein et al., 2011)	X	Chemical manufacture	organic solvents, mixtures in paint production	m	76(36 exposed)	Self-reported information	Clinical examination, B T3, T4, MDA, total antioxidant capacity (TAC), nitric oxide (NO) concentration.	Workers exposed to organic solvents proved to be at risk for hyperthyroidism. Levels of oxidative stress and antioxidants differed significantly different between subjects with elevated vs normal T4 ($p<0.005$ for NO, $p<0.01$ for MDA). Correlation between the duration of exposure and the levels of thyroid hormones, was found particularly for T4 after adjusting for confounders ($p<0.01$).
(Makey et al., 2016)	L	Office workers	PBDEs, flame-retardants	b	51	B PBDEs(11)	B triglycerides, cholesterol, TSH, fT4, T3, T4, TPO antibodies.	T4 was inversely associated with each PBDE congener. After adjusting for confounders, for every-unit increase in BDE-47, there was a 2.6-µg/dL (95% CI: –4.7, –0.35) decrease in T4 ($p = 0.02$) and for every unit increase in BDE-100, a 7.8-µg/dL (95% CI: –14, –1.6) decrease in T4 ($p = 0.01$).
(Persky et al., 2012)	X	Capacitor manufacture	PCBs	m	63	B PCBs(46)	B glucose, triglycerides, cholesterol, GGT, CRP, T4, FTI, T3, TSH, DHEAS, cortisol, LH, insulin, SHBG, oestradiol, testosterone, and SHBG-bound testosterone. U estrone metabolites, 2-hydroxyestrone and 16α – hydroxyestrone. Calculated insulin resistance and β-cell function.	PCB exposure was positively associated with T2D (e.g.: after adjustment, dioxin-like PCBs were significantly associated to T2D, p=.002 OR 2.7, 95%CI 1.3-5.8) and age and inversely associated with TSH and T3. History of diabetes was significantly related to total PCBs and all PCB functional groupings, but not to quarters worked and job score. Results suggested that the measured endogenous hormones did not mediate the associations.
(Fong et al., 2015)	X	Chemical manufacture	phthalates	m	82	Self-reported information. U phthalate metabolites(3)	B SHBG, inhibin B, testosterone, oestradiol, FSH and LH. The free androgen index (FAI) was calculated.	In multiple regression models, adjusted for potential confounders, significant positive associations between U phthalate metabolites and oestradiol ($p<0.01$), and in the ratio of oestradiol to testosterone ($p<0.05$) were found. Quartile analysis showed significant positive relationships between the total U phthalate metabolites and oestradiol ($p_{trend}=0.024$), and in the ratio of oestradiol to testosterone ($p_{trend}=0.031$). Relationships between reproductive hormones and the total U phthalate metabolites were significantly positive. Aromatase activity seemed increased in exposed workers.
(Pan et al., 2011)	DR	Chemical manufacture	phthalates	m	137(74 exposed)	U phthalate metabolites(2). Calculated HQ and HI.	B LH, FSH, free testosterone (fT) and oestradiol	The median of HI value was 53.0-fold for exposed workers than for unexposed workers (0.10). 89.2% of exposed workers and 1.6% of unexposed workers have HI over 1.00. The exposed workers showed inverted long-tailed J-shaped fT and FSH curves, and small changes in the LH curve, whereas unexposed workers had inverted and flattened-S-shaped fT and mirror-S-shaped LH and FSH curves. Both testosterone production and hypothalamus-pituitary-testis axis function were damaged in workers with high HI of phthalate exposures. A feedback function was activated in workers with both high and low HI.

Dose-response (DR), polybrominated diphenyl ethers (PBDEs), arsenic (As), lead (Pb), cadmium (Cd), time-weighted average (TWA), benzene-toluene-ethylbenzene-xylene (BTEX), hazard quotient (HQ), hazard index (HI), free triiodothyronine (fT3), free thyroxine (fT4), thyroglobulin (Tg), glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), thyroid peroxidase (TPO)

Table 4. Occupational exposure to EDCs and effects on sexual function, reproduction, pregnancy and offspring

Ref.	Design	Activity	Clin. Summ.	EDCs	n	Exposure Assessment	Outcome Assessment	Results
(El-Badry et al., 2018)	L	Dental staff	P	Hg	124(64 exposed)	Air and U Hg in every pregnancy trimester	B GSH peroxidase and superoxide dismutase activities. Self-reported information, medical reports for abortion; pre-eclampsia; mode of delivery; post-partum haemorrhage; defective lactation; foetal/neonatal congenital malformations; SGA; prematurity; placental abruption; intrauterine foetal demise; admission to neonatal intensive care unit; neonatal death	The exposed group had a significantly ($p<0.001$) higher mean U Hg level in the three trimesters and lower antioxidant enzymes activity. Exposed women had more frequently spontaneous abortion (RR 3.52, 95% CI 1.29-2.23) and pre-eclampsia (RR 3.67, 95% CI 1.25-10.76) compared to the non-exposed women ($p<0.001$). Babies born to exposed women were smaller for gestational age (RR 6.2, 95% CI 2.3-16.4) compared to the non-exposed women ($p<0.001$).
(Heggland et al., 2011)	X	Dental staff	O	Hg	5493 dental cohort, 1124758 control group	Archives of the public dental healthcare and the national trade unions	Data from the Medical Birth Registry of Norway for all congenital malformations, major congenital malformations, low birth weight, preterm delivery, SGA, multiple births, stillbirth and prenatal death	No excess risks of congenital malformations or other adverse pregnancy outcomes for female dental personnel.
(Miao, Yuan, He, et al., 2011)	X	epoxy resin manufacture	O	BPA	153(56 exposed)	BPA in air (TWA8), personal air sample. A JEM was constructed. U BPA in a subgroup	Measured AGD	Exposure to BPA during pregnancy was associated with shortened AGD in male offspring. The association was stronger for maternal exposure ($p < 0.01$). A dose-response relationship with increased BPA exposure levels in pregnancy was associated with greater magnitude of shortened AGD in male offspring, with a statistically significant trend for the association ($p = 0.008$).
(Miao, Yuan, Zhu, et al., 2011)	X	epoxy resin manufacture	O	BPA	587(143 exposed)	BPA in air (TWA8), personal air sample. A JEM was constructed. U BPA in a subgroup	Self-reported birth outcomes: infant sex, birth weight, gestational age, gravidity, parity and any gross abnormalities of new-borns	Parental exposure to BPA during pregnancy was associated with decreased birth weight. The association was stronger for maternal exposure ($p=0.02$). A dose-response relationship was observed with increased BPA exposure levels and associated with greater magnitude of decrease in birth weight ($P=0.003$).
(Li et al., 2010)	L	epoxy resin manufacture	SF	BPA	550(164 exposed)	BPA in air (TWA8), personal air sample, information from the factory's records, interviews, a walk-through evaluation. U BPA in a subgroup	The International Index of Erectile Function and the Brief Male Sexual Function Inventory for sexual desire, erectile function, orgasmic function and overall satisfaction with sex life, at 1 year or less, 2–5 years and greater than 5 years after employment	BPA-exposed workers had higher risk of male sexual dysfunction than the unexposed [reduced sexual desire (OR 3.9, 95%CI 1.8–8.6), erectile difficulty (OR 4.5, 95%CI 2.1–9.8), ejaculation difficulty (OR 7.1, 95%CI 2.9–17.6), reduced satisfaction with sex life (OR 3.9, 95%CI 2.3–6.6)]. A dose–response relationship was observed with an increasing level of cumulative BPA exposure associated with a higher risk of sexual dysfunction.
(Attarchi et al., 2012)	X	Pharmaceutical industry	P	solvents	406(205 exposed)	Solvent air samples	Self-reported time to pregnancy (TTP). Spontaneous abortion confirmed by medical records	A significant correlation between spontaneous abortion and exposure to organic solvents mixture was found ($p<0.05$) and increased with increasing levels of exposure (OR from 5.21 in the low exposed to 7.70 in high-exposed subjects). A significant correlation between exposure to mixed organic solvents and TTP was shown. A synergistic effect between shift working and occupational exposure to organic solvents mixture on spontaneous abortion was found.

(Katukam et al., 2012)	X	Pharmaceutical industry	SF	benzene	360(160 exposed)	Self-reported duration of exposure, B and seminal fluid benzene	Semen sample: volume, appearance, pH, viscosity, liquefaction, total sperm count, sperm motility, and sperm morphology. Sperm DNA integrity	No significant changes in macroscopic semen parameters. A duration-dependent decrement in total sperm count and the percentage of motility among the benzene-exposed workers ($p < 0.05$) was seen. A duration- dependent increment of abnormal sperm morphology among the benzene-exposed workers ($p < 0.01$) was found. A significant increase in comet tail length was shown in the exposed groups ($p < 0.01$) in comparison to the unexposed.
(Huang et al., 2011)	X	plastic manufacture	SF	phthalates	45	DEHP personal sampling	Semen samples: percentage of abnormal spermatozoa and maturity, concentration, motility, and morphology. Sperm Chromatin Structure Assay (SCSA). Extent of DNA denaturation per cell as alpha-T (aT), expressed as tendency of sperm chromatin DNA damage. DNA fragmentation index (DFI)	In the high-exposed group, significant increases in the tendency for sperm DNA denaturation (aT) induction, in the DNA fragmentation index (DFI), and in propensity for coffee drinking. After adjusting for confounders, personal air DEHP showed positive association with aT ($p = .015$), DFI ($p = .010$) and negative association with sperm motility ($p = .044$).
(Shirangi et al., 2020)	X		O	pesticides, PAHs, PCOCs, phthalates, organic solvents, BPA, alkylphenolic compounds, brominated flame retardants, metals, benzophenones, parabens, siloxanes	4142 pregnancies	A JEM and/or self-reported information. Scores/categories of exposure	SGA, intrauterine growth if percentage of optimal birth weight (POBW)<85	The frequency of POBW<85 significantly increased for mothers exposed to pesticides (RR_{adj} 3.72, 95%CI 1.40–9.91) and phthalates (RR_{adj} 3.71, 95%CI 1.62–8.51). There was a 5-fold increase risk of SGA for mothers exposed to pesticides (RR_{adj} 5.45, 95% CI 1.59–18.62). Veterinary nurses and horticultural trades were most frequently associated with exposure to pesticides while hairdressers, beauticians, and printing machine minders were associated with phthalates.
(Morales-Suarez-Varela et al., 2011)	L/X		O	pesticides, PAHs, PCOCs, phthalates, organic solvents, BPA, alkylphenolic compounds, brominated flame retardants, metals, benzophenones, parabens, siloxanes	45341	A JEM and/or self-reported information. Scores/categories of exposure	National registries' data, self-reported information	The most prevalent occupations conferring exposure were cleaners, laboratory technicians, hairdressers and agricultural workers. The occurrence of hypospadias increased when mothers were probably [HRa = 1.8 (95% CI 1.0-2.6)] or possibly exposed to one or more EDCs [HRa = 2.6 (95% CI 1.8-3.4)]. Possible paternal exposure to heavy metals increased the risk of hypospadias [HRa 2.2 (95% CI: 1.0-3.4)] and cryptorchidism [HRa 1.9 (95% CI: 1.1-2.7)].
(Snijder et al., 2012)	L		P	pesticides, PAHs, PCOCs, phthalates, organic solvents, BPA, alkylphenolic compounds, brominated flame retardants, metals, benzophenones, parabens, siloxanes	4680 mother-child couples	A JEM and/or self-reported information. Scores/categories of exposure	Foetal ultrasound measures: head circumference (HC), femur length (FL), estimated foetal weight (EFW), abdominal circumference (AC) in the second and third trimester. Placental weight, gender at birth, gestational age, weight, length and HC at birth from medical records and hospital registries	Maternal occupational exposure to polycyclic aromatic hydrocarbons, phthalates, alkylphenolic compounds and pesticides adversely influenced several domains of foetal growth. A significant association between pesticide (95%CI 2129.86-21.94) and phthalate (95%CI 285.15-26.60) exposure with decreased placental weight was found.
(Nugteren et al., 2012)	L		P	pesticides, PAHs, PCOCs, phthalates, organic solvents, BPA, alkylphenolic compounds, brominated flame retardants, metals, benzophenones, parabens, siloxanes	4465	A JEM and/or self-reported information. Scores/categories of exposure	Hospital registries for women who had chronic hypertension or reported to have experienced PIH or hypertension related complications. Blood pressure measurements in early, mid and late pregnancy	No association of hypertensive disorders during pregnancy with physically demanding work or exposure to chemicals.

(Burdorf et al., 2011)	L		P, O	pesticides, solvents, phthalates, alkylphenolic compounds, heavy metals, degreasers, anaesthetics, cytostatics, dry cleaning fluids	8880	A JEM and/or self-reported information. Scores/categories of exposure	Self-reported TTP, preterm birth and birth weight. Date of birth and birth weight from mid-wife and hospital registries. Foetal ultrasound to establish gestational age	No self-reported exposure was associated to outcomes. JEM-based maternal occupational exposure to phthalates was associated with prolonged TTP (OR 2.16, 95% CI 1.02-4.57) and exposure to pesticides was associated with decreased birth weight (OR 2.42, 95% CI 1.10-5.34). The population attributable fractions were small.
(Desrosiers et al., 2012)	C		O	solvents	4651: 1674 cases, 2977 controls	A JEM and/or self-reported information. Scores/categories of exposure	Medical records for neural tube defects (anencephaly, craniorachischisis, spina bifida, encephalocele) and orofacial defects (cleft palate alone, cleft lip with or without cleft palate)	Exposure to chlorinated solvents was associated with increased odds of neural tube defects (OR=1.96, CI 1.34-2.87), especially spina bifida (OR=2.26, CI 1.44-3.53). No solvent class was strongly associated with orofacial defects.
(Gilboa et al., 2012)	C		O	solvents	4998: 2047 cases, 2951 controls	A JEM and/or self-reported information. Scores/categories of exposure	Medical records for CHD. Cases confirmed by echocardiography, cardiac catheterization, surgery, or autopsy. Clinical reviewers determined phenotypic subtypes	Using the consensus-based approach, associations for exposure to any solvent and any chlorinated solvent with perimembranous ventricular septal defects (OR 1.6, 95% CI 1.0-2.6 and OR 1.7, 95% CI 1.0-2.8, respectively). Using the literature-based approach, associations for: any solvent exposure with aortic stenosis (OR 2.1, 95% CI 1.1-4.1) and Stoddard solvent exposure with d-transposition of the great arteries (OR 2.0, 95% CI 1.0-4.2), right ventricular outflow tract obstruction defects (OR 1.9, 95% CI 1.1-3.3) and pulmonary valve stenosis (OR 2.1, 95% CI 1.1-3.8).
(Lupo et al., 2012)	C		O	PAHs	4760: 1907 cases, 2853 controls	A JEM and/or self-reported information. Scores/categories of exposure	Medical records for CHD. Cases confirmed by echocardiography, cardiac catheterization, surgery, or autopsy. Clinical reviewers determined phenotypic subtypes	No associations between potential maternal occupational exposure to PAHs and various CHDs. For CHD phenotypic subtypes, only modest nonsignificant associations.
(Estors Sastre et al., 2019)	C		O		420, 210 cases, 210 controls	Scores/categories of exposure	Medical records of patients attending the outpatient clinic of paediatric urology	Associations between maternal and paternal occupational exposure to EDCs (OR 4.08; 95% CI: 2.03-8.96 and OR 3.90; 95% CI: 2.41-6.48, respectively). The DA of the models for the whole sample (AUC 0.75; 95% CI: 0.70-0.79) for cryptorchidism (AUC 0.76; 95% CI: 0.71-0.82) and for hypospadias (AUC 0.75; 95% CI: 0.69-0.81) was moderately high.
(Bengtsson et al., 2017)	X		O	pesticides, PAHs, PCOCs, phthalates, organic solvents, BPA, alkylphenolic compounds, brominated flame retardants, metals, benzophenones, parabens, siloxanes	347746(582 exposed)	A JEM and/or self-reported information. Scores/categories of exposure	Medical records and registries for gestational age, birth weight, preterm birth and low birth weight	No statistically significant associations between exposure to EDCs and reduced birth weight or increased risk of preterm birth were found. Women potentially exposed to EDC had children with a higher birth weight compared to the sample of occupationally active women (in average 63 g higher, 95%CI 22–101), but not compared to other women referred to an Occupational Health Clinic.
(Kalfa et al., 2015)	X		O	pesticides, PAHs, PCOCs, phthalates, organic solvents, BPA, alkylphenolic compounds, brominated flame retardants, metals, benzophenones, parabens, siloxanes	602: 300 cases, 302 matched controls	A JEM and/or self-reported information. Scores/categories of exposure	Clinical diagnosis via direct clinical examination of hypospadias	Foetal exposure to EDCs was more frequent in cases of hypospadias. Maternal job (especially cleaners, hairdressers, beauticians, and laboratory workers) exposure was more frequent in hypospadiac boys ($p = 0.0019$). Paternal job exposure was more frequent in the cases of hypospadias ($p = 0.02$). Industrial areas, incinerators, and waste areas were placed more frequently within a 3-km radius for mothers of hypospadiac boys ($p < 0.00005$). The associations of various type of exposures may increase the risk.

(C. Wang et al., 2015)	C		O	pesticides, polychlorinated compounds, phthalates, bisphenol A, alkylphenolic compounds, heavy metals	1300: 707 cases, 593 matched controls	A JEM and/or self-reported information. Scores/categories of exposure	Clinical diagnosis confirmed by cardiac catheterization	Maternal exposures to phthalates were associated with PmVSD (p=0.001, adjusted OR 3.7, 95%CI 1.7–8.0), PDA (p=0.002, $OR_{adjusted}$ 3.8, 95%CI 1.6–8.9), s-ASD (p=0.008 $OR_{adjusted}$ 3.5, 95%CI 1.4–8.7) and PS (p=0.035, $OR_{adjusted}$ 4.2, 95%CI 1.1–16.0), to alkylphenolic compounds with PmVSD (p=0.003, $OR_{adjusted}$ 2.2, 95%CI 1.3–3.6), PDA (p=0.005, $OR_{adjusted}$ 2.0, 95%CI 1.1–3.5) and PS (p=0.004, $OR_{adjusted}$ 3.8, 95%CI 1.5–9.4), to heavy metals with PmVSD (p=0.003, $OR_{adjusted}$ 7.3, 95%CI 2.0–27.6) and s-ASD (p=0.034, $OR_{adjusted}$ 6.5, 95%CI 1.1–36.7). Paternal occupational exposures to phthalates are associated with PmVSD (p=0.035, $OR_{adjusted}$ 1.6, 95%CI 1.0–2.4) and PS (p=0.026, $OR_{adjusted}$ 2.4, 95%CI 1.1–5.2), and to alkylphenolic compounds with PmVSD (p=0.027, $OR_{adjusted}$ 1.5, 95%CI 1.0–2.2).
(Aguilar-Garduño et al., 2010)	C		O	solvents	302: 151 cases, 151 controls	Self-reported information, literature, periods of exposure	Epidemiological Surveillance System for Neural Tube Defects (ESSNTD) national register, cases identified in maternity hospitals and prenatal clinics	The couples in which at least one of the parents was occupationally exposed to organic solvents compared with non-exposed couples, demonstrated a statistically significant increase in the odds of anencephaly when the exposure was during the periconceptional period (adjusted OR 2.97; 95% CI 1.36-6.52) or at some time during the last 5 years (adjusted OR 2.77; 95% CI 1.35-5.70).
(Giordano et al., 2010)	C		O	pesticides, PAHs, PCOCs, phthalates, organic solvents, BPA, alkylphenolic compounds, brominated flame retardants, metals, benzophenones, parabens, siloxanes	160	A JEM. Serum organochlorine compounds, DDE, HCB, and PCBs(4)	Diagnosis of any form of hypospadias that required surgical treatment.	The risk to bear an hypospadiac infant was associated with perinatal maternal exposure to EDCs. Increase in risk was also found among mothers consuming a diet rich in fish or shellfish. B HCB concentration above the median was significantly associated with the risk of hypospadias ($OR_{adjusted}$, 5.50; 95% CI, 1.24–24.31).

Pregnancy (P), offspring (O), sexual function (SF), polychlorinated organic compounds (PCOCs), dichlorodiphenyldichloroethylene (DDE), hexachlorobenzene (HCB), time weighted average on 8 hours (TWA8), small for gestational age (SGA), pregnancy-induced hypertension (PIH), di(2-ethylhexyl)phthalate (DEHP), congenital heart disease (CHD), job exposure matrix (JEM), perimembranous ventricular septal defect (PmVSD), patent ductus arteriosus (PDA), secundum atrial septal defect (s-ASD), pulmonary valve stenosis (PS)

Table 5. Occupational exposure to EDCs and carcinogenesis

Ref.	Design	Activity	Clinical outcome	EDCs	n	Exposure Assessment	Outcome Assessment	Results
(Ekenga et al., 2014)	X/L		breast cancer	solvents	47661	Self-reported information	Self-reported information, medical records and pathology reports for tumour subtypes and oestrogen receptor status.	Overall, the risk of invasive breast cancer was not associated with lifetime exposure to solvents (HR 1.04; 95%CI 0.88–1.24). Parous women who worked with solvents before their first full-term birth had an increased risk of oestrogen receptor-positive invasive breast cancer compared with unexposed women (HR 1.39; 95%CI 1.03–1.86). A significantly elevated risk for oestrogen receptor-positive invasive breast cancer was associated with solvent exposure among clinical laboratory technologists and technicians (HR 2.00; 95%CI 1.07–3.73). An increased risk for oestrogen receptor–positive breast cancer was found among women whose first solvent job was before 1980 (HR 1.28; 95%CI 1.01–1.62).

(Brophy et al., 2012)	C		breast cancer		2152: 1006 cases, 1156 controls	A JEM and/or self-reported information. Scores/categories of exposure	Diagnosis of histologically confirmed breast cancers, oestrogen receptor (ER) or progesterone receptor (PR) status.	Women with potentially high exposures to carcinogens and EDCs had elevated breast cancer risk (OR = 1.42; 95% CI, 1.18-1.73, for 10 years exposure duration). Specific sectors with elevated risk included: agriculture; bars-gambling; automotive plastics manufacturing, food canning, and metalworking. Oestrogen receptor status of tumours differed by occupational grouping. Premenopausal breast cancer risk was highest for automotive plastics and food canning.
(Peplonska et al., 2010)	C		breast cancer	solvents	4885: 2383 cases, 2502 matched controls	Self-reported information. Industrial hygienists assessed exposure using duration of exposure, probability, intensity, frequency, confidence	Diagnosis cytologically or histologically confirmed from regional population-based cancer registries, data from medical record and pathology forms. Pathology forms and tissue blocks for oestrogen receptor and progesterone receptor status.	Among women with organic solvents exposure a significant association was present for oestrogen receptor- and progesterone receptor-negative tumours (OR 1.40; 95%CI 1.1-1.8). No trends with increasing level of exposure were found.
(Ekenga et al., 2015)	X/L		breast cancer	acids, dyes or inks, petroleum products, glues or adhesives, lubricating oils, metals, paints, pesticides, soldering materials, solvents, stains or varnishes	47640	A JEM and/or self-reported information. Scores/categories of exposure	Self-reported diagnosis among sisters of women suffering from breast cancer	No significant associations between ever use of the evaluated chemicals and breast cancer risk. Women with cumulative exposure to petroleum products at or above the highest quartile cut-off had an elevated risk of total (HR 2.3, 95%CI 1.1–4.9) and invasive breast cancer (HR 2.5, 95%CI 1.1–5.9) compared with women in the lowest quartile (p_{trend} = 0.03). Workplace exposure to soldering materials was associated with an increased risk of premenopausal breast cancer (HR 1.8, 95%CI 1.1–3.0). Occupational petroleum product use was associated with a reduced risk of in situ breast cancer, and a nonsignificant increased risk of hormone receptor- positive breast cancer when highly exposed. A significant excess risk of breast cancer in premenopausal women exposed to soldering materials was found.
(Peremiquel-Trillas et al., 2019)	C		breast cancer; prostate cancer;	alkylphenolic compounds	5663: 2608 cases, 3055 matched controls	A JEM and/or self-reported information. Scores/categories of exposure	Histologically confirmed cases	Exposure to alkylphenolic compounds was modestly associated with breast cancer (OR=1.23; 95% CI=1.01–1.48). The occupational use of domestic surfactants was positively associated with breast cancer (OR=1.28; 95% CI 1.02–1.60). Exposure to nonylphenol ethoxylates was positively associated with breast cancer (OR=1.21; 95% CI 1.00–1.47). No significant associations between alkylphenolic compounds and prostate cancer, except for a positive association among men occupationally exposed to cosmetic, hair and personal hygiene products (OR=2.97; 95% CI 1.15–7.69).
(Mikoczy et al., 2011)	X/L	medical equipment production	cancer incidence, mortality	EtO	2171	JEM, results from statutory hygienic measurements	Classification of Diseases on malignant tumours from the national Cancer Registry and information from the national population registry.	The overall cancer incidence was close to unity (SIR 0.94, 95% CI 0.82–1.08). Eighteen cases of lymphohematopoietic cancer were observed (SIR 1.25, 95% CI 0.74–1.98). A healthy worker effect was indicated. Internal analyses found significantly increased rate ratios for breast cancer for the two upper quartiles of cumulative exposure as compared to the lowest 50% of the cohort (IRR 2.76, 95% CI 1.20–6.33 and IRR 3.55, 95% CI 1.58–7.93).

(Costas et al., 2015)	C		lymphoma	pesticides, PAHs, PCOCs, phthalates, organic solvents, BPA, alkylphenolic compounds, brominated flame retardants, metals, benzophenones, parabens, siloxanes	4635: 2178 cases, 2457 matched controls	A JEM and/or self-reported information. Scores/categories of exposure	incident lymphoma cases	Over 30 years of exposure to EDCs compared to no exposure was associated with a 24% increased risk of mature B-cell neoplasms (p_{trend}=0.02). Associations were observed among men, but not women. Prolonged occupational exposure to endocrine disruptors seems moderately associated with some lymphoma subtypes. Subjects occupationally exposed to any EDC had a modestly elevated risk of mature B-cell lymphoma (OR=1.29, 95%CI 1.04–1.60). Duration of exposure to EDCs showed an upward trend in risk for mature B-cell lymphoma (OR=1.24, 95% CI 1.01–1.51 for >30 years of exposure; P-trend=0.02). Among currently exposed workers, associations were observed for those exposed for 10 years or longer (OR=1.35, 95% CI 1.08–1.70). Between mature B-cell neoplasms and a 10 years increase in exposure to individual chemicals, significant associations were shown for each component in the pesticide group, ethylene glycol ethers, alkylphenolic ethoxylates, and copper.
(Cocco et al., 2010)	C		lymphoma	solvents	4810: 2348 cases, 2462 matched controls	Self-reported information	Clinical diagnosis. A subset of cases was reviewed by a panel of pathologists to ensure diagnostic consistency	Risk of follicular lymphoma significantly increased with independent metrics of exposure to benzene, toluene and xylene (BTX) (combined $p=4\times10^{-7}$) and to styrene ($p=1\times10^{-5}$), and chronic lymphocytic leukaemia (CLL) risk increased with exposure to solvents overall ($p=4\times10^{-6}$), BTX ($p=5x10^{-5}$), gasoline ($p=8\times10^{-5}$) and other solvents ($p=2\times10^{-6}$). For ever exposure to solvents for CLL OR was 1.3 (95%CI 1.1-1.6). Exposure to benzene accounted, at least partially, for the association observed with CLL risk. No association with risk of T-cell lymphoma and Hodgkin's lymphoma was shown. For ever exposure to solvents, follicular lymphoma OR was 1.3 (95%CI 1.0-1.7).
(Villeneuve et al., 2010)	C		MBC	Pesticides, alkylphenolic compounds, phthalates, PCBs, dioxins	2005	A JEM and/or self-reported information. Scores/categories of exposure	Regular contacts with clinical and pathology departments. An expert pathologist reviewed the pathology reports and one slide representative of the tumour	MBC incidence was increased in motor vehicle mechanics (OR 2.1, 95%CI 1.0-4.4) with a dose-effect relationship with duration of employment. It was also increased in paper makers and painters, forestry and logging workers, health and social workers, and furniture manufacture workers. The OR for exposure to alkylphenolic compounds above the median was 3.8 (95%CI 1.5-9.5), this association persisted after adjustment.
(Laouali et al., 2018)	C		MBC	solvents	2005: 104 cases, 1901 matched controls	A JEM and/or self-reported information. Scores/categories of exposure	Regular contacts with clinical and pathology departments. An expert pathologist reviewed the pathology reports and one slide representative of the tumour	Lifetime cumulative exposure to trichloroethylene >23.9 ppm years was associated with an increased MBC risk, compared to non-exposure [OR (95%CI): 2.1 (1.2-4.0); p_{trend} <0.01)]. The risk augmentation persisted only for exposures that occurred ≥10 years before diagnosis. A possible role for benzene and ethylene glycol in MBC risk was suggested, but no exposure-response trend was observed. In all the models for the low benzene exposure levels versus non-exposure, high exposures to gasoline, white spirits and KDF showed OR of 1.9, 1.8, and 1.7. For chlorinated solvents, high exposure to TCE was associated with OR≈2 in all models, with a dose–response trend (P<0.01).
(Videnros et al., 2020)	C		postmenopausal breast cancer	solvents	2400: 731 cases and 1669 matched controls	A JEM and/or self-reported information. Scores/categories of exposure.	Information from the population-based cancer registries	Women exposed to chemicals in their occupational environment had a statistically significantly increased risk (OR 1.59, 95% CI 1.11–2.29) of breast cancer, and the risk correlated positively with duration of exposure but not with exposure intensity. Women exposed to chlorinated hydrocarbon solvents for more than 10 years had a significant higher risk of breast cancer (OR 3.06, 95% CI 1.18–7.96) as well as women exposed to oil mist for more than 10 years (OR 3.08, 95% CI 1.12–8.49).

(Labrèche et al., 2010)	C		postmenopausal breast cancer	fibres, aliphatic aldehydes, CO, inks, MAHs, PAHs, VOCs, solvents	1169: 556 cases, 613 matched controls	A JEM and/or self-reported information. Scores/categories of exposure	Records of pathology departments and cancer registries from the hospitals that provided diagnosis and/or treatment. Histological confirmation was obtained and information on morphology and hormonal receptor status.	ORs increased with occupational exposure to several agents, especially for exposures occurring before age 36 years. Increased ORs were found with duration of exposure, before age 36 years (OR<36), to acrylic fibres (OR <36=7.69) and to nylon fibres (OR<36=1.99). For oestrogen-positive and progesterone-negative tumours, the OR doubled or more for each 10-year increase in exposure to monoaromatic hydrocarbons, and to acrylic and rayon fibres. The OR<36 also doubled for exposure to organic solvents, and to acrylic fibres. A threefold increase was found for oestrogen- and progesterone-positive tumours, with exposure to polycyclic aromatic hydrocarbons from petroleum sources.
(Paoli et al., 2015)	C		TC	HCB; PCBs; PCOCs; pesticides; phthalates; alkylphenolic compounds	223: 122 cases, 101 matched controls	A JEM and/or self-reported information. Scores/categories of exposure. B PCBs(9) and HCB.	Semen samples: ejaculate volume, sperm concentration, total sperm number, total motility, morphology.	A statistically significant increase in TC risk in cases with detectable values of total polychlorinated organic compounds against controls ($p < 0.001$). TC patients with detectable levels of organochlorines had lower total sperm number and total motility, and higher abnormal forms, than those with undetectable levels, although this difference was not statistically significant.
(Olsson et al., 2018)	C		TGCT	solvents, metals	17445:3421 cases, 14024 matched controls	Occupational histories from the Danish Supplementary Pension Fund, companies and jobs coding, a JEM, probability scores/classification.	Information from the population-based cancer registries	The overall analyses showed no significant associations except for paternal exposure to a subgroup of heavy metals and solvents (OR 1.50, 95%CI 1.01–2.24). Most fathers in this category had worked in wood related jobs and were assigned exposure to chromium VI and toluene. Maternal exposure to aromatic hydrocarbon were associated with TGCT risk, in sons born in 1970–1979 (p=0.01), and to heavy metals in sons born in 1980–1998 (OR>2.0, $p \leq 0.02$).
(Le Cornet et al., 2017)	C		TGCT	solvents	34376: 8112 cases, 26264 matched controls	Job codes for both parents from the last census, a JEM, probability scores/classification.	Information from the population-based cancer registries	Overall, no association was found between prenatal maternal exposure to solvents and TGCT risk. In subset analyses, there was an association with maternal exposure to aromatic hydrocarbon solvents (OR 1:53; CI 1.08-2.17), driven by exposure to toluene (OR 1:67; CI: 1.02-2.73). No association was seen for any paternal occupational exposure to solvents with the exception of exposure to perchloroethylene in Finland (OR 2:42; CI: 1.32-4.41).
(Togawa et al., 2016)	C		TGCT	metals, welding fumes	34376: 8112 cases, 26264 matched controls.	Information from censuses, jobs coding, a JEM, probability scores/classification, exposure indices were calculated.	Information from the population-based cancer registries	Not statistically significant TGCT risk associated with presence of heavy metals/welding fumes and no dose-response relationship ($p_{trend} \geq 0.32$). A statistically significant elevated TGCT risk was found in the highest paternal exposure category to chrome (vs. no chrome; OR = 1.37, 95%CI; 1.05-1.79) and the second highest category of paternal exposure to welding fumes (OR = 1.39; 95%CI, 1.10–1.76).
(Zeng et al., 2017)	C		thyroid cancer	pesticides, biocides	960: 462 cases, 498 matched control	A JEM and/or self-reported information. Scores/categories of exposure	Information from cancer registry, the cases were histologically confirmed.	Individuals who were occupationally ever exposed to biocides had an increased risk of thyroid cancer (OR=1.65, 95% CI: 1.16-2.35), and the highest risk was observed for the high cumulative probability of exposure (OR=2.18, 95%CI: 1.28–3.73). The observed associations were similar when we restricted to papillary thyroid cancer and well-differentiated thyroid cancer. Stronger associations were observed for thyroid microcarcinomas (size ≤1cm).

ethylene oxide (EtO), male breast cancer (MBC), testicular cancer (TC), testicular germ cell tumour (TGCT)

Table 6. Occupational exposure to EDCs and effects on immunity, DNA structure or antioxidant systems

Ref.	Design	Activity	Clinical Summary	EDCs	Sex	n	Exposure Assessment	Outcome Assessment	Results
(Kolena et al., 2020)	L	firefighters	I	phthalates	m	32	U phthalate metabolites(11)	Pulmonary volumes and percent predicted values.	Positive association between phthalates and Tiffeneau–Pinelli index (p = 0.001–0.04) and the percent predicted value (%PV) of FEV1/FVC (p = 0.005–0.05), and negative association between MiNP and peak expiratory flow (p = 0.084).
(Makey et al., 2016)	L	office workers	I	PBDEs, flame-retardants	b	51	B PBDEs(11)	Thyroid peroxidase (TPO) antibodies. Levels of urinary iodide	On average, a 1-ng/g serum increase in BDE-47 was associated with a 2.6-μg/dL decrease in total thyroxine (T4) (95% CI: –4.7, –0.35). Total T4 was inversely associated with each PBDE congener. Findings do not indicate effects on the pituitary–thyroid axis.
(Haase et al., 2016)	X/L	recycling company	I	PCBs	b, m>f	258/218/177	B PCBs(12)	fluorescently labelled antibody pairs, leukocytes, total leukocyte counting. Interleukin 6. Immunoglobulin (Ig) levels. Peripheral blood mononuclear cells (PBMC), IFN-γ, NK-cell specific lysis, phagocytosis and oxidative burst.	Several effects on the cellular composition of adaptive immunity, affecting both T-and B-cells, were shown. However, the values were not generally outside the reference ranges for healthy adult individuals and did not indicate overt functional immunodeficiency, even in subjects with the uppermost PCB burden.
(Omotosho, 2019)	X	auto technicians	S	Pb, Cd	m	65(34 exposed)	B Pb and Cd, U Pb and Cd	B total antioxidant capacity (TAC), total plasma peroxides (TPP). Calculated oxidative stress index (OSI)	Significant differences were found in mean B and U Pb, mean U Cd, TPP, and OSI (p≤ 0 006, 0.018, 0.026, 0.001, and 0.001, respectively) in exposed vs non-exposed subjects. Mean TAC was not significantly different in the two groups (p≤ 0 056).
(Kuras et al., 2018)	X	chemical plant	S	Hg	m	198	Air, B and U Hg	B and U Se. Cytosolic GPx (cGPx, GPx-1) and plasma GPx (pGPx, GPx-3) activities. B Selenoprotein P. B pool of low molecular weight antioxidants. Total RNA was isolated from the venous blood. GPX1, GPX3, SEPP1, TRXR1, TRX, PRDX1, PRDX2 gene expression in the B leukocytes.	B Se was significantly higher for chloralkali workers vs. control group (p=0.0001) but correlated inversely with U Hg in chloralkali workers suggesting depletion of the Se protection. The RNA level for GPX1, PRXD1 was significantly higher in the exposed workers compared to the controls (p=0.0002, p=0.0001, respectively). Concentrations of B Hg and U Hg among the exposed workers were significantly positively correlated with selenoprotein P (R=0.32; p=0.0002, R=0.20; p=0.0236; respectively). In the multivariate model, after adjusting to cofounders, U Hg was inversely correlated with gene expression of TRXR1. Findings suggest that exposure to Hg alters gene expression of the antioxidant enzymes and the level of Se-containing selenoproteins.
(Fahim et al., 2020)	X	foundry workers	S	Pb	m	87	B Pb	B T3, fT3, T4, fT4, TSH, MDA and GSH	The exposed group had significantly increased fT3, fT4 and significantly decreased TSH than the control group (p< 0.0001). A state of oxidative stress was indicated by a significant increase in MDA mean levels and significant decrease in GSH (p < 0.0001). A significant positive correlation (r=0.358, p <0.05) between B Pb and duration of employment was found. B Pb showed a significant negative correlation with TSH (r =-0.486, p <0.001), and GSH (r =-0.336, p <0.05). A significant positive relationship between GSH and TSH (β coefficient=0.274, p < 0.05), MDA with FT3 (β coefficient=0.355, p < 0.05) and FT4 (β coefficient = 0.491, p < 0.0001) was shown among exposed workers.
(Saad-Hussein et al., 2011)	X	paints production	S	organic solvents, mixtures in paint production	m	76(36 exposed)	Self-reported information	B MDA, total antioxidant capacity (TAC), NO	T3, T4, MDA and NO were significantly higher in workers compared to controls (p<0.0001, respectively). Total antioxidants were significantly lower in workers than in controls. T3 and T4 were significantly correlated with duration of exposure, while, total antioxidants inversely correlated. In workers, T3 was significantly correlated with MDA and inversely correlated with total antioxidants. MDA and NO were significantly higher in workers with abnormal T4.

(Aisha Mohamed Samir & Wael Mohamed Aref, 2011)	X	dental staff	S, R	Hg	b	69(32 exposed)	B and U Hg	U proteins, albumin, alpha1microgloblin. B GSH-dependent peroxidases, erythrocyte lysate, superoxide dismutase activity	The U indicators of renal function were significantly elevated in exposed workers vs controls ($p < 0.001$). B GSH peroxidase and superoxide dismutase activities were significantly decreased in exposed workers ($p<0.001$, respectively) and were negatively correlated with duration of work ($r = -0.656$ $p <0.001$; $r = -0.407$ $p < 0.05$, respectively).
(Costa-Amaral et al., 2019)	X	filling stations workers, security guards	S, G	benzene	b	86	Air benzene and toluene, U trans,trans-muconic acid (ttMA) and S-phenylmercapturic acid (S-PMA)	B catalase (CAT), superoxide dismutase (SOD), glutathione S-transferase (GST), thiol groups (THIOL), and MDA, metaphases with chromosomal aberrations (MCA), number of chromosome breaks (NCBk), fragments (Frag), premature chromatid separation (PCS), micronuclei (MN), binucleated cells (BNCs), broken egg cells (BECs), and comet assay with FPG (C-FPG). Hematological tests	No differences in ttMA and S-PMA, and no clinical changes were found between both groups, but linearity was observed between leukocyte count and ttMA. No differences were observed between the two groups for THIOL, MDA, MCA, or nuclear abnormalities. A multiple linear relationship was obtained for the biomarkers MCA and C-FPG. MAC showed a significant multiple linear relationship ($F(13.499,30.989) = 2.296$, $p = 0.037$, $R^2 = 0.285$) with significant predictor variables for CAT ($p = 0.020$), GST ($p = 0.012$), and THIOL ($p = 0.044$). A significant multiple linear relationship was also found for MCA when S-PMA was replaced with ttMA. The multiple linear relationship of C-FPG was significant [$F(515,1769) = 3.432$, $p = 0.0005$, $R^2 = 0.338$]; particularly for GST ($p = 0.024$) and THIOL ($p = 0.013$) as predictor variables. A significant correlation was found between length of time in current job and the biomarkers C-FPG, MCA, GST, and MDA.
(Hanchi et al., 2017)	X	foundry workers	S, G		m	93	U PAHs(16) and OHPAHs(8)	U 8-oxodG	The results of this study indicate that the investigated biomarkers of PAH exposure were only minor contributors to U 8-oxodG.
(Tucker et al., 2011)	X	dry cleaning workers; laundry workers	G	PCE	f	36(18 exposed)	Air(TWA), personal air samples and B PCE	B whole chromosome painting analysis for structural chromosome aberrations: translocations, insertions, dicentrics and acentric fragments. Colour junctions were enumerated, and included any chromosome rearrangement (translocations, insertions, dicentrics and acentric fragments)	No significant differences between the PCE-exposed dry cleaners and the laundry workers for chromosome translocation frequencies, but PCE levels were significantly correlated with percentage of cells with acentric fragments ($R^2 = 0.488$, $p < 0.026$).

Immunological effects (I), oxidative stress-antioxidant balance (S), genetic effects (G), renal impairment (R), 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG), perchloroethylene (PCE), selenium (Se), mono-isononyl phthalate (MiNP)

DISCUSSION

This review has addressed the literature of the last decade focusing on the adverse effects resulting from exposure to suspected or proven EDCs in occupational settings.

The analysed studies comprised results on a wide range of topics, including the exposure to numerous different EDCs, with possible effects accounted for by several clinical and biological outcomes. Different methodologies were employed in the assessment of both exposures and outcomes. Moreover, large variations in the different samples in age, sex, conditions of exposure were found. Therefore, it is difficult to outline a general evaluation. However, some observations can be made.

Regarding some issues, conflicting evidence emerged, in particular about the effects of metals at low doses of exposure, those of PCBs on the hormonal axes, and the effects of parental exposure on the development of offspring. Even in other recent reviews, a lack of consensus was underlined on several matters, and a better design and research protocols and other possible ways of improvement were emphasized. For example, a study on occupational exposure to EDCs and breast cancer risk, evaluating also receptor expression, concluded that further investigation was needed to overcome limitations due to the self-reported information on work histories, generalisation in chemical classification, and the lack of environmental or biological monitoring exposure data.(Leso et al., 2019) Another study on *in utero* exposure to persistent and non-persistent EDCs and anogenital distance accounted for a small number of studies per chemical, small sample sizes and difficult replication of the findings. The establishment of associations repeating outcome assessment, evaluating the cumulative impact of exposure to mixtures of chemicals, and a better consideration of confounding factors were desired.(Nelson et al., 2020) A third analysis concluded that more research, mostly long-term longitudinal studies, is needed on the role of EDCs exposure in male reproductive health to assess the outcomes in adulthood.(Rodprasert et al., 2019)

In line with these considerations, more than forty of the articles analysed reported a too small sample size among their limitations, and the authors have not always been able to obtain statistically significant results. It is not unusual in scientific literature.(Vasileiou et al., 2018) Some indications to help calculating a proper sample and the feasibility of a given research have been published.(Zhu et al., 2019;ˏAnderson, 2019;ˏBolarinwa, 2020;ˏX. Wang & Ji, 2020) Moreover, when evaluating the sample characteristics, it is also important to consider factors such as the immortal time bias in cohort studies or the left truncation bias in observational

studies. These elements should be account for, as well as the aspects that influence them, such as the interval between the date of entry and the date the exposure, the proportion of exposed participants and the length of follow-up.(Harding & Weiss, 2019; Hazelbag et al., 2015; Applebaum et al., 2011) Selection bias due to mortality was possible in some of the analysed studies, and it was considered when analysing results.(Karnes et al., 2014; Winquist & Steenland, 2015; A. M. Yang et al., 2015) Some indications have been published to deal with this issue.(Hanley, 2017) Furthermore, in agreement with the conclusions of a recent review, several studies failed in register accurately information on the collective and individual protections in use, introducing another possible bias when evaluating results.(Rim, 2017)

Many of the reviewed articles included stratification, sensitivity analyses or multiple regression models to try to limit the effects of bias. Few of the analysed studies lacked in accounting for several confounders or other everyday life factors or conditions possibly involved in the development of the response. (Persky et al., 2012; Ekpenyong et al., 2013; Heggland et al., 2011; Costa-Amaral et al., 2019) Conversely, when estimating causal effects, the analysis should control for confounders not only of the exposure–primary outcome but also of the exposure–competing outcome effect, otherwise the resulting bias may increase consensually with the incidence of the competing event, following generally a random direction.(Lesko & Lau, 2017) Other articles tried to evaluate accurately even dietary intake or domestic exposure.(Ciarrocca et al., 2012; Ciarrocca et al., 2013; Huang et al., 2011; Giordano et al., 2010; Paoli et al., 2015; Haase et al., 2016; Kuras et al., 2018; Peremiquel-Trillas et al., 2019)

Some reflexions should be made regarding self-reported information, as it is a source of data often used in the analysed literature, as indicated in Tables 2-6. Reliability is a known relevant issue when calculating power, sample size, to interpret and adjust the estimates, and when considering feasibility.(Rosenberg, 1993) Self-reporting could be influenced by several factors that may vary inter- and intra-individually (e.g.: socioeconomic and cultural background, perception at a given moment, comorbidities or disease, proximity to potential hazards, sex, age).(Forastiere & Galassi, 2005) Therefore, the choice of clear and validated protocols or questionnaires, administered by specifically trained staff, is essential.(Forastiere & Galassi, 2005)

Some scientific evidence regards the reliability of self-reported information under different conditions that also apply to the analysed literature. A study evaluated self-reported information from capacitor manufacturing workers. Validity scores ranged widely. Exposure

misclassification tended to be non-random for women (overestimation) for both the early and late periods. The job pattern, sex, duration, time lapse, interviewer skills were significant predictors of validity.(Rosenberg et al., 1987) A second study on the same sample highlighted that reliability decreased for subjects often changing their jobs.(Rosenberg, 1993) Another analysis on cancer patients showed difficulties in recruitment of younger subjects, reliability appeared slightly lower for self-administered than for staff administered questionnaires, the repeatability of coding occupational and industrial status for last jobs was satisfactory, observer variability was large for codes' abbreviated versions.(Rona & Mosbech, 1989) A study about the validity and reproducibility of self-reported working hours among Japanese male employees concluded that the validity of self-reporting was high for all time frames, whereas the reproducibility was moderate to high.(Imai et al., 2016) Other authors concluded that the fair level of validity should discourage from including self-reported age at menarche in middle aged subjects.(Cooper et al., 2006) A research on diabetic patients reporting comorbidities found good reporting of myocardial infarction and amputation, while eye diseases and foot ulceration were rather poorly communicated, particularly in older, male, or less educated subjects.(Hoffmann et al., 2018) A study addressed agreement between self-reported and registered-based data on comorbidities in breast cancer women. There was overall agreement on stroke and myocardial infarction. Older age was associated with better agreement on hypertension, hyperlipidaemia and angina, but poorer agreement on polycystic ovaries, ovarian cysts and preeclampsia. In most subgroups, both sources could confidently identify individuals without the studied conditions.(Ho et al., 2019) Another article regarded agreement between self-reported disease and medical record diagnosis of disease among residents of 45 years of age or older. Questionnaire data were more reliable in respect to life-threatening conditions and chronic disorders requiring ongoing management. They were more accurate in young women and better-educated subjects.(Okura et al., 2004) A further research suggested that detection bias may occur when investigating the association between common medications, and cancer outcomes.(Wirtz et al., 2017) A study taking into account between- and within-subject variability when reporting recurrent events concluded that the availability of the history of previous episodes per subject is important and in the absence of information valid alternatives must be found to tackle analyses.(Navarro et al., 2017)

The use of matrices of exposure has been investigated by Carles et al. regarding pesticides. Two types of matrices were usually employed, generic ones in case–control studies evaluating broad categories of chemicals, and specific ones in cohort studies providing exposure metrics at the

active ingredient level.(Carles et al., 2017) We confirm the same finding in this review, where almost half of the scientific articles that have used matrices employed a generic version and the other half a specific tool. The study stressed also that matrices had rarely been compared with other tools, and that external validity had not been systematically assessed.(Carles et al., 2017) According to other authors, the evaluation of exposure with an unbiased job-exposure matrix in studies on the association between exposure and disease had a statistical power close to that expected with a good expert in several situations.(Bouyer et al., 1995) An article comparing the agreement of occupational exposure assessment by a panel of occupational hygienists with a job exposure matrix and self-reported exposures in a community-based case-control study concluded that the accordance was only poor to fair, and that the attenuation of the odds ratios due to exposure misclassification by the panel was variable and dependent upon the exposure.(Benke et al., 2001) In this review the utilisation of job-exposure matrices was integrated with further expert evaluation in two-thirds of the studies that used matrices (approximately twenty studies, as reported in Tables 2-6).

A study focused on the transportability of a job-exposure matrix from Finland to Canada. For some agents there was considerable disagreement and hence transportability cannot be assumed by default.(Lavoué et al., 2012) The magnitude of the misclassification bias when using a job-exposure matrix was analysed in another context confirming an acceptably valid screening tool also outside the country of reference, provided that the misclassification characteristics of the matrix and the significant differences in exposure between the countries are taken into account. Misclassification depended strongly on the prevalence of exposure and the inclusion criteria for exposure.(Kauppinen et al., 1992) Recently, a letter to the editor emphasized the need to develop and validate a unique matrix at an international level.(Descatha et al., 2019) Several of the analysed studies used matrices built in other countries. We may speculate that sometimes the exposure assessment could be possibly biased by the utilisation of general classes of chemicals rather than single agents. Growing evidence points out the importance of evaluating the effects of mixtures, that are more easily encountered in real life conditions and which may show synergistic or additive effects.(Lazarevic et al., 2019)

An editorial commented on possible misclassifications in occupational exposure data collected from register-based studies. Bias could vary greatly, and very few, not encouraging, validations of the exposure classification were available on census data.(Kogevinas & Hagmar, 2005) The use of registers in the studies of our review is indicated in Tables 2-6.

Environmental and biological monitoring for exposure assessment or a combination of environmental, biological and estimates of exposure, geographical data, data from registries in the enterprise or self-reported information is whished and several of the studies included in our analyses tried to combine different sources. Anyway, only few studies managed to elaborate dose-response curves or define quantitatively relationships or exposure metrics.(Pan et al., 2011; Li et al., 2010; Mikoczy et al., 2011; Miao, Yuan, He, et al., 2011; Miao, Yuan, Zhu, et al., 2011; Attarchi et al., 2012; L. Yang et al., 2017; Laouali et al., 2018)

About the results from exposure monitoring, in several studies not always the levels of a chemical in air samples were proven higher, but also biomonitoring results were significantly higher in respect to non-exposed participants or than the general population.(Huang et al., 2011; Ciarrocca et al., 2012; Ciarrocca et al., 2013; Petra M. Gaum et al., 2014; A. M. Yang et al., 2015; Esser et al., 2016; A. Yang et al., 2017) It should be interesting in these cases to provide more information on the protections in use, and to try to evaluate their efficacy in respect to the specific exposure considered. A comparison with measured levels and values in the general population should be always included, unfortunately acceptable values in the general population are not always available, as discussed by Estors Sastre et al., 2019. In some of the analysed studies the exposure levels were low and comparable to those in the general population or in the residential area.(Pan et al., 2011; Goodrich et al., 2013; Hanchi et al., 2017)

Moreover, a suggestion has been made in the literature about observational studies, as the average hazard ratio (HR) may be uninformative due to potentially time-varying period specific HRs, and built-in selection bias. To solve these possible problems, cumulative measures, the use of a series of average HRs, appropriately adjusted survival curves, or comparisons in the distribution of survival times between the exposed and the unexposed are wished.(Hernán, 2010) Otherwise, a design with active follow-up may significantly shorten the period needed to exclude the bias.(Lin & Lee, 2013) Another study underlined how, in cohort and case-control studies, the use of the proportional hazards model to control for a time-dependent strong risk factor may produce unreliable relative risk estimates unless detailed, time-varying information is incorporated in the analyses.(Moolgavkar et al., 2018) In our review, four scientific articles calculating HRs were included.(Morales-Suarez-Varela et al., 2011; Ekenga et al., 2014; Ekenga et al., 2015; S. Wu et al., 2019) They followed a longitudinal or a mixed cross-sectional/longitudinal design and all comprised adjustment for exposure factors or some of the characteristics of the sample.

Some literature tries also to provide recommendations on the assessment of the exposure to EDCs and possible analytical issues. A study on the variability of urinary metabolites of phthalates, pesticides and bisphenol, on sampling time, and number of needed urinary samples, concluded for a lack of preferred moment for urine collection between first day and added that between 10 and 31 samples were necessary to correctly classify 87.5% of the subjects into quartiles according to their level of exposure.(Faÿs et al., 2020) Some analyses regard the assessment, and especially the choice of methods for adjustment and interpretation of results, when dosing lipophilic chemicals or biomarkers.(Schisterman et al., 2005; O'Brien et al., 2017; Weinberg et al., 2019; Dzierlenga et al., 2019; Cano-Sancho et al., 2018) In the examined literature the applied methods and correcting factors varied from one study to another, in general the collected samples were few, as shown in Tables 2-6.

Another point to stress in this review is the lack of information or accurate description of the mechanisms supposed to be at the base of the tested effects in almost fifty of the cited studies. It should be important, when literature is available, to explicit the possible causal pathways, the known mechanisms of action and, in any case, the hypothesis implied by the scientific investigation, even to allow better assessment of the quality of the study and of the obtained results. Anyway, several mechanisms of action have also been discussed in almost thirty of the included studies, especially when hormonal action was examined. In this context, a definition of the contribution of occupational versus non-occupational factors should be included, whenever possible.

Moreover, windows of susceptibility for EDCs should be carefully considered in the design of the study. Even in the analysed literature, some conclusions reported possible manifestations of different adverse effects, even on the offspring, with different weight in the contribution in the development of disease because of a given specific chemical, depending on the timing of exposure, age and other individual characteristics.(Aguilar-Garduño et al., 2010; Desrosiers et al., 2012; Snijder et al., 2012; Ekenga et al., 2014; Shirangi et al., 2020)

Some of the analysed studies, mostly on metals, reported interesting considerations on the different effects caused by exposure to the same or a similar substance, but in a different physical form.

In conclusion, we cannot fail to mention that the assessment of exposure, outcomes and interpretation of results is still conditioned by the various criteria adopted in each country to define endocrine disruption or adverse effects, depending on the regulation in force in the

country where the study took place and the accepted modes of action. Moreover, environmental and biological acceptable limits for workers and general population are equally potentially different.

CONCLUSIONS

Literature concerning health effects from occupational exposure to EDCs in the last decade still evidenced some critical issues in the studies' design. Especially, exposure assessment should combine as much as possible several data sources (validated questionnaires, registries, records, environmental and biological monitoring, protective measures or equipment, reliable information on non-occupational exposure, geographic information), and, as needed, several time-points measurements, in order to properly define dose-response curves, and to provide better estimates of exposure levels over time. Periods of susceptibility should be considered. In the evaluation, a comparison at least of the levels of exposure in respect to those in the general population should be useful. On the other hand, outcome assessment should rely on validated criteria or diagnosis, and possibly make explicit the assumptions regarding disruption, the suspected mechanisms, and the reasons for the choice of a particular target. If an interplay of factors is suspected to contribute to the effects, an effort should be made to try to consider this context. In both exposure and outcome assessment, validated test methodologies should be used. Efforts should concern the calculation of the power and sample size in order to obtain statistically significant results, notably reliability must be considered as well. Confounders and risk factors contribution to the effect should be taken into account. Anyway, the analysed literature provided some useful indications for prioritizing risk assessment with respect to some occupational categories, and several suggestions could be applied in the health surveillance of exposed workers.

INDUSTRY AND TERTIARY SECTOR IN LYON AREA, FRANCE

French context

According to the last data communicated by the French National Institute of Statistics and Economic Studies (*Institut National de la statistique et des études économiques* - INSEE) in June 2020 (INSEE, 2020a), France was populated by more than 66.500.000 inhabitants on an area of 632,733.9 km^2 in 2017. About 26.400.000 persons were salaried or self-employed workers.(INSEE, 2020a) In the 15-64 age group, the activity rate was 74% and the unemployment rate 13.9% (INSEE, 2020a). The number of active establishments at December 31, 2015 was 6.561.892.(INSEE, 2020a) The agricultural sector accounted for 6% of the active establishments, industry for 5.3%, construction for 10.1%, trade-transport-various services for 64.8% (including trade and auto repair for 16.2%), public administration-education-health-social work for 13.8%. The establishments of one to nine employees were 23.1%, those of 10 employees or more 5.8%.(INSEE, 2020a)

Mêtropole de Lyon (intercommunality)

Since 2015, a local authority has been created by merging of the urban community of Lyon and the General Council of the Rhône region. It regroups 59 municipalities on a territory of 538 km^2, for a total of 1.402.326 inhabitants in 2019.(Grand Lyon, n.d.)

The 20-64 age group represented the 57.8% of the population in 2017, according to the recent statistics of INSEE.(INSEE, 2020b) The 15-64 age group in the same period was constituted by 62.9% of active workers in employment, 14.6% of unpaid students-trainees, 8.3% of inactive people, 10.1% of unemployed workers, 4.1% of retired persons.(INSEE, 2020b)

In 2017, the 15-64 age group was divided into 660,445 (73.0%) active individuals (62.9% employed, 10.1% unemployed) and 244,274 (27.0%) inactive subjects (14.6% of students-trainees, 4.1% retired persons, 8.3% other).(INSEE, 2020b) In 2017, the employed population according to socio-professional category was divided into: farmer operators 0.1%, artisans-traders-company managers 5.3%, executives-higher intellectual professions 26.2%, intermediate professions 29.9%, employees 24.7%, workers 13.8%.(INSEE, 2020b) In the same year, the jobs by sector of activity were distributed between 0.1% agriculture, 11.1% industry, 5.2% construction, 54.2% trade-transports-various services, 29.4% public administration-education-health-social action.(INSEE, 2020b) In the same period, 48.4% of the jobs were occupied by women (35.0% in agriculture, 33.0% in industry, 14.0% in construction, 44.2% in

trade-transports-various services, 68.0% in public administration-education-health-social action).(INSEE, 2020b)

The number of active establishments on December 31, 2015 was 153,330 (71.0% had no employees, 22.3% 0-9 employees, 3.1% 10-19 employees, 2.2% 20-49 employees, 1.4% >50 employees).(INSEE, 2020b) The agricultural sector accounted for 0.2% of the active establishments, industry for 4.3%, construction for 8.1%, trade-transport-various services for 73.3% (including trade and auto repair for 16.1%), public administration-education-health-social work for 14.2%.(INSEE, 2020b) On December 31, 2017 a total of 134,751 establishments could be divided into sectors of activity as follows: 5% in industry, 8.8% in construction, 27.7% in trade-transports-accommodation and catering, 37.9% in commercial services to businesses, 20.6% in commercial services to individuals.(INSEE, 2020b)

On December 31, 2017 a total of 118,337 companies could be divided by sector of activity as follows: 4.8% in industry, 9.5% in construction, 25.9% in trade-transports-accommodation and catering, 38% in commercial services to businesses, 21.8% in commercial services to individuals.(INSEE, 2020b)

HYPOTHESIS FOR AN ADAPTED CHEMICAL RISK ASSESSMENT STRATEGY: CREATION OF AN INFORMATION SYSTEM REGARDING ENDOCRINE-DISRUPTORS

INTRODUCTION

For several decades, concern has raised about the properties of many exogenous substances or mixtures to potentially alter endocrine function in living beings. They are known as endocrine-disrupting chemicals (EDCs). EDCs interfere directly or indirectly with physiologic hormone systems through various mechanisms (Lauretta et al., 2019;ˏCombarnous & Diep Nguyen, 2019;ˏ (Marshall et al., 2013), and the health effects can be felt long after the exposure has stopped till having consequences for the progeny, (sub)populations and the next generations.(Damstra et al., 2002)

It is important to consider that each chemical can show multiple mechanisms of action at a time on different hormonal systems and that many substances at a time can act on the same molecular targets in an additive, modulating, synergistic or antagonist way.(Mantovani, 2017;ˏKortenkamp, 2007;ˏLee, 2018) A cocktail of substance can therefore be more harmful than the single components considered individually.(Kortenkamp, 2007;ˏBopp et al., 2018)

Besides being widespread in the environment and in numerous products of daily consumption, these substances are sometimes present in nature (e.g.: phytoestrogens) as such, or they can be expressly or accidentally synthesized in industrial processes.(Ying, 2012) As these substances can be found in various workplaces and in all economic activities, they can be possibly harmful to the health of the exposed workers and they must be taken in account when carrying out the chemical risk assessment in order to prevent adverse effects.(Å. Bergman et al., 2012;ˏRim, 2017) Furthermore, in this context EDCs can reach exposure levels at concentrations not attained in the general population and they can form mixtures with each other or with other substances displaying different toxic properties.(Lauretta et al., 2019;ˏRibeiro et al., 2017;ˏFucic et al., 2018)

Being these chemicals so widely spread, it is a challenge to find study designs capable to properly analyse single exposures in defined populations *in vivo* or to clarify the role of a single component in mixtures, as well as to understand interactions and accumulation in the human body over a long term.(Lee, 2018;ˏRibeiro et al., 2017)

Moreover, endocrine disruptors (EDs) seem to show other peculiar properties that do not always follow the classic rules of the traditional chemical risk assessment, making sometimes difficult their identification as contributors to risk for human health.

For example, some studies conclude that they cannot always show a threshold effect on a population level, thus adverse effects are possible even at very low doses, without an identifiable cut-off warranting the absence of harmful events under a specific absorbed dose.(Demeneix et al., 2020; Laura N. Vandenberg, 2019) Besides, their dose-response curve seems not to follow linearity: a relationship where primarily low toxic effects and then adverse effects appear more and more pronounced with the augmentation of the delivered dose. Instead, some of these chemicals can follow non-monotonic or inverted dose-response curves.(Lagarde et al., 2015; Beausoleil et al., 2017; L. Vandenberg & Blumberg, 2018)

Moreover, some EDCs can produce effects only in one sex (Monteiro et al., 2020), just in some susceptible subjects (Schuppe et al., 2000; Hatagima, 2002), when some other diseases are occurring (Kato et al., 2013) or if exposure happens at a specific and critical stage in life.(Buser et al., 2019) In particular, during critical windows of exposure, hormonal imbalance can irreversibly modify body functions or development.(Å. Bergman et al., 2012) Some responses can on the one hand be transient, on the other be delayed and not involving evident dysfunctions until later in time.(Gilbert et al., 2017; Lee, 2018; Brehm & Flaws, 2019)

It is of utmost importance in this context to clarify the clinical definition of any adverse effect and the meaning of disruption for each hormonal system: this is the milestone for expanding internationally agreed and validated test methods.(Solecki et al., 2017) Actually, no systematic consensus exists, scientific research models are sometimes missing and only a limited range of the spectrum of effects is detectable.(European Commission, 2018a; Solecki et al., 2017; Coady et al., 2017) This is the reason why hazard and risk assessment still require complementary epidemiological approaches.(Solecki et al., 2017; "Scientific Opinion on the hazard assessment of endocrine disruptors: Scientific criteria for identification of endocrine disruptors and appropriateness of existing test methods for assessing effects mediated by these substances on human health and the environment," 2013)

As a consequence of these considerations, the results of scientific research in humans are sometimes still contradictory and further investigation is needed.(Cho et al., 2020; Predieri et al., 2020; Gorini et al., 2020) In Europe, according to the Classification, Labelling and Packaging (CLP) Regulation, the ED products are not subjected to specific hazard statements,

thus they are not identifiable *via* the regulatory labelling. In a preventive attempt to preserve human health while waiting evidence to be confirmed, European Union (EU) has classified EDs as substances of very high concern in Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Regulation, at the same level as carcinogenic, mutagenic and reprotoxic substances (CMRs), as well as persistent, bio-accumulative and toxic chemicals, consequently making them subject to authorisation. Furthermore, European Union (EU) has developed a regulatory framework to introduce specific legislative obligations, for example regarding water, medical devices, plant protection products and biocides.(European Commission, 2018b;·European Commission, 2016c) Respecting EDs not addressed by specific legislation, EU exploits some environmental legislative instruments, regulations on cosmetics, toys or food contact materials, the legislative framework on Occupational Safety and Health, or adapts existing international legislation.(European Commission, 2018b;·European Commission, 2016c)

The European Commission (EC) has drawn up a program of actions. On one side, the short-term actions involve building information-gathering to provide background data and identify relevant knowledge gaps that may be useful in updating the classification, packaging, labelling, and to ensure safe usage and disposal within the EU. On the other side, some more long-term objectives regard the development of legislation further in order to properly allow the risk management.(European Commission, 2016c) For these reasons, it is important to provide preventers and companies with information adapted to each one's missions, in order to be able to integrate this new hazard into the framework of chemical risk assessment.

The scientific literature and technical publications are numerous, but it is often difficult to find information useful for the prevention of occupational risks. In France, a first national strategy on endocrine disruptors has been published in 2014 (SNPE 2014-2016), in line with REACH Regulation indications. Each year since, ANSES (French Agency for Food, Environmental and Occupational Health and Safety) is evaluating chemicals suspected for endocrine-disrupting properties and their possible substitutes, in order to check their safety, to establish ranked lists by frequency of utilisation and concern, to classify them (as known, presumed or suspected), and to propose adapted recommendations for adapted risk management measures.(*Endocrine disruptors | Anses - Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail*, n.d.;·Ministère de la Transition Ecologique et Solidaire; Ministère des Solidarités et de la Santé, 2019a) A second national strategy followed (SNPE 2019-2022). Some axes of action include training programs on the specific chemical risk related

to EDs for several health professions and other relevant professions with a role in preventing exposure, as professionals in agri-food, chemistry, veterinary sciences, safety engineers, urban planners and early childhood professionals. Some other axes aim at encouraging health professionals to develop prevention campaigns with special attention to couples and parents.(Ministère de la Transition Ecologique et Solidaire; Ministère des Solidarités et de la Santé, 2019a, 2019b) Even in line with the PST3 (3rd Occupational Health Plan) activities, it appears necessary to expand initial training in health and safety at work involving the professional fields.(Ministère du Travail de l'Emploi de la Formation professionnelle et du Dialogue Social - Direction générale du travail, 2016)

Following these PST3 indications, we elaborated a 4-year project that addresses the specific risk assessment needs and the management strategy concerning possible endocrine disruption encountered in the followed companies. This process will warrant uniform decisions, a better adhesion of the staff to evolving norms, conventions of labelling and scientific guidelines. Moreover, it will be useful in prioritizing some actions, as literature search efforts, in view of producing useful information for health surveillance. As end point, on the basis of defined work units, it will include the introduction of a specific alert into electronic health records to help the practitioner being aware of the necessity of formation and information of the workers and the possible necessity of a specific biomonitoring.

This study presents a descriptive starting point in an implementation process of design science methodology. It aims at providing the bases of a decision-making information system to support the preventive activity and the health surveillance of occupational medicine physicians dealing with a possible exposure to endocrine-disrupting chemicals (EDCs) in the workplace.

As a first step, by combining in a single database several sources of data and datasets to create an adapted information system, we tried to warrant clear and simple data visualization techniques to allow the professionals being aware of the presence of the specific ED-hazard in a company having carried out a chemical risk analysis and assessment. The database allows the extraction of current counts, statistics and graphs on the presence of hazard and factors altering the probability of exposure. This pre-implementation phase tries to give some first epidemiological evidence about, for example, the spread of the hazard in a group of selected enterprises or the type of businesses concerned, as well.

MATERIALS AND METHODS

Recruitment

We collected data from each enterprise having requested support to carry out a chemical risk assessment from February 2009 to February 2020. The enterprises joined the occupational health service Agemetra, Oullins, France, member of the *Confédération Nationale des Services de Santé au Travail Interentreprises, Présanse Auvergne-Rhône-Alpes*, St Priest, France. This service develops its preventive activity in line with the indications of the *Directions Régionales des Entreprises, de la Concurrence, de la Consommation, du Travail et de l'Emploi* (DIRECCTE), the *Caisse d'Assurance Retraite et de la Santé au Travail* (Carsat), and the *Agence Régionale de Santé* (ARS) and cooperates for several projects as *the Plan Régional de Santé au Travail 3 Auvergne-Rhône-Alpes* (PRST3 ARA), working in collaboration with Claude Bernard University Lyon I – UCBL, Villeurbanne, France, as well. It follows, mostly in the intercommunality of Lyon in the *Rhône* department, about 1900 enterprises and about 250.000 workers in all sectors except those directly involving construction and agriculture. Almost 95% of the companies have less than 50 employees, 48% of the workers belongs to companies with more than 50 employees.

Chemical risk assessment methodology

The risk assessment methodology followed the guidelines reported in document ND 2233-200-05 of the *Institut National de la Recherche et de Sécurité* (INRS).(*Méthodologie d'évaluation simplifiée du risque chimique : un outil d'aide à la décision - Article de revue - INRS*, n.d.) In brief, the chemical risk assessment process is an iterative procedure starting from the inventory of both the works units and the chemicals found in the workplace, it provides for the identification and qualification of the hazards, proceeds by analysing the exposure, and then allows calculating and prioritizing the risk.

It is important to underline some critical points about the practical application of these guidelines. Firstly, following the current French legislation (*Code du travail* Art. R. 4412-3), a chemical product is considered dangerous if it is classified by the Regulation (EC) N° 1272/2008 on the Classification, Labelling and Packaging of substances and mixtures (CLP Regulation), if Occupational Exposure Limits (OEL) are reported in a decree, if health risks are presumed because of its physical chemical and/or toxicological properties or because of the mode of use in the workplace. Secondly, regarding chemical hazard identification, it must be

considered that Dangerous Substances Directive (DSD – No. 67/548/EEC) and Dangerous Preparations Directive (DPD – No. 99/45/EC) coexisted with the CLP Regulation from January 2009 to June 2017, so it was possible to find a combination of hazard statements in Section 2 or 15 of the Safety Data Sheets (SDS) expressed both as R-Phrases and H-Phrases, subsequently completely replaced by H-Phrases. Hazard identification also included the consideration of exposures to single chemicals or mixtures identified by the International Agency for Research on Cancer (IARC) as carcinogens category 1, 2A and 2B. The multiple criteria cataloguing a substance as dangerous, the H- and R-Phrases in SDSs and IARC classification had to be taken into account in the data analysis process. We defined a product as ED1, if it contained at least one substance whose classification following the PRST3 ARA list(Groupe Risques Chimiques- PRST ARA 2016-2020, 2020) was EDC category 1 (proven endocrine-disrupting properties), and as ED2, if it contained one or more substances classified as EDC category 2 (suspected endocrine-disrupting properties). These definitions were applied irrespective of the percentage of a substance in the chemical composition reported in Section 3 of the SDSs. The PRST3 ARA list (Groupe Risques Chimiques- PRST ARA 2016-2020, 2020) has been elaborated in France using as a base the European Commission Priority List (European Commission, 2013), and it is enriched with information helpful for preventors in developing risk assessment in the enterprises. The list serves to palliate the lack of specifying labelling about endocrine-disrupting properties in European Regulation (EC) No. 1972/2008 (CLP). It exploits the Chemical Abstract Service (CAS) Registry Numbers. The CAS Registry Numbers are reported in the composition in Section 3 of the SDSs as well, which allows the creation of links between tables when elaborating data. To consider properly the properties of EDCs when integrating the INRS methodology, we followed the statements of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Regulation (EC No. 1907/2006). In the REACH Regulation, EDCs are identified of similar regulatory concern as Substances of Very High Concern (SVHC), therefore they are subjected to authorisation. This group of chemicals includes carcinogenic substances category 1A or 1B under CLP Regulation, mutagenic substances category 1A or 1B under CLP Regulation, toxics for reproduction category 1A or 1B under CLP Regulation, persistent-bio accumulative-toxic (PBT) substances under REACH Regulation, very persistent very bio accumulative (vPvB) substances under REACH Regulation, Specific Target Organ Toxicity -Repeat Exposure (STOT RE) under CLP Regulation, and EDs for environment, humans or both (ED env./human/human+env.). Thus, we modified the potential risk scores for a chemical of the original INRS methodology to take into account EDs by assimilating them to Carcinogenic,

Mutagenic or toxic to Reproduction (CMR) or carcinogens. In this way, we assigned a class of hazard 4 to ED1 and a class of hazard 3 to ED2. We calculated the possible risk of exposure by inhalation or by skin or ocular contact following INRS recommendations, using the original and the newly assigned classes of hazard. In this study, we defined some substances as "harmful for human health", when they were already recognised as SVHC for other reasons than classification as EDs.

Construction of the database

We decided to combine different sources of information: 1) general data on the characteristics of all enterprises belonging to the occupational health service; 2) a list of substances classified as EDCs category 1 and 2 and the relative complementary data from PRST3 ARA list (Groupe Risques Chimiques- PRST ARA 2016-2020, 2020); 3) a dataset for each enterprise assembling all the substances reported in Section 3 of the SDSs of the products in use at the time of the chemical risk assessment, by their CAS number, as well as their international classification; 4) a dataset for each enterprise collecting information about each purchased product, comprising data from several sections of the SDS, as composition by CAS Registry Numbers and percentages, data on employment, the dates of the SDS and of the chemical risk assessment, the chemical and physical properties and classes of hazards, classification according to European Regulations; 5) a dataset for each enterprise collecting information about each purchased product according to several sections of the SDS, comprising classes by frequency of use, classes by potentiality of exposure, by volatility, by process, by collective protection, exposed-surface score, score by frequency of exposure, potential exposure scores by inhalation and skin or eye contact; 6) a list of all the business' economic activity codes (NAF codes) in France; 7) a list of some grouped NAF codes we defined by analogy in the type of purchased products and in the type of activity; 8) an excel sheet with the headers elaborated for each type of dataset and their explanation.

The PRST3 ARA list (Groupe Risques Chimiques- PRST ARA 2016-2020, 2020), version 1, 20/11/2019 was used as reference. We filtered the list restricting for EDCs category 1 and 2. This new partial list contained 290 substances by their CAS Registry Number and the relative complementary data reported in the original version.

In France, "*codes Nomenclature des Activités Françaises (NAF)*" are codes used as a national classification of the main business' activity for statistical purposes. The activity is declared by each employer when registering the company. They follow a regularly up-dated list by the

National Institute of Statistics and Economic Studies (INSEE).(*Nomenclature d'activités française | Insee*, 2019) We created a grouping of some business' economic activity codes, to ensure more homogeneity and significant classification regarding the type of exposure and products in use, as shown in Table 7.

Table 7. Definition of a grouping of NAF codes for data processing being more meaningful

Grouped NAF codes contributing to the activity definitions in use in the study	
Research activity and laboratory	71.20B, 72.11Z, 72.19Z, 85.31Z, 85.32Z, 86.90B
Hospital and veterinary activity	75.00Z, 86.10Z, 86.22C
Dental prosthesis	32.50A, 86.23Z
Metal foundry	24.53Z, 24.54Z
Industrial mechanics and metal processing	25.29Z, 25.50B, 25.61Z, 25.62B, 28.14Z, 28.15Z, 28.25Z, 28.30Z, 28.99B, 33.20B
Garage and auto repair	29.20Z, 29.32Z, 45.11Z, 45.19Z, 45.20A, 45.20B, 49.41B, 52.29B
Tires and rubber articles	22.11Z, 22.19Z
Construction and electricity	43.21A, 43.99D
Electronic manufacturing and scientific instrumentation	26.12Z, 26.51B, 27.12Z, 27.32Z, 27.51Z, 28.29A, 33.20D
Manufacture of glass and ceramics	23.19Z, 23.44Z
Cleaning activities	81.21Z, 81.22Z
Textile industry	13.20Z, 13.30Z
Manufacture of jewellery, imitation jewellery and related articles	32.12Z, 32.13Z
Printing and pre-press	18.12Z, 18.13Z

We created a digital folder where we stocked all the datasets from each chemical risk assessment of the recruited enterprises. Every day, the data from this folder are automatically loaded, and the results of analysis updated, by a statistical analysis software, Qlik Sense®, QlikTech International AB©, King of Prussia, Pennsylvania, United States, as result of script modifications. The file listing the headers was used as the reference for charging the data. The collected data have been anonymised, generating automatically a code for each enterprise. Another code was similarly created for each product in use. Substances could be recalled by their CAS Registry Number.

Moreover, we programmed the software to ensure data extraction from the software MEDTRA, Axess Solutions Santé©, Alixan, France. This software is used by the occupational health service to collect the data from all the different companies followed for health surveillance and their workers' medical records. The link between these data and those in the products' datasets was possible by the means of the membership code of the recruited companies.

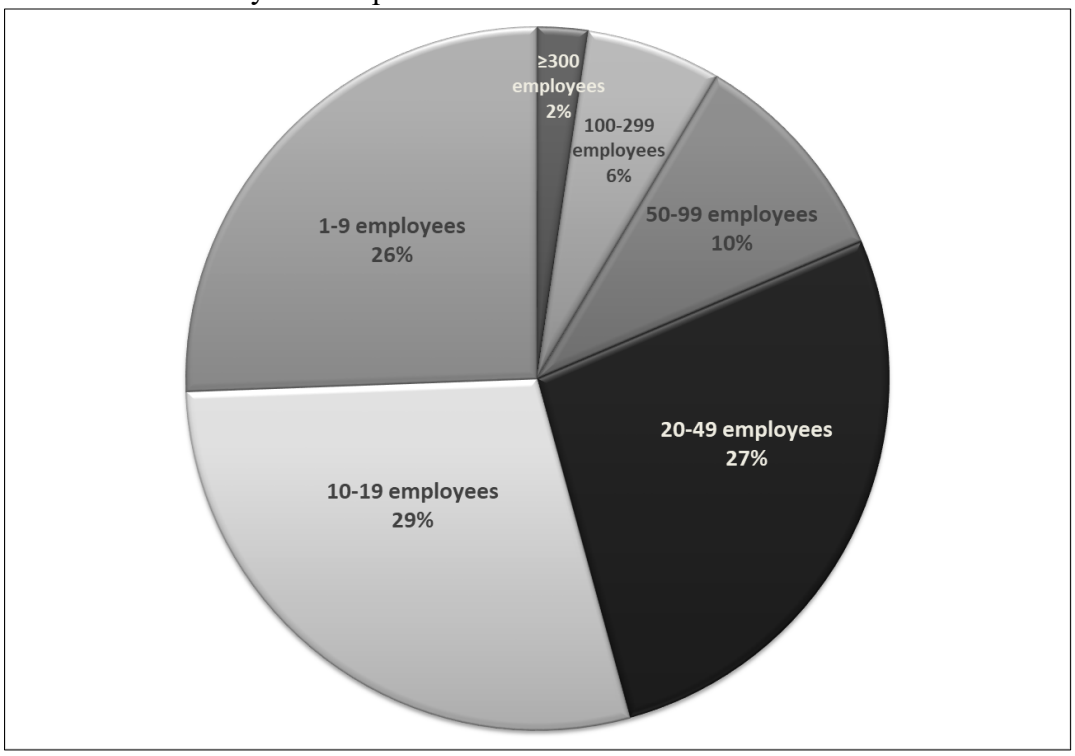
Display of results

We displayed the results using Qlik Sense® software. Calculating the proper formulas directly in the script or when defining the options for data visualisation, we elaborated a common grid for the automatic extraction of counts, figures, graphs and tables. The availability of different filters of interest has made possible to restrict the analysis to several areas of interest. Some examples of the use of filters regard the general characteristics of the enterprises (number of employees, a broader company size category, geographical sector, health professional or preventor in charge, sector of activity, NAF code), the products in use (ED classification and categorisation, harmfulness for health, product name, product family, chemical supplier, physico-chemical state, date of the SDS, date of the chemical risk assessment, IARC or CMR classification), as well as the possible exposures (theoretical gross or residual risk scores, integrating or not EDs into computation, by inhalation or skin and/or ocular exposure).

RESULTS

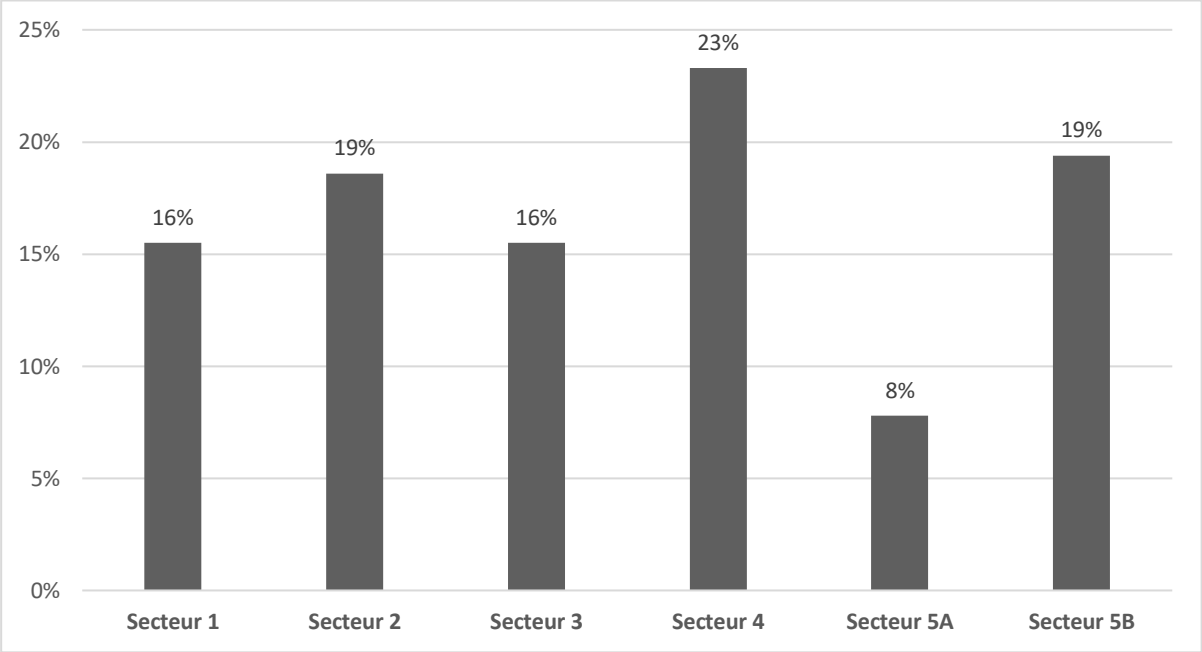
We enrolled 129 enterprises. As shown in Graph 1 they were more frequently small- and medium-sized.

Graph 1. Size of the analysed companies



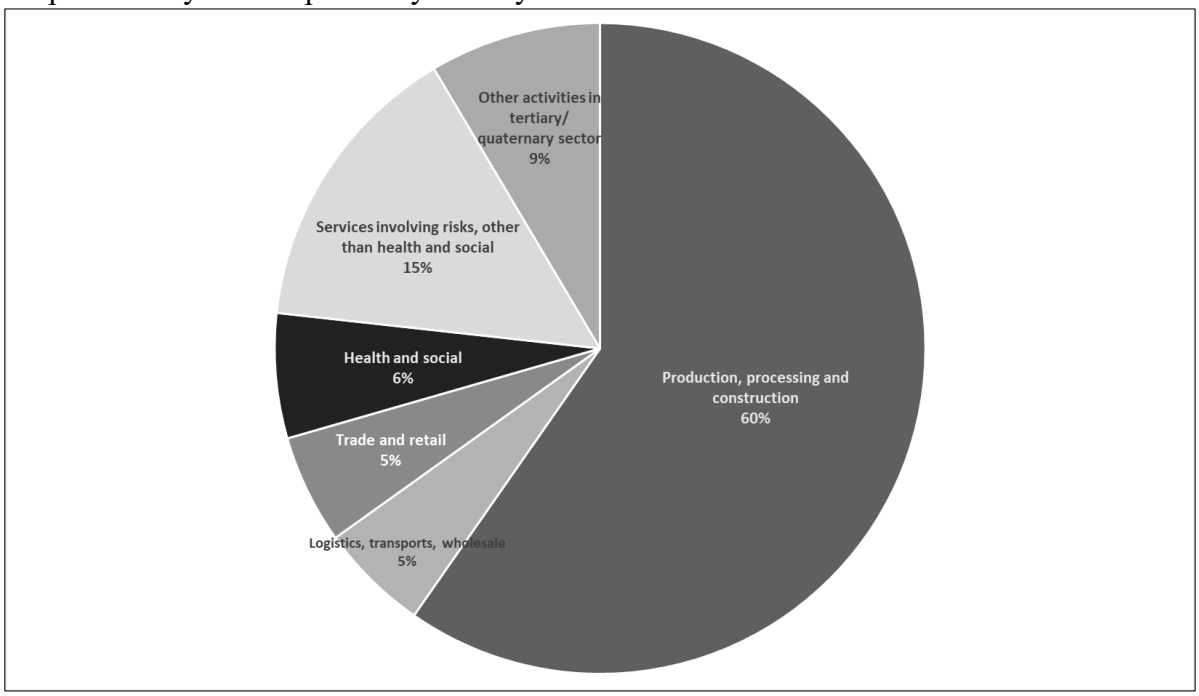
Some geographic sectors have been arbitrarily defined and numbered according to proximity to the city centre (1=periphery->5A or 5B=city centre). Graph 2 reports the relative frequency, expressed as percentage, of the location areas of the analysed enterprises on the overall of the analysed enterprises.

Graph 2. Geographic sectors of the analysed companies

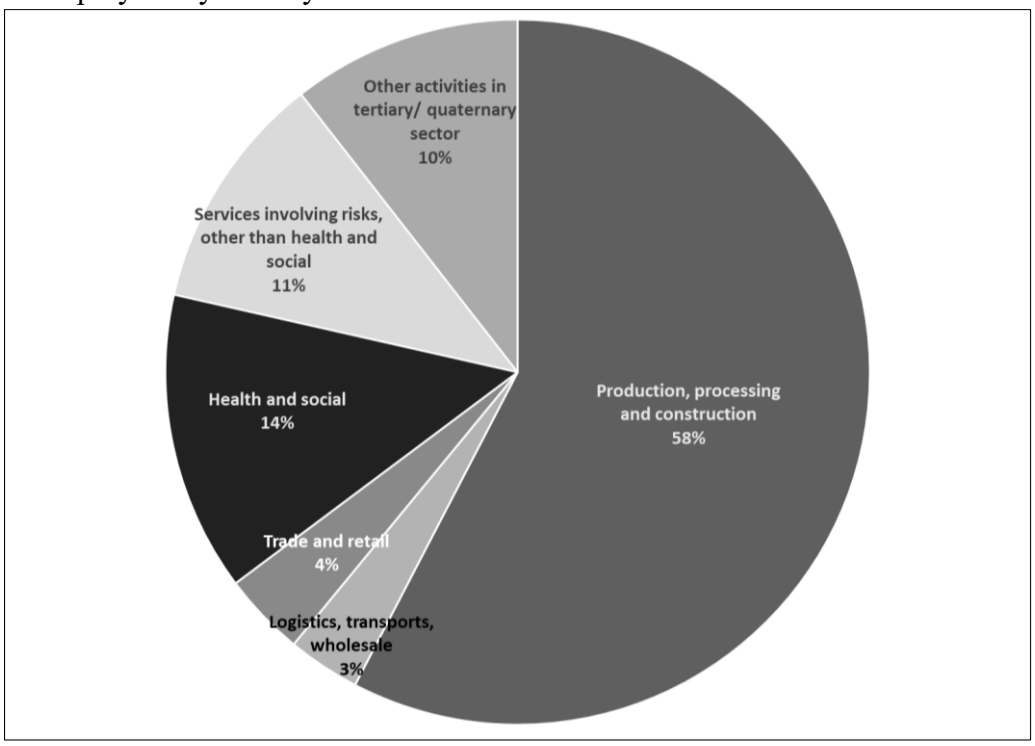


Graph 3 and Graph 4 show the analysed companies and their employees by some arbitrarily defined activity areas.

Graph 3. Analysed companies by activity area

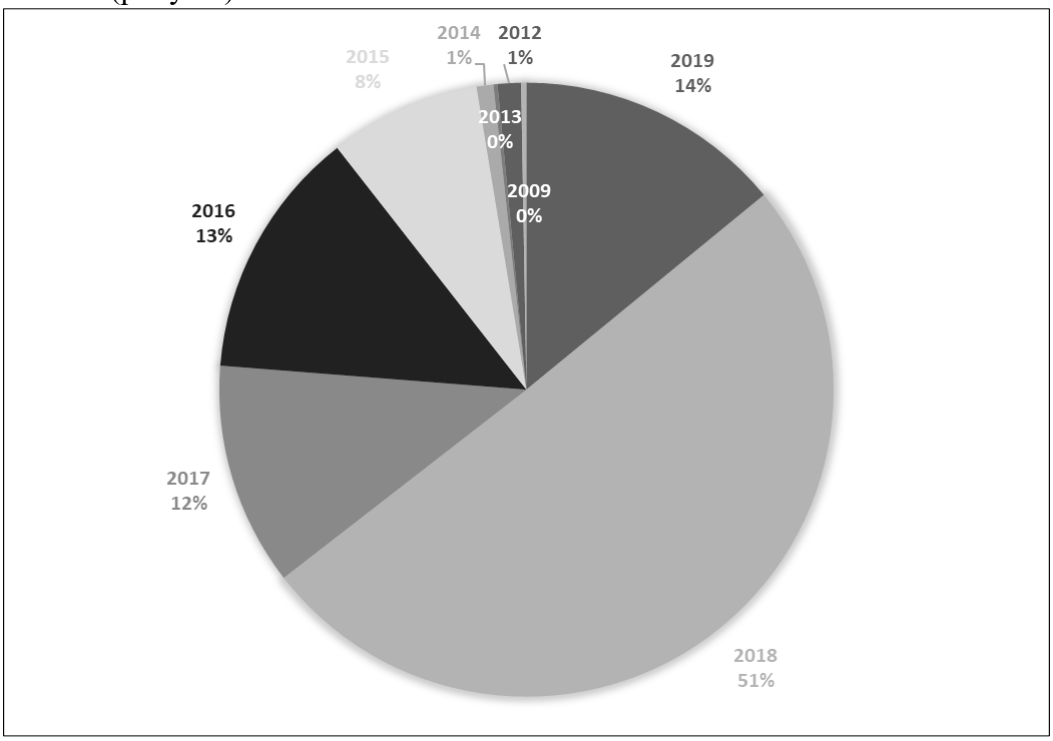


Graph 4. Employees by activity area



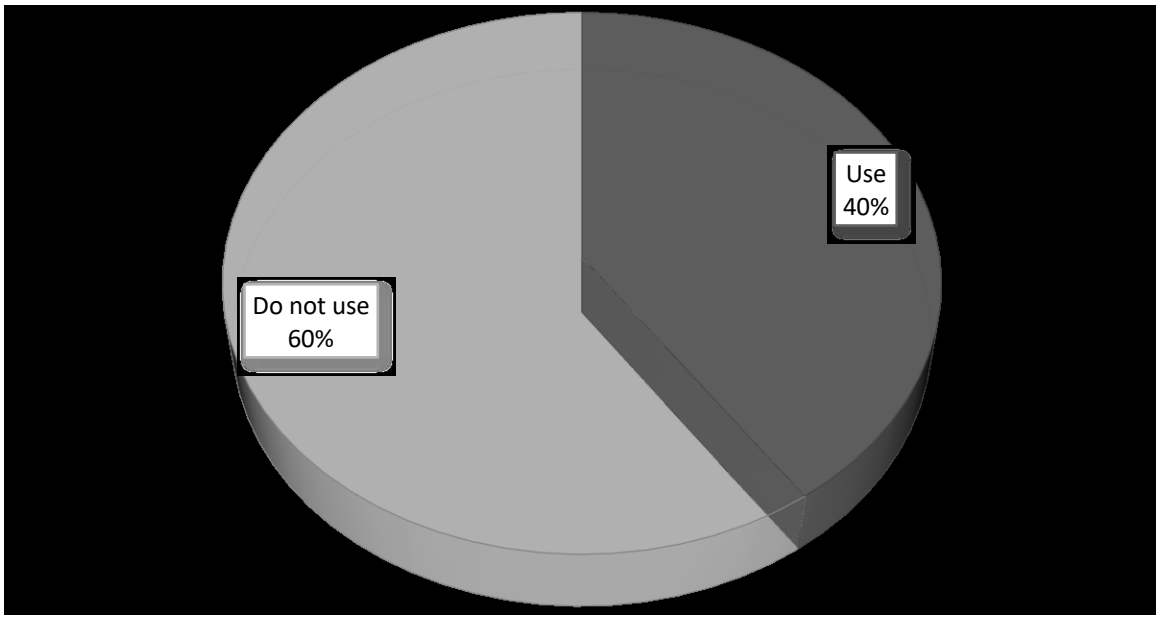
As shown in Graph 5, the chemical risk assessment was performed in the last 5 years for 89.4% of the analysed enterprises.

Graph 5. Date (per year) of the chemical risk assessment



On the total of the enrolled companies, 40.3% used at least one between ED1 and ED2 products, as shown in Graph 6.

Graph 6. Enrolled companies by the use of endocrine-disrupting chemicals



The analysed companies were described by 33 business' economic activity codes (grouped NAF), as listed in Table 8. The activity definitions we elaborated to create a more significant classification, accounted for 5.85% of the firms of our study. Otherwise, the not grouped businesses' economic activity codes we found in our sample were 75, while the whole occupational health service accounted for 558 codes.

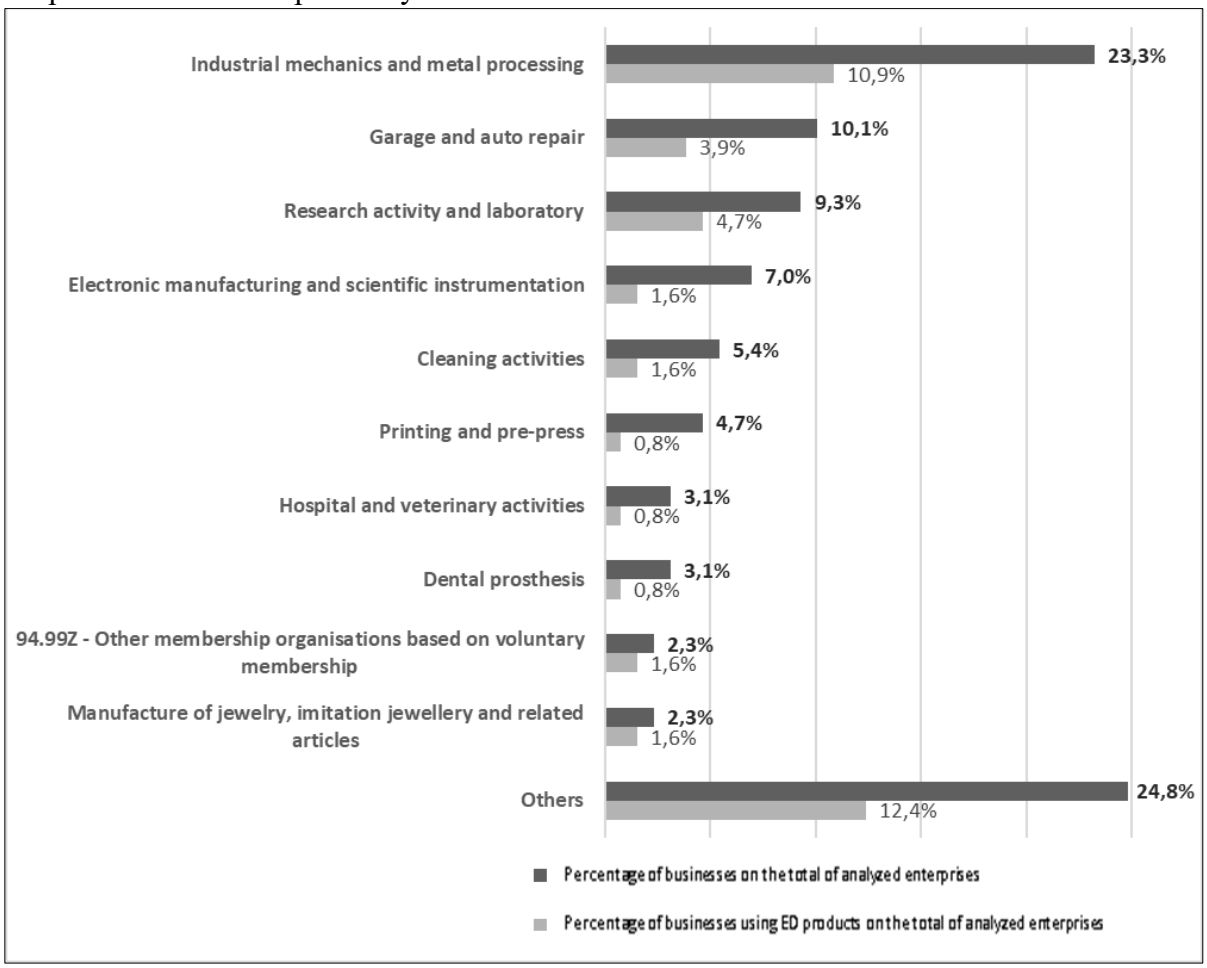
Table 8. NAF codes and activity definition of the analysed companies

Grouped NAF codes	
Production of soft drinks	11.07B
Textile industry	13.20Z, 13.30Z
Printing and pre-press	18.12Z, 18.13Z
Manufacture of plastics in primary forms	20.16Z
Manufacture of perfumes and toilet preparations	20.42Z
Manufacture of other chemical products n.e.c.	20.59Z
Manufacture of pharmaceutical preparations	21.20Z
Tires and rubber articles	22.11Z, 22.19Z
Manufacture of glass and ceramics	23.19Z, 23.44Z
Metal foundry	24.53Z, 24.54Z
Industrial mechanics and metal processing	25.29Z, 25.50B, 25.61Z, 25.62B, 28.14Z, 28.15Z, 28.25Z, 28.30Z, 28.99B, 33.20B
Electronic manufacturing and scientific instrumentation	26.12Z, 26.51B, 27.12Z, 27.32Z, 27.51Z, 28.29A, 33.20D
Garage and auto repair	29.20Z, 29.32Z, 45.11Z, 45.19Z, 45.20A, 45.20B, 49.41B, 52.29B
Manufacture of other furniture and industry closely related to furnishing	31.09B
Manufacture of jewellery, imitation jewellery and related articles	32.12Z, 32.13Z
Dental prosthesis	32.50A, 86.23Z
Construction and electricity	43.21A, 43.99D
Agents involved in the sale of machinery, industrial equipment, ships and aircraft	46.14Z
Wholesale (intercompany trade) of sundry industrial supplies and equipment	46.69B
Wholesale (intercompany trade) of metals and metal ores	46.72Z
Wholesale (intercompany trade) of plumbing and heating equipment and supplies	46.74B
Retail sale of meat and meat products in specialised stores	47.22Z
Letting of land and other own property	68.20B
Activities of head offices	70.10Z
Engineering, technical studies	71.12B
Research activity and laboratory	71.20B, 72.11Z, 72.19Z, 85.31Z, 85.32Z, 86.90B
Hospital and veterinary activity	75.00Z, 86.10Z, 86.22C
Cleaning activities	81.21Z, 81.22Z
Other business support service activities n.e.c.	82.99Z
Fire service activities	84.25Z
Assistance by work	88.10C
Activities of sport clubs	93.12Z
Other membership organisations based on voluntary membership	94.99Z

The most represented codes and activity definitions, as relative frequency on the total of the analysed enterprises, are listed in Graph 7 and expressed as percentage in decreasing order. In this graph, we outlined the percentage of the companies using ED products as well, accounting for 23 business' economic activity codes. We did not find any ED products in the following activities: 20.16Z - Manufacture of plastics in primary forms; 31.09B - Manufacture of other furniture and industry closely related to furnishing; 46.14Z - Agents involved in the sale of machinery, industrial equipment, ships and aircraft; 46.72Z - Wholesale (intercompany trade)

of metals and metal ores; 46.74B - Wholesale (intercompany trade) of plumbing and heating equipment and supplies; 47.22Z - Retail sale of meat and meat products in specialised stores; 68.20B - Letting of land and other own property; 70.10Z - Activities of head offices; 93.12Z - Activities of sport clubs; Construction and electricity. We found that all the analysed companies working in metal foundry, textile industry, tire and rubber articles production were concerned by the employment of ED products.

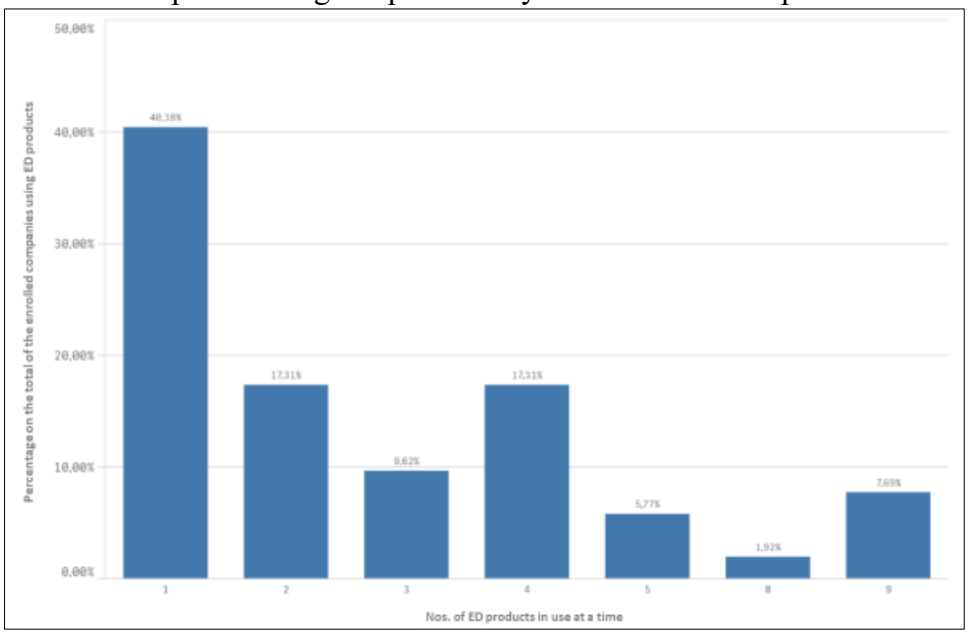
Graph 7. Enrolled companies by the defined economic activities



Among the enterprises using at least one ED product, most of them (59.6%) employed a combination of more than one ED products at a time; about 16% of them used more than 5 EDs products, and 9.6% of them employed more or equal than 8 EDs products at a time, as shown in Graph 8. The companies employing 8 or 9 EDs products at a time belonged to the following economic activities: 21.20Z - Manufacture of pharmaceutical preparations, 94.99Z - Other membership organisations based on voluntary membership (here technological innovation in microbiology), Electronic manufacturing and scientific instrumentation, industrial mechanics and metal processing, Garage and auto repair. In the 8 EDs products used at a time we found

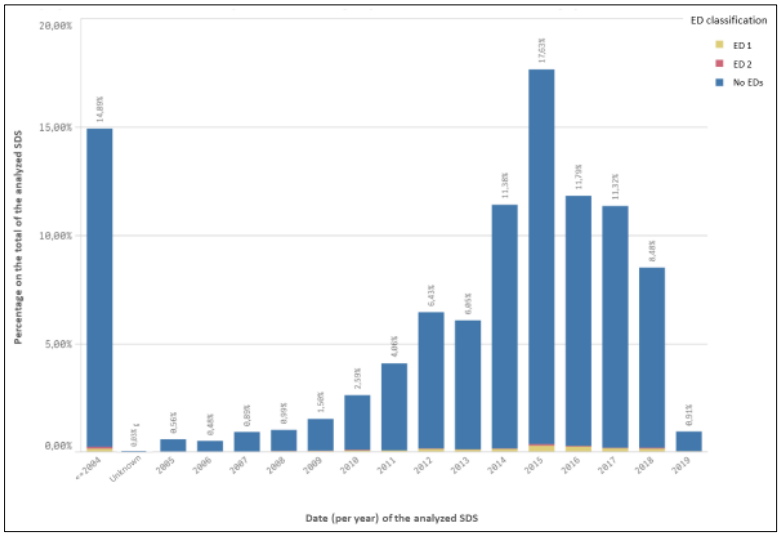
only 3 different substances responsible for their endocrine-disrupting nature. For the companies using 9 EDs products at a time we found 5 or 6 substances responsible for this classification, depending on the enterprise.

Graph 8. Enrolled companies using ED products by the number of ED products in use at a time



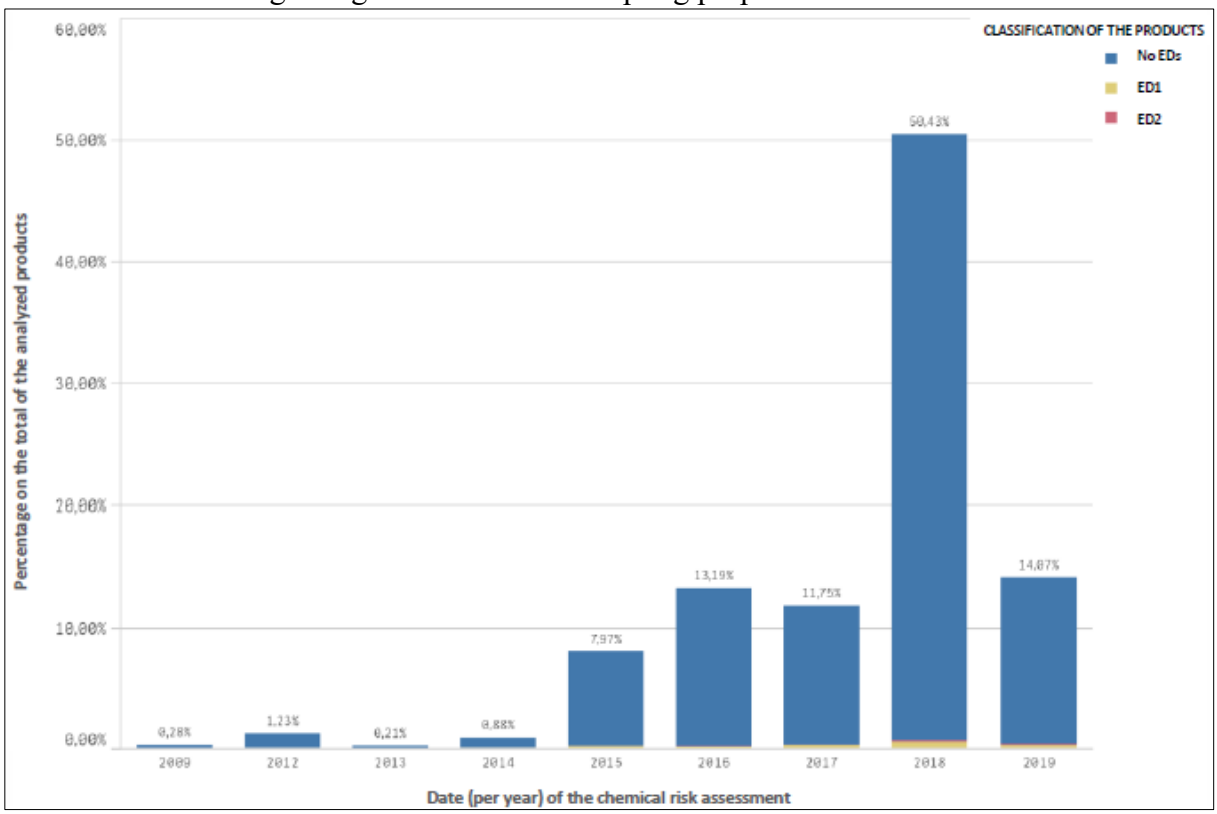
For each company participating in the study, we obtained the SDSs of the purchased products. We analysed 10,792 SDSs, presenting 8,963 different commercial names. Graph 9 reports the relative frequency by the date of the SDSs on the total of the analysed SDSs (one SDS refers to one product), expressed as percentage. The mean time between the chemical risk assessment evaluation and the date of the SDS was about 3 years (data not shown). The SDSs dating after 2010 were 70% of our sample, 10% of the SDSs dated after 2018.

Graph 9. Analysed SDSs by date (per year), showing the relative frequency of the analysed products and their ED classification



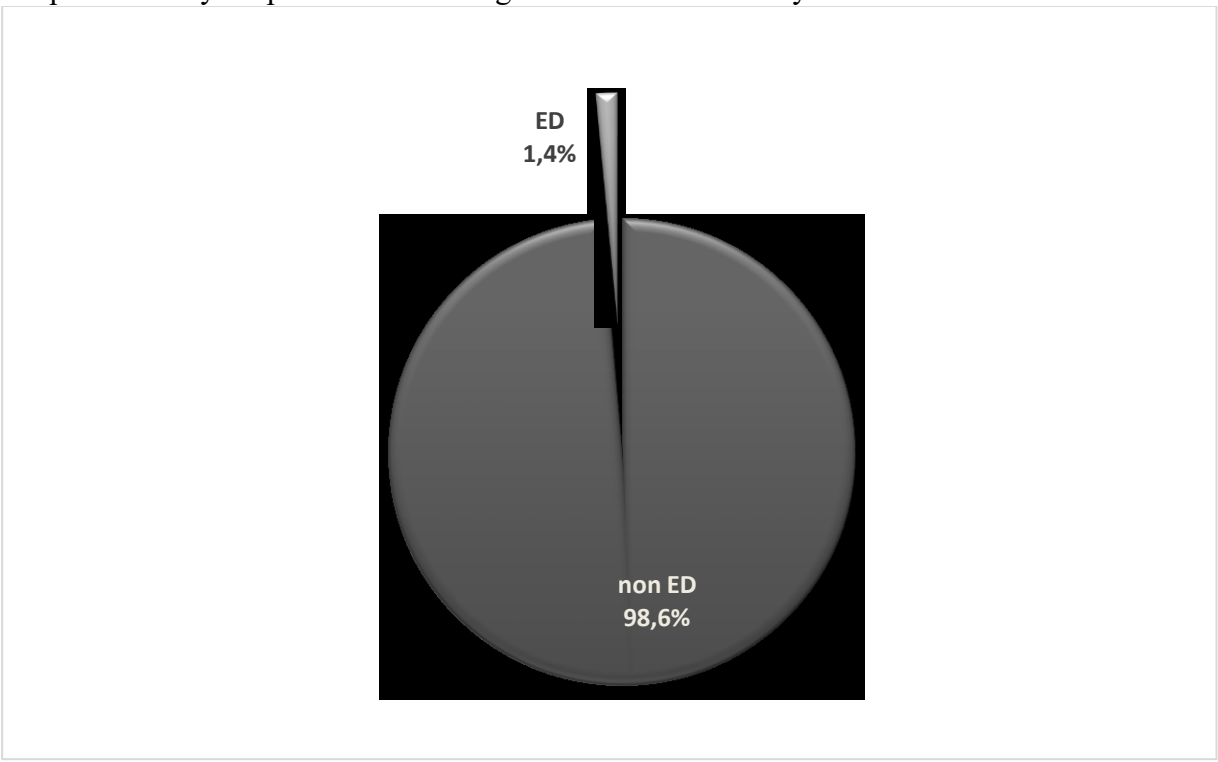
In Graph 10 the relative frequency on the total of the analysed products and their classification with regard to their endocrine-disrupting properties are displayed by the date of the chemical risk assessment and expressed as percentages. Most of the analysed products (76.25%) have been listed and analysed in the last 3 years.

Graph 10. Date (per year) of the chemical risk assessment of the analysed products, showing their classification regarding the endocrine-disrupting properties

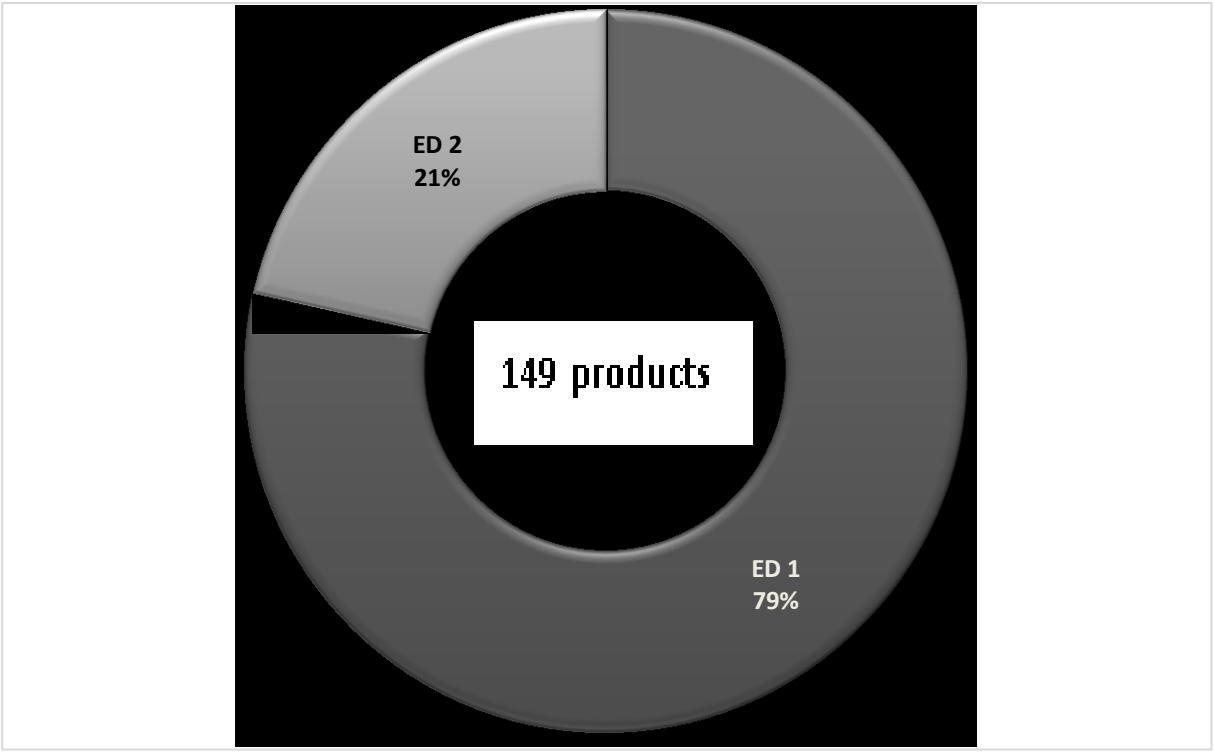


About 1.4% (n=149) of the analysed products, contained at list one EDC, 79% of them being classified as ED1, as shown in Graph 11 and Graph 12.

Graph 11. Analysed products according to the classification by their content of listed EDCs



Graph 12. Analysed ED products by their classification



We summarised in Table 9 the data of the enrolled companies overall, of the enrolled companies using ED1, using ED2, and using ED products not already classified for as harmful for human

health. Up to almost 17% of the employees were potentially exposed to EDs not classified as harmful for human health by European Regulations.

Table 9. Summary of some characteristics of the enrolled enterprises

	All companies enrolled in the study	Companies using EDCs	Companies using EDs1	Companies using EDs2	Companies using EDs not classified for other risks for human health
N°	129	52	45	20	10
N° of different businesses' economic activity codes used (% of «grouped» NAF codes on the total)	37 (5,85)	23 (3,63)	20 (3,16)	12 (1,90)	9 (1,42)
N° of different products analyzed	8.963	149	117	32	13
N° of total SDS analyzed	10.792	149	117	32	13
N° of listed EDCs category 1 or 2 (as reported in Section 3 of the SDS)	41	41	26	15	9
N° of employees	8.596	4.279	3.817	1.772	1.425

In the 149 EDs products, as reported in Section 3 of the SDSs, we found 41 listed EDCs (26 EDCs category 1, 15 EDCs category 2). The list is shown in Table 10.

Table 10. List of all the EDCs found in our study, indicating CAS Registry Numbers, names and their classification

CAS Registry Number	**Name***
EDCs category 1§	
80-05-7	4,4'-isopropylidenediphenol; Bisphenol A (BPA)
556-67-2	Octamethylcyclotetrasiloxane
9016-45-9	Nonylphenol, ethoxylated
50-32-8	Benzo[def]chrysene (fam. Polycyclic aromatic hydrocarbons -PAHs-)
61-82-5	Amitrole
84-66-2	Diethyl phthalate (DEP)
84-74-2	Dibutyl phthalate (DBP)
85-68-7	Benzyl butyl phthalate
87-86-5	Pentachlorophenol
94-26-8	Butyl 4-hydroxybenzoate
99-76-3	Methyl 4-hydroxybenzoate
99-96-7	4-hydroxybenzoic acid
99-99-0	4-nitrotoluene
100-42-5	Styrene
106-89-8	1-chloro-2,3-epoxypropane
108-46-3	Resorcinol; 1,3-benzenediol
117-81-7	Bis(2-ethylhexyl) phthalate
137-26-8	Thiram
4376-20-9	(2-ethylhexyl) hydrogen phthalate
10043-35-3	Boric acid
25036-25-3	Bisphenol (Epoxy Resin)
25154-52-3	Nonylphenol
52918-63-5	α-cyano-3-phenoxybenzyl[1R-[1α(S*),3α]]-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate; Deltamethrin (ISO)
85535-85-9	Alkanes, C14-17, chloro (Intermediate chain chlorinated paraffins)
1634-04-4	Tert-butyl methyl ether (MTBE)
77-09-8	Phenolphthalein
EDCs category 2§	
52315-07-8	α-cyano-3-phenoxybenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate; Cypermethrin
59-50-7	Chlorocresol
84-69-5	Diisobutyl phthalate
90-43-7	Biphenyl-2-ol
98-54-4	4-tert-butylphenol
106-44-5	p-cresol
127-18-4	Tetrachloroethylene
137-30-4	Ziram
330-54-1	Diuron (ISO); 3-(3,4-dichlorophenyl)-1,1-dimethylurea
1570-64-5	4-chloro-o-cresol
1675-54-3	2,2'-[(1-methylethylidene)bis(4,1-phenyleneoxymethylene)]bisoxirane; Bisphenol A diglycidyl ether
3115-49-9	(4-nonylphenoxy)acetic acid
26761-40-0	Di-"isodecyl" phthalate
28553-12-0	Di-"isononyl" phthalate
51-03-6	2-(2-butoxyethoxy)ethyl 6-propylpiperonyl ether

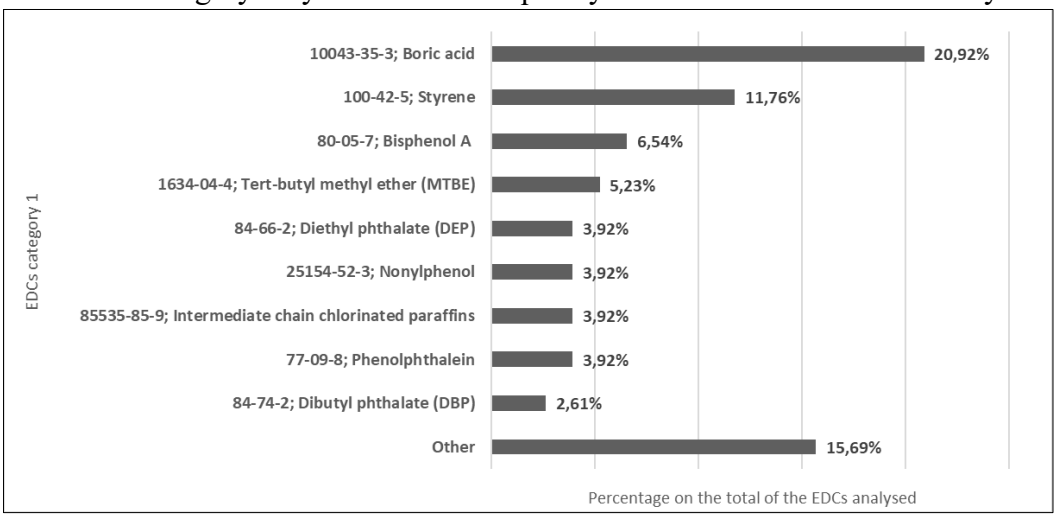
*As reported in European Chemicals Agency (ECHA) site https://echa.europa.eu/it/search-for-chemicals and in the respective substances Infocards

§ Following the classification reported in PRST3 ARA list(Groupe Risques Chimiques- PRST ARA 2016-2020, 2020), version 1, 20/11/2019

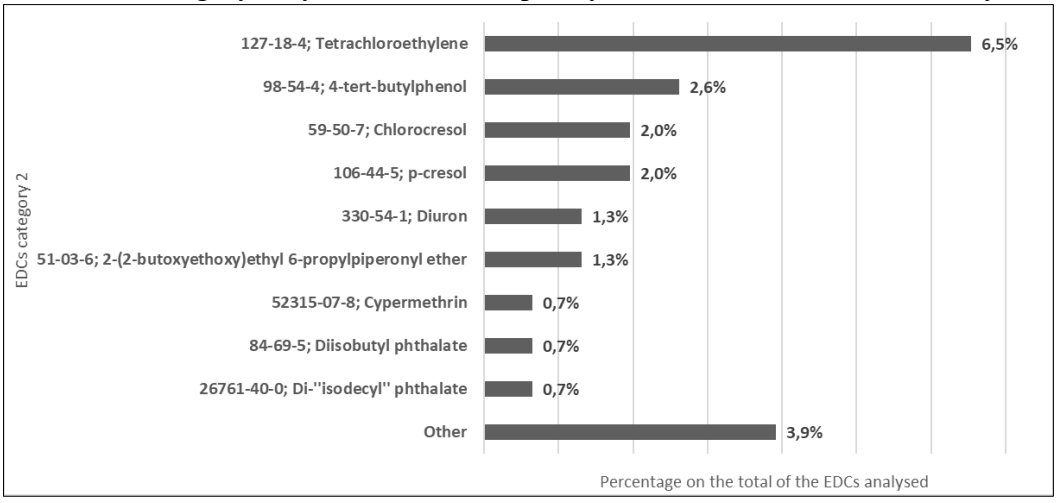
Two products contained two EDCs each. One was used in weaving, the other was an emulsifiable insecticide used for general cleaning of buildings. The other pesticides mentioned in the table were all used in cleaning activities.

In Graph 13 and in Graph 14 we reported the most encountered EDCs by category 1 and category 2; their CAS Registry Number identifies them. The graphs indicate the relative frequency on the total number of EDCs in our sample, in decreasing order, expressed as percentage.

Graph 13. EDCs category 1 by the relative frequency on the total of the EDCs analysed

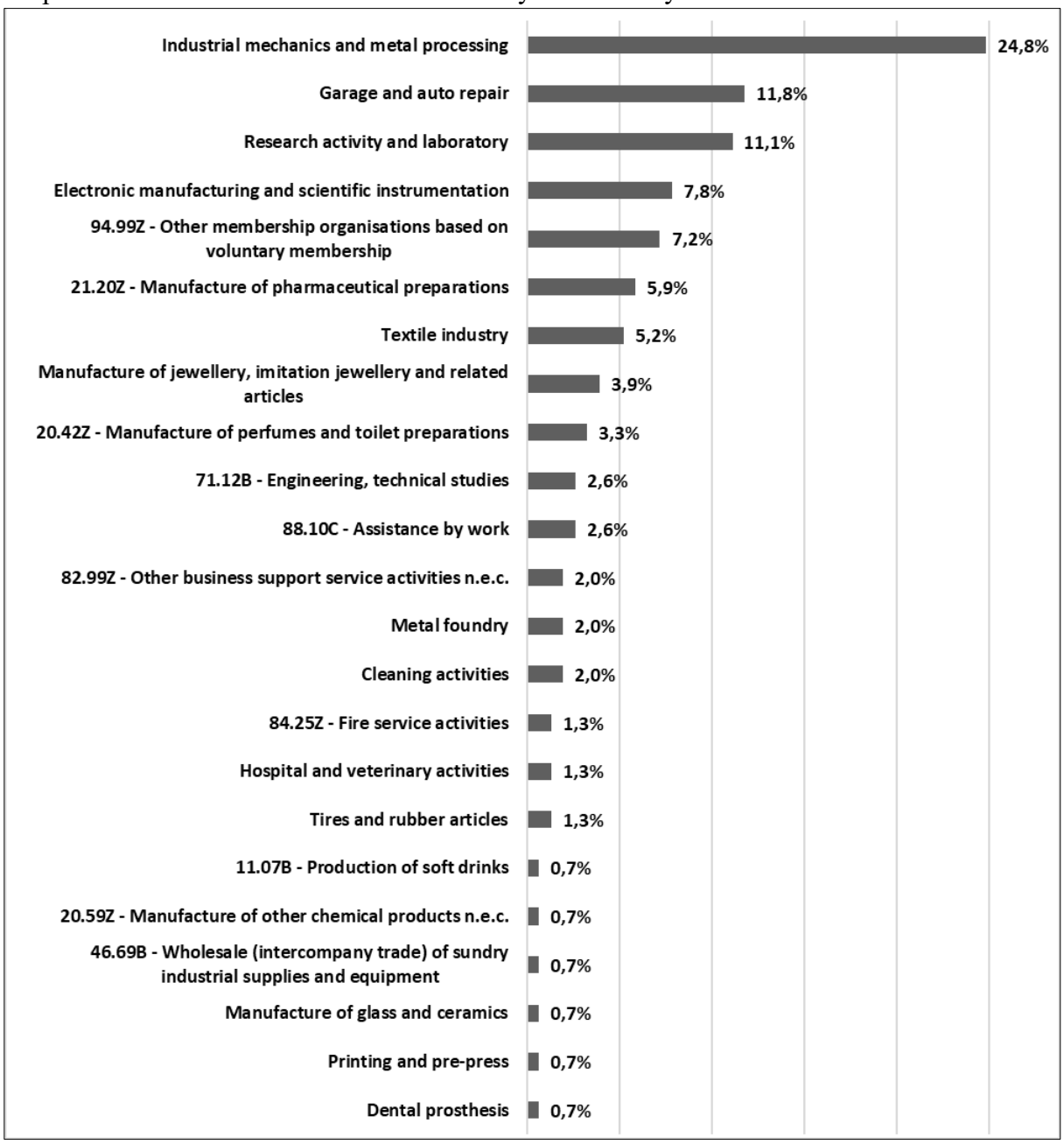


Graph 14. EDCs category 2 by the relative frequency on the total of the EDCs analysed



Graph 15 shows the relative frequency of the EDCs on the total of the analysed EDCs by the defined economic activities, expressed as percentages, in decreasing order.

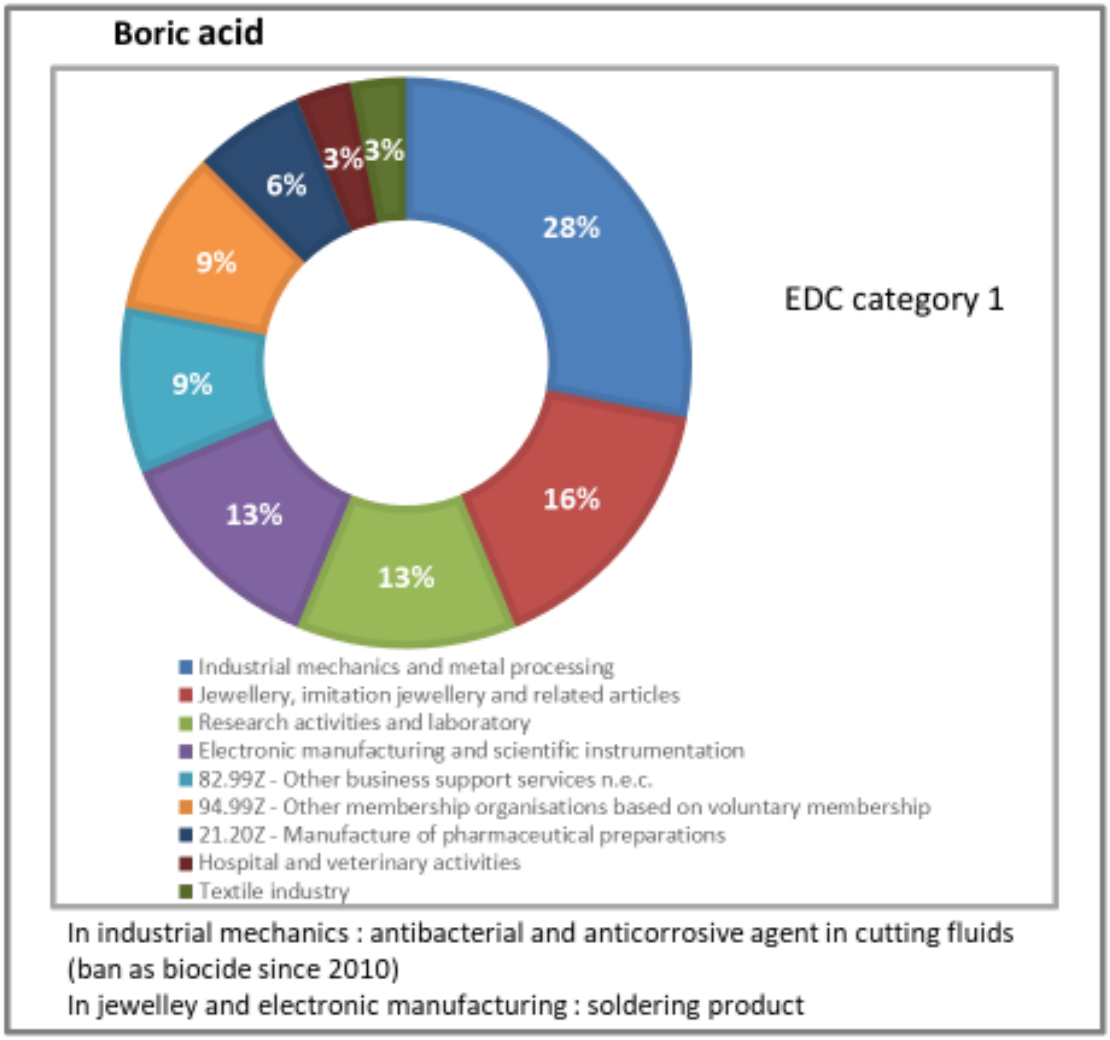
Graph 15. EDCs in use on the total of the analysed EDCs by the defined economic activities



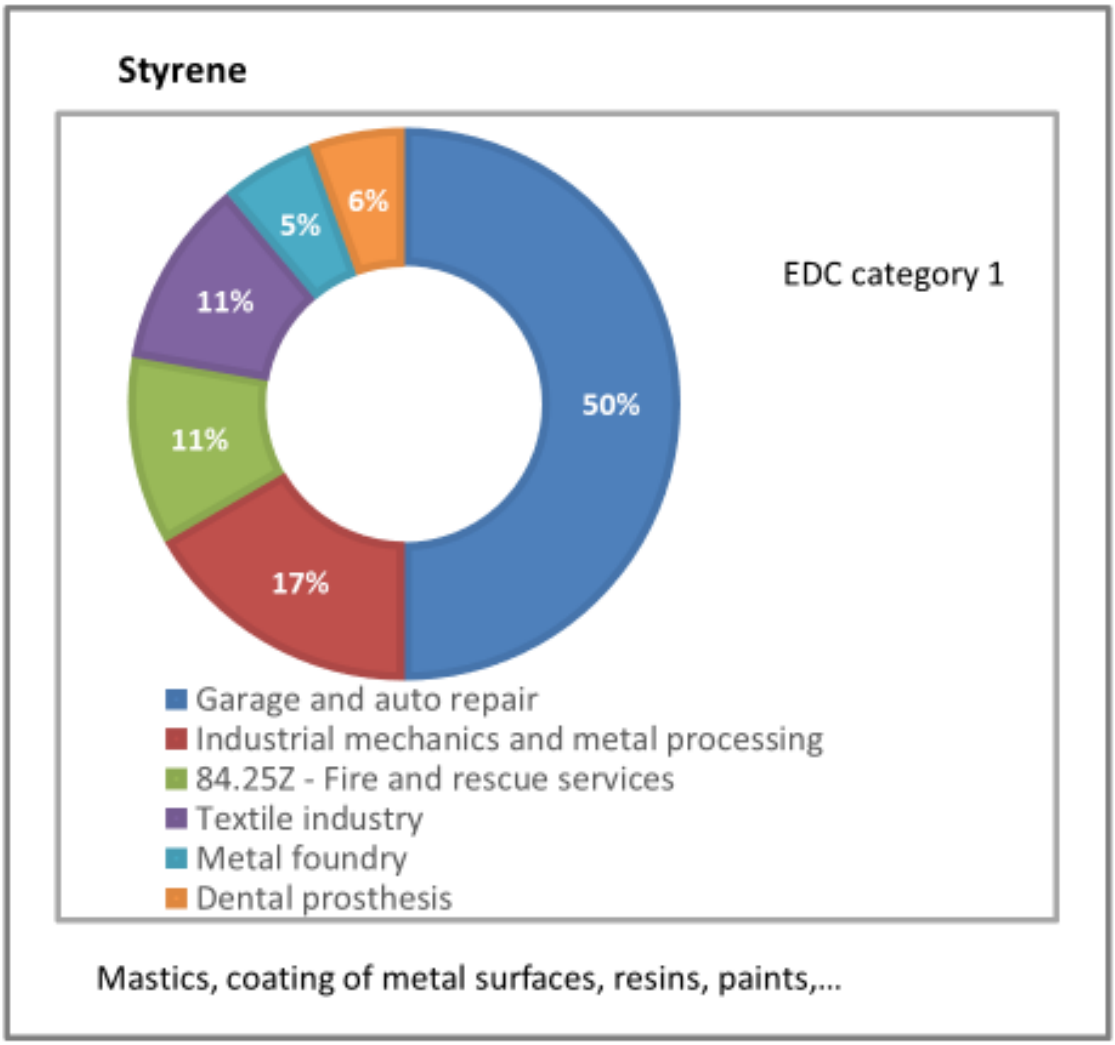
The most encountered EDCs were boric acid, followed by styrene, tetrachloroethylene and bisphenol A, which, alone, constituted about 50% of all the EDCs in our sample.

For each of these substances, we extracted the list of the defined economic activities and we could collect information about the containing products employment. Results are shown in Graph 16, Graph 17, Graph 18, and Graph 19.

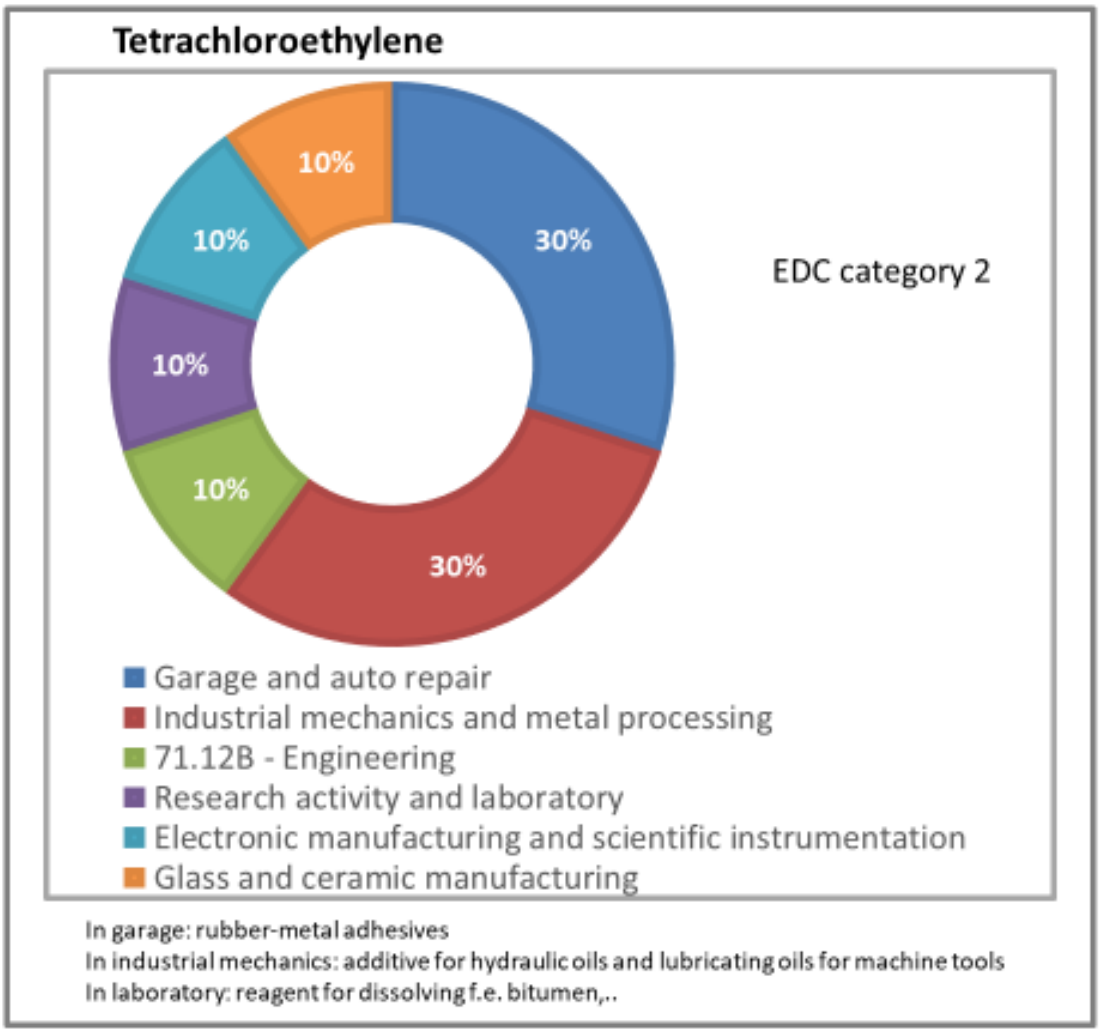
Graph 16. List of the defined economic activities comporting utilisation, EDC category, indications on employment of boric acid



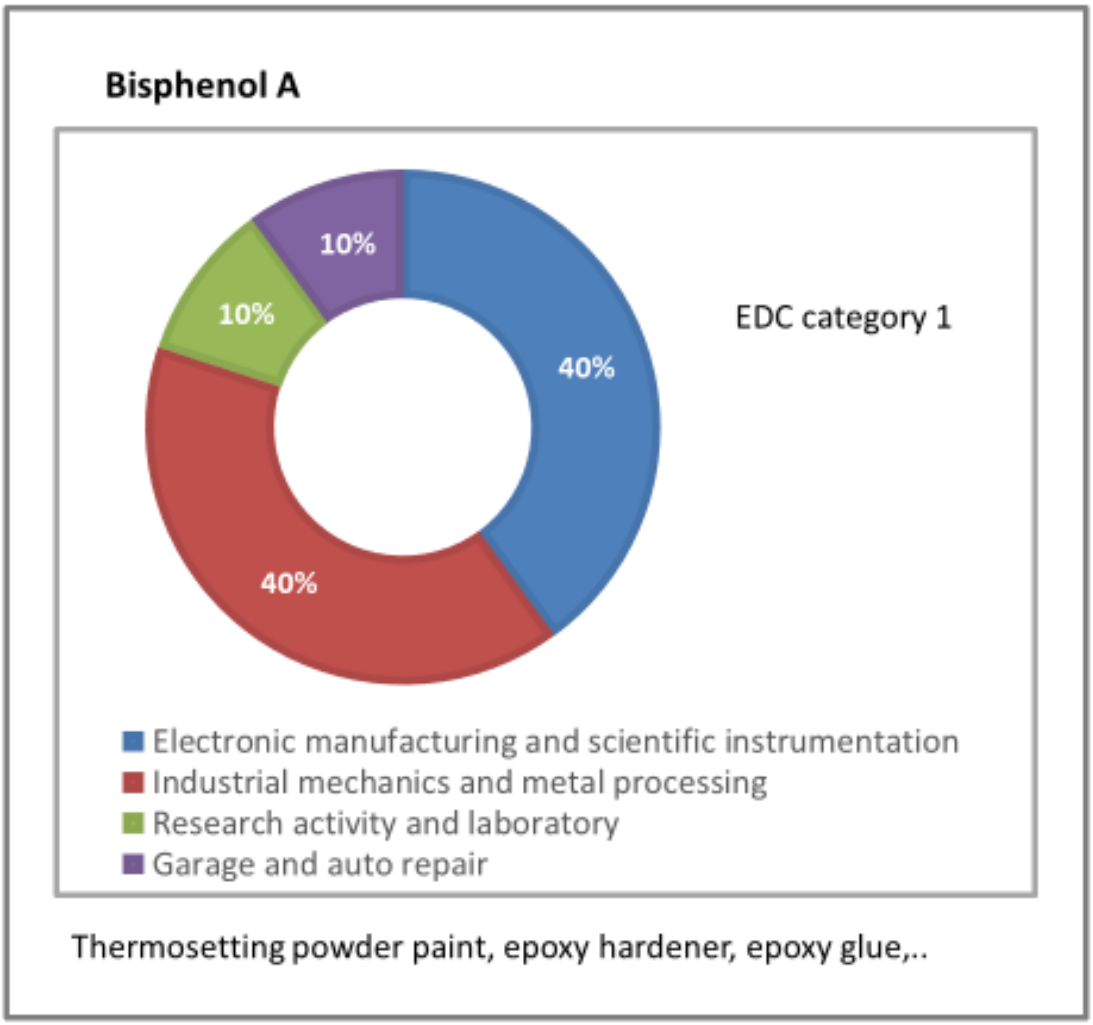
Graph 17. List of the defined economic activities comporting utilisation, EDC category, indications on employment of styrene



Graph 18. List of the defined economic activities comporting utilisation, EDC category, indications on employment of tetrachloroethylene

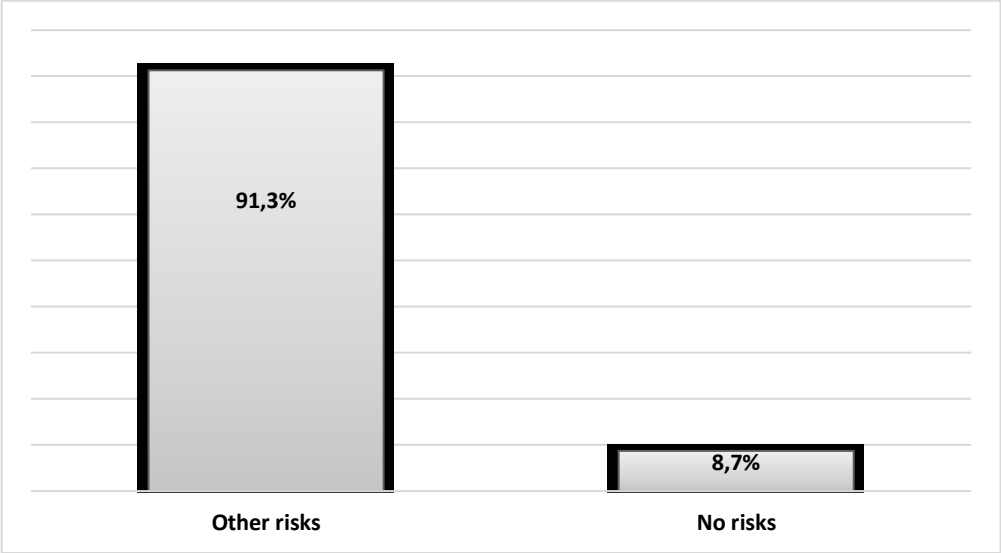


Graph 19. List of the defined economic activities comporting utilisation, EDC category, indications on employment of bisphenol A

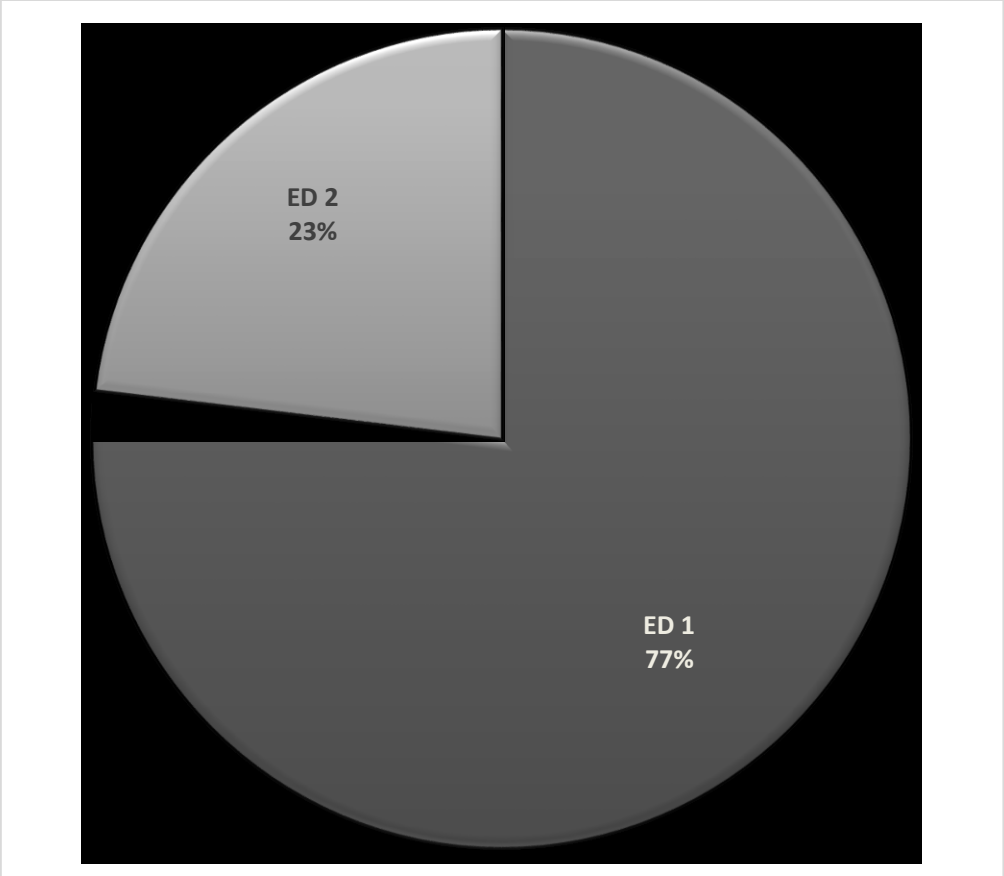


About 10% of the analysed EDs products (n=13) were not classified as harmful for human health (Graph 20). Most of these products were classified as ED1, and they were mostly used alone, as reported in Graph 21 and Graph 22. When used with another ED product, they were still not classified as a danger for health (the same substance being find in different products); while when they were used with more than one ED products, boric acid provides for reprotoxic classification.

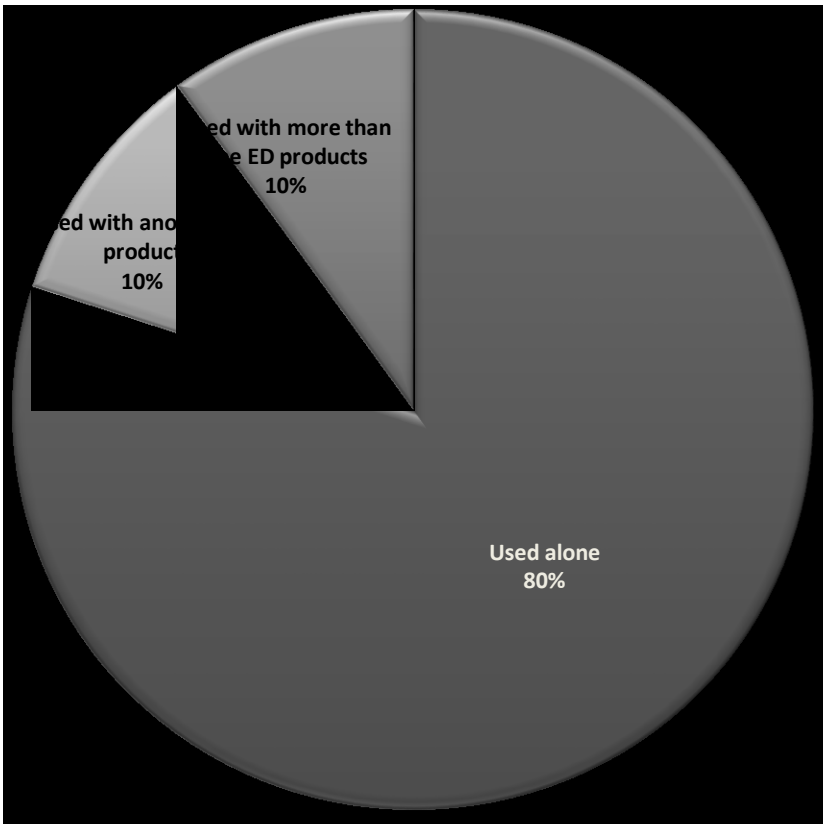
Graph 20. Analysed ED products by the presence of other acknowledged and already classified risks to human health



Graph 21. ED products neither classified nor listed as a risk for human health by their endocrine-disrupting category

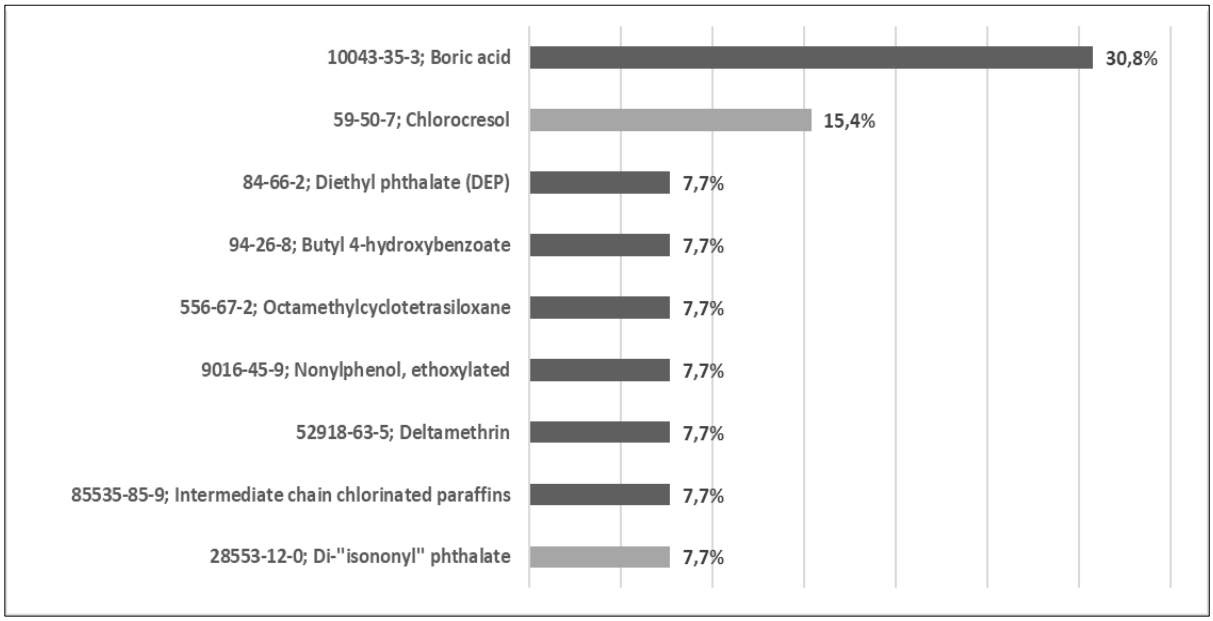


Graph 22. ED products neither classified nor listed as a risk for human health by their use

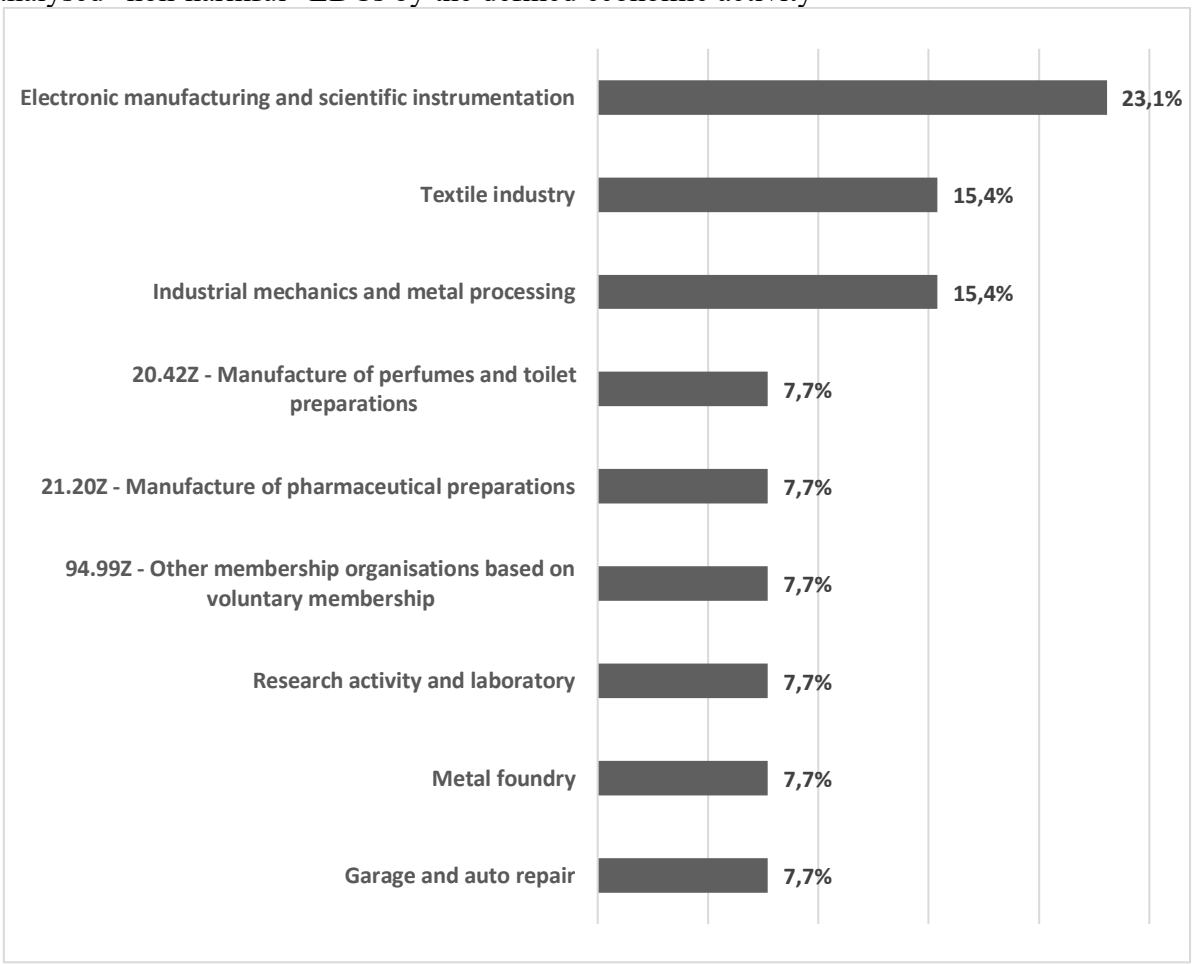


These products contained only nine EDCs in different combinations. These substances are shown in Graph 23 by their classification and CAS Registry Number as relative frequency on the total of EDCs not classified as harmful for human health, expressed as percentage. These EDCs were employed in 10 firms, identified by nine defined economic activities, as expressed in Graph 24.

Graph 23. EDCs category 1 (in dark grey) and category 2 (in light grey) by CAS Registry Number and Name – Relative frequency on the total of EDCs not further classified as harmful for human health

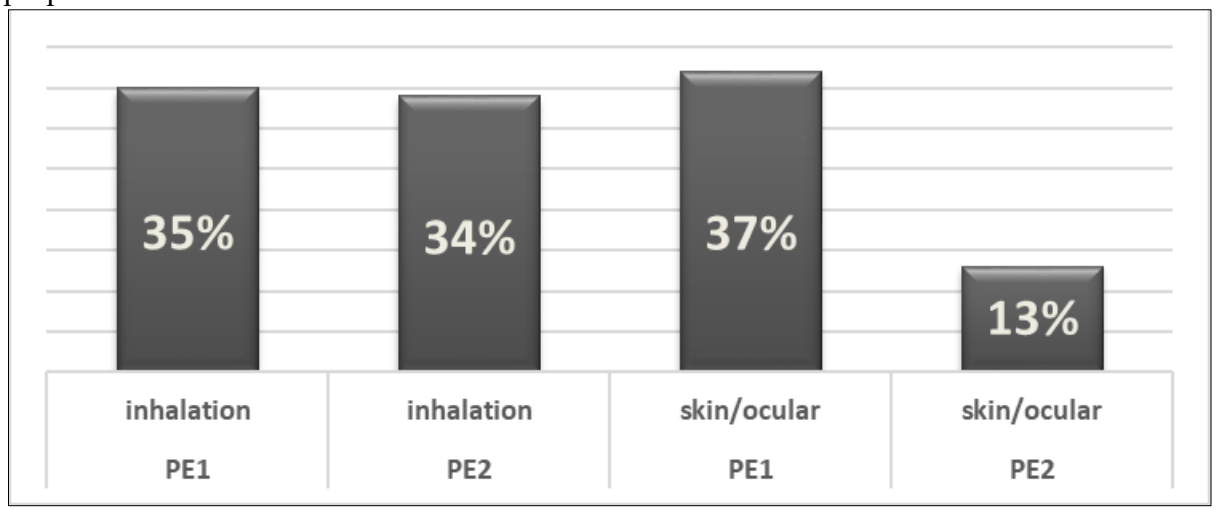


Graph 24. EDCs neither classified nor listed as harmful for human health on the total of the analysed “non-harmful” EDCs by the defined economic activity



Graph 25 shows the relative frequency on the total of the ED products, expressed as percentages, of the change in the calculated theoretical residual risk scores after accounting for ED properties.

Graph 25. Change in the calculated theoretical residual risk scores after accounting for ED properties



DISCUSSION

This study constituted an attempt to provide an information system to deal with the chemical risk assessment in an occupational health service in Lyon, France. This methodology is specifically conceived to consider the EDs and their properties. Structuring the database and automating data extraction allowed us to test and correct the process. It permitted also to verify data import and calculations, as well as the correct creation of tables and charts. A first description of hazards, some considerations on the theoretical residual risk scores and an overview of the actual situation in the analysed enterprises has been done, as a starting point for implementation. This description can be visualized overall or on a particular group of enterprises, products or substances of interest applying the proper filters, as needed.

Some surprising and unexpected observations could be made, as discussed below.

Most of the analysed SDSs dated from 2010 onwards, date on which the CLP Regulation entered into force. Almost 10% of the SDS dated from 2017 onwards, end date of any derogation to the CLP Regulation. It may be considered as an indication of the reliability of the currently collected data. Moreover, every year the number of the transmitted SDSs has

significantly increased, emphasizing a general greater sensitivity in the enterprises about the chemical risk issue.

The occupational health service registered 558 NAF codes, our study focused on 75 NAF codes. This is not a specific indication about the quality of the collected data because many activities may not be concerned by the chemical risk.

Focusing on the most frequently encountered economic activities, we were not surprised, as in 2018 the occupational health service took part in a campaign addressing industrial mechanics and metal processing. Furthermore, the multi-year contract of objectives and means (CPOM), recently launched a prevention program in the garage and auto repair domain. This contract is signed by each regional health agency, the Ministry of Social Affairs and Health and between the ARS and the health establishments in France. Moreover, enterprises in the research-laboratory-scientific sector are historically more sensitive to the chemical risk and health risk issues, and more demanding for counselling for the chemical risk assessment. We can make the general observation that the more a sector is studied, the easier is to encounter ED products. It would be interesting to address specific actions towards companies where 100% of the analysed sample (still numerically limited) was involved in the utilisation of ED products.

Among the enterprises using more than one ED product at a time, almost 15% of the companies employed more than 5 ED products. These activities need to be further investigated and the application of specific strategies to cope with a possible cocktail effect are recommended, as several products easily contain several substances with endocrine-disrupting properties. Their mechanisms of action should be taken into account.

The restricted number of EDCs encountered is somehow reassuring about the bibliographic efforts that are needed to integrate data useful for health surveillance and preventive actions, as few substances are found in many products.

We found ED-pesticide products, the same used in agriculture, in several cleaning activities of buildings; one insecticide even contained two EDCs at a time. Another product, used in a textile industry, contained two EDCs at a time. These kinds of activity should be monitored for possible cocktail effects.

We were extremely surprised when finding that boric acid was used in biocidal products, as since 2010 it is banned for this purpose. Moreover, the analysed SDSs dated in between 2013

and 2019. This finding urges to be very careful when reviewing substances and products actually in use.

Almost 10% of the ED products where not further classified as harmful for human health, possibly leading to not ensuring adequate environmental control or adequate means of protection when performing certain tasks. Most of them were fully recognized and not only suspected for their endocrine-disrupting properties. Few of these products were used in combination with other ED products, possibly forming “unclassified cocktails”. The economic activities concerned were textile industry and electronic manufacturing and scientific instrumentation (e.g. when using chlorinated stainless-steel tapping oils).

Up to more than one third of the theoretical residual risk scores referring to EDs products changed after accounting for their properties, it is a non-negligible fraction, as these products could have been used without the proper protections and be dispersed into the workplace.

A working group has been created including three medical doctors (one expert in toxicology), two chemical engineers, two health prevention advisors, one nurse, a documentary researcher, and a medical secretary. The members of the group had precocious access to the implemented grid, and to the results. They agreed in defining this methodology as very useful for their daily activities.

The actual description has some limits that must be taken into account. The agricultural and construction sectors are not comprised in the description. Because of the agreements of the occupational health service, only industrial and tertiary sector constituted a basis for this study. We focused only on the purchased products, but secondary products, intermediates, waste, mixtures and final products could not be included in the analysis. Methodologies addressing to mixtures and cocktail effects are of general concern and some proposal has been recently advanced (Bornehag et al., 2019), but it is still difficult to transpose this frame in the occupational field. Moreover, we could consider in the calculations only the substances listed in Section 3 of the SDSs. Section 3 may comprise only partial indications on the constituents of a product, as indicated in these ECHA guidelines.(European Chemical Agency, 2020) Critical issues are, for example, the presence of usable identifiers, international classification of substances, impurities, additives or mixtures, presence of cut-offs or concentration limits in regulations. A study of Singh et al. about mining industry concluded that almost 20% of the SDS contained undisclosed information hiding possible hazards and risks for exposed workers.(Singh et al., 2014) We decided to exclude from this study the EDCs indicated in

PRST3 ARA list (Groupe Risques Chimiques- PRST ARA 2016-2020, 2020) in category 3 (absence of scientific basis to consider endocrine-disrupting properties, absence of literature, available evidence is not sufficient), and the subcategories 3a (no literature available on fauna and/or mammals) and 3b (some literature available, but the evidence is not sufficient). This category implies a too weak evidence to be taken into account while evaluating the risks and advising the companies.

The mentioned limitations suggest that our study cannot be conclusive on the extent of the exposure to EDCs in the workplaces. The research project still needs to be further developed. Only a limited number of ED products has apparently been identified, yet sufficient to state that the risk is far from being controlled and that we can see the tip of the iceberg. Besides, this study gives some preliminary useful indications.

Information and decision support systems are increasingly widespread, also in the field of the occupational and environmental medicine, regarding both the pathology and the risk assessment and management.(Ancker et al., 2017; Chen et al., 2012; Yu Semeykin et al., 2019) Our methodology is intended to be part of a broader project that will be settled in the next 4 years to automate and integrate the specific chemical risk assessment and a deeper exposure evaluation of the concerned workers to the already applied procedures. The aim is to create a dynamic cartography of the hazards, to refine the chemical risk assessment with more data about exposure and to complete the process proposing indications for health surveillance and information to enterprises and workers, while developing targeted bibliographic scientific research.

As an in-progress step, the software Quarks Safety, Besançon, France will directly extract data about products and substances in use. The operator will just have to enter the CAS Registry Numbers or the names reported in Section 1 of the SDS, and a map will be added to the grid, allowing geographical visualisation of the density of utilisation of EDs by the number of employees in each area. Moreover, a specific alert about the possible exposure to EDs will appear in the electronic medical records in MEDTRA.

An advantage in the structure of our database is the possibility of charging/recharging or adding specific datasets used as reference, for example the lists of EDCs, allowing an overall updating of results, in line with national and international regulations, and permitting comparisons. Furthermore, by modifying the script or the filters, it is possible to recall data from specific periods in time. Anonymized and updated data could be extracted any time, as import from the

datasets folder has been made automatic. Different type of licence and restrictions guarantee adaptation to privacy policy, confidentiality, impossibility to alter the given grid, security in information system and a specific rendering for the type of user and its necessities.

In the future, when a significant amount of data will be entered, this scheme can be useful in prioritizing further interventions, preventive activities including indications-training-information in the enterprises, in counselling on the products in use and their possible substitution, in developing statistical analyses and bibliographic research. Moreover, this procedure may be useful to the automation in other chemical risk assessment contexts.

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