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Human health problems associated with molecular impact induced by chemical pollutants as endocrine disruptors

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Abstract. Chemicals reaching the human body can affect the endocrine system by inducing hormone agonist or antagonist effects or by altering hormone synthesis reactions. Exposure to the body can be either through ingestion or inhalation (food, drinking water, air) or through direct contact with certain substances in general use (industry, cosmetics, etc.). The human health problems identified and associated with endocrine disrupters are mainly related to dysfunctions of the reproductive system or lipid metabolism. Also, exacerbating exposure can lead to irreversible changes at the molecular level and carcinogenesis. Worryingly, it can have long-term consequences through changes in genetic and epigenetic regulatory pathways. Legislation at the European level seeks to harmonize ways of protecting human health through regulations related to basic research, environmental risk assessment, promotion of sustainable development, protection of vulnerable ecosystems, and continuous information and updating of risk data.

Keywords. endocrine disruptors, human health, genetic/epigenetic mechanisms, European legislation.

1. Chemical pollutants, endocrine disruptors with implications on human health

Chemical substances are a key component of our day to day lives. However, some substances, known as endocrine disruptors, can have negative effects over the organism through a perturbation of the endocrine system. According to the World Health Organization (WHO), endocrine disruptors are defined as "substances or exogenous mixtures that modify the function of the endocrine system and, as a result, cause adverse effects on the health of an intact organism or on its descendants or on a population group" [1].

Human exposure to endocrine disruptors takes place through the consumption of edibles, dust particles, water, through the inhalation of gasses and particles in the air and through the skin. Substances can also be transferred from a pregnant woman to her fetus over the course of its development through the placenta and to the newborn through the mother's milk. Pregnant women and children are the most vulnerable population groups that can suffer direct exposure, but the effects of said exposure may only become obvious later in life [2]. In

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addition, research shows that this can increase susceptibility to non-transmissible genetic diseases [3].

Almost 800 chemical substances are suspected to interfere with endocrine functions. For example, dioxins are a byproduct of the production of herbicides, paper bleaching or in the incineration of waste, while perchlorate is a byproduct of the aerospace, armaments and pharmaceutical industries that is frequently found in drinking water. Other endocrine disruptor substances are perfluoroalkyl and polyfluoroalkyl (PFAS), which has industrial applications as fire extinguishing foams and materials for the manufacture of household items (non-stick pans).

Another category is represented by phytoestrogens that are natural endocrine disruptors from plants, with a similar function to hormones. Part of this group are isoflavones: the genistein and the daidzein found in soy products such as tofu or soy milk, but also in cosmetic products.

Bisphenol A (BPA) and phthalates are of peculiar interest, being investigated on a large scale as obesogenic factors that could interfere with pregnancy physiology and fetal development, thus being a primary cause of pregnancy disorders. BPA is found in numerous common use items such as reusable cutlery and plastic bottles, sports equipment, CDs and DVDs. The epoxy resins containing BPA are utilized as coating layers on the inside of water pipes as well as drink and food cans to extend the period of validity, while also preventing the victuals and drinks from gaining metallic flavors. In addition, BPA is utilized, for example, as a color developer for thermal paper, in order to make the ink visible (https://chemicalsinourlife.echa.europa.eu/ro/bisphenol-a). Fresh meat, fish and vegetables that are wrapped in plastic have a low concentration of BPA and phthalates, while ready-to-eat products and fast food stored in plastic bags and boxes are a major source of exposure.

Other endocrine disruptors can be found in pesticides, metallic materials and in many other day to day products, including plastic containers for edibles, detergents, flame retardants, toys and cosmetic products [4]. All of these are also found in the environment as pollutants in the air, water [5, 6, 7] and later in the human body, or as compounds ingested from some victuals [8, 9]. In certain mechanisms of carcinogenesis an increased risk of breast cancer, as well as of other types of hormone-dependent cancers was observed, under the influence of many different compounds from any given diet, that contribute to the disruption of hormone production, to their metabolism or to action on a cellular level.

Non-chemical compounds with a disruptive effect on the endocrine system also exist; artificial light, radiation, temperature and stress can also influence the endocrine system, thus modulating hormonal functions [10, 11, 12].

Endocrine disruptors, regardless of category, imitate endocrine action through the linking of multiple hormonal receptors of different endocrine glands and act as agonists or antagonists [13].

2. Entry routes and molecular interactions

In general, two interaction paths exist: with receptors binded with the membrane and with nuclear receptors. Endocrine disruptors that link membrane receptors can affect the non-genomic signaling pathways [14], they modify the endocrine functions primarily through the imitation of natural hormones such as estrogens, androgens or thyroid hormones. Furthermore, they can modify hormone metabolism, blocking and antagonizing their interaction with their specific membrane and/or their intracellular receptors [15].

For example, the biological effects of estrogens are mediated through estrogen receptors ERα and ERβ, that are members of a superfamily of nuclear receptors. These receptors act as

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transcription factors, being activated by ligand (direct genomic signaling). The classical mechanism of action involves the binding of estrogen to the receptors in the nucleus, after which the receptors will dimerize and will link to specific elements, known as estrogen response elements (EREs) found in the targeted gene's promoters [16] (Figure 1).

Membrane receptor hormone binding also causes a conformational change in the domain of the binding of the ligand, a change which allows co-activator proteins to induce cellular signaling and the transcription of genes (indirect genomic signaling). That being said, evidence shows explanations for signaling pathways that deviate from this classical model, and now it's widely accepted that hormones are capable of modulating gene expression through a series of distinct mechanisms, through kinases protein (nongenomic signaling).

The pathways of signal transduction can connect the nongenomic actions of estrogen to genomic feedback. The functions of many transcription factors are modulated through the mediated phosphorylation of kinases protein, these transcription factors thus being able to be targeted for the nongenomic actions of estrogens (Figure 1). This type of nongenomic signaling is a distinct mechanism through which receptors can regulate the transcription with the formation of a variety of molecular elements as an alternative answer. This mechanism functions in addition to the genomic actions described previously, which implies protein-protein interactions within the nucleus [17].

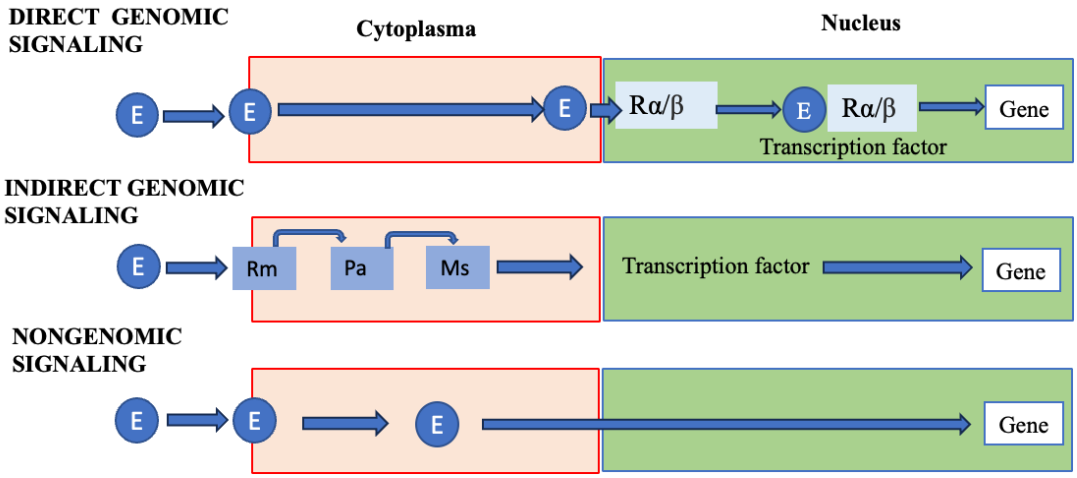

Figure 1 The schematic representation of gene activation pathways by estrogen hormones (E-molecule hormones; Rm - membrane receptor, Pa - the activated protein, Ms - secondary messenger, Rα / β - nuclear receptor)

The estrogenic receptor is involved in many different physiological processes that can be affected by multiple xenobiotics. Some of these compounds can be bisphenols, pesticides, phthalates, phytoestrogens and can influence receptors in conformance with the previous mechanisms or can influence the enzymes that intervene in molecular transformation mechanisms [18, 19, 20].

For example, the phytoestrogens in common foods (isoflavones, flavones and flavonols) such as mycotoxins, pesticides, herbicides, fungicides, surfactants, plasticizers and other substances with applications in the chemical industry can induce changes of aromatase enzymes (CYP 19).

CYP 19 named estrogen synthetase, is a member of the superfamily of the cytochrome P450. The enzyme catalyzes the conversion of the androgens in estrogens (Figure 2).

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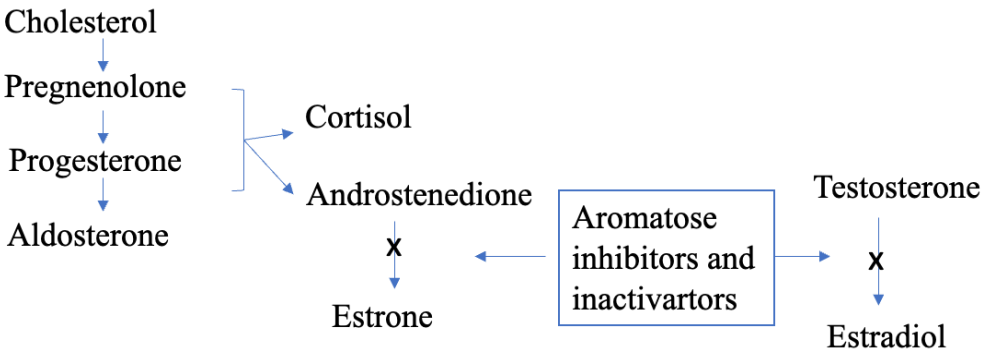

Figure 2 The synthesis mechanism of estrone and estrogen starting from cholesterol and the inhibition of aromatases (estrogen synthetase) [18]

Aromatase is situated in the ovary and placenta and participates in the regulation of reproductive functions. The enzyme is also distributed on a large scale in other tissues or structures, such as the muscles, the liver, hair follicles, the adipose tissue and the brain. This suggests that the estrogen produced by this enzyme has physiological functions not only as a steroid sexual hormone, but also in growth or cellular differentiation [21].

The adipose system is a true endocrine system and as such, is very susceptible to disruption by chemical substances. A group of chemical disruptors, known as obesogens, promote adiposity through the modification of the programing of the development of adipose cells, the increase of energy storage in adipose tissue and interferes with the neuroendocrine control of appetite and fullness (Figure 3).

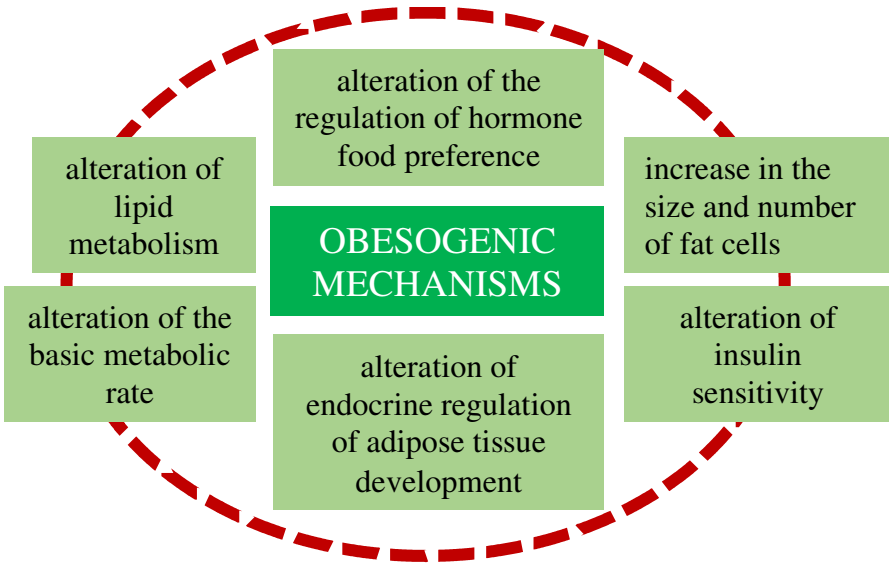

Figure 3 The action pathways of obesogenic substances at a metabolic and cellular level

Amanda S. Janesick and Bruce Blumberg (2016) in their study *Obesogens: an emerging threat to public health* launch a theory according to which the adipogenic stimuli (such as the exposure to chemical obesogenic compounds) received in the perinatal period or during adolescence, permanently increase the number of adipose cells, thus forging a modified metabolic ensemble [22, 23, 24]. If following studies will support this theory, the implications are profound: the increased number of adipose cells at the beginning of life cannot be reduced through diet, physical exercise or even surgery [23].

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Some of the dire consequences of exposure to endocrine disruptors can be transmitted epigenetically to the future generations. This involves modifications in gene expression without mutations to the DNA sequence. The major factors that form the basis of epigenetic inheritance include the expression of uncodified RNAs, modifications of the structure of the chromatin and of the transcriptional activity.

Other modifications of histones (acetylation, phosphorylation, ubiquitination) affect gene expression, though these aren't considered to be hereditary. The most frequent modification of the epigenome that results from the exposure to disruptive endocrine factors is the methylation of DNA. The regular function of DNA methylation is transcriptional, intervening in the regulation of certain specific genes in order to promote and stabilize a certain cellular line. For example, if the osteogenic genes' promoters are methylated in the mesenchymal stem cell population, but those of the adipogenic genes are demethylated, the adipogenic line will be favored due to the increased expression of adipogenic genes.

Although the direct cause-and-effect relation between the specific chemical exposures and the corresponding harm to humans can never be substantially established for certain, potential benefits exist quite evidently in the conciliation of patients, in order to avoid exposure to endocrine disruptors with no perceivable risk. This "principle of precaution" is approved by the American Medical Association and is an eminently sensible strategy to protect public health in comparison as opposed to waiting until the reaching of the legal threshold for the triggering of actions aimed to ban or restrict the use of certain chemical substances [22].

3. Regulations and legislative perspectives

At the European level, an acceleration of the harmonization between the norms of regulation for health research and in the exchange of useful data in the medical field is pursued. The functioning bodies of the EU, as well as the national ones should balance out the best existing practices and to catalyze their adoption in the transnational health research [25].

The list of substances that are suspected to be a part of endocrine disruptors, created by the European Chemicals Agency (ECHA) includes all categories that are subject to evaluations and debated within the group of experts of the ECHA.

In February of 2020, a total of 205 substances have been included in the list of compounds that present reasons for particular concern (the substances of very high concern, SVHC) due to their properties that disrupt the endocrine system and that face an increased regulatory control and of a higher standard of reports. Out of these, 43 substances have been included in the REACH* list, marking the intention to ban their use as soon as appropriate alternatives from a technical and economical point of view are made available.

These pieces of information are further detailed in two separate lists (lists I and II) on the basis of the EU reglementations for REACH (registration, evaluation, authorization and the restricting of the chemical substances; (CE) 1907/2006), BPR (Biological Products Regulation; (EU) 528/2012 and (EU) 2017/2100), PPPR (Plant Protection Products Regulation; (CE) 1107/2009 and (EU) 2018/605) and CR (Cosmetic Regulation; (CE) 1223/2009). The development of list I and II is supported by the competent national authorities from Belgium, Denmark, France, the Netherlands, Spain and Sweden.

A third list, based on the dangers (list III) details the substances that can have endocrine disruptor properties and that were proposed by an individual national authority. As such, these aren't necessarily supported by other member states and it is acknowledged the fact that these substances have never undergone evaluation at the level of the EU Commissions.

These lists are periodically updated and presented for further consultation [26, 27].

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The decline of water quality with a negative impact over human health is one of the major problems of the governments of the world's states, at the dawn of the 3rd millennium. As such, the European Commission has proposed the development of a framework directive regarding water, whose final text was adopted in the October of 2000 and was enforced upon publication in the official journal OJ L327 from December 2000 under the name of *Directive 2000/60/EC of the European Parliament and the Council establishing a framework for Community action in the field of water policy*.

This EU framework directive regarding water represents a cornerstone in the political history of water in Europe. It establishes a common framework for the durable and integrated management of all bodies of water (subterranean waters, interior surface waters, transitional and coastal waters) and demands that all impact factors as well as the economical implications be taken into consideration. The purpose of the directive is the maintenance and the improving of the aquatic environment, while also contributing to the progressive reduction of emission of dangerous substances in water, thus a better water quality will contribute to the ensuring of water supply for the population [28].

In the context of the continuous tracking of pollution sources and of the impact of aquatic micropollutants (parabens, microplastics, pesticides etc.) which later end up through fish and sea foods into the human body, the *Marine Strategy Framework Directive* (2008) aims for an improved ecological state (GES) of the marine waters of the EU as well as protecting the resource base on which economic and social activities related to the marine environment depend.

The directive consecrates in a legislative framework the ecosystemic approach a management of human activities that have an impact over the marine environment, integrating concepts of environmental protection and of durable protection. The new EU strategy regarding biodiversity for 2030 (adopted in 2020) involved the consolidation of protecting the marine ecosystems and their restoration in order to achieve a "good ecological state", including the expansion of protection zones and the creation of strict protection areas for the restoration of habitats and of fish stocks and the fight against practices that lead to the deterioration of water quality.

4. Conclusions

A number of chemical substances that reach the human body become factors with a high health risk through physiological, cellular and molecular modifications. The consequences for such modifications are varied, but the most concerning are those that influence gene regulation and that can be transmitted hereditary.

Since 2020, over 200 substances have been included in the list of compounds that present reasons of concern (the substances of very high concern, SVHC) due to their properties that disrupt the endocrine system and that are subject to a supplementary evaluation, including the finding of alternatives in order to reduce the impact over human health.

Legislative concerns at an European level are directed at the protection of ecosystems and at the limiting of pollutants that affect human health. The politics regarding substances that are suspected to be part of the endocrine disruptors, developed by the *European Chemical Agency* (ECHA) provide in their regularly updated lists substances that undergo evaluation and that are brought up to debate within the group of experts of the ECHA.

References

[1] World Health Organization (WHO) Global Assessment of the State-Of-The-Science of Endocrine Disruptors. [(accessed on 21 April 2020)]; Available online: https://www.who.int/ipcs/publications/new_issues/endocrine_disruptors/
[2] Breton C V., Marsit CJ, Faustman E, et al. Small-magnitude effect sizes in epigenetic end points are important in children's environmental health studies: The children's environmental health and disease prevention research center's epigenetics working group. Environ Health Perspect. 2017;125(4):511-526. doi:10.1289/EHP595
[3] Monneret C. What is an endocrine disruptor? *Comptes Rendus - Biol*. 2017;340(9-10):403-405. doi:10.1016/j.crvi.2017.07.004.
[4] Breton C V., Marsit CJ, Faustman E, et al. Small-magnitude effect sizes in epigenetic end points are important in children's environmental health studies: The children's environmental health and disease prevention research center's epigenetics working group. Environ Health Perspect. 2017;125(4):511-526. doi:10.1289/EHP595
[5] Mousavi SE, Delgado-Saborit JM, Adivi A, Pauwels S, Godderis L. Air pollution and endocrine disruptors induce human microbiome imbalances: A systematic review of recent evidence and possible biological mechanisms. *Sci Total Environ*. 2022;816. doi:10.1016/j.scitotenv.2021.151654.
[6] Zhang L, Ren R, He H, Liu S. Assessing human exposure to phthalate esters in drinking water migrated from various pipe materials and water filter elements during water treatments and storage. *Environ Sci Pollut Res*. 2023;(0123456789). doi:10.1007/s11356-023-25633-1
[7] Bergé A, Cladière M, Gasperi J, Coursimault A, Tassin B, Moilleron R. Meta-analysis of environmental contamination by phthalates. *Environ Sci Pollut Res*. 2013;20(11):8057-8076. doi:10.1007/s11356-013-1982-5
[8] Gálvez-Ontiveros Y, Páez S, Monteagudo C, Rivas A. Endocrine disruptors in food: Impact on gut microbiota and metabolic diseases. *Nutrients*. 2020;12(4):1-40. doi:10.3390/nu12041158
[9] Feng D, Li X, Fan X, et al. Cytotoxicity, endocrine disrupting activity, and chemical analysis of 42 food contact silicone rubber products. *Sci Total Environ*. 2023;872(November 2022):162298. doi:10.1016/j.scitotenv.2023.162298.
[10] Russart, K.L.G.; Nelson, R.J. Light at night as an environmental endocrine disruptor. *Physiol. Behav.* 2018, *190*, 82–89.
[11] Marci, R.; Mallozzi, M.; Di Benedetto, L.; Schimberni, M.; Mossa, S.; Soave, I.; Palomba, S.; Caserta, D. Radiations and female fertility. *Reprod. Biol. Endocrinol.* 2018, *16*, 112.
[12] Palomba, S.; Daolio, J.; Romeo, S.; Battaglia, F.A.; Marci, R.; La Sala, G.B. Lifestyle and fertility: The influence of stress and quality of life on female fertility. Reprod. Biol. Endocrinol. 2018, 16, 113.
[13] Yilmaz, B.; Terekeci, H.; Sandal, S.; Kelestimur, F. Endocrine disrupting chemicals: Exposure, effects on human health, mechanism of action, models for testing and strategies for prevention. *Rev. Endocr. Metab. Disord.* 2020, *21*, 127–147.
[14] Casals-Casas, C.; Desvergne, B. Endocrine Disruptors: From Endocrine to Metabolic Disruption. Annu. Rev. Physiol. 2011, 73, 135–162.
[15] Monneret C. What is an endocrine disruptor? C. R. Biol. 2017;340:403–405. doi: 10.1016/j.crvi.2017.07.004. [PubMed] [CrossRef] [Google Scholar]
[16] Fuentes N, Silveyra P. Estrogen receptor signaling mechanisms. Adv Protein Chem Struct Biol. 2019;116:135-170. doi: 10.1016/bs.apcsb.2019.01.001. Epub 2019 Feb 4. PMID: 31036290; PMCID: PMC6533072.

[17] Linda Björnström, Maria Sjöberg, Mechanisms of Estrogen Receptor Signaling: Convergence of Genomic and Nongenomic Actions on Target Genes, *Molecular Endocrinology*, Volume 19, Issue 4, 1 April 2005, Pages 833–842, https://doi.org/10.1210/me.2004-0486

[18] Stuart-Harris R, Davis A. Optimal adjuvant endocrine therapy for early breast cancer. Womens Health (Lond). 2010 May;6(3):383-98. doi: 10.2217/whe.10.25. PMID: 20426605.

[19] Alva-Gallegos, Raul, Alejandro Carazo, and Přemysl Mladěnka. "Toxicity Overview of Endocrine Disrupting Chemicals Interacting in Vitro with the Oestrogen Receptor." *Environmental Toxicology and Pharmacology* 99 (2023): 104089. https://doi.org/10.1016/j.etap.2023.104089.

[20] Whitehead, Saffron A., and Suman Rice. "Endocrine-Disrupting Chemicals as Modulators of Sex Steroid Synthesis." Best Practice & Research Clinical Endocrinology & Metabolism 20, no. 1 (2006): 45–61. https://doi.org/10.1016/j.beem.2005.09.003.

[21] Harada, N., Ogawa, H., Shozu, M., Yamada, K., Suhara, K., Nishida, E., Takagi, Y. Biochemical and molecular genetic analyses on placental aromatase (P-450-AROM) deficiency. *J. Biol. Chem*. 267: 4781-4785, 1992.

[22] Janesick AS, Blumberg B. Obesogens: An emerging threat to public health. *Am J Obstet Gynecol*. 2016;214(5):559-565. doi:10.1016/j.ajog.2016.01.182

[23] Spalding, K., Arner, E., Westermark, P. *et al.* Dynamics of fat cell turnover in humans. *Nature* **453**, 783–787 (2008). https://doi.org/10.1038/nature06902

[24] Darbre PD. Endocrine Disruptors and Obesity. *Curr Obes Rep*. 2017;6(1):18-27. doi:10.1007/s13679-017-0240-4

[25] Auffray C, Balling R, Barroso I, et al. Making sense of big data in health research: Towards an EU action plan. *Genome Med*. 2016;8(1):1-13. doi:10.1186/s13073-016-0323-y.

[26] https://edlists.org/ed-relevant-legislations

[27] https://echa.europa.eu/da/ed-assessment

[28] Directiva Cadru Apa 2000/60/CE (https://eur-lex.europa.eu/legal-content/RO/TXT/PDF/?uri=CELEX:02000L0060-20141120&from=BG) (accesat martie 2023).