

Hormonal contraception and environmental impact

Piltonen T¹, Gemzell Danielsson K², Petta CA³, Black D⁴

¹ Department of Obstetrics and Gynecology, Research Unit of Clinical Medicine, University of Oulu, Oulu University Hospital, Oulu, Finland

² Department of Women's and Children's Health, Karolinska Institutet, and the Division for Gynecology and Reproductive medicine, Karolinska University Hospital, Stockholm, Sweden

³ Clínica Fertilidade e Vida, Campinas, São Paulo, Brazil

⁴ University of Manitoba, Winnipeg, Manitoba, Canada

Introduction

Environmental pollution has a significant impact on women's health throughout their lives. These compounds enter surface water and treated drinking water, where they act as endocrine-disrupting compounds (EDCs), mimicking or blocking natural hormones and disrupting vital biological processes. Their persistence in aquatic environments not only endangers biodiversity but also poses health risks for women, given the vulnerability of female endocrine systems to environmental pollutants [1]. EDCs contribute to reproductive disorders, pregnancy complications, and adverse prenatal outcomes, with long-term effects on child health and development. Beyond reproduction, they also increase the risks of cancer, cardiovascular and respiratory diseases, and mental health issues in women [2-15]. Given the complex ways in which environmental pollutants, especially EDCs, influence women's health and contribute to environmental injustice, it is vital to assess how common hormonal contraceptives fit into this broader context of exposure effects. In particular, contraceptives containing synthetic estrogens, such as ethinyl estradiol (EE), directly contribute to environmental pollution when excreted and are not sufficiently removed by wastewater treatment systems [16].

Hormonal contraception and its impact on the environment

Estrogens

Estrogens, especially synthetic ones like EE, can act as EDCs in the environment [17,18]. However, their structure, biodegradability, and persistence differ, which in turn influence their ecotoxicological effects. After ingestion, a portion of these hormones is excreted in urine and faeces, entering sewage systems where conventional treatment is often unable to eliminate synthetic estrogens like EE entirely [16]. Nature-based methods, such as algae- and duckweed-based

systems, show promise, especially in resource-limited settings; however, their effectiveness is variable and context-dependent. As a result, EE and other hormone residues frequently persist and enter aquatic ecosystems [19-22].

The presence of synthetic estrogens in the environment is especially concerning due to their strong endocrine-disrupting effects on aquatic life [23]. EE is 100 to 1,000 times more potent than the natural and body-identical estrogen estradiol (E2) in fish. Studies have shown that even extremely low concentrations of EE (as low as 1–5 ng/L) can cause feminisation of male fish, leading to reduced fertility, altered sex ratios, and population declines in some species [24,25]. Feminised male fish have been observed to produce egg yolk proteins, develop ovarian tissue, and show diminished reproductive capabilities [26]. These disruptions threaten aquatic biodiversity and the stability of ecosystems [27]. Beyond aquatic impacts, synthetic hormones can persist in surface water and sediment, where they may undergo limited degradation and continue to exert endocrine-disrupting effects affecting other species over time [17,28,29]. Although the broader implications for human health through exposure to the water and food chain are still being studied, the persistence and mobility of these steroid estrogens raise long-term environmental concerns [30]. This underscores the importance of monitoring not only water but also solid and semi-solid environmental compartments where estrogens may accumulate and persist over time.

The challenge is particularly acute where wastewater treatment infrastructure is limited, resulting in poor removal of synthetic estrogens. Examples of such findings include EE detected in effluents in South Africa, in surface waters near urban centres in South India, in both wastewater and drinking water in Brazil and Mexico, and in irrigation canals in Colombia [29,31-35]. In coastal sediments from Chile and Brazil, EE has also been reported at high concentrations, sometimes exceeding 40–80 ng/g dry weight, highlighting its persistence in marine systems and the impact of inadequate sewage treatment and direct discharges [36,37].



Similar patterns are seen elsewhere: in China, EE accounts for most estrogenic activity in municipal effluents and downstream rivers [38,39]; in Japan, both free and conjugated estrogens persist in treated effluent, particularly in winter when removal efficiency declines [40,41]; and in Australia, EE resists biological treatment and often requires advanced filtration or sludge sorption for effective removal [42,43].

In contrast, recent EU-wide monitoring suggests that estrogen concentrations in European surface waters are now relatively low, typically below 1–2 ng/L, with most samples under the effect-based trigger value of 0.4 ng/L. This likely reflects improvements in wastewater treatment and stricter regulatory oversight, although methodological limitations in detection mean that low-level risks cannot be excluded [44–46].

Collectively, these findings illustrate that the widespread reliance on EE-containing contraceptives, particularly in regions with suboptimal or poorly maintained wastewater infrastructure, can significantly contribute to environmental estrogen loads [47,48]. Combined with broader structural and social determinants, such as limited access to healthcare, poverty, and occupational exposures, this pattern amplifies environmental and health inequities [49]. Women in low-resource settings are more likely to live near industrial emissions, vehicular air pollution, and hazardous waste sites [50]. They are disproportionately represented in occupations with high chemical exposure, including agriculture, domestic cleaning, beauty services, and textile work, where regulatory protections are often weak [51–54]. These exposures can worsen physiological vulnerabilities during sensitive life stages like pregnancy, puberty, and menopause, raising risks of preterm birth, endocrine disorders, and cancer [10]. Children are also particularly vulnerable: even low-level exposure during development can disrupt hormonal, neurological, and reproductive systems, and while direct causal links between environmental EE exposure and developmental harm remain under investigation, such risks are plausible given EE's high estrogenic potency [18,55]. Limited healthcare access may further delay or prevent diagnosis and treatment, while structural inequities such as racism, housing segregation, and gender bias heighten cumulative risks [49,56]. Moreover, many sources of pollution that drive hormone contamination, such as fossil fuel combustion, industrial emissions, and deforestation, also contribute to climate change, creating overlapping and compounding threats to women's and children's health [57–59]. Moreover, beyond reproductive toxicity, EE, as an environmental pollutant, disrupts adipose tissue biology, increases adiposity, and promotes insulin resistance and type 2 diabetes, a risk that persists throughout the lifespan [60]. EDCs like EE complicate diagnoses and treatment of infertility, cancer and thyroid disorders [61].

Table 1. Estrogens as EDC: estradiol (E2), estetrol (E4) and ethinyl estradiol (EE)

	EE	E2	E4
Potency	High (binds strongly to estrogen receptors)	High (binds strongly to estrogen receptors)	Low (weaker binding to estrogen receptors)
Metabolism in humans	Extensive liver metabolism Forms glucuronide and sulphate conjugates Some enterohepatic recycling	Converted to estrone and estriol Conjugated in the liver Undergoes enterohepatic recirculation	Mostly excreted unchanged or as glucuronide/sulphate conjugates Minimal recycling
Excreted forms	EE-glucuronide EE-sulphate Minor unmetabolized EE	- Estradiol, estrone, estriol - Glucuronide and sulphate conjugates	Estetrol-3-glucuronide Estetrol-16-glucuronide
Environmental persistence	High Environmental half-life ~12–17 days in water Resistant to microbial degradation High potential for bioaccumulation Moderate water solubility. But varies by formulation	Moderate Environmental half-life ~2.8–4.5 days in water Degraded by microbes in soil and water Moderate water solubility Moderate to low potential for bioaccumulation	Low Rapid degradation; expected to degrade quickly, although precise half-life is still under study Degraded by microbes in soil and water Moderate water solubility Low potential for bioaccumulation
Impact on aquatic life	Altered gene pathways related to metabolism and organ development Feminizes male fish at ≤5 ng/L	Disrupts reproduction in fish (e.g., intersex, altered vitellogenin levels)	Minimal effects in comparative studies; significantly lower risk in aquatic life
Environmental impact	High Very potent EDC. Highly estrogenic even at nanogram levels. Detected widely in surface waters, sediments, and biota. Not effectively removed in wastewater plants	Moderate High to moderate estrogenic activity. Present but moderately transient. It can disrupt aquatic life at higher levels. Partial removal in wastewater plants (inefficient in conventional plants)	Low Weak estrogenic activity. Present but highly transient. Low impact on aquatic life.

Refer to Sections 3 and 4 for more details and literature on potency, metabolism, and excreted forms. Refer to the text in this section for additional information and references on environmental persistence, its impact on aquatic life, and its overall environmental effects. EDC: endocrine-disrupting compound.

Altogether, disadvantaged communities face the double burden of higher pollution exposure and the environmental load of contraceptive-derived EE, underscoring an urgent need for environmental justice approaches. Equitable solutions must therefore combine improvements in wastewater treatment, stronger occupational protections, expanded access to healthcare, and the promotion of non-EE contraceptive options.

As a result, interest is growing in hormonal contraceptives that contain natural and body-identical estrogens instead of synthetic EE. Natural and body-identical estrogens, such as E2 and E4, degrade more readily in the environment, reducing ecological risk compared to EE [62]. E2, though potent, is rapidly biodegraded in aquatic systems and thereby less likely to cause

endocrine disruption in wildlife [25]. E4, with weak estrogenic activity in non-reproductive tissues and rapid biodegradability, facilitates an environmentally sustainable contraception. In zebrafish, E4 showed a markedly lower ecotoxicological impact than EE: even at doses 1000 times the predicted environmental concentration, it did not affect reproductive output and caused only minimal molecular and histological changes, while EE reduced fecundity, altered gonadal histology, and triggered widespread transcriptomic disruptions. Consistent with this, a metamorphosis study demonstrated that EE delayed development and disrupted nutrient metabolism pathways, whereas E4 produced no adverse morphological effects, even at concentrations 10,000-fold above predicted environmental levels. [63,64].

A mixture of steroid hormones, including EE and progestins, has been shown to additively suppress egg production in fish, illustrating that combined exposures can cause complex biological effects not seen with individual compounds. [65,66]. In this respect, a multigenerational zebrafish study confirmed that E4, when combined with drospirenone (DRSP), produced far fewer adverse effects across three generations than EE/DRSP [67]. The latter impaired sex differentiation, reduced fecundity, skewed sex ratios, and induced severe gonadal and transcriptomic disruptions.

Taken together, current evidence indicates substantially lower ecotoxicological impact of natural and body-identical estrogens (E2, E4) compared to EE. Promoting these alternatives, alongside educational efforts (including unused medication disposal), and upgrading wastewater treatment infrastructure, offers a promising path to align contraceptive access with environmental sustainability [68].

Progestins

Like estrogens, progestins in hormonal contraceptives are excreted into aquatic environments, often resisting removal in wastewater treatment. Similar to estrogens, progestins, as environmental pollutants, affect non-target species, particularly marine species [69].

Their endocrine-disrupting potential includes interference with the hormonal regulation of reproduction and development. In particular, their ability to activate androgen receptors in fish is a significant environmental risk, as this can disrupt sex differentiation, fertility, and population balance [69]. A common challenge in assessing the environmental impact of progestins is

their low environmental concentrations, as well as the lack of sensitive, standardised biomarkers to detect their sublethal effects in aquatic organisms. Unlike estrogens, whose feminising effects are well-characterised, androgenic or anti-androgenic impacts of progestins are more complex and more challenging to quantify, often requiring species-specific assays and long-term exposure studies to detect reproductive or developmental disruption [69,70].

Certain progestins, such as levonorgestrel (LNG), have androgenic properties and seem to be several orders of magnitude more potent in terms of reproductive impairment in fish than non-androgenic progestins [69]. In a study by Zeilinger et al., where LNG was compared with DRSP, LNG was shown to inhibit egg production in fish at concentrations of ≥0.8 ng/L, while requiring ≥6.5 µg/L of DRSP to achieve the same effect [71]. Hua et al. reported completed sex reversal in zebrafish embryos exposed to ≥10 ng/L LNG. This result was still confirmed at 142 days, suggesting that even low levels of LNG can interfere with normal sex development in fish [72]. Zhao et al. found that progesterone (P4) and DRSP can disrupt the internal circadian rhythm in zebrafish. Adult fish exposed to even low, environmentally relevant levels of these hormones (7 ng/L P4 and 99 ng/L DRSP) showed changes in brain gene activity related to circadian rhythms. However, their reproductive organs were less affected. These changes were linked to reduced fertility and appeared in the offspring. The findings suggest that environmental progestins may also affect the daily biological cycles in fish [73]. Although their primary impact is on aquatic ecosystems, potential indirect risks for human health cannot be excluded.

Table 2. Androgenic potencies of progestins [86-89]

Parameter	LNG	ENG	NETA	DRSP	DNG	NOMAC
Androgenic activity	+++	+	++	-	-	-
Anti-androgenic activity	-	-	-	+++	++	++

LNG: levonorgestrel; ENG: etonogestrel; NETA: norethisterone-acetate; DRSP: drospirenone; DNG: dienogest; NOMAC: nomegestrol-acetate

Global policy responses

Growing awareness of the ecological risks posed by synthetic estrogens, notably EE, has led to significant regulatory action worldwide [74] (Table 3). The European Union Water Framework Directive lists EE as a priority substance for environmental monitoring [74,75]. Some progestins (e.g., LNG) have been considered in risk assessments but are not yet designated as priority substances. Germany and Sweden have taken leadership in implementing advanced wastewater treatment to reduce micropollutants, including estrogens, from effluents [76]. In the United States, the Environmental Protection Agency (EPA) supports research on contaminants of emerging concern, including hormones, through its CompTox Chemicals Dashboard [77]. EE is included on the EPA's Contaminant Candidate List 4 (CCL 4), which compiles unregulated contaminants that may warrant regulation under the Safe Drinking Water Act [74,78]. Estrogens (E1, E2, EE) were added to Canada's Priority Substances List (PSL2) in 2001 for risk assessment under the Canadian Environmental Protection Act (CEPA) [79]. Although they were not subsequently added to Schedule 1, their PSL status prompted monitoring and research programs, which have since demonstrated estrogenic effects in Canadian surface waters and whole-lake experiments [18,22,35,68]. Japan's SPEED

98 initiative has expanded national monitoring and control of endocrine disruptors, including synthetic estrogens [80]. Brazil has reinforced effluent control through the CONAMA Resolution 430/2011, which regulates liquid waste discharge [22,74,81]. South Africa has not officially recognised estrogens as emerging pollutants requiring regulatory attention; however, a Water Research Commission framework exists that utilises "trigger values" for estrogenicity, expressed as estrogen equivalents. These are applied in risk assessments for aquatic life and drinking water safety [34,82,83].

Pharmaceutical innovation is shifting towards 'greener' contraceptives that, for instance, contain natural estrogens (e.g., E2, E4). Proposals now advocate including environmental impact data, such as biodegradability, persistence, and ecotoxicity, into the benefit-risk assessment of therapeutic products. Giovagnoni et al. emphasise that when clinical alternatives offer comparable efficacy and safety, environmental profiles should guide therapeutic choices [84]. Further impact could also be achieved by policies promoting contraceptive-induced amenorrhoea through reduced sanitary waste. All this aligns with planetary health principles and the One Health approach, recognising the interdependence between human and environmental well-being [84].



Table 3. Examples of governmental initiatives to reduce environmental pollution by EDCs

Region/Country	Policy/Initiative	Focus Area	Reference
Brazil	CONAMA Resolution 430/2011	Strengthened wastewater regulations and pharmaceutical residue monitoring.	CONAMA Resolution 430/2011 [81]
European Union	EU Water Framework Directive (2013/39/EU)	Monitoring and Reporting Synthetic Estrogens in Surface Water.	European Union [75]
Germany	Five-Point Plan of the Federal Government on Protection against EDCs	Improving regulation; providing information; promoting joint action; advancing knowledge on EDCs; strengthening international cooperation.	BMUKN [85]
Japan	Strategic Program on Environmental EDCs (SPEED 98)	Environmental Impact Research and Endocrine Disruptor Management.	Ministry of Environment [80]
South Africa	National Environmental Management Act (No. 107 of 1998). National Health Act (Act No. 61 of 2003). National Drug Policy for South Africa, 1996	Provide practical tools to monitor, assess, and manage EDCs in water resources, specifically addressing how chemicals in water may interfere with the endocrine system.	WRC [83] Kalebaila and Hlophe-Ginindza [82]
Sweden	Advanced wastewater treatment upgrades targeting pharmaceutical residues	Advanced wastewater treatment upgrades targeting pharmaceutical residues.	Swedish Environmental Protection Agency [76]
United States	National Emerging Contaminant Research Initiative (NECRI)	EPA funding research on contaminants of emerging concern, including hormones.	U.S. Environmental Protection Agency [77]

BMUKN: Federal Ministry for the Environment, Nature Conservation, Nuclear Safety and Consumer Protection, CONAMA: Conselho Nacional do Meio Ambiente, EPA: Environmental Protection Agency, EDC: endocrine-disrupting compound, WRC: Water Research Commission

Conclusion

Eco-friendlier estrogens and progestins, along with enhanced wastewater treatment technologies, represent a promising strategy to balance women's health needs with environmental sustainability. Evidence strongly supports that E4 has a significantly lower ecological footprint compared to EE and better aligns with environmental safety goals. E2, while still environmentally impactful, also poses relatively lower risks than EE. The EU's Water Framework Directive and related regional and local policies are crucial drivers in the monitoring and mitigation of estrogenic pollutants, directly supporting the shift toward more eco-friendly contraceptive options.

Globally, however, EE-containing contraceptives remain the most accessible and widely distributed option, often through public health programs. In low-resource countries, limited wastewater treatment capacity increases the risk of environmental contamination. Promoting alternatives like E2 and E4 and investing in sustainable infrastructure can reduce hormone pollution, advancing both health equity and planetary health.

Current knowledge gaps

Human health consequences of chronic low-level environmental exposure to EE remain underexplored. While the impact of EE on aquatic ecosystems is well-established, evidence on its long-term effects in humans, particularly in children and pregnant women, is still emerging.

Environmental risks from hormone mixtures and progestins are insufficiently characterised. Most research examines individual compounds, yet combined exposures (e.g., EE with progestins like LNG) may have additive or synergistic effects that current risk assessments do not capture.

Global and regional policy efforts are beginning to address hormone pollution, but further integration of environmental data into drug regulation is needed. Initiatives such as the EU Water Framework Directive and green pharmaceutical development are promising, yet environmental impact assessments should become standard in contraceptive benefit-risk evaluations.

Environmental monitoring and data collection are limited in countries with high EE-CHC use and weak wastewater infrastructure. Critical data from regions in Africa, South America, and South Asia are scarce, impeding risk mitigation and sustainable policy development.

Key messages

Environmental pollution harms women's health. Women are especially vulnerable to pollutants like phthalates and bisphenol A, which disrupt hormonal systems and contribute to menstrual irregularities, reproductive disorders, pregnancy complications, and long-term diseases such as cancer and metabolic disorders.

Social and structural inequalities amplify environmental health risks for women in low-resource settings. Disadvantaged populations face greater pollution exposure due to inadequate infrastructure, occupational hazards, and limited healthcare access, exacerbating environmental injustice and health disparities.

EE, the most widely used estrogen in CHCs, is a persistent and potent environmental pollutant. EE enters aquatic systems via human excretion and resists removal in wastewater treatment, leading to reproductive disruption in fish and long-term ecological damage.

Natural estrogens, particularly E4, offer environmentally safer alternatives to EE. E4 is rapidly degradable and minimally toxic to the environment. While E2 is more biodegradable than EE, it still poses moderate risks to aquatic life, making E4 the most environmentally sustainable option for CHCs.

References

- [1] Gore AC, Chappell VA, Fenton SE, et al. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. *Endocr Rev*. 2015;36(6):E1-E150.
- [2] Buck Louis GM, Sundaram R, Schisterman EF, et al. Heavy metals and couple fecundity, the LIFE Study. *Chemosphere*. 2012;87(11):1201-1207.
- [3] Patel S, Zhou C, Rattan S, et al. Effects of Endocrine-Disrupting Chemicals on the Ovary. *Biol Reprod*. 2015;93(1):20.
- [4] Pilsner JR, Hall MN, Liu X, et al. Influence of prenatal arsenic exposure and newborn sex on global methylation of cord blood DNA. *PLoS One*. 2012;7(5):e37147.
- [5] Pedersen M, Giorgis-Allemand L, Bernard C, et al. Ambient air pollution and low birthweight: a European cohort study (ESCAPE). *Lancet Respir Med*. 2013;1(9):695-704.
- [6] Burton GJ, Jauniaux E. Oxidative stress. *Best Pract Res Clin Obstet Gynaecol*. 2011;25(3):287-299.
- [7] Vrijheid M, Martinez D, Manzanares S, et al. Ambient air pollution and risk of congenital anomalies: a systematic review and meta-analysis. *Environ Health Perspect*. 2011;119(5):598-606.
- [8] Kalkbrenner AE, Daniels JL, Chen JC, et al. Perinatal exposure to hazardous air pollutants and autism spectrum disorders at age 8. *Epidemiology*. 2010;21(5):631-641.
- [9] Bellinger DC. A strategy for comparing the contributions of environmental chemicals and other risk factors to neurodevelopment of children. *Environ Health Perspect*. 2012;120(4):501-507.
- [10] Woodruff TJ, Axelrad DA, Kyle AD, et al. Trends in environmentally related childhood illnesses. *Pediatrics*. 2004;113(4 Suppl):1133-1140.
- [11] Brody JG, Rudel RA. Environmental pollutants and breast cancer. *Environ Health Perspect*. 2003;111(8):1007-1019.
- [12] Fonken LK, Xu X, Weil ZM, et al. Air pollution impairs cognition, provokes depressive-like behaviors and alters hippocampal cytokine expression and morphology. *Mol Psychiatry*. 2011;16(10):987-995, 973.
- [13] Miller KA, Siscovick DS, Sheppard L, et al. Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med*. 2007;356(5):447-458.
- [14] Salam MT, Millstein J, Li YF, et al. Birth outcomes and prenatal exposure to ozone, carbon monoxide, and particulate matter: results from the Children's Health Study. *Environ Health Perspect*. 2005;113(11):1638-1644.
- [15] Rachon D. Endocrine disrupting chemicals (EDCs) and female cancer: Informing the patients. *Rev Endocr Metab Disord*. 2015;16(4):359-364.
- [16] Silva CP, Otero M, Esteves V. Processes for the elimination of estrogenic steroid hormones from water: a review. *Environ Pollut*. 2012;165:38-58.
- [17] Adeel M, Song X, Wang Y, et al. Environmental impact of estrogens on human, animal and plant life: A critical review. *Environ Int*. 2017;99:107-119.
- [18] Kidd KA, Blanchfield PJ, Mills KH, et al. Collapse of a fish population after exposure to a synthetic estrogen. *Proc Natl Acad Sci U S A*. 2007;104(21):8897-8901.
- [19] Snyder SA, Westerhoff P, Yoon Y, & Sedlak D. L. . Pharmaceuticals, personal care products, and endocrine disruptors in water: Implications for the water industry. *Environmental Engineering Science*. 2003;20(5):449-469.
- [20] Shi W, Wang L, Rousseau DP, et al. Removal of estrone, 17alpha-ethinylestradiol, and 17beta-estradiol in algae and duckweed-based wastewater treatment systems. *Environ Sci Pollut Res Int*. 2010;17(4):824-833.
- [21] Liyanage S, Lay M, Glasgow G, et al. Nature based solutions for removal of steroid estrogens in wastewater. *Front Microbiol*. 2024;15:1437795.
- [22] Ternes TA, Stumpf M, Mueller J, et al. Behavior and occurrence of estrogens in municipal sewage treatment plants--I. Investigations in Germany, Canada and Brazil. *Sci Total Environ*. 1999;225(1-2):81-90.
- [23] Jobling S, Tyler CR. Endocrine disruption, parasites and pollutants in wild freshwater fish. *Parasitology*. 2003;126 Suppl:S103-108.
- [24] Vajda AM, Barber LB, Gray JL, et al. Reproductive disruption in fish downstream from an estrogenic wastewater effluent. *Environ Sci Technol*. 2008;42(9):3407-3414.
- [25] Lerdsuwanrut N, Zamani R, Akrami M. Environmental and Human Health Risks of Estrogenic Compounds: A Critical Review of Sustainable Management Practices. *Sustainability*. 2025;17(2).
- [26] Lange A, Paull GC, Coe TS, et al. Sexual reprogramming and estrogenic sensitization in wild fish exposed to ethinylestradiol. *Environ Sci Technol*. 2009;43(4):1219-1225.
- [27] Tyler CR, Jobling S, Sumpter JP. Endocrine disruption in wildlife: a critical review of the evidence. *Crit Rev Toxicol*. 1998;28(4):319-361.

- [28] Johnson AC, Belfroid A, Di Corcia AD. Estimating steroid oestrogen inputs into activated sludge treatment works and observations on their removal from the effluent. *Sci Total Environ.* 2000;256(2-3):163-173.
- [29] Odinga ES, Zhou X, Mbaio EO, et al. Distribution, ecological fate, and risks of steroid estrogens in environmental matrices. *Chemosphere.* 2022;308(Pt 2):136370.
- [30] Baronti C, Curini R, D'Ascenzo G, et al. Monitoring Natural and Synthetic Estrogens at Activated Sludge Sewage Treatment Plants and in a Receiving River Water. *Environmental Science & Technology - ENVIRON SCI TECHNOL.* 2000;34.
- [31] Ferreira AP, Rocha JC, Oliveira DG, et al. Detection of hormones in surface and drinking water in Brazil by LC-ESI-MS/MS and ecotoxicological assessment with *Daphnia magna*. *Environmental Monitoring and Assessment.* 2015;187(1):1-12.
- [32] Pessoa GP, Rodgher S, Zaiat M. Occurrence and removal of estrogens in Brazilian wastewater treatment plants. *Environmental Science and Pollution Research.* 2014;21(14):8565-8575.
- [33] Sodré FF, Montagner CC, Jardim WF. Occurrence of natural and synthetic hormones in Brazilian surface waters. *Journal of the Brazilian Chemical Society.* 2007;18(4):816-821.
- [34] Manickum T, John W. Occurrence, fate and environmental risk assessment of endocrine disrupting compounds at the wastewater treatment works in Pietermaritzburg (South Africa). *Sci Total Environ.* 2014;468-469:584-597.
- [35] Aleán-Florez JD, Márquez-Mendez DA, Burgos-Núñez SM, Enamorado-Montes GH, Marrugo-Negrete JL. Presencia de contaminantes emergentes (CE) en los distritos de riego del departamento de Córdoba, Colombia. *Orinoquia.* 2021:57-63.
- [36] Pusceddu FH, Sugauara LE, de Marchi MR, et al. Estrogen levels in surface sediments from a multi-impacted Brazilian estuarine system. *Mar Pollut Bull.* 2019;142:576-580.
- [37] Bertin A, Inostroza PA, Quinones RA. Estrogen pollution in a highly productive ecosystem off central-south Chile. *Mar Pollut Bull.* 2011;62(7):1530-1537.
- [38] Lei B, Qiao M, Liu Y, et al. Occurrence, risk assessment and source apportionment of estrogens in the Beijing-Tianjin-Hebei region, China. *Ecotoxicology and Environmental Safety.* 2020;189:109982-109982.
- [39] Zhou H, Liu X, Zhang Y. Fate of steroid estrogens in a municipal wastewater treatment plant in Beijing, China. *Environmental Monitoring and Assessment.* 2012;184(1):405-415-405-415.
- [40] Komori K, Suzuki Y, Minamiyama M, et al. Occurrence of selected pharmaceuticals and hormones in untreated wastewater and rivers in Japan. *Water Science and Technology.* 2004;50(5):145-152-145-152.
- [41] Kumar V, Johnson AC, Nakada N, et al. The application of an indicator approach to assess the risk of estrogenic discharges in the aquatic environment. *Environmental Monitoring and Assessment.* 2014;186:7335-7352-7335-7352.
- [42] Allinson M, Shiraishi F, Salzman SA, et al. In vitro and immunological assessment of the estrogenic activity and concentrations of 17beta-estradiol, estrone, and ethinyl estradiol in treated effluent from 45 wastewater treatment plants in Victoria, Australia. *Arch Environ Contam Toxicol.* 2010;58(3):576-586.
- [43] Braga O, Smythe GA, Schafer AI, et al. Fate of steroid estrogens in Australian inland and coastal wastewater treatment plants. *Environ Sci Technol.* 2005;39(9):3351-3358.
- [44] Simon E, Duffek A, Stahl C, et al. Biological effect and chemical monitoring of Watch List substances in European surface waters: Steroidal estrogens and diclofenac – Effect-based methods for monitoring frameworks. *Environment International.* 2022;159:107033.
- [45] Profita M, Fabbri E, Vasumini I, et al. Endocrine disrupting chemicals in Italian drinking water systems: Insights from a three-year investigation combining chemical and effect-based tools. *Heliyon.* 2024;10(5):e26785.
- [46] Cargouet M, Perdiz D, Mouatassim-Souali A, et al. Assessment of river contamination by estrogenic compounds in Paris area (France). *Sci Total Environ.* 2004;324(1-3):55-66.
- [47] Teal S, Edelman A. Contraception Selection, Effectiveness, and Adverse Effects: A Review. *JAMA.* 2021;326(24):2507-2518.
- [48] United Nations. World Family Planning 2022: Meeting the changing needs for family planning: Contraceptive use by age and method: Department of Economic and Social Affairs, Population Division; [Accessed 05 September 2025]. Available from: https://www.un.org/development/desa/pd/sites/www.un.org/development/desa/pd/files/files/documents/2023/Feb/undesapd_2022_world-family-planning.pdf
- [49] Morello-Frosch R, Shenassa ED. The environmental “risky” and social inequality: implications for explaining maternal and child health disparities. *Environ Health Perspect.* 2006;114(8):1150-1153.
- [50] Brender JD, Maantay JA, Chakraborty J. Residential proximity to environmental hazards and adverse health outcomes. *Am J Public Health.* 2011;101 Suppl 1(Suppl 1):S37-52.

- [51] Atinkut Asmare B, Freyer B, Bingen J. Women in agriculture: pathways of pesticide exposure, potential health risks and vulnerability in sub-Saharan Africa. *Environmental Sciences Europe*. 2022;34(1):89.
- [52] Quach T, Gunier R, Tran A, et al. Characterizing workplace exposures in Vietnamese women working in California nail salons. *Am J Public Health*. 2011;101 Suppl 1(Suppl 1):S271-276.
- [53] Padula AM, Monk C, Brennan PA, et al. A review of maternal prenatal exposures to environmental chemicals and psychosocial stressors-implications for research on perinatal outcomes in the ECHO program. *J Perinatol*. 2020;40(1):10-24.
- [54] Fouad M. Females and occupational exposures: Review article. *Egyptian Journal of Occupational Medicine*. 2024;48(3):15-28.
- [55] Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, et al. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *Endocr Rev*. 2009;30(4):293-342.
- [56] Perry MJ, Arrington S, Freisthler MS, et al. Pervasive structural racism in environmental epidemiology. *Environ Health*. 2021;20(1):119.
- [57] World Economic Forum. Climate change impacts women more. We must legislate to protect their health [Accessed 4 September 2025]. Available from: <https://www.weforum.org/stories/2024/01/women-health-climate-change/>
- [58] Landrigan PJ, Fuller R, Acosta NJR, et al. The Lancet Commission on pollution and health. *Lancet*. 2018;391(10119):462-512.
- [59] United Nations Environment Programme. Healthy Environment, Healthy People 2016 [Accessed 04 September 2025]. Available from: <https://wedocs.unep.org/bitstream/handle/20.500.11822/17602/K1602727%20INF%205%20Eng.pdf?sequence=1&isAllowed=y>
- [60] Bardhi O, Dubey P, Palmer BF, et al. Oestrogens, adipose tissues and environmental exposures influence obesity and diabetes across the lifecycle. *Proc Nutr Soc*. 2024;83(4):263-270.
- [61] Genco M, Anderson-Shaw L, Sargis RM. Unwitting Accomplices: Endocrine Disruptors Confounding Clinical Care. *J Clin Endocrinol Metab*. 2020;105(10):e3822-3827.
- [62] Leusch FD, Chapman HF, van den Heuvel MR, et al. Bioassay-derived androgenic and estrogenic activity in municipal sewage in Australia and New Zealand. *Ecotoxicol Environ Saf*. 2006;65(3):403-411.
- [63] Baekelandt S, Leroux N, Burattin L, et al. Estetrol has a lower impact than 17alpha-ethinylestradiol on the reproductive capacity of zebrafish (*Danio rerio*). *Aquat Toxicol*. 2023;259:106505.
- [64] Leroux N, Baekelandt S, Robert JB, et al. Assessment of the effects of estetrol and 17alpha-ethinylestradiol on zebrafish (*Danio rerio*) metamorphosis: a morphological and transcriptomic approach. *Environ Pollut*. 2025;376:126423.
- [65] Rossier NM, Chew G, Zhang K, et al. Activity of binary mixtures of drospirenone with progesterone and 17alpha-ethinylestradiol in vitro and in vivo. *Aquat Toxicol*. 2016;174:109-122.
- [66] Thrupp TJ, Runnalls TJ, Scholze M, et al. The consequences of exposure to mixtures of chemicals: Something from 'nothing' and 'a lot from a little' when fish are exposed to steroid hormones. *Sci Total Environ*. 2018;619-620:1482-1492.
- [67] Baekelandt S, Leroux N, Lambert J, et al. Evaluating the toxicity of estetrol, 17alpha-ethinylestradiol, and their combination with drospirenone on zebrafish larvae: A behavioural and proteomic study. *Aquat Toxicol*. 2024;271:106941.
- [68] Kidd KA, Paterson MJ, Rennie MD, et al. Direct and indirect responses of a freshwater food web to a potent synthetic oestrogen. *Philos Trans R Soc Lond B Biol Sci*. 2014;369(1656).
- [69] Rocha MJ, Rocha E. Synthetic Progestins in Waste and Surface Waters: Concentrations, Impacts and Ecological Risk. *Toxics*. 2022;10(4).
- [70] Stavreva DA, Varticovski L, Raziuddin R, et al. Novel biosensor for high-throughput detection of progesterone receptor-interacting endocrine disruptors. *Sci Rep*. 2024;14(1):5567.
- [71] Zeilinger J, Steger-Hartmann T, Maser E, et al. Effects of synthetic gestagens on fish reproduction. *Environ Toxicol Chem*. 2009;28(12):2663-2670.
- [72] Hua J, Han J, Guo Y, et al. The progestin levonorgestrel affects sex differentiation in zebrafish at environmentally relevant concentrations. *Aquat Toxicol*. 2015;166:1-9.
- [73] Zhao Y, Castiglioni S, Fent K. Environmental Progestins Progesterone and Drospirenone Alter the Circadian Rhythm Network in Zebrafish (*Danio rerio*). *Environ Sci Technol*. 2015;49(16):10155-10164.
- [74] da Cunha DL, da Silva SM, Bila DM, et al. Regulation of the synthetic estrogen 17alpha-ethinylestradiol in water bodies in Europe, the United States, and Brazil. *Cad Saude Publica*. 2016;32(3):e00056715.
- [75] European Union. Directive 2013/39/EU of the European Parliament and of the Council of 12 August 2013 amending Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy Text with EEA relevance. Available from: <https://eur-lex.europa.eu/eli/dir/2013/39/oj>

- [76] Swedish Environmental Protection Agency. Advanced wastewater treatment for separation and removal of pharmaceutical residues and other hazardous substances - report 6803 April 2017 [Accessed 05 September 2025].
- [77] U.S. Environmental Protection Agency. Drinking Water Contaminant Candidate List (CCL) and Regulatory Determination [Accessed 06 September 2025]. Available from: <https://www.epa.gov/ccl>
- [78] U.S. Environmental Protection Agency. Contaminant Candidate List 4 - CCL 4 [Accessed 10 September 2025]. Available from: <https://www.epa.gov/ccl/contaminant-candidate-list-4-ccl-4-0>
- [79] Environment and Climate Change Canada. Canadian Environmental Protection Act: priority substances list: Government of Canada; [Accessed 06 September 2025]. Available from: <https://www.canada.ca/en/environment-climate-change/services/canadian-environmental-protection-act-registry/substances-list/priority-list.html>
- [80] Japan Environment Agency. Strategic Programs on Environmental Endocrine Disruptors '98 (SPEED '98) [Accessed 05 September 2025]. Available from: <https://www.env.go.jp/en/chemi/ed/speed98/sp98.html>
- [81] Conselho Nacional do Meio Ambiente. Conselho Nacional do Meio Ambiente. Resolução CONAMA no 430, de 13 de maio de 2011. Dispõe sobre as condições e padrões de lançamento de efluentes, complementa e altera a Resolução no 357, de 17 de março de 2005, do Conselho Nacional do Meio Ambiente-CONAMA. Diário Oficial da União 2011; 16 ma [Accessed 05 September 2025]. Available from: <https://www.legisweb.com.br/legislacao/?id=114770>
- [82] Kalebaila N, Hlophe-Ginindza S. Evolution of Water Research in South Africa from Legacy Pollutants to Contaminants of Emerging Concern: Successes and Opportunities. In: Zandaryaa S, Fares A, Eckstein G, editors. Emerging Pollutants: Protecting Water Quality for the Health of People and the Environment. Cham: Springer Nature Switzerland; 2025. p. 131-158.
- [83] Heath R MO, Masoabi D. Introduction to the management of EDCs Volume I: Water Research Commission; [Accessed 6 September 2025]. Available from: <https://www.wrc.org.za/wp-content/uploads/mdocs/TT%20560-13.pdf>
- [84] Giovagnoni E, Mattoli L, Cossu A, et al. Integrating environmental effects in the benefit-risk assessment of therapeutic products: a proposal and example for sustainable health and healthcare [Review]. *Frontiers in Drug Safety and Regulation*. 2025;Volume 4 - 2024.
- [85] The Federal Ministry for the Environment CA, Nature Conservation and Nuclear Safety. Five-point plan of the federal government on protection against endocrine disruptors [Accessed 05 September 2025]. Available from: <https://www.bundesumweltministerium.de/en/download/five-point-plan-of-the-federal-government-on-protection-against-endocrine-disruptors>
- [86] Sitruk-Ware R, Nath A. The use of newer progestins for contraception. *Contraception*. 2010;82(5):410-417.
- [87] Stanczyk FZ. All progestins are not created equal. *Steroids*. 2003;68(10-13):879-890.
- [88] Schindler AE, Campagnoli C, Druckmann R, et al. Classification and pharmacology of progestins. *Maturitas*. 2003;46 Suppl 1:S7-S16.
- [89] Oelkers W. Drospirenone, a progestogen with antimineralocorticoid properties: a short review. *Mol Cell Endocrinol*. 2004;217(1-2):255-261.