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REVIEW ARTICLE

Bone Disruption and Environmental Pollutants

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Abstract: ***Background*:** Endocrine Disrupting Chemicals (EDCs) are ubiquitous and may significantly contribute to environmental pollution and contamination in humans and wildlife. Ecological pollutants could interfere with bone homeostasis through different mechanisms, including hormonal imbalance, direct osteoblast toxicity, and enhancement of osteoclasts activity, leading to either osteopenia or osteoporosis. Among these chemicals, bisphenols, dioxins, polycyclic aromatic hydrocarbons, polychlorobiphenyls, poly- and perfluoroalkyl, phthalates, parabens, organotins, and cadmium may play a role in the bone disruption.

***Methods*:** Authors searched PubMed/MEDLINE, ISI-web of knowledge, and Google scholar databases for medical subject headings terms and free-text words related to the classes mentioned above of chemicals and bone metabolism and remodeling for better clarifying and understanding the main mechanisms of bone disruption.

***Results*:** Several EDCs act as xeno-estrogens. Considering that estrogens play a significant role in regulating bone remodeling, most of these chemicals generate hormonal imbalance with possible detrimental consequences on bone tissue structure and its mechanical and non-mechanical properties.

***Discussion*:** Much evidence about bone disruptors was obtained from *in vitro* studies or animal models with equivocal results. Besides, a few data have been acquired from humans, and most of these data focused on the impact of EDCs on bone mineral density without considering their influence on long-term fracture risk. Moreover, humans may be exposed to a mixture of EDCs, and the final effect on bone metabolism might be attributable to either synergistic or antagonist effects. Age of first exposure, cumulative exposure over time, and the usually observed non-monotonic dose-response curve for EDCs should be considered as other essential variables influencing bone metabolism's final effect.

***Conclusion*:** Given these variables, observational studies are needed to analyze this issue for ecological purposes better and preserve bone health.

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1. INTRODUCTION

The concept of endocrine-disrupting was addressed for the first time in 1991 during the Wingspread Congress [1]. The US Environmental Protection Agency (EPA) defined an endocrine-disrupting chemical as "an exogenous agent interfering with the synthesis, release, clearance, transport, metabolism, or elimination of natural hormones that are responsible for the homeostasis, reproduction, and developmental process [2]. EDCs are a broad class of synthetic compounds primarily employed to manufacture different products for over 70 years. These chemicals mostly diffuse into the environment, thus contaminating the ecosystems. These chemicals may contact the human body by skin, airway, and intestine [3], whereas placental nourishment and breastfeed-

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ing are responsible for both fetal and neonatal exposure to EDCs [4].

EDCs display estrogenic, androgenic, and antiandrogenic actions and may act as thyroid disruptors [2]. EDCs work as selected modulators of estrogen, androgen, and thyroid receptors and peroxisome proliferator-activated receptor gamma and retinoid receptors [4]. Besides the direct action on nuclear receptors (NRs), some EDCs can activate the aryl hydrocarbon receptor (AhR), which is involved in the metabolism of many xenobiotic substances [5]. AhR was first characterized due to its affinity binding for tetrachlorodibenzo-dioxin and regulating insulin secretion during pregnancy and myocardial development in embryo mice [6]. Dioxins can activate NRs signaling and induce metabolic dysfunctions leading to hyperglycemia, adipogenesis, and adipose tissue dysfunction [7]. Moreover, EDCs can negatively affect sexual development, growth, stress response, insulin production, gender behavior, reproduction, and even fetal development [8].

Bone metabolism results from a complex dynamic equilibrium among several types of resident cells, including osteocytes, osteoclasts, and osteoblasts, which finely regulate bone deposition and reabsorption. A wide range of hormones influences bone metabolism, such as parathyroid hormone, prostaglandins, thyroid hormones, and sex steroid hormones [9-11]. Given this consideration, EDCs may consequently disrupt bone metabolism, leading to bone mineral density impairment, loss in plasticity, strength, hardness, and bending force [12].

Given these considerations, this narrative review aims to report the current status of knowledge about the direct and indirect effects of EDCs on bone health. For this purpose, the authors searched PubMed/MEDLINE, ISI-web of knowledge, and Google scholar databases. Medical subject headings terms and free-text word related to "endocrine disruptors," "endocrine-disrupting chemicals," "bone structure," "bone turnover," "bone metabolism," "Bisphenol A," BPA, Cadmium, Dioxin, "Polycyclic Aromatic Hydrocarbons," Polychlorobiphenyls, Polyfluoroalkyls, Perfluoroalkyls, Phthalates, Parabens, Organotins were used in various combinations to find relevant information. We extended the search to reference lists of original articles and reviews written in English.

1.1. Bisphenol A

Bisphenols are organic compounds with two hydroxyphenyl groups and are employed mainly as plasticizers in plastic products, household appliances, electronic devices, toys, kitchen tools, tubes, plastic bottles, and food packaging [13-15]. Bisphenol A (BPA) may enter in contact with the human body through oral and bronchial mucosae, and it is usually conveyed by environmental pollution, food chain, and close dermal contact [16-19].

According to the Registration, Evaluation, Authorization, and Restriction of Chemicals legislation, BPA has been classified as a disruptor, and since 2006 a tolerated daily dose exposure to BPA has been set at 0.05 mg/Kg of body weight (bw) (https://www.efsa.europa.eu/en/topics/-topic/bisphenol). Over time, further limitations have been applied, especially for reducing infants' levels of exposure. Thus, a novel tolerated daily dose has been restricted to 0.4 mcg/Kg of bw per day since 2014 (https://www.efsa.europa.eu/en/topics/topic/bisphenol). BPA may affect bone homeostasis even if the underlying mechanisms of bisphenol-related bone disruption remain unclear [20]. BPA is chemically similar to 17β-Estradiol (E2) and can bind both the α and β receptors of E2; however, BPA displays a receptor affinity approximately 2,000 - 10,000 times lower than E2 [21, 22]. *In vitro*, BPA seems to inhibit bone turnover by suppressing both the proliferation and maturation of osteoblasts and promoting the apoptosis of osteoblasts and osteoclasts, thus remarkably reducing the bone turnover [23, 24]. BPA suppresses bone turnover by acting on the receptor activator of nuclear kappa B (RANK) - RANK ligand system and Wnt/β-catenin signaling pathways, thus reducing the levels of bone morphogenic protein-2 and alkaline phosphatase expression.

Moreover, individuals exposed to BPA have lower serum testosterone (T) levels than controls, suggesting that BPA may act as a direct antiandrogen, too [25]. Additionally, BPA increases aromatase enzyme levels and activity in men [26, 27]. Moreover, BPA stimulates the release of some cytokines such as tumor necrosis factor-α and interleukin-6, modulates inflammation and bone catabolism, deteriorates bone quality, thus triggering degenerative bone processes [28, 29]. Given these results, it is expected that BPA can affect skeletal development and determine loss of bone mass and osteoporosis (OP) *in vivo*, although the current state of the art does not provide conclusive results [30, 31]. Kim *et al*. observed a slow ossification of the fetal rat skeleton after BPA administration to mated females. The main findings were represented by a reduction in the number of ossification centers, enlarged fontanel, malformations of ribs, pelvis, and other different skeletal districts [32].

Conversely, in another study, a diet rich in BPA completely reversed the femoral trabecular bone mass loss in mice lacking the aromatase gene (Cyp19) [33]. BPA displayed estrogenic activity without any evident adverse effects, and further findings suggested the higher the levels of exposure to BPA, the higher the increase in femoral bone mass density according to a dose-dependent manner [33]. In a mice model, BPA exposure through the gestational period and during a few postnatal days may increase the femoral length in both male and female pups with a few significant alterations in bone strength [34]. Similarly, low-dose exposure to xeno-estrogens increases the femoral length and tensile strength in adult mice [20]. In ovariectomized female rats, BPA determines bone mass loss and reduces both the mineral content and bone resistance; conversely, in prenatal male rodents, BPA exhibits the opposite effects [13], hence leading to suppose a possible gender dimorphism in bone response to BPA.

Bone response to BPA seems to be diphasic [35, 36] (inverted - U shaped); thus, low-dose exposure to BPA may promote bone apposition, while a higher exposure to BPA may deteriorate bone homeostasis with potentially harmful consequences. Although evidence suggested that BPA may affect skeletal homeostasis *in vitro* and animal models, only a few studies evaluate BPA effects on bone metabolism in humans. The first study was conducted in 51 Korean postmenopausal women (mean age 64.5 years) who assumed an active treatment for OP. In these patients, serum BPA levels did not show a statistically significant correlation with lumbar and femoral bone mineral density [BMD], body mass index (BMI), serum concentrations of 25-Hydroxy Vitamin D, and sera markers of bone turnover. On the other hand, the study's main limitation was related to a concomitant effect of current active treatment for OP, which could have possibly attenuated detrimental effects of BPA on bone metabolism [37]. Another study was carried out in 246 Chinese women (mean age 35 ± 0.6 years) in pre-, and postmenopausal phases. Urinary BPA concentrations were positively correlated with body fat mass and leptin levels, while the correlation with BMD [lumbar and femoral], bone turnover markers, and serum E2 were not statistically significant after the adjustment for BMI [38]. Premenopausal women were healthy, had a normal BMI (21.2 ± 0.2 Kg/m^2), and a regular menstrual cycle, thus being at shallow risk of OP even if a lower body mass strongly predicted a lower BMD [38].

BPA could also affect calcium-phosphorus metabolism. In one study, pregnant mice exposed to high doses of BPA exhibited a significant reduction in calcium plasma levels by reducing the intestine and renal absorption [39, 40]. Vitku *et al*. [41] observed a positive association between plasmatic BPA levels and plasmatic calcium concentration in humans, even if any relationship between circulating levels of BPA and BMD was conclusively found.

Despite some controversy, available evidence from cross-sectional studies revealed a negligible relationship between plasmatic BPA levels and BMD. However, more comprehensive longitudinal studies are needed to clarify the relationship between BPA and bone health in humans [42], especially concerning fracture risk assessment.

1.2. Dioxin, Polycyclic Aromatic Hydrocarbons, Polychlorobiphenyls, Perfluoroalkyl substances, and Phthalates

Dioxin and dioxin-like compounds are widespread toxic pollutants, causing metabolic disturbances, cancer, reproductive and developmental change in experimental conditions [43]. The predominant exposure to dioxins is represented by oral ingestion of contaminated food [44]. Dioxins exhibit lipophilic properties, and after ingestion, they accumulate in adipose tissue and, consequently, may be released slowly in the bloodstream. Similarly, dioxins might be delivered through breast milk, hence leading to overexposure of breastfed new-borns and children [45].

The 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is considered the most potent dioxin compound. The AhR mostly mediates its effects in osteoblasts and osteoclasts [46, 47]. After the binding between TCDD and AhR, the complex receptor-ligand moves towards the nucleus, where it binds to specific DNA recognition sites, and finally activates the transcription of the so-called dioxin's responsive genes [48]. However, TCDD possibly simulates estrogenic effects, too.

TDCC seems to suppress osteogenesis and consequently induces detrimental effects on bone health, as demonstrated in *in vitro* studies [49, 50]. Moreover, according to the results of several observations in rat models [51-53], TCDD affects bone remodeling, mainly by reducing bone growth and development with long-term adverse effects. Other rats' findings suggested that exposure to TCDD during gestation and postnatal breastfeeding impaired bone geometry, mineral density, and bone mechanical properties [54]. Finnila *et al*. [12] and Nishimura *et al*. [55] showed that TCDD, administered to mice dams, elicited a marked increase in the amount of unmineralized osteoid matrix and a dramatic reduction in the mineralized bone of the proximal margin of tibiae in the offspring. Given these findings, it is thought that TCDD may disrupt bone tissue deposition as the consequence of an osteoblast impairment rather than excessive osteoclastic bone resorption [55]. However, compared to the previous reports, the effect of TCDD on bone formation, composition, and geometry were dissimilar in primates [56]. Indeed, pregnant rhesus monkeys exposed to TCDD gave birth to offspring with bone dimorphism in femurs: in female pups, there was a relevant increase in bone formation, whereas, in males, there was a lower bone strength, thinner cortical bone thickness, and osteoporotic fractures.

None longitudinal studies have been carried out beyond an Italian observational study in Seveso (Lombardy) started after the so-called Seveso's disaster (July 10^{th}, 1976) when an electric center burst due to an accident. Since that, a very high quantity of dioxin has spread into the environment, leading to detrimental effects on human and wildlife species' health. Skeletal anomalies were not found in 267 women, even if, at the time of the accident, 219 women had not yet reached the peak of bone mass, and 48 were already in menopause [57]. Thus, other observational studies in humans are needed to recognize dioxin-related skeletal disruption better.

1.3. 3-Methylcholanthrene

3-Methylcholanthrene (3MC) is an aromatic hydrocarbon with a similar chemical structure compared to TCDD. It can bind to the AhR, exerting immunologic, toxic, and tumorigenic effects [58, 59]. *In vitro*, 3MC decreases osteoblasts differentiation as demonstrated by a reduction of the expression of alkaline phosphatase activity and osteocalcin and ossification process *in vivo* [60]. Additionally, 3MC was also found to inhibit the differentiation and activation of osteoclasts, impairing the osteoclastogenesis [61]. As observed by Naruse *et al*., pregnant female mice exposed to this compound displayed adverse effects on fetus bone remodeling, including a delayed ossification in several skele-

tal districts [60]. Since these detrimental effects, it is expected that 3MC may induce skeletal damage in both animal models and humans, hence giving necessary observational studies focused on the specific theme.

1.4. Benzo[a]Pyrene

Benzo[a]Pyrene (BaP) is a polycyclic aromatic hydrocarbon typically found in tobacco smoke and tar. It is an agonist of AhR, and it is thought that BaP could be implicated in the induction of cell proliferation with a potential for tumorigenesis [62, 63], including osteosarcoma [64]. In animal models, BaP disrupted bone architecture and impair bone remodeling by inhibiting osteoclastogenesis and affecting bone resorption [65, 66]. BaP may interfere with osteoblast differentiation, significantly impairing the morphogenetic protein-2/Smad pathway through AhR [67]. This interference has also been observed in humans and is mediated by AhR signaling. When exposed to BaP, human periodontal ligament cells reduced the expression of osteogenic genes, and consequently, several activities decreased, such as alkaline phosphatase activity, mineralization, and collagen synthesis. Simultaneously, the treatment with CH-223191 (an antagonist of AhR) reverted these effects, thus confirming that BaP may impair osteogenesis by binding to the AhR with possible detrimental effects on periodontal tissue, especially in cigarette smokers [68]. Besides, BaP regulated osteoblasts' proliferation through an estrogen receptor-related cyclooxygenase-2 pathway [64] and was found to impair chondrogenesis, accelerating chondrocyte differentiation in mice through its interaction with the AhR pathway [69]. BaP led to toxic effects on skeletal development, bone modeling, and remodeling by possible epigenetic interferences in animal models. In conclusion, BaP exposure (as in the example by cigarette smoke) may induce detrimental effects on bone health.

1.5. Polychlorinated Biphenyls

Polychlorinated biphenyls (PCBs) are a group of more than 200 different halogenated aromatic hydrocarbon compounds widely spread into the environment since they are generally used as diluents, lubricants, and cutting oils, flame retardants, fluids for capacitors and transformers. They are employed in thermal and electrical insulators [70]. Some chemical structure differences exist among PCBs, leading to different physical-chemical properties and biological activities. Notably, the 3,30,4,40,5-Pentachlorobiphenyl (PCB126) is one of the most toxic compounds of the class, highly affine to the AhR. Moreover, it might lead to estrogenic or anti-estrogenic actions depending on individual oestrogenic balance [71]. In rats, these compounds induce structural and functional modifications in estrogen-responsive tissues, including the skeleton. Mainly, PCBs display estrogenic activities in estrogen-deprived female models, thus contributing to bone formation.

Conversely, in a female with an adequate hormonal milieu, PCBs exhibit a significant antiestrogenic effect leading to an impaired bone strength due to a substantial decrease in skeletal collagen contents [72, 73]. Another observation by Alvarez-Lloret *et al*. found that PCB126-exposed female rats had a significantly lower vertebral mineralization than controls, even though an increase in vertebral trabecular bone density was observed. Authors speculated that bone mineralization might have been disrupted during the observation due to a PCBs-related interference with thyroid hormone synthesis and vitamin D metabolism [74]. The Italian Institute of Health confirmed that PCBs could reduce bone mass and cortical thickness in male rats [75].

It should be considered that PCBs bioaccumulate in adolescents who lived in polluted regions [76]. A delayed sex maturation and pubertal development in both boys and girls living in polluted areas have also been described. These alterations were attributable to either an impaired hormonal secretion or a direct interference of PCBs (and dioxins) with sexual hormone receptors [77]. Finally, Guo *et al*. found in adults an inverse correlation between 9 urinary metabolites' concentrations of Polycyclic Aromatic Hydrocarbons (U--PAHs) and bone mineral density of the femoral neck in postmenopausal women [78]. In conclusion, PCBs may act as a polymodal disruptor as they interfere with thyroid and gonadal secretion and interrupt vitamin D metabolism. As the consequences of this mechanism of action, possible skeletal consequences could be expected. Prevention programs should be focused on this theme to reduce the spread of PCBs into the environment. On the other hand, more knowledge is needed to prevent long-term toxic effects on humans.

1.6. Poly- and Perfluoroalkyl Substances

Poly- and Perfluoroalkyl substances (PFAS) are widely used in several industrial sectors and could be found in a wide range of consumer products such as firefighting foam, non-stick cookware, and food packaging [79]. PFAS are challenging to be biodegradable; therefore, they persist in the environment and bioaccumulate in the human body [79]. Toxicological studies indicate that PFAS accumulates in bone tissue, disrupting bone metabolism. In a multicentre study, plasma concentrations of 76 prenatal maternal EDCs were assessed in a cohort of 2,106 healthy pregnant women of different ethnicities followed until the delivery. These data were compared with seven neonatal anthropometric endpoints (weight, length, head and umbilical circumference, and mid-upper arm and thigh length). For the overall cohort, the perfluorooctanoic acid, PCBs congeners 118/106 and 146/161, and other seven PFAS were inversely related to whole neonatal length and arm length, whereas the perfluorohexanesulfonic acid was inversely related with umbilical circumference [80].

Di Nisio *et al*. recently examined the association between PFAS exposure and bone status assessed by quantitative ultrasound at the heel level in a cohort of 117 young men resident in a polluted area. Patients exposed to a high concentration of environmental PFAS showed a significantly lower stiffness index, lower T-score, and higher prevalence of medium to high fracture risk [81].

The toxic potential of phthalate esters is well known [82]. Given their widespread use and considering their relatively high biodegradation resistance, phthalates accumulate in food and drinking water [83]. It is currently acknowledged that phthalates display estrogenic activity in mammalians [84, 85] and were found to induce skeletal defects, embryopathy, and embryo-lethality in rat models [86-88]. According to the results of molecular studies, phthalates were demonstrated to disrupt the intracellular signaling of fibroblast growth factor 2, one of the most important regulators of bone remodeling [89-94]. Furthermore, phthalates were found to interfere with actin microfilaments' distribution across the cytoskeleton, thus compromising the preservation of cellular polarization and plasticity essential for a physiological osteocyte activity [95, 96]. The actin microfilaments disruption was found to stimulate cell proliferation [97]. Benzyl-butyl-phthalate increased osteoclast proliferation in rats by inducing cyclin D3 over-expression [98, 99].

Although several kinds of research confirmed that phthalates might exert toxic effects on bone tissue, data referred to humans are currently lacking. In one observational study in the United States, urinary phthalates were assessed in 480 postmenopausal women from 2005 to 2010. The results showed an inverse correlation between urinary phthalate concentrations and lumbar but not femoral bone mineral density, even if this effect was modulated by age and BMI [100].

1.7. Methylparaben, Butylparaben, and Metoxychloride

Methylparaben (MPB) and Butylparaben have mainly been employed to manufacture cosmetics and personal care and hygiene products. In rats, parabens seem to favor obesity and reduce the expression of N-terminal pro-peptide but not that of the C-terminal Telopeptide of Collagen 1. Consequently, parabens decrease the neoformation of bone tissue but do not affect its reabsorption [101]. Serum concentrations of MPB have been reported to be higher in people who exhibit a frequent use of paraben-containing products [102]. Parabens display estrogenic activity in humans, and a high--exposure to parabens might induce detrimental effects at the levels of estrogen-responsive tissue [103-107]. However, a few studies have been carried out to evaluate the impact of chronic exposure to parabens on bone health. One observation suggests that MPB could have a "positive" effect on skeletal metabolism by reducing bone resorption, similar to that observed for estrogens [41]. However, other data are needed to confirm this observation.

Methoxychloride (MXC) is a synthetic estrogen used as a pesticide. MXC and its metabolites have oestrogenic, antiestrogenic, and antiandrogenic activity in mammalians. In male rats, the MXC reduces BMD at the level of vertebral skeleton and tibia, significantly increasing porosity in cortical bone [102].

1.8. Organotin Compounds

Organotin compounds result from the addition of organic moieties to inorganic tin, which can bind to four hydrocarbon groups [mono-, di-, tri-, and tetra-substituted], and are ubiquitous in the environment since they have been employed in agriculture and industry as biocides, wood preservers, and stabilizers for polyvinyl chloride polymers. Notably, tributyltin (TBT) and triphenyltin (TPT) have been widely used in boat antifouling paint and fishing nets, contributing to contaminate seawaters and the marine ecosystem. Indeed, the accumulation of these organotin compounds has been reported in marine fish and mammalians, leading to endocrine disruption [108-110]. Humans are consequently exposed to organotin mainly via seafood consumption [111]. In a rat model, Adeeko *et al*. investigated the consequences of chronic exposure to TBT during pregnancy outcomes. Fetal skeletal ossification was significantly reduced in exposed strains and was associated with thyroid disruption and maternal hypothyroidism [112].

In contrast, no considerable bone formation changes in monobutyltin-treated rats have been described [113]. Delayed ossification of fetal skeleton observed in animals exposed to TBT could be attributable to an essential signaling cascade interference in osteoblasts [113]. Low concentrations of TBT and TPT can suppress osteoclast differentiation in mice by decreasing the expression of the nuclear factor of activated T cells (NFAT) c1 and by activating protein-1 (AP-1) expression via a retinoic acid receptor RAR/RXR-dependent pathway [114]. In a mice model, organotin compounds were also found to interfere with the physiological epithelial-to-mesenchymal transition process, essential for normal dental development [115].

TBT regulates multipotent stem cells' differentiation in both humans and mice. Particularly, TBT leads to an increase in the number of adipose-derived stromal stem cells, predisposing them to differentiate toward an adipocyte instead of osteogenic lineage via PPARc signaling [116]. *In vivo* studies exploring the effects of TBT on mouse stromal stem cells, supporting the previous finding. Synergism among organotin compounds leads to impaired bone homeostasis [102] because of their harmful effects on mesenchymal stem cells' differentiation. Moreover, TBT enhances macrophage activation and the systemic production of reactive oxygen species [117-119]. Many of the deleterious effects of TBT are related to hormonal disruption, particularly at the adrenal and gonadal axis level and with osteoblast differentiation interference [120-123]. In rats, TBT was found to impair the transition from mesenchymal cells to osteoblasts, conversely stimulating the former's differentiation into adipocytes [124]. Sturgeon *et al*. hypothesized that TBT disrupts bone metabolism *in vivo*, but they found the opposite effects [125]. However, plasmatic levels of biomarkers of bone resorption, such as the urinary deoxypyridinoline excretion ratio, were increased in TBT-treated animals versus controls. Similarly, the levels of other biomarkers of bone formation, such as osteocalcin and alkaline phosphatase, were also elevated, suggesting that TBT might induce a higher bone matrix turnover than control [126]. Finally, TBT was found to increase urinary calcium excretion rate, even if serum Ca concentration (total and ionized) remains unchanged.

1.9. Cadmium

Cadmium (Cd) is a heavy metal employed mainly in manufacturing nickel-cadmium rechargeable batteries and is also used for its anti-corrosive properties as the coat of metal surfaces (iron and steel). Cd was used as a dye to paint (of known, Vincent Van Gogh used Cd pigments for painting his "sunflowers"), but due to its toxicity, the European commission activated tight surveillance to ban the metal when used for that purpose [2014].

The Italian Ministry of Health, through the so-called Integrated National Plan (2015 - 2018), indicated the Italian Institute of Health as the reference laboratory for assessing the levels of Cd (and lead) in foodstuffs. According to several measurements, plants resulted in a relevant Cd source since they absorb the metal similar to zinc. Additionally, Cd has also been found in fishes, bivalve mollusks (mussels, oysters), and cephalopods (octopus, cuttlefish, squid, ink fish, and mollusks with internal "bone"). Cd is also found in tobacco; thus, usual cigarette smokers are typically exposed to a high ion concentration.

In vitro studies highlighted that Cd addition to a culture of human osteoblasts induced necrosis by disrupting the Wnt/β-catenin pathway [127]. This process was partially blocked by adding caspase 8 and 3 inhibitors into culture media [128]. Cd also appears to have a biphasic action on OB, leading to a significant induction of cell proliferation during the first 6 hours of exposure, while the opposite effects [both apoptosis and necrosis] occurred after prolonged exposure (15 and 24 hours, respectively) [129].

1.10. Palmitic Acid

Palmitic Acid (PA) is naturally found in a particular food, including palms (palm oil). PA can also be found in meats, cheeses, butter, other dairy products and cocoa butter, soybean oil, and sunflower oil. It is inexpensive and adds texture to processed foods. For these reasons, PA is widely used as an ingredient in many industrial products.

In rats, PA interferes with the RANK-RANK ligand signaling and activates osteoclastogenesis leading to bone reabsorption and loss in skeletal mineral contents [130]. Furthermore, high PA concentrations reduce mice osteoblasts' efficiency in *in vitro* experiments, while high levels of PA lead to a C16-ceramide accumulation *in vivo* [130]. Interestingly, Oleic acid inhibits this PA-induced bone disruption [131]; thus, a diet rich in OA should be preferred.

1.11. Atmospheric Pollutants and Bone Health

Prada *et al*. explored the association between outdoor air pollution, mostly particulate matter (a mixture of particles floating in the air), and bone disruption [132]. According to the results of this observation, floating particles were an independent risk factor for low bone mineral density and osteoporosis-related fractures through different putative mechanisms, possibly summarized as follows: a) induction of low-grade systemic inflammation, hence affecting osteoblast and osteoclast differentiation (tumor necrosis factor-α, interleukin-1β, IL-6, and IL-17); b) increased intracellular oxidative damage, also in bone resident cells; c) disruption of receptor signaling in bone cells; d) interference with vitamin D absorption and metabolism.

2. DISCUSSION

EDCs were found to interfere with the endocrine system by different pathways. However, several determinants influence the endocrine outcomes in exposed organisms, including the age of exposure, latency from exposure, possible exposure to a mixture of chemicals, dose-response dynamics, and long-term latent effects (transmission to further generations) [2]. The economic burden is not negligible, since it has been estimated that the deleterious effects of the EDCs on humans may cost approximately 163 billion Euros in the European Union and even more in the United States.

A complex hormonal interchange finely regulates bone homeostasis; thus, it can be a target tissue of EDCs. Bone is a dynamic tissue regulating body stability and mobility, mineral metabolism, mesenchymal or stromal, and hematopoietic progenitor or stem cells breeding. Furthermore, bone is also an endocrine organ producing different hormones, including osteocalcin and fibroblast growth factor 23, currently known to regulate systemic inflammation and vascular reactivity [133]. The so-called xeno-estrogens interfere with bone remodeling and modulate hormone and cytokine/chemokine release [134]. ERs bind to several physiological steroids exhibiting structural differences, including estradiol, Δ5-androstenediol, 5α-androstenediol, and 27-hydroxycholesterol. This characteristic could explain the estrogenic activity of a variety of plant-derived chemicals such as genistein, coumestrol, and resveratrol and synthetic chemicals such as bisphenol A, DDT, and other EDCs in vertebrates [135-137].

Therefore, EDCs interfere with bone tissue health, but the results of studies (both *in vitro* and *in vivo*) from animal models are heterogeneous and often inconclusive. First, it should be considered that EDCs activate both the formation and reabsorption of the bone matrix. Furthermore, the action of EDCs seems to be variable according to the dose of exposure. On the other hand, epidemiological studies in humans were lacking and exhibit inconclusive results [8, 15]. Moreover, it should be considered that humans may be simultaneously exposed to several EDCs; therefore, it is difficult to explain every chemical's contribution to bone disruption specifically.

Although the possible relationship between EDCs and BMD has so far been investigated, it has not been evaluated whether and how EDCs increase the risk of fracture and the impact of EDCs exposure on bone health in patients taking medications for treating osteopenia or OP. In any case, the action of EDCs on bone health should be carefully monitored by national and international commissions and departments to provide accurate surveillance on this phenomenon and possibly implement consistent epidemiological data in the next future.

CONCLUSION

Much evidence about bone disruptors has been published. Most of them have been inherited from *in vitro* studies or animal models, but they led to equivocal results. Conversely, a few data have been obtained from humans, and most of these data focused on the impact of EDCs on bone mineral density without considering their influence on the more relevant long-term fracture risk. Considering that humans are exposed to a mixture of EDCs, bone metabolism's final effect might be the result of either synergism or antagonist effects among them. Other variables that may influence bone response against EDCs include the age of first exposure, cumulative dose-exposure over time, and the usually observed non-monotonic dose-response curve for EDCs. Therefore, long-term observational studies are needed to better analyze this issue for ecological and medical purposes.

LIST OF ABBREVIATIONS

3MC	=	3-Methylcholanthrene
AhR	=	Aryl Hydrocarbon Receptor
BaP	=	Benzo[a]Pyrene
BMD	=	bone mineral density
BMI	=	body mass index
BPA	=	Bisphenol A
Cd	=	Cadmium
E2	=	17β-Estradiol
EDCs	=	Endocrine Disrupting Chemicals
MPB	=	Methylparabene
MXC	=	Methoxychloride
NRs	=	Nuclear Receptors
OP	=	Osteoporosis
PA	=	Palmitic Acid
PCB 126	=	3,30,4,40,5-Pentachlorobiphenyl
PCBs	=	Polychlorinated biphenyls
PFAS	=	Poly- and Perfluoroalkyl substances
RANK	=	receptor activator of nuclear kappa B
T	=	Testosterone
TBT	=	Tributyltin
TCDD	=	The 2,3,7,8-tetrachlorodibenzo-p-dioxin
TPT	=	Triphenyltin
U-PAHs	=	Polycyclic Aromatic Hydrocarbons

AUTHORS' CONTRIBUTION

Raffaele Giannattasio conceived the review. Raffaele Giannattasio, Giuseppe Lisco, Vincenzo Triggiani carried-out databases' search and drafted the manuscript. All authors read the text, provided feedback and criticisms, and accepted the manuscript's final version.

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The authors declare no conflict of interest, financial or otherwise.

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