J Oral Res
research in oral sciences

REVIEW

EXPOSURE TO ENDOCRINE DISRUPTORS AND ALTERATIONS IN MINERALIZED TISSUES: A NARRATIVE REVIEW.

Exposición a disruptores endocrinos y alteraciones en tejidos mineralizados: Revisión Narrativa.

Paula Contreras Meza.[1]
Jaime A. Jacques.[2]

AFFILIATIONS:
[1]Unidad de Patología, Departamento de Estomatología, Facultad de Odontología, Universidad de Talca, Talca, Chile.
[2]Unidad de Periodoncia, Departamento de Estomatología, Facultad de Odontología, Universidad de Talca, Talca, Chile.

CORRESPONDING AUTHOR:
Jaime Jacques.
Facultad de Odontología, Universidad de Talca, Av. Lircay, Talca, Chile. Phone: (56-71) 2201546. E-mail: jjacques@utalca.cl

CITE AS:
Contreras Meza P & Jacques JA. Exposure to endocrine disruptors and alterations in mineralized tissues: A Narrative Review.
J Oral Res.2022;11(5):1-16.
doi:10.17126/joralres.2022.060

ABSTRACT:

Background: Endocrine Disrupting Chemicals (EDCs) would cause alterations in organs/systems of exposed individuals or their progeny.

Objetive: To identify and analyze the main published findings on the effects of exposure to EDCs on teeth, cartilage, and bone.

Material and Methods: Two databases were analyzed: Medline and Web of Science. Only observational studies analyzing the effect of EDCs on mineralized tissues published since 2006 were included in the study.

Results: 25 articles were selected, most of them involving EDCs pesticides, plasticizers, or personal care products, highlighting organochlorine compounds, bisphenols, phthalates, dioxins, parabens, and perfluoroalkyls. Thirty-six per cent of the studies reported an accumulation of EDCs in teeth or bones, while 64% reported alterations in their development or morphology, mainly at the bone level, primarily affecting their mineral density and size, as well as that of the bones of exposed individuals or their progeny. The type of effect observed was related to the EDCs analyzed, and it seemed to depend on variables such as age, sex, ethnicity/race, and even the metabolic status of the individuals in the different species analyzed. No evidence associated with effects on cartilage was found.

Conclusion: EDCs in the environment, at work, or at home, under different exposure routes, are capable of accumulating in teeth and bone, particularly affecting the latter. It is necessary to study the effect of EDCs on mineralized tissues in agro-industrial areas, especially on teeth.[1]

KEYWORDS:

Endocrine disruptors; bone and bones; cartilage; tooth; bioaccumulation; review.

Received: September 30, 2021 | **Accepted:** January 26, 2022 | **Published online:** June 30, 2022.

RESUMEN:

Antecedentes: Los Químicos Disruptores Endocrinos (EDCs) causarían alteraciones en órganos/sistemas de individuos expuestos, o su progenie.

Objetivo: Identificar y analizar los principales hallazgos publicados sobre el efecto de la exposición a EDCs en dientes, cartílago y hueso.

Material y Métodos: Se analizaron dos bases de datos: Medline y Web of Science, incluyendo solo estudios observacionales publicados desde el 2006, analizando el efecto de los EDCs sobre tejidos mineralizados.

Resultados: 25 artículos fueron seleccionados, siendo la mayoría de los EDCs pesticidas, plastificantes o productos de cuidado personal, destacando los compuestos Organoclorados, Bisfenoles, Ftalatos, Dioxinas, Parabenos y los Perfluoroalquilos. Un 36% de los estudios reportaron un acúmulo de EDCs en dientes o huesos, mientras que un 64% informaron de alteraciones en su desarrollo o morfología, particularmente a nivel de huesos, afectando principalmente su densidad mineral y su tamaño, así como el de los individuos expuestos o su progenie. El tipo de efecto observado tuvo relación con el EDCs analizado, pareciendo depender de variables tales como edad, sexo, etnia/raza e incluso el estado metabólico de los individuos, en las diferentes especies analizadas. No se encontraron evidencias asociadas a efectos en el cartílago.

Conclusión: Los EDCs en el medio ambiente, ámbito laboral o doméstico, bajo distintas rutas de exposición, son capaces de acumularse en diente y hueso, afectando particularmente a este último. Es necesario estudiar el efecto de los EDCs en los tejidos mineralizados en zonas agroindustriales, particularmente a nivel de dientes.

PALABRAS CLAVE:

Disruptores endocrinos; huesos; cartílago; diente; bioacumulación; revisión.

INTRODUCTION.

Endocrine Disrupting Chemicals (EDCs) can alter the hormonal balance and the regulation of embryonic development,[1] altering the function of the endocrine system.[2] These compounds produce adverse effects on the hypothalamus, thyroid, mammary glands, pancreas, liver, adrenal glands, intestine, gonads, and the immune system ,[3–8] causing alterations in glucose regulation and predisposing to obesity.[9] EDCs, contained in pesticides, plastics, flame retardants or personal care products, are released into the environment, contaminating ecosystems and exposed living beings;[10] they can cross the placental barrier, exposing the fetus to their harmful effects.[1]

Observational studies (OS) allow to establish an association between environmental contaminants and their harmful effect on exposed populations. The external validity and strength of association of the studies will depend on their design, not allowing for causality to be established.

However, OS are the first step in the research of potential risk factors.[11] Thus, the exposure of populations to EDCs – organophosphate and pyrethroid pesticides, bisphenol A (BPA), manganese (Mn) and perfluoroalkyl substances (PFAS) – has been associated with alterations in the nervous system, cognitive performance,[12–15] renal system,[16] reproductive system,[17] diabetes,[18,19] in addition to an increase in deformities of the maxillofacial complex in newborns from rural areas of Chile.[20]

Consequently, since the introduction of the term Endocrine Disrupting Chemicals (EDCs) in 2006, there has been an increase in the literature on the effects of exposure to these substances, with growing interest in the effect of these compounds on mineralized tissues. In this sense, the development of dental, cartilage, and bone tissues, which share a common neuroectodermal embryological origin,[21-23] are closely linked to hormonal control, being susceptible to exposure to EDCs.[24]

Alterations during the formation of mineralized tissues, due to exposure to toxic substances, can result in morphological or structural damage both at the dental,[25,26] bone,[27] and cartilaginous[28-30] levels. Subsequently, exposure to EDCs should negatively affect these tissues,[24,31-34] which may explain the consequences observed at the oral and maxillofacial levels. The aim of this study is to identify and analyze the main published findings on the effects of exposure to EDCs on teeth, cartilage, and bone.

MATERIALS AND METHODS.

A narrative review of the literature was carried out using the PRISMA criteria[35] as a reference. Two databases were searched: Medline and Web of Science. The following search strategy was used for each database: ("endocrine disruptors" OR "endocrine disrupting chemicals" OR pesticides OR pesticide) AND ("dental enamel" OR enamel OR dentin OR dentin* OR bone OR "bone tissue" OR bones OR cartilage OR cartilages). OS published in English or Spanish, which analyzed the effect of EDCs on the development of bone, cartilage, or dental tissue, since 2006 —the year in which this term was introduced in the scientific literature— were included in the study. Experimental studies and other narrative reviews were excluded (Figure 1).

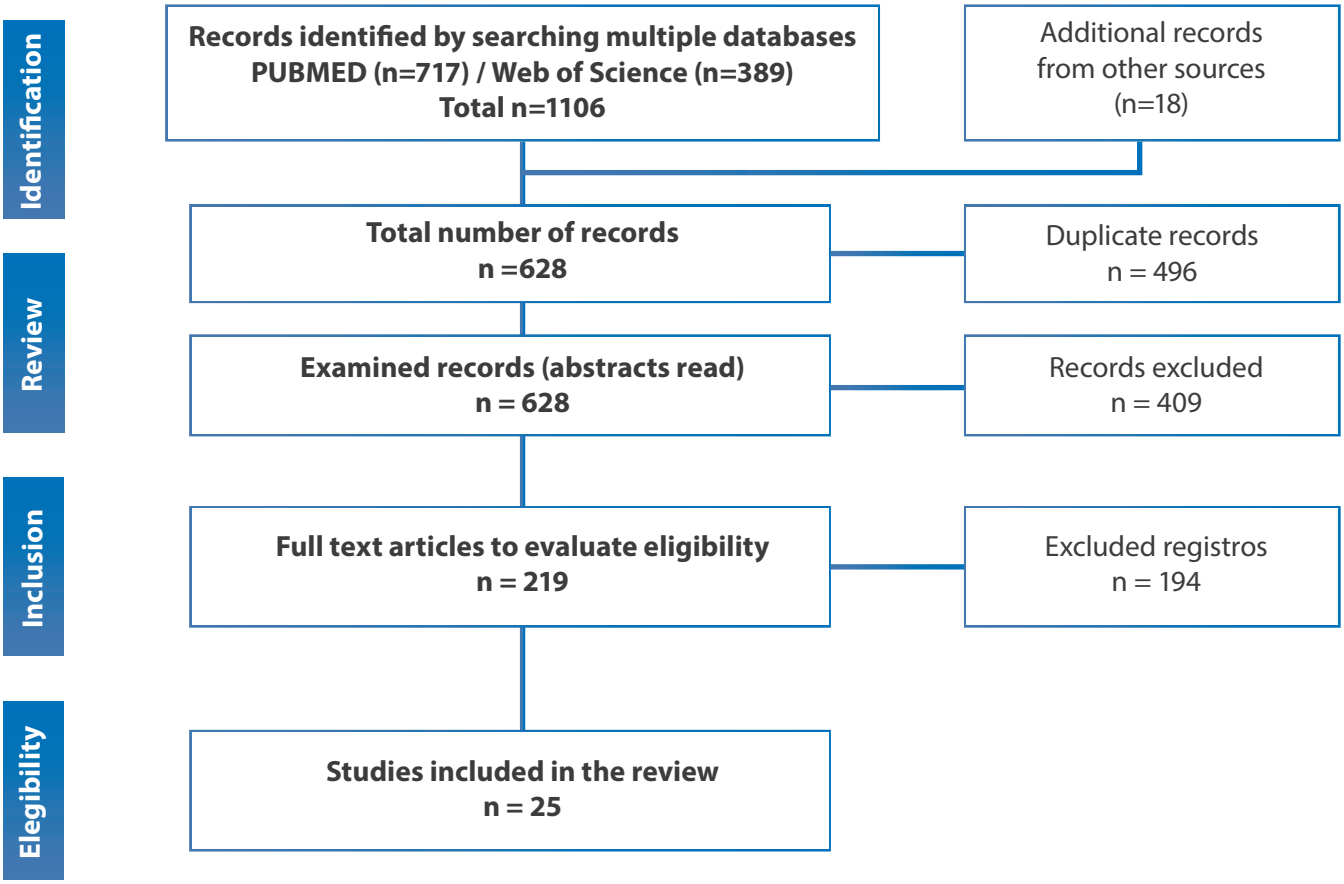
RESULTS.

Twenty-four studies were selected of the 1106 identified articles (Table 1):

11 cross-sectional, seven retrospective, and seven prospective. The most frequently studied EDCs in the articles selected were:

1. perfluoroalkyl substances (PFAS) (36%);
2. bisphenols (16%);

Figure 1. PRISMA flowchart adapted from the bibliographic systematic review process carried out and its results.[35]



ISSN Print 0719-2460 - ISSN Online 0719-2479.

3. phthalate esters (12%);
4. dioxins (24%);
5. organochlorines (20%);
6. parabens (4%);

in addition to other EDCs such as atrazine, lead, Mn, chlorpyrifos (CPF) (32%). Some articles studied more than one compound.

Accumulation of EDCs

Thirty-six per cent of the studies showed that one of the main effects observed was the accumulation of these compounds in bone and teeth. In this way, environmental exposure to Mn during pregnancy could be detected by its accumulation in the teeth of the progeny of exposed individuals (dentin and enamel). Its levels were measured in the dentin layer immediately adjacent to the enamel in 7-year-old children (36–38). In addition, it was also observed that other EDCs, such as mono-(2-ethylhexyl) phthalate (MEHP), a compound used as a plasticizer,[39] and the 3,5,6-trichloro-2-pyridinol metabolite of CPFs, organophosphate pesticide.[40] also deposited in deciduous molars of the children examined.[41]

Regarding bone tissue, polychlorinated biphenyls (PCB),[42,43] polybrominated diphenyl ethers (PBDE): congeners 47, 99 and 153[42,43] —both compounds present in electrical insulators, plasticizers, and flame retardants[44,45]– lead,[46] and perfluoroalkyl substances (PFAS),[47–50] which are highly fluorinated aliphatic substances,[51] were detected in the bones of different environmentally exposed species (mammals and birds).

This is how perfluorooctanoic acid (PFOA) and perfluoro octane sulfonic acid (PFOS), compounds used in the surfactant and polymer industries,[52] were detected in bone marrow and trabecular bone, with a preferential distribution in the former, while PFOS was evenly distributed in both.[50]

In humans, PFAS concentrations increased with socioeconomic status and body mass index (BMI) (p<0.001), with higher concentrations observed in smokers (p<0.001).[47,49] On the other hand, people with osteoarthritis were found to have higher levels of PFOA and PFOS (p<0.001).[47] Finally, higher concentrations of PFAS were observed in women with osteoporosis versus women without this condition (p<0.05).[53]

Morphological defects

The selected studies detected morphological defects only in bone tissue. This is how exposure to water contaminated with high concentrations of pesticides such as atrazine, dicamba, bentazone, CPF, mecoprop, dimethoate, 2,4-dichlorophenoxyacetic acid (2,4-D) and 4-chloro-2-methylphenoxyacetic acid (MCPA), in agricultural areas, was associated with a decrease in total length of the skeleton of exposed frogs, while in sites with low concentrations of EDCs only a decrease in tibial length was observed.[54]

Likewise, high concentrations of environmental contaminants would be responsible for the bone morphological alterations reported in otters and polar bears, which would be the reflection of histological alterations of the mineralized tissues, induced by exposure to EDCs. Thus, the presence of dioxins in the femur of marine mammals exposed to PCBs would be related to an increase in the area, content, density, and thickness of the cortical bone of the femur[55] and a decrease in the bone mineral density (BMD) of the penis bone of polar bears, affecting their reproductive capacity.[56] This decrease in bone density would be significantly lower compared to PCB 74 and 153, hexachlorobenzene (HCB), PBDE-153, and other organochlorines.[43]

In humans, exposure to EDCs also had effects on the bone structure of obese children aged 8 to 12 years environmentally exposed to PFAS, showing an association between the concentration of perfluorononanoic acid (PFNA) in the children's serum with a decrease in the density of their calcaneal bone (p=0.01).[57] Similarly, the presence of a diet rich in shellfish from marine areas contaminated with PCB 153 and HCB, fungicides for seed treatment,[58] was related to a decrease in the size of the same bone in exposed postmenopausal women (p<0.001), showing limited evidence that exposure to organochlorines and dioxins is related

to the presence of osteoporosis in this population.[59]

According to studies in post-menopausal women, BPA, which is used in the lining of cans, in polycarbonate containers for food use, in dental sealants and resins, and in thermal paper receipts,[60–62] was associated with increased plasma calcium levels in women with osteoporosis (p<0.05).[63] In addition, in these women, exposure to methylparaben was related to an increase in markers of osteoclastogenesis, with an association between concentrations of urinary phthalate metabolites and decreased BMD in the femur and spine (p<0.05).[64]

Finally, exposure to EDCs during pregnancy revealed important effects on the offspring. A longitudinal study reported on the association between prenatal concentrations of PFAS and bone health in 17-year-old girls, showing that prenatal exposure to these EDCs was associated with inverse effects on body size and bone mass of the tibia, femur, and hip (p<0.05).[65]

Modulating Factors

The following factors seem to influence the concentrations of EDCs detected, as well as the morphological alterations observed in exposed individuals.

Sex: Populations exposed to PFOA and PFOS showed higher concentrations in male individuals (p<0.001).[48] Interestingly, these EDCs have been associated with the presence of osteoarthritis only in females (p<0.001).[47] For its part, PFNA was associated with an increase in bone mineral content (BMC), preferably in the tibia, femur, and hip of females (p<0.05),[65] while PFOA was associated with a higher prevalence risk of fracture, mainly in males.[66] On the contrary, a third study showed that there would be no association between serum levels of PFOA and PFOS with the report of fractures in both females and males (p>0.05).[49]

Finally, the concentration of 2,4-dichlorophenol was associated with a lower BMD and a higher prevalence of osteopenia and osteoporosis in males (p<0.05).[67]

Ontogenetic Status: Populations exposed to PFOA and PFOS showed serum concentrations that increased with age (p<0.001).[47,49] Likewise, the appearance of bone abnormalities also seems to be dependent on age. This is how the exposure of pregnant women to bisphenol S (BPS) during the first trimester was associated with a decrease in the BMD and BMC of the progeny at ten years (p<0.01).

However, this was not noted at six years (p>0.05), showing that the harmful effect at the bone level would be evidenced in the long term.[68] For its part, exposure to high concentrations of low molecular weight phthalates, phthalic acid, and di-(2-ethylhexyl)-phthalate (DEHP), plasticizers present in personal care and medical products,[69,70] in the third trimester of gestation, was associated with a high BMC at six years, while exposure to high concentrations of di-n-octylphthalate (DNOP), present in plasticizers, coatings, and pesticides,[71] were associated, not significantly (p>0.05), to a lower BMC at ten years.[68]

It should be noted that in other cases no correlation was observed between bone PFAS concentrations and age or bone volume, however a negative trend was observed between bone PFOS concentration and bone volume (p=0.06).[50]

Ethnic Differences: PFOA and PFOS showed serum concentrations in exposed populations that differed by race/ethnicity, being higher in white and non-Hispanic black individuals, while the lowest mean concentrations of both exposures were observed in Mexican-Americans (p<0.001).[47] Regarding the differences in observed effects, exposure to high concentrations of PBDE 28 and 153 was associated with smaller birth size in Hispanic women, while exposure to PFOA was associated with smaller birth size only in black women. Finally, perfluorooctanesulfonamide (PFOSA) exposure was associated with an increase in total length in newborns of white women (p<0.001).[72]

Hormonal Variations: Exposure to certain substances such as parabens,[69] and benzophenone-3, was associated with an increase in bone BMD preferentially in men, and premenopausal women.

ISSN Print 0719-2460 - ISSN Online 0719-2479.

Table 1. Observational studies of the effects on dental and bone tissue due to exposure to EDCs.

Observational studies in dental tissue					
Population	EDCs studied	Target Tissue-Cell	Comparison /Control	Results	Author
Pregnant women exposed to Mn present in the floor dust of their homes	Mn	Deposit of EDCs in dental tissue of children	No	Detection in dentin and enamel	Arora, 2012[36]
			No	Detection in dentin mainly formed in the third trimester	Gunier, 2013[37]
Rural population exposed to pesticides such as Maneb and Mancozeb			No	Detection in dentin	Gunier, 2015[38]
Children with perinatal exposures to pollutants	DEP, MEHP, CPF, 3-PBA, cyfluthrin	Deposit of EDCs in deciduous molars of children	No	Higher concentrations of MEHP and CPF	Camann, 2013[41]
Observational studies in bone tissue					
Population	EDCs	Target Tissue-Cell	Comparison	Results	Author
Populations exposed to high concentrations of organochlorines and dioxins through the diet	PCB 28, 52, 101, 105, 118, 128, 138, 153, 156, 170, 180, 183, 187, Aldrin, β-HCH, γ-Chlordane, cis-Nonachlor, p,p'-DDE, p,p' -DDT, HCB, Mirex, trans-Nonachlor	Morphological analysis of the right calcaneal bone	No	PCB 153 and HCB ↓size. Other compounds without association. No association with significant predictors of bone stiffness.	Côté, 2006[59]
Small mammals exposed to EDCs through environmental water	PCB and DDE	Femur	No	PCB ↑ cortical bone (area, content, and thickness) and ↓ trabecular density DDE does not cause alterations	Roos, 2010[55]
Large mammals exposed to dioxins and organochlorines due to environmental pollution	PCB: 28, 52, 101, 105, 118, 138/163, 153, 156, 170, 180, 183, 187, 194. DDT:p,p´-DDT, o,p ´-DDT, p,p´-DDE, p,p´-DDD PBDE: 47, 99, 100, 153 and 154	Metacarpus and metatarsus	No	Bone marrow PCB 99, 105, 118, 138/163, 153, 156, 170, 180 and 187 detection DDT, DDE, DDD below limit PBDE 138 below limit PBDE 138 not detected PBDE 47, 99 and 153 detected in MO	Hassan, 2013[42]
Large mammals exposed to dioxins due to environmental contamination	PCB	Penis	No	PCB↓ BMD	Sonne, 2015[56]
Pregnant women exposed to organochlorines due to environmental exposure	β-HCH, γ-HCH, HCB, trans-nonacloro, p,p-DDE, o, p´-DDD, p,p´-DDD, PBDE 28, 47, 85,99, 100, 153, 183, 209	Body analysis in newborns	No	PBDEs 28-153 ↓ total length Other compounds without association	Louis, 2018[72]
Large mammals exposed to dioxins and organochlorines due to environmental pollution	PCB 74, DDT3, p, p'-DDE, HCH3, α-HCH, PBDE 153, HCB, HCH, β-HCH	Penis	No	PCB 74 in higher concentrations PCB 74 and 153, HCB, HCH, β-HCH, ClBz, PBDE-153 ↑ BMD	Daugaard, Petersen, 2018[43]
Small amphibians exposed to EDCs in high and low concentrations through environmental water	Atrazine, deisopropylatrazine, diethylatrazine, dicamba, bentazone, CPF, mecoprop, dimethoate, 2,4-D, MCPA	Tibia	No	↓ total length in high exposure sites ↑ tibial length in low exposure sites	Spear, 2009[54]

The Table continues on the next page. ↳

Observational studies in bone tissue					
Population	EDCs	Target Tissue-Cell	Comparison	Results	Author
Population exposed to EDCs due to environmental contamination	Barium, Cadmium, Cesium, Mn, Lead, BPA, Triclosan, 2-Hydroxyfluorene, 1-Hydroxypyrene,1-Naphthol, 2-Naphthol/ Cobalt, Molybdenum, Antimony, Strontium, Thallium, Tin, Tungsten, Uranium, Benzophenone 3, 3 -hydroxyfluorene, 9-hydroxyfluorene, 1-hydroxyphenanthene, 2-hydroxyphenanthene, 3-hydroxyphenanthene	Perioral bone	No	↑ bone loss in the presence of high levels of Cadmium, Nitrate, Thiocyanate, propyl paraben, and PAH	Shiue, 2015[73]
Birds exposed to lead due to environmental contamination	Lead	Femur	No	Detection in bone tissue	Baxter, 2015[46]
Population exposed to phthalates in plastic products femoral BMD	Phthalates: MNBP, DEP, DEHP, BBP, DINP, DNOP, DIDP	Femur and spine	No	Phthalates ↓ Spinal and (primarily MNBP)	DeFlorio-Barker, 2016[64]
Population exposed to phthalates and parabens in plastic products	Bisphenols: BPA, BPS, BPF and BPAF Parabens: methyl, ethyl, propyl, butyl, and benzyl paraben	Plasma	Healthy women of the same age	BPA was associated with ↑ plasma calcium levels, unrelated to the presence or absence of osteoporosis MP abundant in plasma, positively associated with CTx in women with osteoporosis	Vitku, 2018[63]
Pregnant women exposed to bisphenols and phthalates in plastic products	Bisphenols (BPA-BPS-BPF) Phthalates (Phthalic acid,DEHP, DNOP) BMC	Bone mass in children	No	BPS associated with < BMD and BMC Phthalic acid and DEHP associated with high DNOP was associated with low BMC	Van Zwol-Janssens, 2020[68]
Population exposed to PFAS due to environmental contamination	PFOA and PFOS	NS	No	Men had > levels of PFOA and PFOS Relationship between levels of PFAS (PFOS and PFOA), and the presence of osteoarthritis	Uhl, 2013[47]
		Lumbar spine and femur	No	PFOA and PFOS: > concentration in men Association between PFOS and ↓spinal BMD in non-menopausal women. No association between PFOA, PFOS and femoral neck BMD	Lin, 2014[49]
Population environmentally exposed to high and low concentrations of PFAS	PFAS	NS	Unexposed population	PFOA: Lowest Stiffness Index. High affinity for hydroxyapatite	Di Nisio, 2020[66]

The Table continues on the next page. ↳

ISSN Print 0719-2460 - ISSN Online 0719-2479.

end of table. ↓

Observational studies in bone tissue					
Population	EDCs	Target Tissue-Cell	Comparison	Results	Author
Population exposed to PFAS due to environmental contamination	PFOA, PFOS, PFHxS, PFNA, PFOSA	Ribs	No	Low accumulation of PFAS in ribs, with PFOA being the main substance	Pérez, 2013[48]
	PFOA, PFOS, PFHxS, and PFNA	Lumbar spine and femur	No	Higher PFAS in women with osteoporosis. No association between PFAS and BMD in men and pre-menopausal women	Khalil, 2016[53]
	PFOA, PFOS, and PFNA	Skull, humerus, rib, femur, tibia, and fibula	No	>accumulation of PFOS and PFOA. PFNA was present in long bones. Negative association bet-ween PFOS and relative bone volume	Koskela, 2017[50]
Obese children exposed to PFAS due to environmental contamination	PFOA, PFOS, PFNA, and PFHxS	Calcaneus	No	Negative association between PFAS and bone health in obese children PFAS influence bone turnover	Khalil, 2018[57]
Population exposed to PFAS due to environmental contamination	PFOS, PFOA, PFHxS, and PFNA	Tibia, femur, and hip	Girls from a previous study by the authors	Negative association between PFOS, PFOA, PFHxS and PFNA, and bone size and mass PFNA was positively associated with bone mineral content	Jeddy, 2018[65]
Pregnant women exposed to PFAS due to environmental contamination	PFOA, PFOSA, PFHxS	Anthropometric evaluation of newborns	No	PFAS associate ↓ the length of the bones and affects the size of new borns according to ethnicity	Louis, 2018[72]
Population exposed to EDCs in personal care and parabens and Benzophedaily consumer products	BPA, Benzophenone-3, Triclosan, Butylparaben, Ethylparaben, Methylparaben, Propylparaben, 2, 5-Dichlorophenol, and 2, 4-Dichlorophenol	Femur; inter-trochanteric and lumbar spine	No	Ethyl, methyl, propyl none-3 were associated with > BMD in men and premenopausal women 2,4-dichlorophenol was associated with lower BMD and > prevalence of osteopenia + osteoporosis in men BPA was associated with a higher prevalence of osteopenia + osteoporosis in postmenopausal women	Wang, 2020[67]

2,4-D: 2,4-dichlorophenoxyacetic acid, **3-PBA:** 3-phenoxybenzoic acid, **4,4-DDE/p,p´-DDE:** Dichlorodiphenyldichloroethylene, **α/β-HCH:** α/β Hexachlorocyclohexane, **BBP:** Benzyl butyl phthalate, **BMC:** Bone Mineral Content, **BMD:** Bone Mineral Density, **BPA:** Bisphenol A, **BPAF:** Bisphenol AF, **BPF:** Bisphenol F, **BPS:** Bisphenol S, **ClBz:** Chlorobenzene, **CPF:** Chlorpyrifos, **CTx:** C-Telopeptide bonds collagen crosslinked, **DDT3:** Dichlorodiphenyltrichloroethane, **DEHP:** Di (2-ethylhexyl) phthalate, **DEP:** Di ethyl phthalate, **DIDP:** Di isodecyl phthalate, **DINP:** Di isononyl phthalate, **DNOP:** Di-n-octyl phthalate, **HCB:** Hexachlorobenzene, **HCH3:** Hexachlorohexane, **MCPA:** 4-Chloro-2-Methylphenoxyacetic Acid, **MEHP:** Mono-(2-Ethylhexyl) Phthalate, **Mn:** Manganese, **MNBP:** Mono-n-Butyl Phthalate, **MO:** Bone Marrow, **PAH:** Polycyclic Aromatic Hydrocarbon, **PBDE :** Polybrominated diphenyl ethers, **PCB:** Polychlorinated Biphenyls, **PFAS:** Perfluoroalkyl Substances, **PFHxS:** Perfluorooctane Sulfonic Acid or Perfluorohexane Sulfonate, **PFNA:** Perfluorononanoic Acid, **PFOA:** Perfl Acid uorooctanoic, **PFOS:** Perfluorooctane Sulfonic Acid, **PFOSA:** Perfluorooctanesulfonamide, **p,p'-DDT:** Dichloro diphenyl trichloroethane, **NS:** Not Specified, **TCPy:** 3,5,6-trichloro-2-pyridinol.

In contrast, BPA led to a higher prevalence of osteopenia and/or osteoporosis in the lumbar spine only in postmenopausal women ($p<0.05$).[67]

Likewise, the increase in serum PFOS level was associated with a decrease in lumbar spine BMD in non-menopausal women; no association between serum PFOA and PFOS concentration with femoral neck BMD in non-menopausal women, compared with men or menopausal women ($p>0.05$).[49]

DISCUSSION.

EDCs are found in a wide range of consumer and personal care products and items in many daily activities,[73] An important part of the chemicals studied in this review are part of the composition of pesticides that are widely used in agricultural areas,[74] contaminating fruits and vegetables, consumed by the population.[74,75]

This exposure has been related to neurodevelopmental alterations in individuals, motor disorders, poor cognitive performance, memory difficulties, as well as genotoxicity and neoplasms.[76–78] According to the articles selected in this study, EDCs would accumulate in dental[36-38] and bone[41-43,46-50] tissues, particularly in children. They can cross the placenta, an important barrier for the fetal protection during pregnancy, which responds to endocrine signals induced by these compounds,[79] eventually affecting fetal development.[80]

Likewise, it has been shown that some EDCs can accumulate in placental tissues, disturbing the function of this structure.[79] In relation to morphological and structural alterations, or chemical constitution, of mineralized tissues, a relevant finding was the association between high environmental concentrations of EDCs and decreased bone density, particularly in premenopausal women,[49] where the effect of EDCs could depend on the levels of circulating estrogens – or their receptors – in exposed individuals,[81] affecting bone turnover through mechanisms such as:

a) The alteration of osteoblastic and osteoclastic activity;[27,82]

b) Interference with cell survival through 17β-estradiol;[32]

c) Induction of apoptosis of osteoblasts;

d) Competition for 17β-estradiol receptors (estrogenic receptors (ER-α and ER-β)[83]), as is the case of phthalate esters (benzyl butyl phthalate [BBP] and di-butyl phthalate [DBP]), which mimic the effect of 17β-estradiol on rat osteoblasts, altering proliferative signaling.[84]

A similar effect has been observed in dental tissue, where the dental epithelium (ameloblasts) of rats would express ER-α,[85] whose activity would be inhibited, affecting amelogenesis, mainly in males.[86] In parallel, certain EDCs, such as Bisphenols, could interfere with the function of thyroid hormones – thyroxine (T4), triiodothyronine (T3) and thyroid-stimulating hormone (TSH) – affecting their synthesis, transport, metabolism or acting as an antagonist of their receptors.[87]

In this way, the effects on mineralized tissues could also be an indication of endocrine alterations, especially in regions where the environmental concentrations of these compounds are particularly high. Despite the presence of ER in dental and bone cells, and the existence of a common neuroectodermal embryological origin, between osteoblasts, odontoblasts, and pulp cells,[21–23] it is surprising to find that most OS only record abnormalities at the bone level.

However, a growing number of *in vitro*[85,88] and *in vivo*[34,88,89] studies reveal an effect of EDCs on dental tissue, similar in appearance to molar incisor hypomineralization (MIH), defined by the presence of opacities and abnormalities in the translucency of the enamel, in one of the four first permanent molars.[90–92] The anomalies would be the result of the activity of the EDCs on ER present in the dental epithelium, increasing the proliferative activity of ameloblasts, affecting the quality of the enamel.

The detection of high concentrations of EDCs in exposed individuals, as well as the presence of morphological alterations in mineralized tissues, particularly teeth,[47,53,59,63] may be relevant:

ISSN Print 0719-2460 - ISSN Online 0719-2479.

a) as a warning sign of chronic exposure to EDCs of certain populations at risk;

b) as an early marker of the presence of other systemic pathologies related to exposure to environmental contaminants;

c) contributing to the prevention of conditions such as obesity, diabetes[9] or reproductive and behavioral disorders.[8] In this way, the detection of pathologies such as MIH, frequently detected from 6 to 9 years of age and predominant in rural areas and with low socioeconomic status,[93] may be associated with exposure to substances contained in the pesticides commonly used in Chile.[75]

It is interesting to note that sex, age, ethnicity/race, as well as the presence of certain physiological states (menopause), habits (smoking), or chronic pathologies (obesity and arthritis) would influence the effect of some EDCs. Thus, the effect of PFOA and PFOS would differ according to the sex of the individuals, probably due to differences between the hormonal mechanisms –and the excretion of these compounds–.[94]

Regarding ethnic factors, the observed differences seem to reflect a certain *"biological fingerprint"* unique to each specific group of pregnant women, depending also on the route and source of exposure to EDCs (use of consumer products, diet, or environment),[95,96] factors that seem to have an influence on fetal growth.[97,98]

Regarding other modulating factors, such as the presence of chronic pathologies of inflammatory origin, the results still seem contradictory, not ruling out an association between the concen-trations of some EDCs and the presence of osteoarthritis.[99] Likewise, the metabolic state of the exposed population seems to be a relevant factor, where high concentrations of EDCs could mainly affect the bone health of obese individuals.[57]

These results suggest a possible relationship between the presence of certain pre-existing chronic inflammatory processes and the magnitude of the damage observed by exposure to EDCs.

This is possibly the result of chemicals inducing inflammatory responses.[100] It is necessary to include the analysis of this aspect in future research. Some studies have suggested that the presence of high levels of several metabolites of EDCs in the urine of adult individuals has been related to the presence of gum disease, bone loss in the perioral region or dental mobility,[73]consequently, it is relevant to analyze the effect of EDCs on periodontal tissues and their relationship with other chronic pathology of inflammatory origin such as periodontitis.

CONCLUSION.

In conclusion, the exposure of the population to EDCs in the environment, such as bisphenols or organophosphate and pyrethroid pesticides,[101] as well as the evidence of the accumulation of these compounds affecting the development and health of children, particularly in agricultural areas,[13,15,74,102] highlights the importance of financing and carrying out studies –epidemiological or experimental– to analyze the biological impact of EDCs in mineralized tissues of exposed populations, in order to reveal causal relationships between exposure to EDCs and the harmful effects observed, as well as their underlying pathophysiological mechanisms, particularly at the level of the dental-periodontal complex.

Conflict of interests:

The authors declare no conflict of interest.

Ethics approval:

Not applicable.

Funding:

Guillermo Blanco Martínez Scholarship, University of Talca.

Authors' contributions:

Authorship included participation in the conception of the study, writing and approval of the manuscript.

Acknowledgements:

This work was carried out with the support of the Master's program in Biomedical Sciences of the University of Talca, Chile, (Guillermo Blanco Martínez Scholarship).

REFERENCES.

1. Monneret C. What is an endocrine disruptor? Endocr Disruptors Perturbateurs Endocriniens. 2017;340(9):403-5.
2. Kortenkamp A, Martin O, Faust M, Evans R, McKinley R, Orton F, et al. State of the art assessment of endocrine disruptors. Final Rep. 2011;2011:1-135.
3. Silva M. Silva, M.H., Gammon, D., 2009. An assessment of developmental, reproductive and neurobehavioral toxicology of endosulfan. Birth Defects Research: Part B. 86(1), 1-28. Birth Defects Res B Dev Reprod Toxicol. 2009;86:1-28.
4. Poimenova A, Markaki E, Rahiotis C, Kitraki E. Corticosterone-regulated actions in the rat brain are affected by perinatal exposure to low dose of bisphenol A. Neuroscience. 2010;167(3):741-9.
5. Braniste V, Jouault A, Gaultier E, Polizzi A, Buisson-Brenac C, Leveque M, et al. Impact of oral bisphenol A at reference doses on intestinal barrier function and sex differences after perinatal exposure in rats. Proc Natl Acad Sci U S A. 2010;107(1):448-53.
6. Menard S, Guzylack-Piriou L, Leveque M, Braniste V, Lencina C, Naturel M, Moussa L, Sekkal S, Harkat C, Gaultier E, Theodorou V, Houdeau E. Food intolerance at adulthood after perinatal exposure to the endocrine disruptor bisphenol A. FASEB J. 2014;28(11):4893-900. doi: 10.1096/fj.14-255380. Epub 2014 Aug 1. PMID: 25085925.
7. Haeno S, Maeda N, Yagi T, Tahata S, Sato M, Sakaguchi K, Miyasho T, Ueda H, Yokota H. Diethylstilbestrol decreased adrenal cholesterol and corticosterone in rats. J Endocrinol. 2014;221(2):261-72. doi: 10.1530/JOE-13-0460. PMID: 24578295.
8. Tavares RS, Escada-Rebelo S, Correia M, Mota PC, Ramalho-Santos J. The non-genomic effects of endocrine-disrupting chemicals on mammalian sperm. Reprod Camb Engl. 2016;151(1):R1-13.
9. Vom Saal FS, Nagel SC, Coe BL, Angle BM, Taylor JA. The estrogenic endocrine disrupting chemical bisphenol A (BPA) and obesity. Mol Cell Endocrinol. 2012;354(1-2):74-84.
10. Kabir ER, Rahman MS, Rahman I. A review on endocrine disruptors and their possible impacts on human health. Environ Toxicol Pharmacol. 2015;40(1):241-58.
11. Manterola C, Otzen T. Estudios Observacionales: Los Diseños Utilizados con Mayor Frecuencia en Investigación Clínica. Int J Morphol. 2014;32:634-45.
12. Muñoz Q MT, Iglesias Á VP, Lucero M BA. Exposición a organofosforados y desempeño cognitivo en escolares rurales chilenos: un estudio exploratorio. Rev Fac Nac Salud Pública. 2011;29:256-63.
13. Muñoz-Quezada MT, Lucero BA, Gutiérrez-Jara JP, Buralli RJ, Zúñiga-Venegas L, Muñoz MP, Ponce KV, Iglesias V. Longitudinal exposure to pyrethroids (3-PBA and trans-DCCA) and 2,4-D herbicide in rural schoolchildren of Maule region, Chile. Sci Total Environ. 2020;749:141512. doi: 10.1016/j.scitotenv.2020.141512. Epub 2020 Aug 4. PMID: 32846350.
14. Mora AM, Arora M, Harley KG, Kogut K, Parra K, Hernández-Bonilla D, Gunier RB, Bradman A, Smith DR, Eskenazi B. Prenatal and postnatal manganese teeth levels and neurodevelopment at 7, 9, and 10.5 years in the CHAMACOS cohort. Environ Int. 2015;84:39-54. doi: 10.1016/j.envint.2015.07.009. Epub 2015 Jul 24. PMID: 26209874; PMCID: PMC4570875.
15. Muñoz-Quezada MT, Lucero BA, Iglesias VP, Muñoz MP, Cornejo CA, Achu E, Baumert B, Hanchey A, Concha C, Brito AM, Villalobos M. Chronic exposure to organophosphate (OP) pesticides and neuropsychological functioning in farm workers: a review. Int J Occup Environ Health. 2016;22(1):68-79. doi: 10.1080/10773525.2015.1123848. Epub 2016 Apr 29. PMID: 27128815; PMCID: PMC4894272.
16. Krieter DH, Canaud B, Lemke HD, Rodriguez A, Morgenroth A, von Appen K, Dragoun GP, Wanner C. Bisphenol A in chronic kidney disease. Artif Organs. 2013;37(3):283-90. doi: 10.1111/j.1525-1594.2012.01556.x. Epub 2012 Nov 12. PMID: 23145999.
17. Zhang J, Liu XF, Liu Y, Xu LZ, Zhou LL, Tang LL, Zhuang J, Li TT, Guo WQ, Hu R, Qiu DS, Han DW. Environmental risk factors for women with polycystic ovary syndrome in china: a population-based case-control study. J Biol Regul Homeost Agents. 2014;28(2):203-11. PMID: 25001653.
18. Cardenas A, Hivert MF, Gold DR, Hauser R, Kleinman KP, Lin PD, Fleisch AF, Calafat AM, Ye X, Webster TF, Horton ES, Oken E. Associations of Perfluoroalkyl and Polyfluoroalkyl Substances With Incident Diabetes and Microvascular Disease. Diabetes Care. 2019;42(9):1824-1832. doi: 10.2337/dc18-2254. Epub 2019 Jul 11. PMID: 31296647; PMCID: PMC6702604.
19. Cardenas A, Hauser R, Gold DR, Kleinman KP, Hivert MF, Fleisch AF, et al. Association of Perfluoroalkyl and Polyfluoroalkyl Substances With Adiposity. JAMA Netw Open. 2018;1(4):e181493.
20. Rojas A, Ojeda ME, Barraza X. [Congenital malformations and pesticide exposure]. Rev Med Chil. 2000;128(4):399-404.
21. MacNeil RL, Somerman MJ. Development and regeneration of the periodontium: parallels and contrasts. Periodontol 2000. 1999;19:8-20.
22. Thesleff I. The genetic basis of tooth development and dental defects. Am J Med Genet A. 2006;140(23):2530-5.
23. Yuan Y, Chai Y. Regulatory mechanisms of jaw bone and tooth development. Curr Top Dev Biol. 2019. 2019;133:91-118.
24. Windahl SH, Andersson G, Gustafsson JA. Elucidation of estrogen receptor function in bone with the use of mouse models. Trends Endocrinol Metab TEM. 2002;13(5):195-200.
25. Cangussu MCT, Narvai PC, Castellanos Fernandez R, Djehizian V. [Dental fluorosis in Brazil: a critical review]. Cad Saude Publica. 2002;18(1):7-15.
26. Kellerhoff NM, Lussi A. ["Molar-incisor hypomineralization"]. Schweiz Monatsschrift Zahnmed Rev Mens Suisse Odonto-Stomatol Riv Mens Svizzera Odontol E Stomatol. 2004;114(3):243-53.

27. Suzuki N, Hattori A. Bisphenol A suppresses osteoclastic and osteoblastic activities in the cultured scales of goldfish. Life Sci. 2003;73(17):2237-47.
28. Rath NC, Richards MP, Huff WE, Huff GR, Balog JM. Changes in the tibial growth plates of chickens with thiram-induced dyschondroplasia. J Comp Pathol. 2005;133(1):41-52.
29. Hwang YH, Son YJ, Paik MJ, Yee ST. Effects of diisononyl phthalate on osteopenia in intact mice. Toxicol Appl Pharmacol. 2017;334:120-8.
30. Welshons WV, Nagel SC, vom Saal FS. Large effects from small exposures. III. Endocrine mechanisms mediating effects of bisphenol A at levels of human exposure. Endocrinology. 2006;147(6 Suppl):S56-69.
31. Smith EP, Boyd J, Frank GR, Takahashi H, Cohen RM, Specker B, et al. Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. N Engl J Med. 1994;331(16):1056-61.
32. Sabbieti MG, Agas D, Palermo F, Mosconi G, Santoni G, Amantini C, Farfariello V, Marchetti L. 4-nonylphenol triggers apoptosis and affects 17-β-estradiol receptors in calvarial osteoblasts. Toxicology. 2011;290(2-3):334-41. doi: 10.1016/j.tox.2011.10.014. Epub 2011 Oct 25. PMID: 22056370.
33. Holz JD, Sheu T jen, Drissi H, Matsuzawa M, Zuscik MJ, Puzas JE. Environmental agents affect skeletal growth and development. Birth Defects Res Part C Embryo Today Rev. 2007;81(1):41-50.
34. Jedeon K, De la Dure-Molla M, Brookes SJ, Loiodice S, Marciano C, Kirkham J, Canivenc-Lavier MC, Boudalia S, Bergès R, Harada H, Berdal A, Babajko S. Enamel defects reflect perinatal exposure to bisphenol A. Am J Pathol. 2013;183(1):108-18. doi: 10.1016/j.ajpath.2013.04.004. Epub 2013 Jun 10. PMID: 23764278; PMCID: PMC3703547.
35. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1. doi: 10.1186/2046-4053-4-1. PMID: 25554246; PMCID: PMC4320440.
36. Arora M, Bradman A, Austin C, Vedar M, Holland N, Eskenazi B, Smith DR. Determining fetal manganese exposure from mantle dentine of deciduous teeth. Environ Sci Technol. 2012;46(9):5118-25. doi: 10.1021/es203569f. Epub 2012 Apr 11. PMID: 22455722; PMCID: PMC3341525.
37. Gunier RB, Bradman A, Jerrett M, Smith DR, Harley KG, Austin C, Vedar M, Arora M, Eskenazi B. Determinants of manganese in prenatal dentin of shed teeth from CHAMACOS children living in an agricultural community. Environ Sci Technol. 2013;47(19):11249-57. doi: 10.1021/es4018688. Epub 2013 Sep 23. PMID: 24053404; PMCID: PMC4167759.
38. Gunier RB, Arora M, Jerrett M, Bradman A, Harley KG, Mora AM, Kogut K, Hubbard A, Austin C, Holland N, Eskenazi B. Manganese in teeth and neurodevelopment in young Mexican-American children. Environ Res. 2015 Oct;142:688-95. doi: 10.1016/j.envres.2015.09.003. PMID: 26381693; PMCID: PMC4696558.
39. Wang Y, Zhu H, Kannan K. A Review of Biomonitoring of Phthalate Exposures. Toxics. 5 de abril de 2019;7(2).
40. Lozowicka B. Health risk for children and adults consuming apples with pesticide residue. Sci Total Environ. 2015;502:184-98. doi: 10.1016/j.scitotenv.2014.09.026. Epub 2014 Sep 26. PMID: 25260164.
41. Camann DE, Schultz ST, Yau AY, Heilbrun LP, Zuniga MM, Palmer RF, Miller CS. Acetaminophen, pesticide, and diethylhexyl phthalate metabolites, anandamide, and fatty acids in deciduous molars: potential biomarkers of perinatal exposure. J Expo Sci Environ Epidemiol. 2013;23(2):190-6. doi: 10.1038/jes.2012.71. Epub 2012 Jul 18. PMID: 22805989.
42. Hassan AA, Rylander C, Brustad M, Sandanger TM. Persistent organic pollutants in meat, liver, tallow and bone marrow from semi-domesticated reindeer (Rangifer tarandus tarandus L.) in Northern Norway. Acta Vet Scand. 2013;55(1):57. doi: 10.1186/1751-0147-55-57. PMID: 23938064; PMCID: PMC3751901.
43. Daugaard-Petersen T, Langebæk R, Rigét FF, Dyck M, Letcher RJ, Hyldstrup L, Jensen JB, Dietz R, Sonne C. Persistent organic pollutants and penile bone mineral density in East Greenland and Canadian polar bears (Ursus maritimus) during 1996-2015. Environ Int. 2018;114:212-218. doi: 10.1016/j.envint.2018.02.022. Epub 2018 Mar 6. PMID: 29522985.
44. Erickson MD, Kaley RG 2nd. Applications of polychlorinated biphenyls. Environ Sci Pollut Res Int. 2011;18(2):135-51. doi: 10.1007/s11356-010-0392-1. Epub 2010 Sep 17. PMID: 20848233.
45. McGrath TJ, Ball AS, Clarke BO. Critical review of soil contamination by polybrominated diphenyl ethers (PBDEs) and novel brominated flame retardants (NBFRs); concentrations, sources and congener profiles. Environ Pollut. 2017;230:741-757. doi: 10.1016/j.envpol.2017.07.009. Epub 2017 Jul 18. PMID: 28732337.
46. Baxter CE, Pappas S, Abel MT, Kendall RJ. Organochlorine pesticides, lead, and mercury in northern bobwhite (Colinus virginianus) and scaled quail (Callipepla squamata) from the Rolling Plains ecoregion of Texas and Oklahoma. Environ Toxicol Chem. 2015;34(7):1505-10. doi: 10.1002/etc.2917. Epub 2015 Apr 30. PMID: 25663380.
47. Uhl SA, James-Todd T, Bell ML. Association of Osteoarthritis with Perfluorooctanoate and Perfluorooctane Sulfonate in NHANES 2003-2008. Environ Health Perspect. 2013;121(4):447-52. doi: 10.1289/ehp.1205673. Epub 2013 Feb 14. PMID: 23410534; PMCID: PMC3620767.
48. Pérez F, Nadal M, Navarro-Ortega A, Fàbrega F, Domingo JL, Barceló D, Farré M. Accumulation of perfluoroalkyl substances in human tissues. Environ Int. 2013;59:354-62. doi: 10.1016/j.envint.2013.06.004. Epub 2013 Jul 25. PMID: 23892228.
49. Lin LY, Wen LL, Su TC, Chen PC, Lin CY. Negative association between serum perfluorooctane sulfate concentration and bone mineral density in US premenopausal women: NHANES, 2005-2008. J Clin Endocrinol Metab. 2014;99(6):2173-80. doi: 10.1210/jc.2013-3409. Epub 2014 Feb 28. PMID: 24606077.

ISSN Print 0719-2460 - ISSN Online 0719-2479.

50. Koskela A, Koponen J, Lehenkari P, Viluksela M, Korkalainen M, Tuukkanen J. Perfluoroalkyl substances in human bone: concentrations in bones and effects on bone cell differentiation. Sci Rep. 2017;7(1):6841.

51. Authority EFS. Perfluoroalkylated substances in food: occurrence and dietary exposure. EFSA J. 2012;10(6):2743.

52. Buck RC, Franklin J, Berger U, Conder JM, Cousins IT, de Voogt P, Jensen AA, Kannan K, Mabury SA, van Leeuwen SP. Perfluoroalkyl and polyfluoroalkyl substances in the environment: terminology, classification, and origins. Integr Environ Assess Manag. 2011;7(4):513-41. doi: 10.1002/ieam.258. PMID: 21793199; PMCID: PMC3214619.

53. Khalil N, Chen A, Lee M, Czerwinski SA, Ebert JR, DeWitt JC, Kannan K. Association of Perfluoroalkyl Substances, Bone Mineral Density, and Osteoporosis in the U.S. Population in NHANES 2009-2010. Environ Health Perspect. 2016;124(1):81-7. doi: 10.1289/ehp.1307909. Epub 2015 Jun 9. PMID: 26058082; PMCID: PMC4710590.

54. Spear PA, Boily M, Giroux I, Deblois C, Leclair MH, Levasseur M, Leclair R. Study design, water quality, morphometrics and age of the bullfrog, Rana catesbeiana, in sub-watersheds of the Yamaska River drainage basin, Québec, Canada. Aquat Toxicol. 2009;91(2):110-7. doi: 10.1016/j.aquatox.2008.09.011. Epub 2008 Oct 1. PMID: 19027968.

55. Roos A, Rigét F, Orberg J. Bone mineral density in Swedish otters (Lutra lutra) in relation to PCB and DDE concentrations. Ecotoxicol Environ Saf. 2010;73(5): 1063-70.

56. Sonne C, Dyck M, Rigét FF, Beck Jensen JE, Hyldstrup L, Letcher RJ, Gustavson K, Gilbert MT, Dietz R. Penile density and globally used chemicals in Canadian and Greenland polar bears. Environ Res. 2015;137:287-91. doi: 10.1016/j.envres.2014.12.026. Epub 2015 Jan 16. PMID: 25601730.

57. Khalil N, Ebert JR, Honda M, Lee M, Nahhas RW, Koskela A, Hangartner T, Kannan K. Perfluoroalkyl substances, bone density, and cardio-metabolic risk factors in obese 8-12 year old children: A pilot study. Environ Res. 2018;160:314-321. doi: 10.1016/j.envres.2017.10.014. Epub 2017 Oct 15. PMID: 29040951.

58. Starek-Świechowicz B, Budziszewska B, Starek A. Hexachlorobenzene as a persistent organic pollutant: Toxicity and molecular mechanism of action. Pharmacol Rep PR. 2017;69(6):1232-9.

59. Côté S, Ayotte P, Dodin S, Blanchet C, Mulvad G, Petersen HS, Gingras S, Dewailly E. Plasma organochlorine concentrations and bone ultrasound measurements: a cross-sectional study in peri-and postmenopausal Inuit women from Greenland. Environ Health. 2006;5:33. doi: 10.1186/1476-069X-5-33. PMID: 17184534; PMCID: PMC1770911.

60. Olea N, Pulgar R, Pérez P, Olea-Serrano F, Rivas A, Novillo-Fertrell A, Pedraza V, Soto AM, Sonnenschein C. Estrogenicity of resin-based composites and sealants used in dentistry. Environ Health Perspect. 1996;104(3):298-305. doi: 10.1289/ehp.96104298. PMID: 8919768; PMCID: PMC1469315.

61. Krishnan AV, Stathis P, Permuth SF, Tokes L, Feldman D. Bisphenol-A: an estrogenic substance is released from polycarbonate flasks during autoclaving. Endocrinology. 1993;132(6):2279-86.

62. Biedermann S, Tschudin P, Grob K. Transfer of bisphenol A from thermal printer paper to the skin. Anal Bioanal Chem. 2010;398(1):571-6.

63. Vitku J, Kolatorova L, Franekova L, Blahos J, Simkova M, Duskova M, Skodova T, Starka L. Endocrine disruptors of the bisphenol and paraben families and bone metabolism. Physiol Res. 2018;67(Suppl 3):S455-S464. doi: 10.33549/physiolres.934005. PMID: 30484672.

64. DeFlorio-Barker SA, Turyk ME. Associations between bone mineral density and urinary phthalate metabolites among post-menopausal women: a cross-sectional study of NHANES data 2005-2010. Int J Environ Health Res. 2016;26(3):326-45. doi: 10.1080/09603123.2015.1111312. Epub 2015 Nov 20. PMID: 26586408.

65. Jeddy Z, Tobias JH, Taylor EV, Northstone K, Flanders WD, Hartman TJ. Prenatal concentrations of perfluoroalkyl substances and bone health in British girls at age 17. Arch Osteoporos. 2018;13(1):84.

66. Di Nisio A, De Rocco Ponce M, Giadone A, Rocca MS, Guidolin D, Foresta C. Perfluoroalkyl substances and bone health in young men: a pilot study. Endocrine. 2020;67(3):678-84.

67. Wang N, Wang Y, Zhang H, Guo Y, Chen C, Zhang W, Wan H, Han J, Lu Y. Association of bone mineral density with nine urinary personal care and consumer product chemicals and metabolites: A national-representative, population-based study. Environ Int. 2020;142:105865. doi: 10.1016/j.envint.2020.105865. Epub 2020 Jun 22. PMID: 32585503.

68. van Zwol-Janssens C, Trasande L, Asimakopoulos AG, Martinez-Moral MP, Kannan K, Philips EM, Rivadeneira F, Jaddoe VWV, Santos S. Fetal exposure to bisphenols and phthalates and childhood bone mass: a population-based prospective cohort study. Environ Res. 2020;186:109602. doi: 10.1016/j.envres.2020.109602. Epub 2020 May 1. PMID: 32668547; PMCID: PMC8336628.

69. Guo Y, Wang L, Kannan K. Phthalates and parabens in personal care products from China: concentrations and human exposure. Arch Environ Contam Toxicol. 2014;66(1):113-9.

70. Luo H, Sun G, Shi Y, Shen Y, Xu K. Evaluation of the Di(2-ethylhexyl) phthalate released from polyvinyl chloride medical devices that contact blood. Springer Plus. 2014; 3:58-58.

71. David RM, McKee RH, Butala JH, Barter RA, Kayser M. Esters of Aromatic Mono-, Di-, and Tricarboxylic Acids, Aromatic Diacids and Di-, Tri-, Or Polyalcohols. En: Patty's Toxicology [Internet]. American Cancer Society; 2001.

72. Buck Louis GM, Zhai S, Smarr MM, Grewal J, Zhang C, Grantz KL, Hinkle SN, Sundaram R, Lee S, Honda M, Oh J, Kannan K. Endocrine disruptors and neonatal anthropometry, NICHD Fetal Growth Studies - Singletons. Environ Int. 2018;119:515-526. doi: 10.1016/j.envint.2018.07.024. Epub 2018 Jul 26. PMID: 30055518; PMCID: PMC6267852.

73. Shiue I. Urinary heavy metals, phthalates, phenols, thiocyanate, parabens, pesticides, polyaromatic hydrocarbons but not arsenic or polyfluorinated compounds are associated with adult oral health: USA NHANES, 2011-2012. Environ Sci Pollut Res Int. 2015;22(20):15636-45. doi: 10.1007/s11356-015-4749-3. Epub 2015 May 28. PMID: 26018285.

74. Grillo Pizarro Á, Achú Peralta E, Muñoz-Quezada MT, Lucero Mondaca B. [Exposure to organophosphate pesticides and peripheral polyneuropathy in workers from Maule Region, Chile]. Rev Esp Salud Publica. 2018;92.

75. Muñoz-Quezada MT, Lucero B, Iglesias V, Muñoz MP. Vías de exposición a plaguicidas en escolares de la Provincia de Talca, Chile. Gac Sanit. 2014;28(3):190-5.

76. Garry VF. Pesticides and children. Toxicol Appl Pharmacol. 2004;198(2):152-63.

77. Mie A, Rudén C, Grandjean P. Safety of Safety Evaluation of Pesticides: developmental neurotoxicity of chlorpyrifos and chlorpyrifos-methyl. Environ Health Glob Access Sci Source. 2018;17(1):77.

78. Guo J, Zhang J, Wu C, Lv S, Lu D, Qi X, Jiang S, Feng C, Yu H, Liang W, Chang X, Zhang Y, Xu H, Cao Y, Wang G, Zhou Z. Associations of prenatal and childhood chlorpyrifos exposure with Neurodevelopment of 3-year-old children. Environ Pollut. 2019;251:538-546. doi: 10.1016/j.envpol.2019.05.040. Epub 2019 May 10. PMID: 31108286.

79. Tang ZR, Xu XL, Deng SL, Lian ZX, Yu K. Oestrogenic Endocrine Disruptors in the Placenta and the Fetus. Int J Mol Sci. 2020;21(4):1519.

80. Murphy VE, Smith R, Giles WB, Clifton VL. Endocrine regulation of human fetal growth: the role of the mother, placenta, and fetus. Endocr Rev. 2006;27(2):141-69.

81. Liu C, Du Y, Zhou B. Evaluation of estrogenic activities and mechanism of action of perfluorinated chemicals determined by vitellogenin induction in primary cultured tilapia hepatocytes. Aquat Toxicol Amst Neth. 2007;85(4):267-77.

82. Hwang JK, Min KH, Choi KH, Hwang YC, Jeong IK, Ahn KJ, et al. Bisphenol A reduces differentiation and stimulates apoptosis of osteoclasts and osteoblasts. Life Sci. 2013;93(9-11):367-72.

83. Kim JC, Shin HC, Cha SW, Koh WS, Chung MK, Han SS. Evaluation of developmental toxicity in rats exposed to the environmental estrogen bisphenol A during pregnancy. Life Sci. 2001;69(22):2611-25.

84. Agas D, Sabbieti MG, Capacchietti M, Materazzi S, Menghi G, Materazzi G, Hurley MM, Marchetti L. Benzyl butyl phthalate influences actin distribution and cell proliferation in rat Py1a osteoblasts. J Cell Biochem. 2007;101(3):543-51. doi: 10.1002/jcb.21212. PMID: 17171637.

85. Jedeon K, Loiodice S, Marciano C, Vinel A, Canivenc Lavier MC, Berdal A, Babajko S. Estrogen and bisphenol A affect male rat enamel formation and promote ameloblast proliferation. Endocrinology. 2014;155(9):3365-75. doi: 10.12 10/en.2013-2161. Epub 2014 Jul 8. PMID: 25004094.

86. Jedeon K, Loiodice S, Salhi K, Le Normand M, Houari S, Chaloyard J, Berdal A, Babajko S. Androgen Receptor Involvement in Rat Amelogenesis: An Additional Way for Endocrine-Disrupting Chemicals to Affect Enamel Synthesis. Endocrinology. 2016157(11):4287-4296. doi: 10.12 10/en.2016-1342. Epub 2016 Sep 29. PMID: 27684650.

87. Kim MJ, Park YJ. Bisphenols and Thyroid Hormone. Endocrinol Metab Seoul Korea. 2019;34(4):340-8.

88. Jedeon K, Marciano C, Loiodice S, Boudalia S, Canivenc Lavier MC, Berdal A, Babajko S. Enamel hypomineralization due to endocrine disruptors. Connect Tissue Res. 2014;55 Suppl 1:43-7. doi: 10.3109/03008207.2014.923857. PMID: 25158179.

89. Jedeon K, Berdal A, Babajko A. Impact of three endocrine disruptors, Bisphenol A, Genistein and Vinclozolin on female rat enamel. Bull Group Int Rech Sci Stomatol Odontol. 2016;53(1):e28.

90. Weerheijm KL, Jälevik B, Alaluusua S. Molar-incisor hypomineralisation. Caries Res. 2001;35(5):390-1.

91. Weerheijm KL. Molar incisor hypomineralisation (MIH). Eur J Paediatr Dent. 2003;4(3):114-20.

92. Weerheijm KL. Molar incisor hypomineralization (MIH): clinical presentation, aetiology and management. Dent Update. 2004;31(1):9-12.

93. da Costa-Silva CM, Jeremias F, de Souza JF, Cordeiro R de CL, Santos-Pinto L, Zuanon ACC. Molar incisor hypomineralization: prevalence, severity and clinical consequences in Brazilian children. Int J Paediatr Dent. 2010;20(6):426-34.

94. Betts KS. Perfluoroalkyl acids: what is the evidence telling us? Environ Health Perspect. 2007;115(5):A250-6.

95. James-Todd TM, Chiu YH, Zota AR. Racial/ethnic disparities in environmental endocrine disrupting chemicals and women's reproductive health outcomes: epidemiological examples across the life course. Curr Epidemiol Rep. 2016;3(2):161-80.

96. Nelson JW, Scammell MK, Hatch EE, Webster TF. Social disparities in exposures to bisphenol A and polyfluoroalkyl chemicals: a cross-sectional study within NHANES 2003-2006. Environ Health Glob Access Sci Source. 2012;11:10.

97. Buck Louis GM, Grewal J, Albert PS, Sciscione A, Wing DA, Grobman WA, Newman RB, Wapner R, D'Alton ME, Skupski D, Nageotte MP, Ranzini AC, Owen J, Chien EK, Craigo S, Hediger ML, Kim S, Zhang C, Grantz KL. Racial/ethnic standards for fetal growth: the NICHD Fetal Growth Studies. Am J Obstet Gynecol. 2015;213(4):449.e1-449.e41. doi: 10.1016/j.ajog.2015.08.032. PMID: 26410205; PMCID: PMC4584427.

98. Kiserud T, Piaggio G, Carroli G, Widmer M, Carvalho J, Neerup Jensen L, Giordano D, Cecatti JG, Aleem HA, Talegawkar SA, Benachi A, Diemert A, Kitoto AT, Thinkhamrop J, Lumbiganon P, Tabor A, Kriplani A, Gonzalez R, Hecher K, Hanson MA, Gülmezoglu AM, Platt LD. Correction: The World Health Organization Fetal Growth Charts: A Multinational Longitudinal Study of Ultrasound Biometric Measurements and Estimated Fetal Weight. PLoS Med. 2017;14(3):e1002284.

ISSN Print 0719-2460 - ISSN Online 0719-2479.

doi: 10.1371/journal.pmed.1002284. Erratum for: PLoS Med. 2017 Jan 24;14 (1):e1002220. Erratum in: PLoS Med. 2017 Apr 20;14 (4):e1002301. PMID: 28339475; PMCID: PMC5365101.

99. Innes KE, Ducatman AM, Luster MI, Shankar A. Association of osteoarthritis with serum levels of the environmental contaminants perfluorooctanoate and perfluorooctane sulfonate in a large Appalachian population. Am J Epidemiol. 2011;174(4):440-50.

100. Loffredo LF, Coden ME, Berdnikovs S. Endocrine Disruptor Bisphenol A (BPA) Triggers Systemic Para-Inflammation and is Sufficient to Induce Airway Allergic Sensitization in Mice. Nutrients. 2020;12(2):343.

101. Ramírez-Santana M, Farías-Gómez C, Zúñiga-Venegas L, Sandoval R, Roeleveld N, Van der Velden K, Scheepers PTJ, Pancetti F. Biomonitoring of blood cholinesterases and acylpeptide hydrolase activities in rural inhabitants exposed to pesticides in the Coquimbo Region of Chile. PLoS One. 2018;13(5):e0196084. doi: 10.1371/journal.pone.0196084. PMID: 29718943; PMCID: PMC5931667.

102. Muñoz-Quezada MT, Iglesias V, Lucero B, Steenland K, Barr DB, Levy K, Ryan PB, Alvarado S, Concha C. Predictors of exposure to organophosphate pesticides in schoolchildren in the Province of Talca, Chile. Environ Int. 2012;47:28-36. doi: 10.1016/j.envint.2012.06.002. Epub 2012 Jun 23. PMID: 22732215; PMCID: PMC3408779.