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THE ROLE OF PLASTICIZERS ON TOOTH DEVELOPMENTAL DEFECTS: A SCOPING REVIEW

O PAPEL DOS PLASTIFICANTES NOS DEFEITOS DE DESENVOLVIMENTO DENTÁRIO: UMA REVISÃO DE ESCOPO

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ABSTRACT

This review evaluated the role of plasticizers on tooth developmental defects (TDD). Six electronic databases were searched without language or date restrictions. Studies with humans and animals that evaluated the effect of any plasticizer on dental structures were considered eligible. From 1,716 studies, nine were included: eight experimental studies with rats and one case-control in humans. All studies observed TDD clinically that verified enamel opacities (n=8) and shorter incisors with blunted tips (n=1). Bisphenol A (BPA) and di-(2-ethylhexyl) phthalate (DEHP) were associated to TDD. Children of pregnant women exposed to BPA are 2.9 times more likely to have Molar Incisor Hypomineralisation (MIH); and rats exposed to BPA + fluoride presented more severe enamel defects. One article states that male rats exposed to BPA had more enamel defects during amelogenesis due to disruption of estrogen receptors; other three observed lower amounts of calcium and phosphorus from teeth of rats treated with BPA. Two papers reported that rat molar surfaces were opaque and rough in the BPA group, while another showed besides opacities, scratches, and enamel breakdown in incisors of rats exposed to DEHP. Almost of all investigated proteins and genes affected by BPA (n=7) and DEHP (n=1), and detected alterations in levels of the Enamelin, Amelogenin, Ameloblastin, and polymorphisms in H3K27me3, Klk4 and Mmp12 genes. BPA and DEHP exposure leads to enamel defects and changes in length and shape of the incisors of rats. BPA transmutes preferentially amelogenesis in male rats and may be a causative agent of MIH in humans.

Keywords: Plasticizers; Bisphenol A; Phthalic Acids; Tooth Abnormalities; Dental Enamel Hypoplasia

RESUMO

Avaliou-se o papel dos plastificantes nos defeitos de desenvolvimento dentário (DDD). Estudos em humanos e animais que avaliaram o efeito de qualquer plastificante nos dentes foram elegíveis. De 1.716 estudos, nove foram incluído: oito experimentais em ratos e um caso-controle em humanos. Todos observaram DDD clinicamente (em oito, opacidades de esmalte e, em um, incisivos mais curtos com bordas rombas). Entre os plastificantes, Bisfenol A (BFA) e di(2-etilhexil)ftalato (DEHP) estavam associados com DDD. Crianças de mães expostas, na gestação, ao BFA são 2.9 vezes mais sujeitas a hipomineralização molar incisivo (HMI); já em ratos, se expostos ao BPA+fluoreto, apresentaram defeitos de esmalte (DE) mais severos. Um artigo afirmou que ratos machos expostos ao BFA têm mais DE durante a amelogênese devido à ruptura dos receptores de estrogênio; outros 3 observaram níveis menores de cálcio e fósforo nos dentes de ratos tratados com BFA. Dois manuscritos reportaram que as superfícies de molares de ratos eram opacas e rugosas no grupo BFA, enquanto outro, mostrou, além das opacidades, arranhões e quebra do

esmalte em incisivos de ratos expostos ao DEHP. Quase todos investigaram proteínas e genes afetados pelo BFA (n=7) e DEHP (n=1), e detectaram alterações nos níveis de enamelina, amelogenina, ameloblastina, além de polimorfismos nos genes H3K27me3, Klk4 e Mmp12. Exposição a BFA e DEHP leva a DE e mudanças no comprimento e forma de incisivos em ratos. Além disso, o BFA altera preferencialmente a amelogênese em ratos machos e pode ser um agente etiológico de HMI em humanos.

Palavras chave: Plastificantes; Ácidos Ftálicos; Anormalidades Dentárias; Hipoplasia do Esmalte Dentário

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INTRODUCTION

Plasticizers have been, since 2017, the most consumed plastic additives in the world. Two of the most common and harmful plasticizer categories are phthalic acid esters (phthalates) and bisphenol A (BPA) [1]. Phthalates, mainly di-(2ethylhexyl) phthalate, constitute chemical compounds usually found in toys, food containers, cosmetics, and medical devices [2] .BPA is a synthetic organic compound widely used in the production of polycarbonate plastics, epoxy resins, dental materials [3], in food and drink can/packaging, and in the environment [4]. Despite concerns of health agencies and safety policies, most of the population is contaminated with BPA [4] and di-(2ethylhexyl) phthalate. The di-(2ethylhexyl) phthalate may still be present in many medical devices and equipment in neonatal intensivecare units, which may lead to contamination of hospitalized children [5]. BPA has been described as a typic endocrine-disrupting chemical (EDC) and has been associated with complex diseases, such as obesity [6], diabetes [7], cardiovascular diseases [8], carcinogenesis, and reproductive and immune response dysregulations [9, 10].

In addition to BPA association with complex diseases, concern arises on their adverse effect on tooth. The impact of EDC is greater during fetal and perinatal stages of life, when tooth development is initiated. Teeth have been found to be a target of BPA, which disrupts amelogenesis leading to enamel hypomineralisation [11]. Studies in rats have indicated an intricate relationship between developmental defects of enamel (DDE) and BPA exposure, accompanied by proliferative changes, serum albumin retention, and calcium deficiency [11, 12]. In the same way, recently, Bui et al. [2] found alterations on structural, biochemical, and mechanical properties of enamel of rats' teeth after exposed daily to di-(2ethylhexyl) phthalate (DEHP).

Amelogenesis occurs through a series of precisely regulated and minutely timed molecular, biochemical, and cellular events. Any abnormalities that originate during this process are referred to as DDE [13], with a specific pattern of gene expression [14]. The investigation of DDE caused by environmental factors has been the focus of intense research and debate due to the increased incidence and gravity of developmental diseases associated with environmental exposure [15].

DDE, such as enamel hypoplasia, enamel opacity, and molar-incisor hypomineralisation (MIH might affect both the primary and permanent dentitions [16]. DDE shows visible alterations to the appearance of tooth enamel as a result of damage from the enamel organ during amelogenesis. Enamel defects may be categorized as quantitative defects such as hypoplasia, or qualitative ones such as opacities [17].

Even though the etiology of DDE is already known to be multifactorial, it remains unclear. During amelogenesis, ameloblasts are primarily responsible for enamel formation and mineralization. However, although any environmental influences or genetic alterations during this period might affect ameloblasts leading to DDE [18], how environmental factors are biologically integrated during enamel formation is still poorly understood [15]. Human

deciduous teeth enamel mineralization occurs between the 13th week of intrauterine life and the 1st year of life [19]. For permanent teeth (excluding third molars), it occurs between birth and the 8th year of life [20]. Therefore, searching for the probable etiology of DDE requires feedback from pre, peri and posnatal period [21 - 24].

Understanding the current knowledge is necessary to better clarify the role of plasticizers, including phthalates and BPA, in the etiology of DDE, thus, increasing awareness, identifing barriers and opportunities in the field of scientific research. The present article performed a scoping review of the current literature on the role of plasticizers on tooth developmental defects, including DDE.

MATERIALS AND METHODS

This scoping review was registered in the Open Science Framework (OSF) (DOI: https://archive.org/details/osf-registrations-tfx4g-v1) and adhered to the Preferred Reporting Items guidelines (PRISMA-ScR) using the extension for scoping reviews [24] and to the methodology by Joanna Briggs Institute [26]. Based on Population, Concept, and Context (PCC) framework [25], studies with deciduous and permanent teeth (P) that investigated any damage to teeth (C) from exposure to plasticizers in the odontogenesis period (C) were included. Moreover, in vivo studies (in animals or humans) with a full publication in peer-reviewed journals that evaluated the effect of exposition of any plasticizer in dental structures were also included. No publication date and language restrictions were imposed. In vitro studies, letters, editorials, unpublished grey literature, guidelines, conference proceedings, case reports, methodology papers, reviews, and book chapter were excluded.

Search strategy:

Six electronic databases (MEDLINE via PubMed, Scopus, Web of Science, Cochrane Library, Embase and Latin American and Caribbean Health Sciences Literature database (LILACS) via Virtual Health Library (VHL) were searched to identify relevant studies up to July 2022, with no restriction on the language and year of publication of the studies.

For this search, a controlled vocabulary (MeSH and Entry terms) and free terms regarding plasticizers, bisphenol A, Phthalic Acids and tooth development defects together with boolean operators "OR" and "AND" were used to make search keys. The search strategy was firstly performed in PubMed and then adapted respecting syntax standards for each database, as presented in Table 1.

Study selection:

All articles retrieved from the search strategy's electronic databases were exported to a reference manager software (RayyanTM), where duplicate articles were removed. Then, in the same software, after preliminary screening of the title and the abstract performed by two independently reviewers (ALV and CSC), articles considered eligible were retrieved for full reading. If any disagreement occurred between the two reviewers and no consensus was reached, a third reviewer (AF) was contacted to resolve the conflict. In cases where the full article was not available for reading, the corresponding author or co-authors were contacted via email or social media with an article request. Studies published in languages other than the knowledge of the present authors were translated using the Google® Translate Tool at https://translate.google.com.

Table 1. Descriptors and their combinations of search strategy in each database.

ELECTRONIC DATABASES		NUMBER OF STUDIES
PubMed	(Plasticizers[mesh] OR bisphenol A[Supplementary Concept] OR Phthalic Acids[mesh] OR Plasticizer*[tiab] OR bisphenol A[tiab] OR bisphenol A sodium salt[tiab] OR bisphenol A disodium salt[tiab] OR Phthalic Acid*[tiab] OR Acids Phthalic[tiab] OR bisphenol[tiab]) AND (Tooth Abnormalities[mesh] OR Dental Enamel[mesh] OR Amelogenesis[mesh] OR AmelogenesisImperfecta[mesh] OR Dental Enamel Hypoplasia[mesh] OR Tooth Abnormalities[tiab] OR Abnormalities Tooth[tiab] OR Abnormality Tooth[tiab] OR Tooth Abnormality[tiab] OR Tee th Abnormalities[tiab] OR Abnormality Teeth[tiab] OR Dental Enamel*[tiab] OR Enamel Dental[tiab] OR Enamel*[tiab] OR Enamels Dental[tiab] OR Amelogenesis[tiab] OR Amelogenesis Imperfecta[tiab] OR Congenital Enamel Hypoplasia[tiab] OR Dental Enamel Hypoplasia[tiab] OR Hypoplastic Enamel[tiab] OR Enamel Hypoplastic[tiab] OR Enamel Hypoplasia Dental[tiab] OR Hypoplasia Dental Enamel[tiab] OR Agenesis Enamel[tiab] OR Enamel Hypoplas ia[tiab] OR Enamel Hypoplasias[tiab] OR Hypoplasias Enamel[tiab] OR Molar Incisor Hypomineralization[tiab] OR enamel developmental d efect*[tiab] OR developmental defect of enamel[tiab])	63
Scopus	TITLE-ABS-KEY (plasticizers OR "Phthalic Acids" OR plasticizer OR "bisphenol A" OR "bisphenol A sodium salt" OR "bisphenol A disodium salt" OR "Phthalic Acid" OR "Acids Phthalic" OR bisphenol) AND TITLE-ABS-KEY ("Tooth Abnormalities" OR "Dental Enamel" OR amelogenesis OR "AmelogenesisImperfecta" OR "Dental Enamel Hypoplasia" OR "Tooth Abnormalities" OR "Abnormalities Tooth" OR "Abnormality Tooth" OR "Tooth Abnormality" OR "Teet h Abnormalities" OR "Abnormality Teeth" OR "Dental Enamel" OR "Enamel Dental" OR enamel OR "Enamels Dental" OR amelogenesis OR amelogeneses OR "Amelogenesis Imperfecta" OR "Congenital Enamel Hypoplasia" OR "Dental Enamel Hypplasia" OR "Hypoplastic Enamel" OR "Enamel Hypoplastic" OR "Enamel Hypoplasia Dental" OR "Hypoplasia Dental Enamel" OR "Agenesis Enamel" OR "Enamel Hypoplasia" OR "Enamel Hypoplasias" OR "Hypoplasias Enamel" OR "Molar Incisor Hypominerali zation" OR "enamel developmental defect" OR "developmental defect of enamel")	1004
COCHRANE	#1 MeSH descriptor: [Plasticizers] explode all trees #2 MeSH descriptor: [Phthalic Acids] this term only #3 (Plasticizer* OR bisphenol A OR bisphenol A sodium salt OR bisphenol A disodium salt OR Phthalic Acid* OR Acids Phthalic OR bisphenol):ti,ab,kw #4 #1 OR #2 OR #3 #5 MeSH descriptor: [Tooth Abnormalities] explode all trees #6 MeSH descriptor: [Dental Enamel] explode all trees #7 MeSH descriptor: [Amelogenesis] explode all trees #8 MeSH descriptor: [Amelogenesis Imperfecta] explode all trees #9 MeSH descriptor: [Dental Enamel Hypoplasia] explode all trees #10 (Tooth Abnormalities OR Abnormalities Tooth OR Abnormality Tooth OR Tooth Abnormality OR Teeth Abnormalities OR Abnormality Teeth OR Dental Enamel* OR Enamel Dental OR Enamel* OR Enamels Dental OR Amelogenesis OR AmelogenesisImperfecta OR Congenital Ename l Hypoplasia OR Dental Enamel Hypoplasia OR Hypoplastic Enamel OR Enamel Hypoplastic OR Enamel Hypoplasia Dental OR Hypoplasia Dental Enamel OR Agenesis Enamel OR Enamel Hypoplasia OR Enamel Hypoplasias OR Hypoplasias Enamel OR Molar Incisor Hypomineralization OR enamel developmental defect* OR developmental defect of enamel):ti,ab,kw #11 #5 OR #6 OR #7 OR #8 OR #9 OR #10 #12 #4 AND #11	197
EMBASE	('plasticizer'/exp OR 'benzhydryl derivative'/exp OR 'phthalic acid derivative'/exp OR bisphenol:ti,ab,kw OR 'acids phthalic':ti,ab,kw OR 'phthalic acid':ti,ab,kw OR 'bisphenol a disodium salt':ti,ab,kw OR 'bisphenol a sodium salt':ti,ab,kw OR '4,4` isopropylidenediphenol':ti,ab,kw OR plasticizer:ti,ab,kw) AND ('tooth malformation'/exp OR 'enamel'/exp OR 'amelogenesis'/exp OR 'amelogenesisimperfecta'/exp OR 'enamel hypoplasia'/exp OR 'developmental defect of enamel':ti,ab,kw OR 'enamel developmental defect* ':ti,ab,kw OR 'molar incisor hypomineralization':ti,ab,kw OR 'hypoplasias enamel':ti,ab,kw OR 'enamel hypoplasias':ti,ab,kw OR 'enamel hypoplasia':ti,ab,kw OR 'agenesis enamel':ti,ab,kw OR 'hypoplasia dental enamel':ti,ab,kw OR 'enamel hypoplasia dental':ti,ab,kw OR 'enamel hypoplastic':ti,ab,kw OR 'hypoplastic enamel':ti,ab,kw OR 'dental enamel hypoplasia':ti,ab,kw OR 'congenital enamel hypoplasia':ti,ab,kw OR 'amelogenesis imperfecta':ti,ab,kw OR amelogenesis:ti,ab,kw OR 'enamels dental':ti,ab,kw OR ename l:ti,ab,kw OR 'enamel dental':ti,ab,kw OR 'dental enamel*':ti,ab,kw OR 'abnormality teeth':ti,ab,kw OR 'teeth abnormalities':ti,ab,kw OR 'tooth abnormality':ti,ab,kw OR 'abnormality tooth':ti,ab,kw OR 'abnormalities tooth':ti,ab,kw OR 'tooth malformation':ti,ab,kw)	54

Charting the Data:

The data mapping included the following data fields: a. author(s); b. year of publication; c. origin/country of origin (where the study was published or conducted); d. aims/purpose; e. study population and sample size (if applicable); f. methodology/ methods; g. intervention type, comparator and details of these (if applicable); h. duration of the intervention (if applicable); i. outcomes and details of these (e.g. how measures) (if applicable); j. key findings that relate to the scoping review question/s [26].

A thematic analysis was used to identify, analyze, and report patterns (themes) that arise through the review process [27]. The data set was also organized, described, and interpreted through a thematic analysis. Themes were identified from common patterns in the included papers and are described in the results.

RESULTS

Study selection:

The distinct steps that were carried out the search process are represented in the flow diagram (Figure 1). A total of 1,716 studies were identified and 1,408 records remained after the removal of duplicates using the reference manager software (RayyanTM). Posteriorly, 1,392 studies were removed after reading their titles and abstracts because they did not meet the inclusion criteria. Sixteen full texts were read and seven were excluded due to not fulfilling the inclusion criteria. Ultimately, nine studies were included in the review.

Study characteristics:

The data mapping of the nine included studies is shown in Table 2. The studies were published between 2013 and 2022. Six were carried out in France, one in Lebanon, one in China, and another one in Turkey. Eight experimental studies in rats and one case-control in humans were selected.

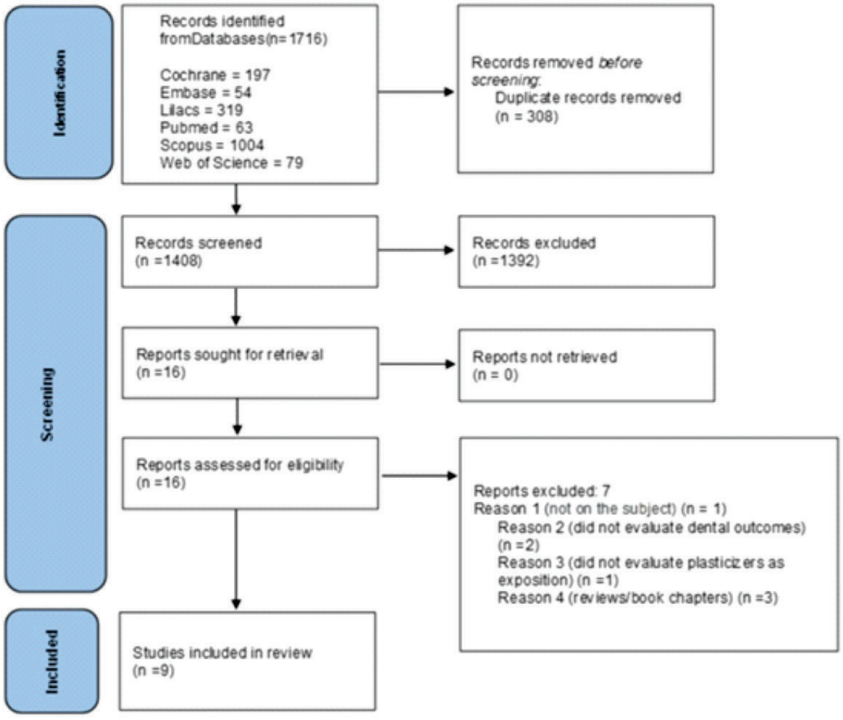

Figure 1: Flow diagram of databases searched according to PRISMA guidelines.

Thematic analysis:

Matters identified in the selected studies are described thematically in six separate headings according to the following findings: (1) Clinical tooth developmental defects; (2) BPA and Molar Incisor Hipomineralisation (MIH); (3) BPA+ fluoride (NaF); (4) BPA and estrogen; (5) Mineral analysis; (6) Proteins and genes affected by BPA and DEHP. All themes but MIH were addressed only by studies in rats.

Theme 1: Clinical tooth developmental defects

Considering the clinical outcomes related to tooth defects,the study conducted by Jedeon et al. [28] showed that 75% of mice exposed only to BPA, and 37.5% to 50% exposed to a combination of BPA and two different EDC (genistein and vinclozolin) exhibited white spot opacities on their mandibular incisors. In contrast, in another study [29] of the same group of authors same results were reported only in female rats and the prevalence was 31% and 20%, respectively. When only the results of the BPA group were shown by sex, there was a prevalence of 31% in females while 75% of males exhibited white opacities reflecting enamel hypomineralization [12]. Moreover, the teeth in the group exposed only to BPA displayed an anarchic distribution of white spots, in some cases asymmetrically and with loss of tooth substance [28; 29] or broken enamel in teeth occlude areas (molar cusps and incisor tips) emphasizing enamel fragility due to enamel hypomineralization [11]. Recently, two papers reported that all enamel rat molar surfaces were opaque and rough, along with vertical cleft areas on tubercles in the BPA group [30], while incisors presented various dose-dependent dental lesions such as opacities, scratches, and enamel breakdown in rats exposed to di-(2-ethylhexyl) phthalate (DEHP) [2].

When changes in the anatomy of the tooth were investigated, Jedeon et al. [12] did not find differences in length between control and BPA-treated mice; while Li et al. [15] reported that BPA exposed group showed shorter incisors with blunted tips, as compared with the sharp and intact cutting edge in control mice.

Theme 2: BPA and MIH

A case-control study [31] that investigated the association of molar incisor hypomineralisation (MIH) with prenatal, natal, and postnatal factors amongst 659 Lebanese children aged 7–9 years reported that the multivariate logistic regression model showed that only three risk factors were found to be associated to MIH. Among prenatal variables, children whose mothers had consumed canned food and drinks during pregnancy were 2.9 (CI: 1.367–6.187) times more likely to have MIH. In addition, no significant association between MIH and birth factors were found. In postnatal period, MIH was significantly associated to mothers who had consumed canned food and drinks during breastfeeding. However, no significant association was found between MIH and baby bottle type (plastic or glass).

In addition, in an animal study [11] that performed a phenotypic comparison between BPA-treated rat incisors and human teeth affected by MIH showed that both presented asymmetrical white spots that affected the enamel. A phenotype completely consistent with the human MIH phenotype was present in the 30th day of life in mice. Interestingly, in 100-day-old rats, erupting incisor enamel was normal, suggesting amelogenesis is only sensitive to MIH-causing agents throughout a specific time window during development (as reported for human MIH).

Theme 3: BPA+ fluoride (NaF)

Rats exposed to BPA exhibited a moderate phenotypeof enamel breakdown, while rats exposed to NaF + BPA showed a more severe phenotype with a pronounced discoloration of incisors. A transversal section of the zone of incisor eruption from the bone show a notable lower enamel density in rats exposed to BPA alone or in combination with NaF than in control animals [3].

Theme 4: BPA and estrogen

BPA has estrogen receptors (ER), ER-dependent and ER-independent, which have effects on the ameloblast proliferation and

gene transcription, impacting, preferentially, on the amelogenesis in male rats. The estrogen signaling pathway is involved in tooth development and the enamel mineralization process.These results are consistent with the steroid hormones that have effect on ameloblasts, raising the issues of the hormonal influence on amelogenesis and possible differences in enamel quality between genders [12].

Theme 5: Mineral analysis

There was a noticeable difference between the elemental composition of incisors from BPA-treated and control rats. The calcium/phosphorus (Ca/P) ratio were lower in BPA-treated rats than in controls, indicating a significant increase in the concentration of organic material relative to the mineral phase and a calcium deficiency compared with controls. These compositional differences were also mirrored in human MIH [11].

Similarly, remarkably lower calcium and phosphorus levels were detected by SEM-EDX spectra in BPA-treated mice than in control mice, although the Ca/P ratio remained unchanged [15].

More recently, Bui et al. [2] described mineral alterations in teeth of rats exposed to DEHP.

Theme 6: Proteins and genes affected by BPA and DEHP

Analysis of mRNAs extracted from microdissected dental epithelium of female rats did not show any significant difference of enamel genes expression in the various treated groups compared to the control one [29]. Levels of amelogenin (AMELX), ameloblastin (AMBN), amelotin, tuftelin, and matrix metalloprotease 20 mRNAs in whole dental enamel epithelia were unaffected by BPA. However, levels of AMELX and AMBN of all groups of rats exposed to different prenatal environmental factors, between then, BPA, were significantly lowerthan that of the control group in the secretory, transitional, and maturation stages of amelogenesis, showing the effect of this plasticizer on enamel formation [30]. The expression of Amelx, Ambn, and Enam was higher in males treated with DEHP, whereas Klk4 was not affected [2]. The levels of the mRNAs encoding the major enamel matrix proteins and proteases did not differ between mice exposed to the various combinations of EDC (genistein and vinclozolin and BPA). The only effect detected was with BPA group, which significantly increased enamelin mRNA levels and decreased klk4 mRNA levels [11; 28].

The combination of NaF and BPA affected ameloblast gene expression largely than BPA or NaF alone. The enamel genes (Amelx, Enam and Klk4) had significant differences in the expression in the maturation stage of ameloblasts in male rats exposed to BPA and BPA+NaF. Amelx and Enam were the most highly unregulated genes. Klk4 and Mmp12 were downregulated for exposure to BPA [3].

Proliferating Cell Nuclear Antigen (PCNA mRNA) levels in the cervical loop (a proliferative niche of dental cells) were determined by RT-qPCR and were significantly higher in BPA-treated mice than controls [12].

Li et al. [15] demonstrates a developmental effect of BPA on enamel formation, which is partially mediated byup regulation of repressive mark H3K27me3. The increase of EZH2 expression and function demonstrated after exposure to BPA is a potential mechanism for the increased risk of DDE.

DISCUSSION

Although animal studies are not at the top of the evidence pyramid, the continually growing rodent incisor is a model of choice to study disruption of amelogenesis because all stages of ameloblast differentiation can be investigated regardless of the age of the animal [3; 11]. Case control studies constitute a fast, practical, and low-cost method to test the effect and interaction of a large number of factors that are related to the event studied. Thus, such studies were included in the present review.

Human and animal populations are exposed to many EDC simultaneously. Consequently, the effects of combinations of EDC are unpredictable: they can potentiate each other's actions or suppress them [28; 32], making it difficult to identify which EDC is the cause of the investigated change. Therefore, studies in rats that compared exposure to

various groups of EDC (control – corn oil; bisphenol A; genistein / vinclozolin; Genistein / bisphenol A; vinclozolin / bisphenol A; genistein / vinclozolin / bisphenol A; genistein / vinclozolin) are extremely important. Jedeon et al. [29] showed that groups of mice exposed solely to BPA were the most affected. The epigenetic mechanisms of EDC, including BPA, phthalates, and diethylstilbestrol, have recently expanded our understanding of the etiology of complex human diseases [33] and disturbances in amelogenesis, which may lead to tooth development defects, including enamel defects (DED).

Identifying DED predictors and monitoring its occurrence may help reduce the risk for oral diseases such as dental caries [34] and its impact in quality of life related to oral health [35]. Enamel quality is an important marker of mother-childhood environmental conditions and of early life stressors because any environmental stress that disrupts its formation is irreversibly recorded in a time-specific manner [36; 37]. The prevalence of DDE is high, especially in regards to MIH, which is considered one of the most common pandemic health problems in the world, creating a major treatment burden [38]. However, the etiology of MIH among other defects is still unclear; the present data indicate that ameloblasts are susceptible to BPA and that BPA may be a causative agent in human MIH etiology [31].

The second most important enamel hypomineralising pathology also due to an environmental factor is dental fluorosis (DF), which is the consequence of excessive intake of systemic fluoride [39]. The current review showed interaction between exposure to NaF and BPA [3]. Rats exposed to both NaF and BPA showed a more severe phenotype than those exposed to NaF alone, characterized by the more pronounced discoloration of incisors. Similar phenotype was observed with higher doses of NaF. These results may help to explain high prevalence of enamel hypomineralsation, even in areas where the concentration of fluoride in water was reduced [40; 41].

In addition to the results of the action of plasticizers on amelogenesis can vary when associated with other ECD or NaF, it can also diversify according to hormonal influenceand probably result on sexual differences of enamel quality as reported by Jedeon et al. [12] in rat enamel. In contrast, Ludarnelli et al. [42] did not find differences between the average numbers of enamel defects and of hypoplasia in both human male and female.

Genes are also targets of plasticizers as BPA and ethyl hexyl phthalate (DEHP) on enamel structure, which makes the elucidation of the etiology of DDE quite complex. It is known that enamel isproduced by ameloblasts that secrete enamel matrix proteins (amelogenin, enamelin, ameloblastin, amelotin and tuftelin) and proteases (klk4 and mmp20) that degrade theenamel matrix allowing subsequent mineral crystalgrowth. The two maintarget genes of BPA are klk4 and enamelin, and that modulations of their expression lead to enamel hypomineralisation [11; 12; 43; 44].

CONCLUSION

This scoping review shows results from exposure to plasticizers as BPA and di-(2ethylhexyl) phthalate (DEHP) on enamel structure. It has been reported that both plasticizers exposure leads to enamel developmental defects and changes in the anatomy of the tooth in mice incisors, and that BPA may be a causative agent of human MIH. BPA has shown to mainly impact amelogenesis in male rats, and the combination of systemic NaF and BPA affected ameloblast gene expression to a greater extent than BPA or NaF alone. In addition, BPA and DEHP affect the proteins and genes involved to amelogenesis.

DECLARATIONS

Ethics approval: Not applicable

Informed consent: Not applicable

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