Mini Review

Serena Bianchi, Sara Bernardi*, Manuel Belli, Giuseppe Varvara and Guido Macchiarelli

Exposure to persistent organic pollutants during tooth formation: molecular mechanisms and clinical findings

https://doi.org/10.1515/reveh-2019-0093
Received November 17, 2019; accepted March 9, 2020

Abstract: Persistent organic pollutants (POPs) constitute a relevant part of environmental pollution. POPs are chemical compounds that persist for a long time in the environment, bio-accumulate in the human body and determine significant adverse consequences to human health. The characteristics of these substances are lipo-affinity, semivolatility and resistance to the degradation processes. Results deriving from several different studies attest that exposure to the main classes of POPs results in multiple toxic effects on humans and experimental animal models. Among the various alterations caused by exposition to and bio-accumulation of POPs, there are abnormalities in tooth formation and related hard dental tissue structure, especially enamel. This review aimed to describe the close association between the exposure of these compounds during the development of the tooth germ and the occurrence of tooth structural anomalies. Indeed, structural defects of the enamel have as possible consequences higher susceptibility of the tooth to caries disease and higher fragility of the crown to the occlusal trauma.

Keywords: developmental enamel defects; environmental exposure; persistent organic pollutants.

***Corresponding author: Sara Bernardi,** Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy; and Microscopy Centre, Universiyt of L'Aquila, L'Aquila, Italy, E-mail: sara.bernardi@univaq.it.
https://orcid.org/0000-0001-6130-8533
Serena Bianchi, Manuel Belli and Guido Macchiarelli: Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy
Giuseppe Varvara: Department of Medical, Oral and Biotechnological Sciences, 'G. d'Annunzio' University of Chieti–Pescara, Chieti, Italy

Introduction

Persistent organic pollutants (POPs) include hydrophobic organic pollutants that are toxic and persistent, and they can undergo long-range atmospheric transport and bio-accumulation (1). The main POPs present in the environment are agricultural and industrial compounds. These compounds have become a focus of global attention because of their persistent presence in the environment and their constant detection in the food reserve and drinking water (2).

The most abundant POPs in the environment are dioxins, organochlorine, and polychlorinated compounds. These are chemically stable and lipophilic, and due to their slow degradation rates, they tend to bio-accumulate primarily in lipid-rich tissues (3). Previous studies have shown how organochlorine and polychlorinated compounds accumulate in organisms and have defined their role in alterations to the endocrine and developmental systems at environmental exposure levels (4–6). As is well acknowledged, tissues and cells of human reproduction are under the control of hormones and the endocrine system (7, 8), and dysregulation of any part of these can result in significant morphological alterations to the others (9–11). As a consequence, POPs with estrogen-like effects influence the reproductive system, which can decrease embryo implantation rates and alter the development of tissues during embryo formation.

The most abundant organochlorine and polychlorinated contaminants in the environment are 1,1,1-trichloro-2,2-bis[4-chlorophenyl]ethane, better known as DDT, polychlorinated biphenyls (PCBs) with dioxin-like structures, not-dioxin-like PCBs, hexachlorocyclohexanes (HCHs), and related compounds. The commercial production and distribution of these organic compounds are for various, mainly agricultural purposes (Table 1). Due to their environmental distribution, low degradation rates, bio-accumulation, and high toxicity, the potential effects of these compounds on humans have been studied

Published online April 17, 2020

Table 1: The main persistent organic pollutants according to the Stockholm Convention list.

Chemical class	Type of use
Aldrin	Organochlorine insecticide
α-Hexachlorocyclohexane	Organochlorine insecticide
β-Hexachlorocyclohexane	Organochlorine insecticide
Chlordane	Organochlorine insecticide
Chlordecone	Organochlorine agricultural pesticide
Dieldrin	Organochlorine insecticide
Endrin	Organochlorine insecticide
Heptachlor	Organochlorine insecticide
Hexabromobiphenyl	Organobromine flame retardant
Hexabromodiphenyl ether	Organobromine flame retardant
Hexachlorobenzene	Organochlorine fungicide
Lindane	Organochlorine insecticide
Mirex	Organochlorine insecticide
Pentachlorobenzene	Chlorinated aromatic hydrocarbon insecticide
Polychlorinated biphenyls	Organochlorine compounds with several industrial applications, such as lubricating and cutting oils, plasticizers in paints and cement, pesticides, flame retardants
Tetrabromodiphenyl	Organobromine flame retardant
Toxaphene	Organochlorine insecticide

over the past several decades. Indeed, the studies on the effect of chemical pollution on animal and human health included model on dioxin-like molecules and not-dioxin-like molecules, which affect the development of hard and soft tissues during the embryological and childhood periods (12). The molecules produced by the chemical pollution and that affects human health are endocrine-disrupting chemicals (EDCs) which act on the cellular receptors in the steroid axis of the endocrine system (12). One particular effect relates to increased rates of developmental defects of tooth enamel in recent years (13). The developing enamel is sensitive to a wide range of local and systemic disturbances (14), and permanent alterations to the chemical structure can arise due to an imbalance in the metabolic homeostasis during development.

Indeed, the histological history of the dental tissues, specifically the enamel, represents one of the key markers of the Developmental Origins of Health and Disease (DOHaD) approach, allowing to date back to eventual maternal exposure to environmental factors which might affect the future adult health (15).

Thus, exposure to environmental pollutants is a likely contributor to this increased prevalence (16–18).

The aim of this review is to examine the long-term effects of exposure to the main POPs on the development of hard dental tissues. Indeed, the particular developmental stages of teeth (19) and the high resistance and availability of the dental tissues (20, 21) might make them a target in terms of prenatal exposure to POPs, as well as providing the burden of proof of the exposure itself.

Polychlorinated biphenyls

PCBs are highly persistent organochlorine environmental toxins (22). PCBs are lipophilic compounds that are known to increase in concentration up the food chain, and thus to bioconcentrate in animal and human tissues. Humans are exposed to PCBs generally through their diet, and also fetuses can receive PCBs transplacentally and infants via lactation (23). In this way, PCBs can promote developmental defects and abnormalities (24). PCBs have always been in the spotlight due to their high environmental exposure and the possibly greater sensitivity of children (25, 26). Different studies have shown that human tooth development is a sensitive target of PCB toxicity. Animal studies in several species have demonstrated that PCB exposure can cause morphological changes to ameloblasts, which are the cells depositing the enamel during tooth development (27, 28). However, the specific risk to humans from such PCB exposure remains unclear. In two cases of epidemic PCB exposure in Asia, this was associated with an excess of ectodermal defects and developmental delay (23), which included a variety of dental changes, such as mottled, chipped and carious teeth (29, 30). However, it appears that the co-exposition to polychlorinated dibenzofurans was mostly responsible for the overall toxicity (31, 32).

Hexachlorocyclohexanes

HCHs are available in two formulations: technical HCHs and lindane B. A total of eight HCH isomers have been identified in technical HCHs. Of these, only the α, β, γ, δ, and ε isomers are stable, and these are the ones commonly identified in technical HCHs. The toxicities of lindane and the various HCH mixtures depend on their metabolite hexachlorobenzene (HCB) (5, 33). Human exposure to and ingestion of HCB-treated seeds resulted in serious health effects (34). Although dental lesions have not been reported in humans, exposure to HCBs has been associated with skeletal lesions, arthritis, and defects in the hands and stature development (34). Hence, HCB appears

to have effects on mineralized tissue, and can potentially also alter the dental hard tissues.

Interactions of dioxin and dioxin-like compounds with the aryl hydrocarbon receptor

The aryl hydrocarbon receptor (AhR) is a member of the basic helix-loop-helix (bHLH) and Period/AhR nuclear translocator (ARNT)/Single-minded (PAS) protein family (35). AhR is involved in the physiological functions of the cell, such as regulation of gene transcription, protein interactions, cell proliferation, migration, and adhesion, and xenobiotic metabolism (36).

Activation of AhR can follow both genomic and non-genomic pathways. In the former, the nonactivated form of the AhR is in the cell cytosol as a complex with different chaperones (37). When a compound binds to AhR, this promotes AhR migration into the nucleus, where it can then activate ARNT protein, as an active heterodimer (38). This heterodimer can interact with the xenobiotic response element (XRE) region of target genes, to thus regulate the expression of their related molecules and the elements involved in transcriptional mechanisms. Steroid receptor coactivator 1 binding protein, cyclic adenosine monophosphate (cAMP)-response-element-binding protein, nuclear receptor coactivator 2, glucocorticoid receptor-interacting protein 1, and transcriptional intermediate factor 2 are some of the proteins that are expressed following activation of the XRE region of the target genes, depending on the ligand that binds and activates AhR (35). The most dioxin molecule studied to understand the activation of AhR has been 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). The binding of TCDD with AhR results in genomic pathway activation (Figure 1), and the consequent cytochrome P450 1 (*CYP1*) gene expression (35).

Also, the binding of TCDD with AhR defines the activation of the nongenomic pathway (Figure 2) (35). Indeed, when TCDD binds to AhR, the intracellular Ca^{2+} levels increase due to the opening of the Ca^{2+} channel in the cell membrane and the endoplasmic reticulum (35). The high Ca^{2+} concentrations activate the pathways that involve adhesion and migration of the cells, and also the production of arachidonic acid and prostaglandins, with the development of inflammation (35, 39).

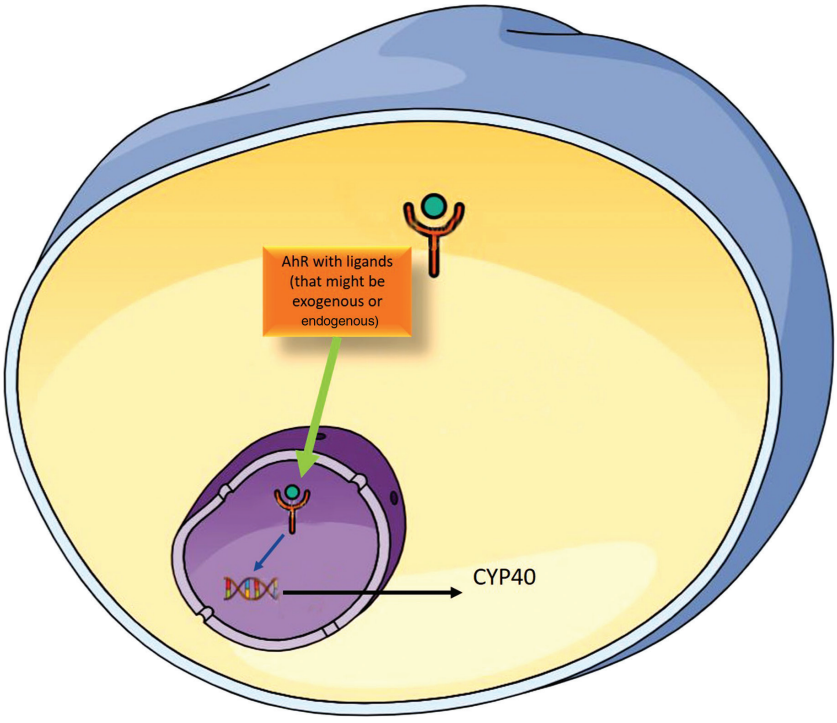

Figure 1: The genomic pathway of the activation of the AhR receptor.
Once the AhR is bonded to a ligand (which can be exogenous such as a dioxin or endogenous such as a steroid), it determines in the nucleus the activation of the genetic transcription of cytochromes.

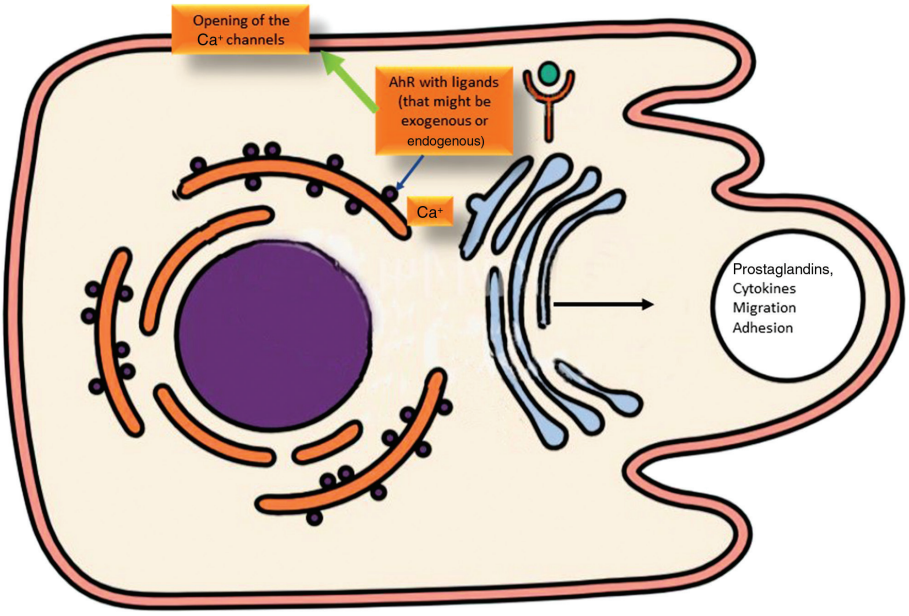

Figure 2: The not-genomic pathway of the activation of the AhR receptor.
Once the AhR is bonded to a ligand (which can be exogenous such as a dioxin or endogenous such as a steroid), the not-genomic consequences are the increase of the level of calcium, which determines adhesions and migration phenomena, together with the production of cytokines and prostaglandins.

Developmental dental defects due to exposure to dioxins, polychlorinated biphenyls, and hexachlorobenzene

The effects of POPs on developmental enamel defects have been studied both from the epidemiological and bio-morphological points of view (Table 2). Indeed, some historical environmental disasters have led to studies of people exposed over the long term, such as contamination of oil in northern Kyūshū, Japan, in 1968, contamination of the Bela Krajina region of Slovenia in the 1970s, and the Seveso disaster in 1976. These have included the pregnancies and births occurred after those periods, including studies on developmental enamel defect frequency.

Alaluusua et al. (17) conducted epidemiological studies on the association between developmental enamel defects in children and the levels of TCDDs in maternal milk. For hypomineralization of teeth, which are known to mineralize during the first 24 months of life, they demonstrated a positive association of TCDD concentrations and duration of breastfeeding (17). Later Alaluusua et al. (40) investigated the population exposed to the Seveso disaster, with analysis here of TCDD serum levels and developmental defects in tooth enamel. Indeed, as the serum samples from the time of the accident were stored for further analysis, it was possible to analyze the TCDD levels in people aged <5 years at the time of the disaster. The results of this epidemiological study showed a positive correlation between developmental enamel defects and dioxin exposure (40).

More recently, Ngoc et al. (41) conducted an observational study on Vietnam populations living in a region that had been exposed to dioxin contamination. They compared this sample population with a control sample and showed that for the population living in dioxin-contaminated regions, the frequency of developmental enamel defects was doubled (41). A similar epidemiological outcome was obtained when Jan et al. (26) studied the frequency of developmental enamel defects in children exposed to PCBs. The cohort group under investigation showed a significant association of developmental enamel defects with exposure to PCBs (26).

The epidemiological data available in the literature are supported by morphological data derived from animal model studies. Kattainen et al. (42) reported that exposure to TCDDs affected the size and even the full development of the third molar, proportional to the TCDD dosing. Indeed, the mesiodistal size of the first and second molars decreased according to TCDD dosing (42). In a similar study in 2004, Gao et al. confirmed morphological changes in the development of enamel, dentin, and

Table 2: Main studies in the literature of the effects of persistent organic pollutants on developmental enamel defects.

Study, year	Type of study	Conclusions
Alaluusua S, Lukinmaa P, Koskimies M, Pirinen S, Hölttä P, Kallio M, et al. Developmental dental defects associated with long breast feeding. Eur J Oral Sci 1996;104:493–7	Epidemiological study	Long breast feeding in case of environmental exposure may increase the risk of developmental enamel defect
Kattainen H, Tuukkanen J, Simanainen U, Tuomisto JT, Kovero O, Lukinmaa PL, et al. In utero/lactational 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin exposure impairs molar tooth development in rats. Toxicol Appl Pharmacol 2001;174:216–24	Animal model	Tooth development is influenced by the exposure to dioxins and dioxin-like compounds
Gao Y, Sahlberg C, Kiukkonen A, Alaluusua S, Pohjanvirta R, Tuomisto J, et al. Lactational exposure of Han/Wistar rats to 2,3,7,8-tetrachlorodibenzo-p-dioxin interferes with enamel maturation and retards dentin mineralization. J Dent Res 2004;83:139–44	Animal model	Dioxin-like compounds interfere with the mineralization process via AhR
Long PH, Herbert RA, Nyska A. Hexachlorobenzene-induced incisor degeneration in Sprague-Dawley rats. Toxicol Pathol 2004;32:35–40	Animal model	HCB is related to enamel defect in incisors
Alaluusua S, Calderara P, Gerthoux PM, Lukinmaa PL, Kovero O, Needham L, et al. Developmental dental aberrations after the dioxin accident in Seveso. Environ Health Perspect 2004;112:1313–8	Epidemiological study	Developmental dental defects were associated with the serum level of exposure to TCDD in children
Jan J, Sovcikova E, Kočan A, Wsolova L, Trnovec T. Developmental dental defects in children exposed to PCBs in eastern Slovakia. Chemosphere 2007;67: S350–4	Epidemiological study	The exposure to PCB was significantly related to the frequency of developmental enamel defects in permanent teeth
Guo H, Zhang L, Wei K, Zhao J, Wang Y, Jin F, et al. Exposure to a continuous low dose of tetrachlorodibenzo-p-dioxin impairs the development of the tooth root in lactational rats and alters the function of apical papilla-derived stem cells. Arch Oral Biol 2015;60:199–207	Animal model	TCDD negatively affects the development of the dental root
Ngoc VTN, Van Nhon B, Tan NTM, Van Thuc P, Hien VTT, Dung TM, et al. The higher prevalence of developmental defects of enamel in the dioxin-affected region than non-dioxin-affected region: result from a cross-sectional study in Vietnam. Odontology 2019;107:17–22	Epidemiological study	The prevalence of developmental defects of enamel was higher in the regions exposed to dioxin compounds and in particular, the lesions occurred in the anterior teeth on the vestibular side

pulp organs, with the conclusion that dioxin compounds influence tooth mineralization by acting through the AhR pathway (43).

Then, in 2015, Guo et al. focused on the effects of TCDDs on tooth root development in lactating rats. They not only confirmed that prenatal exposure to low-dose TCDDs could negatively affect dentin and enamel development but also showed how the action of dioxin on the AhR pathways impaired stem cells derived from the apical papilla and therefore caused alterations in tooth root morphology (13).

Another POP that is considered to influence tooth formation is HCB, which is contained in pesticides. Similar to dioxins, HCB binds AhR, which leads to similar genomic effects. Long et al. (33) studied incisor degeneration in rats exposed to HCB treatments. Their study showed that dental injuries from HCB exposure were dependent on the HCB dose and were specific for incisors, with alterations to the dentinogenesis for the length of the tooth. Potential secondary damage from such developmental defects was seen as perforations or root fractures, which can lead to tooth loss (33).

Discussion

Different studies have confirmed that exposure to POPs can cause multiorgan functional and morphological alterations, including various types of teeth disorders if exposure occurs in the developmental stages of life. Indeed, POPs act in the steroid axis and interfere in the formation of the hard tissues, such as bone and teeth (12). Yilmaz et al. in their study showed how organochloride interferes with the estradiol's role in the bone turnover in exposed mice (44). Bio-accumulation of POPs in the human body, as mostly dioxins, dioxin-like, and not-dioxin-like compounds, takes place through consumption of contaminated food, inhalation of polluted air, and penetration through the skin. However, about 90% of the bio-accumulated dioxin compounds arise from food intake (45).

Earlier studies demonstrated that dioxins and dioxin-like compounds mainly accumulate in fat tissue (46, 47). A more recent study indicated that these toxins are stored in human and animal fat tissues and that their elimination is correlated to life expectancy and the energy rates of

the entire metabolic processes of an organism. In humans, this period of elimination lasts 9 years (48). The accumulation of these compounds in the human body over time influences several biological functions and induces developmental disorders (48).

The influence of POPs on humans and mammals in terms of oral health has been analyzed in several studies. A morphological and structural analysis of mice teeth exposed to different concentrations of TCDD showed damage on the incisal edge of the anterior teeth and gray and spotted bleaching (49). Histological examination of mice teeth exposed to dioxin revealed a reduction in the thickness of the dentin and hypoplastic, pigmented, and poorly mineralized enamel (49). Experimental studies performed by Alaluusua and collaborators showed that POPs, in particular, and dioxin-like compounds affect the morphology and structure of the teeth in rats (50). Furthermore, TCDD causes different morphological alterations, such as thin layers of dentin and enamel, and it also influences the maturation of the enamel matrix and alters the development of crowns and roots (48). Recently, Romero et al. (51) pointed their attention to the skeletal and dental effects of not-dioxin-like pollutants. Indeed, if the endocrine disruptive mechanism of PCBs with a dioxin-like structure has been studied, the other molecules have not been considered so far. The not-dioxin-like PCBs have similar effects, but their mechanism is different. Indeed they act on the constitutive androstane receptor (CAR) and the pregnane X receptor (PXR) inducing a sexual dimorphism in the activation of the *CYP2B1* and *CYP3A1* genes in mammals (51).

Long et al. (33) demonstrated that HCB could also induce tooth damage. High exposure to HCB can predispose rat incisors to perforation or fracture through alterations in the quality or quantity of dentin (33). Different studies have confirmed the toxic effects of HCB in humans. A study performed in Japanese children whose mothers were exposed to dioxins showed an increased predisposition to caries formation and vulnerability of the hard-dental tissues (29). All these findings have demonstrated dose-response correlations between POPs' exposure and teeth abnormalities. Thus, these studies confirm an association between POPs' exposure and the prevalence of enamel and dentin alterations.

Conclusion

Exposure to POPs during the prenatal and childhood periods affects the formation of organs undergoing development, such as teeth and the related dental tissues. The present literature review includes valuable studies using animal models and epidemiological methods that demonstrate dose-dependent associations between exposure to dioxin-like compounds and prevalence of dental tissue defects. When more quantitative data are available, future systematic reviews and meta-analyses are recommended to highlight the weight of environmental exposure in the etiopathogenesis of these dental developmental defects. Future research direction should focus on the molecular mechanism of action on the endocrine axes of the other POPs, such as the not-dioxin-like molecules.

Authors' statement
Research funding: Authors state no funding involved.
Conflict of interest: Authors state no conflict of interest.
Informed consent: Informed consent is not applicable.
Ethical approval: The conducted research is not related to either human or animal use.

References

1. Lohmann R, Breivik K, Dachs J, Muir D. Global fate of POPs: current and future research directions. Environ Pollut 2007;150:150–65.
2. Snedeker SM. Pesticides and breast cancer risk: a review of DDT, DDE, and dieldrin. Environ Health Perspect 2001;109:35–47.
3. Bajwa A, Ali U, Mahmood A, Chaudhry MJ, Syed JH, Li J, et al. Organochlorine pesticides (OCPs) in the Indus River catchment area, Pakistan: status, soil–air exchange and black carbon mediated distribution. Chemosphere 2016;152:292–300.
4. Vos JG. Health effects of hexachlorobenzene and the TEF approach. Environ Health Perspect 2000;108:A58–8.
5. Palmerini MG, Zhurabekova G, Balmagambetova A, Nottola SA, Miglietta S, Belli M, et al. The pesticide lindane induces dose-dependent damage to granulosa cells in an in-vitro culture. Reprod Biol 2017;17:349–56.
6. Palmerini MG, Belli M, Nottola SA, Miglietta S, Bianchi S, Bernardi S, et al. Mancozeb impairs the ultrastructure of mouse granulosa cells in a dose-dependent manner. J Reprod Dev 2018;64:75–82.
7. Nottola SA, Cecconi S, Bianchi S, Motta C, Rossi G, Continenza MA, et al. Ultrastructure of isolated mouse ovarian follicles cultured in vitro. Reprod Biol Endocrinol 2011;9:3.
8. Palmerini MG, Nottola SA, Tunjung WAS, Kadowaki A, Bianchi S, Cecconi S, et al. EGF-FSH supplementation reduces apoptosis of pig granulosa cells in co-culture with cumulus-oocyte complexes. Biochem Biophys Res Commun 2016;481:159–64.
9. Khalili MA, Maione M, Palmerini MG, Bianchi S, Macchiarelli G, Nottola SA. Ultrastructure of human mature oocytes after vitrification. Eur J Histochem 2012;56:e38.
10. Bianchi S, Macchiarelli G, Micara G, Linari A, Boninsegna C, Aragona C, et al. Ultrastructural markers of quality are impaired in human metaphase II aged oocytes: a comparison

between reproductive and in-vitro aging. J Assist Reprod Genet 2015;32:1343–58.
11. Zhurabekova G, Balmagambetova A, Bianchi S, Belli M, Bekmukhambetov Y, Macchiarelli G. The toxicity of lindane in the female reproductive system: a review on the Aral Sea. EuroMediterranean Biomed J 2018;13:104–8.
12. Babajko S, Jedeon K, Houari S, Loiodice S, Berdal A. Disruption of steroid axis, a new paradigm for molar incisor hypomineralization (MIH). Front Physiol 2017;8:343.
13. Guo H, Zhang L, Wei K, Zhao J, Wang Y, Jin F, et al. Exposure to a continuous low dose of tetrachlorodibenzo-p-dioxin impairs the development of the tooth root in lactational rats and alters the function of apical papilla-derived stem cells. Arch Oral Biol 2015;60:199–207.
14. Small BW, Murray JJ. Enamel opacities: prevalence, classifications and aetiological considerations. J Dent 1978;6:33–42.
15. Behie AM, Miszkiewicz JJ. Enamel neonatal line thickness in deciduous teeth of Australian children from known maternal health and pregnancy conditions. Early Hum Dev 2019;137:104821.
16. Kierdorf U, Kierdorf H, Fejerskov O. Fluoride-induced developmental changes in enamel and dentine of European roe deer (Capreolus capreolus L.) as a result of environmental pollution. Arch Oral Biol 1993;38:1071–81.
17. Alaluusua S, Lukinmaa P, Koskimies M, Pirinen S, Hölttä P, Kallio M, et al. Developmental dental defects associated with long breast feeding. Eur J Oral Sci 1996;104:493–7.
18. Brook AH, Fearne JM, Smith JM. Environmental causes of enamel defects. Ciba Found Symp 1997;205:212–21.
19. Caruso S, Bernardi S, Pasini M, Giuca MR, Docimo R, Continenza MA, et al. The process of mineralisation in the development of human tooth. Eur J Paediatr Dent 2016;17:322–6.
20. Bernardi S, Bianchi S, Continenza MA, Pinchi V, Macchiarelli G. Morphological study of the labial grooves' pattern in an Italian population. Aust J Forensic Sci 2018:1–10.
21. Bernardi S, Bianchi S, Fantozzi G, Leuter C, Continenza MA, Macchiarelli G. Morphometric study on single-root premolars in a European population sample: an update on lengths and diameters. Eur J Anat 2019;23:17–25.
22. Ashraf MA. Persistent organic pollutants (POPs): a global issue, a global challenge. Environ Sci Pollut Res 2017;24:4223–7.
23. Ahlborg UG, Brouwer A, Fingerhut MA, Jacobson JL, Jacobson SW, Kennedy SW, et al. Impact of polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls on human and environmental health, with special emphasis on application of the toxic equivalency factor concept. Eur J Pharmacol Environ Toxicol Pharmacol 1992;228:179–99.
24. Ghosh S, Mitra PS, Loffredo CA, Trnovec T, Murinova L, Sovcikova E, et al. Transcriptional profiling and biological pathway analysis of human equivalence PCB exposure in vitro: indicator of disease and disorder development in humans. Environ Res 2015;138:202–16.
25. Brouwer A, Ahlborg UG, Van den Berg M, Birnbaum SL, Boersma ER, Bosveld B, et al. Functional aspects of developmental toxicity of polyhalogenated aromatic hydrocarbons in experimental animals and human infants. Eur J Pharmacol Environ Toxicol Pharmacol 1995;293:1–40.
26. Jan J, Sovcikova E, Kočan A, Wsolova L, Trnovec T. Developmental dental defects in children exposed to PCBs in eastern Slovakia. Chemosphere 2007;67:S350–4.
27. Hashiguchi I, Akamine A, Hara Y, Maeda K, Anan H, Abe T, et al. [Effects on the hard tissue of teeth in PCB-poisoned rats]. Fukuoka Igaku Zasshi 1985;76:221–8.
28. McNulty WP. Toxicity and fetotoxicity of TCDD, TCDF, and PCB isomers in rhesus macaques (Macaca mulatta). Environ Health Perspect 1985;60:77–88.
29. Hara I. Health status and PCBs in blood of workers exposed to PCBs and of their children. Environ Health Perspect 1985;59:85–90.
30. Rogan WJ, Gladen BC, Hung KL, Koong SL, Shih LY, Taylor JS, et al. Congenital poisoning by polychlorinated biphenyls and their contaminants in Taiwan. Science 1988;241:334–6.
31. Safe SH. Polychlorinated biphenyls (PCBs): environmental impact, biochemical and toxic responses, and implications for risk assessment. Crit Rev Toxicol 1994;24:87–149.
32. Masuda Y. Approach to risk assessment of chlorinated dioxins from Yusho PCB poisoning. Chemosphere 1996;32:583–94.
33. Long PH, Herbert RA, Nyska A. Hexachlorobenzene-induced incisor degeneration in Sprague-Dawley rats. Toxicol Pathol 2004;32:35–40.
34. Gocmen A, Peters H, Cripps D, Bryan G, Morris C. Hexachlorobenzene episode in Turkey. Biomed Env Sci 1989;2:36–43.
35. Larigot L, Juricek L, Dairou J, Coumoul X. AhR signaling pathways and regulatory functions. Biochim Open 2018;7:1–9.
36. Mulero-Navarro S, Fernandez-Salguero PM. New trends in aryl hydrocarbon receptor biology. Front Cell Dev Biol 2016;4:45.
37. Petrulis JR, Perdew GH. The role of chaperone proteins in the aryl hydrocarbon receptor core complex. Chem Biol Interact 2002;141:25–40.
38. Robert B, Martine A, Lawrence A, Xavier C. The aryl hydrocarbon receptor system. Drug Metabol Drug Interact 2012;27:3.
39. Varvara G, Bernardi S, Cutilli T, Bianchi S, Sinjari B, Piattelli M. Anti-inflammatory steroid use in impacted third molar surgery: a systematic review. J Biol Regul Homeost Agents 2017;31:1095–9.
40. Alaluusua S, Calderara P, Gerthoux PM, Lukinmaa PL, Kovero O, Needham L, et al. Developmental dental aberrations after the dioxin accident in Seveso. Environ Health Perspect 2004;112:1313–8.
41. Ngoc VTN, Van Nhon B, Tan NTM, Van Thuc P, Hien VTT, Dung TM, et al. The higher prevalence of developmental defects of enamel in the dioxin-affected region than non-dioxin-affected region: result from a cross-sectional study in Vietnam. Odontology 2019;107:17–22.
42. Kattainen H, Tuukkanen J, Simanainen U, Tuomisto JT, Kovero O, Lukinmaa PL, et al. In-utero/lactational 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin exposure impairs molar tooth development in rats. Toxicol Appl Pharmacol 2001;174:216–24.
43. Gao Y, Sahlberg C, Kiukkonen A, Alaluusua S, Pohjanvirta R, Tuomisto J, et al. Lactational exposure of Han/Wistar rats to 2,3,7,8-tetrachlorodibenzo-p-dioxin interferes with enamel maturation and retards dentine mineralization. J Dent Res 2004;83:139–44.
44. Yilmaz B, Seyran AD, Sandal S, Aydin M, Colakoglu N, Kocer M, et al. Modulatory effects of Aroclors 1221 and 1254 on bone turnover and vertebral histology in intact and ovariectomized rats. Toxicol Lett 2006;166:276–84.
45. Dobrzyński M, Kaczmarek U, Kuropka P, Reichert P, Grzech-Leśniak K, Całkosiński I. Tooth development disorders in infants of rat dams exposed to 2,3,7,8 tetrachlorodibenzo-p-dioxin and

protective role of tocopherol and acetylsalicylic acid. Pol J Vet Sci 2017;20:769–78.
46. Schlatter J, Zimmerli B, Dick R, Panizzon R, Schlatter C. Dietary intake and risk assessment of phototoxic furocoumarins in humans. Food Chem Toxicol 1991;29:523–30.
47. Heimler I, Trewin AL, Chaffin CL, Rawlins RG, Hutz RJ. Modulation of ovarian follicle maturation and effects on apoptotic cell death in holtzman rats exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in utero and lactationally. Reprod Toxicol 1998;12:69–73.
48. Całkosiński I, Dobrzyński M, Cegielski M, Sieja A. The multifaceted effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in organisms, especially dentition changes. Postep Hig Med Dosw 2006;60:237–40.
49. Madhukar BV, Brewster DW, Matsumura F. Effects of in-vivo–administered 2,3,7,8-tetrachlorodibenzo-p-dioxin on receptor binding of epidermal growth factor in the hepatic plasma membrane of rat, guinea pig, mouse, and hamster. Proc Natl Acad Sci USA 1984;81:7407–11.
50. Alaluusua S, Lukinmaa PL, Pohjanvirta R, Unkila M, Tuomisto J. Exposure to 2,3,7,8-tetrachlorodibenzo-para-dioxin leads to defective dentin formation and pulpal perforation in rat incisor tooth. Toxicology 1993;81:1–13.
51. Romero AN, Herlin M, Finnilä M, Korkalainen M, Håkansson H, Viluksela M, et al. Skeletal and dental effects on rats following in utero/lactational exposure to the non-dioxin-like polychlorinated biphenyl PCB 180. PLoS One 2017;12:e0185241.

Article note: The figures were realized using the infographic software MindTheGraph®.