BPA from dental resin material: where are we going with restorative and preventive dental biomaterials?

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Since a number of years, the question of the impact of BPA released from dental resins and/or sealants (or other dental materials) is open. These materials contain different monomers and many additives that are used to induce or inhibit the polymerization reaction. The monomers are mainly urethane dimethacrylate, BPA glycidyl dimethacrylate (Bis-GMA), its ethoxylated version (Bis-EMA), and BPA dimethacrylate (Bis-DMA). Comonomers such as triethylene glycol dimethacrylate are used to dilute the thick consistency and provide a higher degree of cure because of their relatively lower molecular weight [1]. BPA is used in the manufacturing process of Bis-GMA, Bis-EMA, and Bis-DMA or other similar molecules, and thus, minute amounts of BPA residues may be present in the final material. Interestingly, it has been shown that some patients treated with Bis-DMA containing materials present salivary and urinary BPA concentrations two to tenfold higher than control patients [2], which, however, decreased to almost normal after 24 h. For Bis-GMA materials, very small amounts of BPA could be detected in saliva and only neglectable amounts in urine, which also decreased 24 h after placement.

It has been published that BPA may act as an endocrine disruptor (ED), thus being able to alter functions of the endocrine system and cause adverse health effects to an intact organism or its progeny (World Health Organization (WHO) definition 2002). EDs with an estrogenic activity have been

proposed to be associated with estrogenic effects such as testicular dysgenesis, inducing testicular, prostate, and mammary gland cancers, impairing semen quality, diabetes, and obesity [3]. Some authors [3–5] claim that a series of diseases including cancer risks, type 2 diabetes, obesity, and developmental impairments are related to exposure towards BPA [3–5]. In human cross-sectional studies, BPA plasma or urine concentrations were reported to be associated among others with prostate dysplasias and abnormal birth weight [4]. A main problem in this context is the correct chemical analysis of BPA, the sensitivity of the analytical methods, and the question of BPA conjugation/glucoronization. Whereas the measurements in urine may be considered reliable, unconjugated BPA is apparently difficult to be measured in plasma because the sensitivity of the methods may not allow the measure the concentrations in the picogram per milliliter range. It is accepted that reported results in plasma/serum may be artifacts due to external contamination of the samples. Experimental studies in animals could not confirm results from reported observational studies in humans and showed general toxicity of BPA of doses above 5 mg/kg bw/day. Proliferation of mammary gland at doses of 400 µg/kg bw/day in monkeys [6] and behavioral effects in rodents at the same dose level. Although there are effects to be noted in in vitro studies on cell and tissue cultures and in vivo animal experiments, which may indicate adverse endocrine related effects due to BPA, it is still difficult to extrapolate these findings to the human clinical situation. Its precise mechanism of action is still not clear, as the signaling pathways seem to be dependent on the BPA concentrations. However, its functional interaction with estrogen receptors has been recently demonstrated and could explain at least in part its endocrine disrupting effects [4]. In the EU, USA, and Canada, BPA was banned from feeding bottles.

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The question of risk due to BPA released from dental resin fillings, fissure sealants, or other dental materials is also still debated. With respect to dental resins and sealants, Olea et al. [7] reported that between 89.8 and 931 μg of BPA was found in the saliva of patients treated with a BPA-releasing material resulting in an exposure of between 1.3 and 13.3 $\mu\text{g}/\text{kg}$ bw per person. As the release was measured to be spread over 3 days, the short-term exposure would be between 0.43 and 4.43 $\mu\text{g}/\text{kg}$ bw/day. These in vitro data could not be confirmed by other groups, but small amounts of BPA released from dental resins were found immediately and within a day or two after placement (e.g., [2, 8]). The question remains, which impact these data have for the patient, the dental personnel and the environment.

Other authors conclude from their chemical analysis that no BPA was released from polymerized sealants tested and therefore that the risk was regarded to be minimal or null [9]. Again, these data depend upon the sensitivity of the analytical method. However, it could be clarified that Bis-DMA containing resins rather than Bis-GMA-based resins released BPA shortly after placement and that collected saliva showed estrogenic activity in vitro [10–12]. Under hydrolytic conditions, the release of BPA from a fissure sealant into the saliva occurs immediately after the placement of the sealant. BPA was found in the saliva within few minutes after a dental treatment, but at considerably lower levels than previously reported. BPA became undetectable 1 and 24 h after the placement of the sealant [10, 12]. It was concluded that due to the low level of BPA, there was no clinical risk after placement of fissure sealants, an assumption that was confirmed by other authors [10, 13, 14]. Indeed, considering the dose–response, the BPA level was too low to be toxic if the disease is linked to the amount of BPA released during dental treatment. Some authors concluded that BPA-containing resins were safe and unable to induce noxious effects even considering the fact that some BPA residues due to the manufacturing process were present.

However, the discussion on BPA in general and in dentistry has not at all come to an end. Diverging views have been expressed during the last few years, including BPA differences between blood and urine analysis. Some authors claim that low doses of EDs could elicit effects, which were not seen at higher doses, these non-monotonic dose–response effects are named hormesis [15, 16]. In addition, one should keep in mind that different EDs could have potentiated impacts, which is why effects of BPA should be considered in association with other EDs. This might be especially an interesting aspect in the context of environmental effects of BPA. So, many experimental and epidemiologic studies are still needed before concluding on non-adverse effects of BPA-containing dental resins. Relevant endpoints including genomic and epigenomic effects must be defined and the

presently used limit values critically analyzed including the potential effect of low doses [16]. The recently mentioned fact that BPA is detectable in human sweat [17] might be an interesting approach as well as the recently reported route of BPA uptake through the oral mucosa [18].

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