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The safety of the use of bisphenol A in medical devices

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The European Commission's independent Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) recently published its risk assessment of exposure to BPA via medical devices that are manufactured with materials that potentially leach BPA leading to oral (via dental material), subcutaneous and intravenous (e.g. during hemodialysis) routes of exposure.

1. Background

Most people – between 91 and 99% – have Bisphenol A (BPA) conjugates in their bodies because they are exposed to BPA by eating food that contains BPA leached out from food packaging and to thermal paper that they touch (e.g. from many store and automatic bank teller receipts). For oral exposure, it is quickly absorbed from the gastro-intestinal tract and because of a high pre-systemic metabolism in the gut wall and the liver to non-toxic conjugation metabolites; BPA has a low systemic bioavailability (around 1–10% in humans) and has a half-life of a few hours.

Although BPA is mainly flushed out of the body fairly quickly if the exposure is through the oral route, BPA toxicity has nonetheless been linked to various health issues like hormonal disruption because it mimics estrogen, which has led to consumer demand for BPA-free plastic products. Yet substitutes for this key building block of polycarbonate plastic also raise concerns about possible associated health risks and more research is needed to assess these alternative materials.

Still, consumers can make choices to reduce their BPA exposure by limiting their exposure to food packaging and thermal paper, but medical and dental patients do not usually have a choice when they need medical treatment that requires the use of medical devices that may leach BPA like implants, catheters, tubing and some dental materials. European PVC manufacturers reported that they *no longer* use BPA in PVC production, but BPA-containing medical devices made of PVC outside of the EU may still be available in Europe.

Unlike BPA exposure through the oral route, by exposure through parental routes BPA is 100% systemically bioavailable and the full dose reaches the systemic circulation intact. However, BPA will also be conjugated in the liver and the clearance of free BPA from the circulation appeared to be relatively fast.

The NOAELs identified in several studies, including multigeneration reproductive toxicity studies, after repeated oral exposure were approximately 5 mg/kg b.w./day for effects on the liver and 50 mg/kg b.w./day for effects on the kidney. Because of the low oral systemic bioavailability, effects on kidney weight were the most sensible effects and the European Food and Safety Authority (EFSA) derived a BMDL10 of 8.96 mg/kg b.w./day based on those changes. BPA is unlikely to pose a genotoxic hazard to humans and has no carcinogenic activity, but there have been some proliferative effects on the mammary gland, of unknown significance. Neither reproductive nor prenatal developmental toxicity are critical end-points in BPA toxicity, but at doses higher than those that cause liver and kidney damage (40 mg/kg b.w./day) it has been associated with reproductive toxicity.

BPA may also have biological effects below the recently determined BMDL but the evidence is inconclusive and contradictory. Some concerns remain about low-dose effects on the mammary gland, metabolism, adiposity and neurobehaviour.

As a useful base for carrying out this risk assessment for the use of BPA in medical devices, the SCENIHR adopts the temporary oral TDI (t-TDI) of 4 μg/kg b.w./day derived by EFSA. The BMDL10 dose found in mice was translated into a human dose inducing similar effects, known as the human equivalent dose (HED). The HED of 609 μg/kg b.w./day was established considering the ratio of internal exposure in mice (on which experimental data are available) versus the internal exposure in humans, based on toxicokinetic studies.

Various exposure scenarios for medical devices were evaluated, considering things like the type of material used, information (although very scant) related to BPA leaching, the duration of a single treatment and the frequency of treatments in order to derive toxicologically relevant information regarding acute, short and long term exposure. There is little data to go on and often only estimates were used in lieu of hard data. Due to the high degree of uncertainty related to the exposure assessment, only the highest value obtained in the estimate was used.

The estimated relevant BPA exposures were: 1) 3000 ng/kg b.w./day (3 μg/kg b.w./day) for premature infants in neonatal intensive care units NICU); 2) 685 ng/kg b.w./day for prolonged medical procedures (like transplantation/implantation of an artificial organ or extracorporeal circulation) in infants (b.w. around 5 kg); 3) 57 ng/kg b.w./day for dialysis patients; 4) 0.4–12 ng/kg b.w./day for long-term exposures to medical devices; 5) 140–200 ng/kg b.w./day for, respectively, children and adults due to contact with dental materials (<24 h); 6) 2–12 ng/kg b.w./day due to long-term contact with dental materials.

For medical devices made with BPA-containing PVC, exposure might be higher with values estimated for adults up to 5000 ng/

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kg b.w./day and infants up to 12,000 ng/kg b.w./day. However estimates of exposure were based on extrapolation from data on phthalate leakage from PVC and the values are highly uncertain.

Long-term oral exposure to BPA via dental material poses only a negligible risk to human health as it is below the t-TDI of 4 μg/kg b.w./day.

For the other scenarios, differing from the long term oral exposure, the SCENIHR applied a margin of safety (MoS) approach using a dose of 6 μg/kg b.w./day (=HED/100), taking into account the bioavailability after oral route of exposure (around 1–10%) and the parenteral one (assumed as 100%).

Applying the MoS approach, the results were as follows: for the 3 μg/kg b.w./day, corresponding to medical devices use in NICU, the MoS is 2; for repeated medical procedures in infants the MoS is 10; for the other short-term exposure scenarios estimated for different medical devices it ranges from 43 to 100 and for dialysis treatments the MoS is 105.

For other scenarios the exposure ranges from 0.4 ng/kg b.w./day to 12 ng/kg b.w./day, resulting in a MoS range from 500 to 15,000.

The uptake by the oral mucosa can be significant. Assuming 100% as a worst case scenario, for the highest exposures of 200 ng/kg b.w./day the MoS would be 30. However, peak exposure occurs for <24 h, whereas the MoS of 150 is related to chronic exposure. The differences in exposure duration can be more than 5 − so a MOS of 30 for acute exposure to dental materials would suffice.

It is important to consider the duration of exposure for this risk assessment. Except for dialysis patients, who undergo repeated treatments over long periods of time, and oral exposure to BPA via dental materials, exposure to BPA via medical devices is usually limited and brief. Nonetheless, BPA may have adverse effects and represent a potential risk when it is directly available for systemic exposure after non-oral exposure routes, especially for neonates in intensive care units, infants undergoing prolonged medical procedures and for dialysis patients (for which the MoS value is ≤ 100). The benefit of medical devices must also be considered − the patients' survival may depend on their use − but whenever possible, the SCENIHR recommends that medical devices that do not leach BPA should be used.

This assessment may be updated and refined when new data on exposure via medical devices (in the actual condition of use) becomes available.

The Opinion in full may be read on the website of the European Commission's independent Scientific Committees: http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_040.pdf.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.yrtph.2016.01.014.

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