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SCENIHR final Opinion on the safety of the use of bisphenol A in medical devices [official text]

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the ECJ stated that it is for the German court to determine whether that is appropriate for correcting the defect in those products or whether it is necessary to replace the product for that purpose.

Reference

1. http://curia.europa.eu/juris/document/document.jsf;jsessionid=9ea7d2dc30ddb3dafa10683d49e992b5fde6ab85a2e5.e34KaxiLc3qMb40Rch0SaxuPc3v0?text=&docid=162686&pageIndex=0&doclang=EN&mode=req&dir=&occ=first&part=1&cid=461530.

Directive 2011/65/EU amended to exempt use of mercury and lead in specific circumstances

Annex IV to Directive 2011/65/EU on the restriction of certain hazardous substances in electrical and electronic equipment has been amended to exempt the following two specific uses of lead and mercury in medical devices:

- The use of lead as a thermal stabiliser in polyvinyl chloride (PVC) used as a base material in amperometric, potentiometric and conductometric electrochemical sensors, which are used in *in vitro* diagnostic medical devices for the analysis of blood and other body fluids and body gases; the exemption is until 31 December 2018[1].
- The use of mercury in electric rotating connectors used in intravascular ultrasound imaging systems capable of high operating frequency modes of operation (>50 MHz); the exemption is until 30 June 2019[2].

References

1. http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2015.094.01.0004.01.ENG.
2. http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2015.094.01.0006.01.ENG.

SCENIHR final Opinion on the safety of the use of bisphenol A in medical devices [official text]

In February 2015, the European Commission and its non-food Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) published their final Opinion on *The safety of the use of bisphenol A (BPA) in medical devices*[1].

For medical devices, several exposure scenarios were evaluated taking into account the material used, information related to BPA leaching, duration of a single treatment and the frequency of treatments, giving rise to toxicologically-relevant acute, short- and long-term exposure.

The SCENIHR concluded that long-term exposure to BPA via dental material is below the temporary oral tolerable daily intake (t-TDI) of 4 µg/kg bw/day, thus posing a negligible risk for human health.

For non-oral exposure routes, although based on a limited data set, the SCENIHR concluded that when the BPA is directly available for systemic exposure, the highest estimated exposure to BPA occurs during prolonged medical procedures especially for neonates in intensive care units, for infants undergoing prolonged medical procedures and for dialysis patients. Therefore, risk of adverse effects from BPA might exist in such cases, since the exposure exceeds the reference value and the exposed population can be particularly vulnerable.

Background

The use of BPA is widespread because it is a key building block of polycarbonate plastic and is used in the manufacture of monomers of epoxy resins. Some studies in various countries suggest that 91% to 99% of the population has detectable levels of BPA conjugates in their urine, mainly due to oral exposure through BPA leaching from food containers and food packaging material and dermal exposure associated with BPA use in thermal paper[2].

As a result of its durability, high heat resistance, electrical resistance and other qualities, polycarbonate with BPA as the main building block is often used in the manufacture of medical devices. Exposure routes are not limited to oral applications (i.e. for dental material) because exposure via other applications such as subcutaneous and intravenous routes may also occur (e.g. during haemodialysis).

Concerns about BPA exposure through leakage/release from medical devices, including implants, catheters and dental devices, have recently been raised, in particular with regard to the safety of vulnerable groups such as infants, pregnant and breast-feeding women. This Opinion assesses whether these concerns are warranted and provides indications on limit values for BPA release from medical devices whilst identifying any patient group that might be particularly at risk.

BPA toxicological profile

After oral exposure, BPA is readily absorbed from the gastrointestinal tract and due to the first pass effect in the liver and the small intestine it is rapidly conjugated to BPA-glucuronide and to a lesser extent to BPA-sulphate, which are not toxic. For this reason, by the oral route BPA has a low systemic bioavailability in animals (2.8%, 0.2%, 0.9% and less than 1% in rats, mice, monkeys and dogs, respectively) as well as in humans (1–10%), where the half-life is a few hours. For parenteral routes of exposure that may be relevant for medical devices, due to the lack of the hepatic first pass effects, BPA can be considered 100% systemically bioavailable. However, in this case it is then readily detoxified and eliminated in the urine.

Several toxicity studies indicate that the kidney and the liver are relevant targets for BPA toxicity. Indeed the lowest no observed adverse effect level (NOAEL) after repeated oral exposure identified in several studies, including multi-generation reproductive toxicity studies, was approximately 5 mg/kg bw/day. By applying the benchmark dose (BMD) approach, a BMDL10 of 8.96 mg/kg bw/day was derived based on the alteration in kidney weight.

Considering all data available, BPA is not likely to pose a genotoxic hazard to humans and has no carcinogenic activity, although there are some effects observed in the mammary gland, the biological significance of which is currently unknown for human health. A large number of studies is available on the effects of BPA on reproduction and pre-natal development, from which it can be concluded that reproductive or developmental toxicity are not the critical endpoints in BPA toxicity, although it does cause reproductive toxicity at doses higher than those causing liver and kidney damage.

There are studies suggesting that BPA might have biological effects below the health-based reference value; however, results are contradictory and dose-response relationships could not be established. Regarding possible low dose effects, some concern remains for effects on the mammary gland, metabolism, adiposity and neurobehaviour.

The SCENIHR has adopted the t-TDI of 4 µg/kg bw/day derived by the European Food Safety Authority,

which considers the BMDL10 as the point of departure and the uncertainties related to some effects using a BPA-specific assessment factor of 150. This t-TDI represents a useful base for carrying out a BPA risk assessment for the use of BPA in medical devices. The BMDL10 dose was translated into a human dose inducing similar effects, which is referred to as the human equivalent dose (HED). The HED of 609 µg/kg bw/day was determined using the ratio of internal exposure in mice (the species used in the study from which BMDL10 was derived) versus the internal exposure in humans based on toxicokinetic studies.

Exposure assessment

Little information was available on BPA exposure from the use of medical devices and, in many cases, estimates had to be used due to a lack of experimental data. Various exposure scenarios regarding medical devices were identified for this assessment, taking into account the type of material used, information related to BPA leaching, the duration of single treatments and frequency of treatments, which were then evaluated for toxicologically-relevant acute, short- and long-term exposure. Scenarios included external short-term contact with a medical device, short- and long-term contact with dental materials, short- and long-term contact with an implanted medical device, long-term contact via haemodialysers and contact in intensive care units with various medical devices. Exposure due to medical devices is usually for a short period of time, except in the case of haemodialysis. Implanted medical devices (including dental fillers) release high levels of BPA immediately after implantation, which quickly decrease to zero; therefore, even in this case, exposure is limited to short periods.

Risk assessment

For exposure via the oral route, it can be concluded that the long-term exposure to BPA via dental material is far below the recently derived t-TDI of 4 µg/kg bw/day.

For parenteral exposure via medical devices, the SCENIHR considered it appropriate to use the internal dose (expressed as HED/100 = 6 µg/kg bw/day) rather than the external t-TDI because of the BPA kinetic differences between routes of exposure. Applying a margin of safety (MOS) approach for the release in the oral cavity itself – taking a very conservative approach of 100% bioavailability in the oral cavity and that the peak of exposure occurs for <24 hours (representative of acute exposure in a toxicological context) – the MOS for acute exposure to dental materials is considered sufficiently large.

For the 3 µg/kg bw/day, corresponding to medical device use in intensive care, the MOS is 2; for prolonged medical procedures in infants the MOS is 10; for dialysis treatments the MOS is 105. These three medical procedures represent an area of concern. For the other scenarios, the MOS range was considered sufficiently large considering the duration of exposure. Nevertheless, scenarios related to multiple treatments of neonates in intensive care units, prolonged treatments in infants and long-term exposure of dialysis patients still raise concerns.

Conclusions

For exposure via the oral route, the SCENIHR has concluded that long-term exposure to BPA via dental material is far below the recently derived t-TDI and the risk to human health is therefore negligible.

Adverse effects may exist after non-oral exposure routes when the BPA is directly available for

systemic exposure, especially for neonates in intensive care units, for infants undergoing prolonged medical procedures and for dialysis patients.

Having said this, any possible risk must be weighed against the obvious benefits of using these medical devices. Neonates, for example, often owe their very survival to the use of medical devices which result in relatively high BPA exposure. Nevertheless, research should continue into how BPA might be replaced in these products if this substitution does not negatively impact treatment, and the toxicological profile of the alternative materials indicates an acceptable and reduced risk when compared to BPA.

When new data on exposure via medical devices become available, the current risk assessment may be refined and revised.

References

1. http://ec.europa.eu/health/scientific_committees/consultations/public_consultations/scenihr_consultation_18_en.htm.
2. The European Food Safety Authority performed risk assessments mainly related to the oral route of exposure to BPA in foodstuffs. The latest results (2015) can be found on http://www.efsa.europa.eu/en/topics/topic/bisphenol.htm.

Please note: this article has been supplied by the SCENIHR and is an official summary of the Opinion. The authors of this Opinion are: Bustos J, Castle L, De Jong WH, Gundert-Remy U, Hartemann P, Hensten A, Kopperud HM, Olea N, Piersma A, Rodriguez-Farré E, Rastogi SC and Testai E.

New German medical device rules come into effect in October 2015

On 1 October 2015, a new legal provision will come into force that will oblige German hospitals to provide patients who have been implanted with devices according to Appendix 3 of the Medical Devices Operator Ordinance (e.g. cardiac pacemakers, artificial heart valves) with information on aftercare, as well as to issue implant cards for better traceability of patients[1]. Hospitals will be required to store this information so that in the case of a corrective measure, affected patients can be identified within three working days.

Also, on this date, the processing for the re-use of critical medical devices in Germany must be certified by a Notified Body.

Reference

1. http://www.bvmed.de/download/bvmed-annual-report-2015.

Ireland's HPRA updates its guide to CFS applications for medical devices

On 28 February 2015, an updated version of the *Guide to Applications for Certificates of Free Sale [CFS] for Medical Devices*[1] was published by the Health Products Regulatory Authority (HPRA) in Ireland.

The amended guide explains that notarised proof of manufacture documents must be stamped and signed by a public notary based within Ireland. If a notarised document is being submitted by a European Authorised Representative then it will additionally need to be signed by a designated representative of the manufacturer.

In addition to the current Notified Body certificate for the relevant device(s), the application should include the Full Quality Assurance certificate listing sites of manufacture and the address of the European Authorised Representative. Notified Body certificates for quality management systems are not sufficient.