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The safety of medical devices containing DEHP plasticized PVC or other plasticizers on neonates and other groups possibly at risk (2015 update)

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The European Commission recently asked its independent Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR) for an update on its 2008 Opinion on the safety of medical devices containing di(2-ethylhexyl) phthalate (DEHP) or alternative plasticizers for their polyvinylchloride (PVC) based components in the light of new studies on DEHP activity and alternative plasticizers.

New scientific information published from 2008 and onwards was reviewed and evaluated by the SCENIHR for this Opinion, which mainly focuses on the potential health risks for patients with high exposure to DEHP or related plasticising compounds leaching from medical devices.

From the evidence analysed, it appears that the general population is mainly exposed to DEHP through a variety of routes, food being the main source from DEHP leakage from packaging. The range of body burden values from all sources, excluding medical and occupational exposure, is estimated at 1–30 μg/kg bw/d. Recent biomonitoring research suggest a current median exposure of 2–5 μg/kg bw/d. In infants and children, the 95th percentile is estimated at 6–17 μg/kg bw/d.

Patients who are exposed to medical devices that contain PVC may, however, have a higher exposure to DEHP than the general public, and some procedures in particular may expose patients to levels of DEHP significantly higher than the everyday sources resulting in exposure of the general population. Indeed, DEHP has been demonstrated to leach from the medical devices being used. The medical procedures include haemodialysis, peritoneal dialysis, heart transplantation or coronary artery bypass graft surgery, the extracorporeal membrane oxygenation treatment of neonates and adults, exchange transfusion of blood and total parenteral nutrition in neonates, enteral nutrition in neonates and adults, and the massive blood transfusion of red blood cells and plasma. The extent of exposure depends on the frequency and duration of the medical procedures and what type of medical device is being used.

Maximal and rapid oral absorption of DEHP in humans was estimated at 50–75%, but absorption can be regarded near 100% due to the underestimation of metabolites and bile excretion (ECHA, 2013). The bioavailability following parenteral exposure is considered 100%. DEHP metabolic profiles in humans are different than in rats, in which biologically active biotransformation products are excreted in urine. At variance in humans DEHP is mainly metabolised to non toxic conjugates, which are then excreted in urine. This is relevant for setting the markers of exposure in biomonitoring studies, which have to include both the free DEHP form as well as the conjugates, and to explain possible species-differences. The metabolic pathway as well as the excretion pattern of DEHP in humans is qualitatively independent on the exposure routes (oral or i.v.).

DEHP has a low oral acute toxicity, but repeated toxicity tests in rodents revealed that DEHP induces toxicity in the kidney, liver and testis. The tumours that developed in rodents, however, were formed through a mechanism (involving the peroxisome-proliferator activated receptor alpha, PPARα) that is thought to be species specific and therefore not relevant for humans. However, new studies, though, seem to indicate that other pathways may also be involved in hepatic tumour induction, so the relevance of liver cancer in rodents cannot be completely ruled out. However, the lack of genotoxicity for DEHP and its major metabolites implies that a threshold mechanism is involved and the doses inducing hepatic tumours are higher than those eliciting non-neoplastic effects. The International Agency for Research on Cancer (IARC) found sufficient evidence for the carcinogenicity of DEHP in experimental animals, and DEHP has therefore been classified since the 2008 Opinion as possibly carcinogenic to humans (Group 2B).

On the basis of reproductive and developmental toxicity studies in rats, mice, hamsters, ferrets and marmosets, DEHP is classified as category 1B for reproductive toxicity. The testis toxicity of DEHP is age dependent, with immature young animals being more susceptible to testicular toxicity by DEHP than older mature animals. However, it should be noted that rodents are more sensitive to testicular toxicity than non-human primates.

Recent epidemiological studies concerning DEHP exposure and possible effects on testosterone production, breast tumours, hypospadias and cryptorchism, decreased anogenital distance, childhood growth and pubertal development, endometriosis, neurobehaviour, obesity and insulin resistance and type 2 diabetes were either inconclusive or inconsistent.

Previously, the Tolerable Daily Intake (TDI) value of DEHP was

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set at 48 μg per kg bw per day, based on a NOAEL of 4.8 mg/kg/d for reproductive toxicity in rats and applying an assessment factor of 100 (RAR 2008 and ECB 2008). The EFSA rounded the TDI to 50 μg/kg bw/d (EFSA 2005) based on the same studies. The SCENIHR supports the previously derived TDI value and considers that the new studies are not sufficiently robust to justify the derivation of a new TDI.

The TDI is a value set up for a lifelong continuous exposure, while exposure to DEHP through medical devices is transient. It is therefore conservative to use a TDI value for risk assessment associated to exposure via medical devices, because exposure to medical devices is usually high but brief, except in the case of dialysis patients subject to long term exposure. Their median exposure levels has been estimated to exceed the TDI by 2–12 fold with peak values (up to 2200 μg/kg/d) >40 fold higher than the TDI. These exposure values thus have a small Margin of Safety (MoS) (lower than 100) using the NOAEL in rodents for induction of kidney toxicity (around 30 mg/kg/day), which is particularly relevant for that kind of patient. Therefore patients subject to hemodyalisis procedure may be at risk of DEHP induced effects.

Other groups at risk have been identified in the premature neonates in intensive care units (NICU) and infants and neonates experiencing ECMO. The survival of the former is often dependent on multiple medical procedures, which can result DEHP levels of exposure (6000 μg/kg bw/d), as high as the No Observed Adverse Effect Level (NOAEL) (4.8 mg/kg/d) for reproductive toxicity in mice.

ECMO is the medical treatment which may give the highest daily repeated exposure to neonates and infants over a short period of time (up to 35,000 μg/kg over 10 days treatment in 4 kg bw infants: assuming an equal distribution over time, this would correspond approximately to 3500 μg/kg bw/d). Therefore for these patients there is no MoS.

While examining possible risks, the obvious benefits of using medical devices cannot be forgotten: patients' survival often depends on procedures using the very medical devices that subject them to DEHP exposure.

Concerning the analysed alternative plasticisers di(2-ethylhexyl) adipate (DEHA), tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate (TOTM), 1,2-Cyclohexanedicarboxylic acid, diisononylester (DINCH), ATBC (acetyl tri-N-butyl citrate), BTHC (N-butyryl-tri-N-hexyl citrate), DINP (di-iso-nonyl phthalate), DEHT (di(2-ethylhexyl) terephthalate) and di-iso-nonyl phthalate (DINP) they showed lower or no reproductive toxicity in animal studies when compared to DEHP. The relevant endpoint for toxicity is in some cases different from reproductive effects. However, the paucity of data on their release from medical devices and consequent human exposure does not allow an appropriate risk assessment to be carried out. Glycerides, Castor-oil-mono-, hydrogenated, acetates (COMGHA) and TOTM could not be properly evaluated, since the only data available are from oral studies and since they are very poorly absorbed via the gastrointestinal tract, these data are of limited use for the parenteral route of exposure. Therefore information is insufficient to identify the hazards and limits an evaluation of alternative plasticizers.

SCENIHR recommends that researchers should continue to look for DEHP replacements in these products. More information is needed about alternative materials, about their toxicological profile and leaching properties in actual conditions of use in order to develop alternative materials that are both efficient and safe.

The full Opinion is published on the Scientific Committees website: http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_046.pdf.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.yrtph.2016.01.013.

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