Biocompatibility of the alternative plasticizer DEHT after intravenous administration based on the animal testing study: "Subacute Toxicity Study in Rats; Intravenous Infusion of DEHT for 12 hour daily for 3 weeks"

This animal testing study, which was sponsored by B|Braun, is an essential part of a comprehensive program to proof that the new plasticizer DEHT[a] is safe to patients.

By the order of the EU, the potential risk of the most frequently used plasticizer DEHP has been evaluated by the independent Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). The results have been published in a well researched report [1], which (among other things) also includes a list of potential alternative plasticizers[b]. This list and the recommendations of SCENIHR for evaluating alternative plasticizers forms the basis of the examinations carried out by B|Braun.

In the first step, the available information concerning alternative plasticizers was compiled from the literature and evaluated. Parallel to this, discussions were held with the manufacturers of these plasticizers to receive more thorough internal company information. A large portion of confidential and unpublished information was therefore made accessible to B|Braun. Based on this extensive information, it was possible to perform a comprehensive evaluation of alternative plasticizers with regard to possible risks for patients. For this evaluation, B|Braun was

[a] The chemical specification of DEHT is (Di(2-ethylhexyl) terephtalate);
Synonyms are 1.4 Benzenedicarboxylic acid, bis(2-ethylhexyl) ester, dioctylterephthalate (DOTP)

[b] Page 41 and following from the SCENIHR report

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advised by a number of independent toxicologists. After a further evaluation with regard to quality (e.g. contamination) and ensured availability, the plasticizer DEHT from the Eastman[c] company was selected as a possible candidate. This

plasticizer has already successfully replaced the potentially dangerous plasticizer DEHP used to manufacture children's toys.

The application of the plasticizer candidate DEHT in tubes for IV sets was then proven to be safe by BBraun in an extensive series of bio-compatibility and toxicity examinations.

According to the bio-compatibility requirements of ISO 8536, ISO 1135 and especially ISO 10993 for IV-Sets, all of the tests[d] suggested by the norms were carried out and passed without exception or deviations. These formed the foundation of the additional animal testing studies that were carried out.

The toxicological compatibility after oral administration[e] of DEHT had already been observed thoroughly and did indicate better compatibility compared to DEHP (see SCENIHR report). In these studies especially, the known effects of DEHP did not appear in the reproductive organs and the liver. However, for a conclusive risk evaluation, studies after intravenous administration of DEHT were still needed. Since the plasticizer can migrate from the tubes and enter the patient through the veins, this is the relevant clinical exposure. Studies after oral or intravenous administration may lead to different results, since:

1. After intravenous administration, more substance enters the body.

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[c] Trade name Eastman 168

[d] Cytotoxcicity, Hemolysis with Resonance Thromgography, Genotoxicity (Ames Test), Systemic Toxicity, Irritation, Sensitization.

[e] i.e. administered in feed or via gavage

2. After intravenous administration (in contrast to oral administration), the substance does not reach the circulatory system primarily via the liver where it is metabolized, but rather directly and unchanged.

Intravenous toxicity studies are therefore essential for the selection of a suitably alternative plasticizer.

According to the recommendations of the SCENIHR report[f], B|Braun carried out a leaching study at the Labor für medizinische Materialprüfung GmbH (BMP). This study established the maximum daily quantity of DEHT that may be released from an IV-Set during clinical use[9]. A maximum daily quantity of 0.241 mg DEHT was determined. Compared to similar studies carried out with the potentially dangerous plasticizer DEHP [2], only half was measured with DEHT. Using this quantity, a preliminary study with rats was performed by BMP in collaboration with Bayer Schering Pharma AG, where daily, up to 90-times more (21.69 mg) was administered for 21 days via intravenous infusion. In relation to the weight of a newborn child, this dose is more than a factor 1000 higher than the maximum quantity applied during clinical use. In this preliminary study, no DEHT-related effects were observed.

In the currently running main study, a higher number of animals per group are treated with intravenous doses of up to 600-times (144.6 mg per day) the expected clinical exposure during 28 days, to examine possible toxicological effects of DEHT. The In-Life phase is finished. Currently, no clinically related DEHT effects have been observed. Histopathological examinations are still upcoming. The finalization of the study report is planned for the end of 2009.

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[f] Page 45, section 2 „...The risk and benefit should be carefully evaluated for each individual medical device and each medical procedure in which the alternative needs to be used. ..."

[9] 24 h interior volume extraction with 20% fat emulsion at room temperature of a 2 m long tube

The intravenous toxicity of DEHP has been tested in a few smaller studies [3, 4, 5] showing effects on testes and liver. In contrast, no intravenous toxicity studies similar to the one carried out by B|Braun.have been reported with any of the potential alternatives. According to the current level of knowledge BBraun has

therefore fulfilled its obligation with regard to patient safety to a higher degree as it is the case with other known plasticizers.

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[1] http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_014.pdf

[2] Pharama International 3 / 2005, pages 17 to 21

[3] Agarwal D.K. et al.: Effects of parenteral di-(2-ethylhexyl)phthalate (DEHP) on gonadal biochemistry, pathology and reproductive performance of mice, J. Toxicol.Environ. Health, 26, 39-59 (1989).

[4] Nair K.G.P. et al.: Toxic effect of systemic administration of low doses of the plasticizer di-(2-ethylhexy)phthalate (DEHP)n in rats. Ind. J. Exp. Biol, 36, 264-272 (1997)

[5] Sjöberg P. et al.: Age-dependent response of the rat testes to di-(2-ethylhexy) phthalate. Environ. Health. Persp. 65, 237-242 (1986).