

## **Eucomed position on the use of DEHP-plasticized PVC in medical products**

The medical technology industry's role is to provide therapies for diseases and medical conditions including those that are life-threatening. The industry's primary responsibility is to the patient, and there is total commitment to manufacture therapeutically effective products in which the risks to patients are minimized and to use the most appropriate materials in doing so. Indeed minimization of risks is a key feature of the European medical device directives.

Medical products containing plasticized PVC were originally developed as replacements for natural rubber and glass. Products made from this material are easier to sterilize, more transparent, flexible, physically reliable, chemically stable and cost-effective. In addition, plasticized PVC often has important functional attributes such as convenience in use, softness and flexibility to avoid trauma to sensitive tissue or discomfort to the patient. Furthermore, it improves the collection of whole blood by preventing clotting and increases the range of blood treatment options available.

Soft PVC used in medical products is usually plasticized by using DEHP, di-(2-ethylhexyl) phthalate to render it softer and more flexible. According to the most recent scientific data today, there is no known cancer risk to humans at any tested exposure levels, a view endorsed by the WHO's International Association for Research in Cancer. This contradicts earlier assumptions based upon inappropriate animal models. Moreover, DEHP is the only plasticizer listed by the European Pharmacopoeia ("quality specifications for pharmaceutical preparations and their ingredients") for use in pharmaceutical and medical products.

Eucomed fully agrees with the American Council on Science and Health when it highlighted in the 1999 Koop Report: "It is important for the medical community and the public to understand that removing the phthalate would actually pose a significant health risk to individuals who depend on these devices."

Eucomed has closely followed the work being done in the EU on the risk assessment of phthalates and will take into account in the most appropriate way any recommendations made by the Commission as a result. The EU Scientific Committee on Medicinal Products and Medical Devices (SCMPMD) was asked to review the issue and on 26 September 2002 issued a report .

The report concludes that the contribution of DEHP-plasticized PVC to the delivery of health care is significant and should be taken into account in the consideration of the potential risks of adverse effects of DEHP in patients. It discusses the scientific evidence and states that:

*"There are no concerns over carcinogenicity in humans on the basis of animal studies. The general view of DEHP toxicity is therefore that mechanisms for adverse effects do seem to exist in rodents, but that these do not appear to be of great significance in non-human primates and that the evidence that such mechanisms could be operative in humans is lacking."*

However, the report goes on to say that the levels of DEHP that induce toxic effects in rodents are of the same order as the exposure that could be experienced by some neonates in clinical practice and that *"this is the basis of concerns that have been expressed by a number of organizations concerning the potential of DEHP toxicity in humans."* Mention is made of the groups of patients who experience prolonged periods of elevated DEHP exposure. Reference is also made to the need to consider alternatives, while stating that it is always necessary to evaluate the risks and benefits of these alternatives.

The report concludes that in view of the lack of a full analysis of all risks associated with potential alternative materials, no specific recommendations can be made to limit the use of DEHP in any particular patient group. Nevertheless it recommends that detailed studies are performed and further data collected in order to monitor the situation. Finally, it states, *“On the basis of the evidence presented in this report, no Tolerable Intake Value for DEHP in medical devices can be recommended.”*

In the Federal Register of 20 August 2004, the US Department of Health and Human Services announced and requested public comment on a number of nominated toxicological studies including one on DEHP proposed by the FDA in relation to possible long term risks associated with the medical exposure of infants to DEHP.

Since the publication of the SCMPMD report, a paper was presented at the American Pediatrics Society by Khodayar Rais-Bahrami et al concerning a follow-up study of adolescents exposed to DEHP as neonates on extracorporeal membrane oxygenation (ECMO) support. This follow-up study, the first of its type in humans, examined 19 children who experienced life-saving medical procedures as newborns that may have led to relatively high exposures to the phthalate DEHP. However such exposure showed no ill effects in their teenage years. The report concluded:

*“In conclusion our study of adolescents exposed to significant quantities of DEHP as neonates showed no significant adverse effects of DEHP on their physical growth and pubertal maturity. Thyroid, liver, renal, and male and female gonadal functions tested were within normal range for age and sex distribution. We hypothesize that the acute and short-term exposure to DEHP in an intravenous form and lack of significant conversion of DEHP to (mono ethylhexyl phthalate) MEHP may be protective against its long term side effects.”*

In relation to alternative materials to DEHP-plasticized PVC, the medical industry is continuously evaluating new materials and, indeed, already has a number of non-PVC alternatives. If the overall performance and safety of an alternative material is proven to be superior to DEHP-plasticized PVC, and assuming the necessary regulatory approval is obtained, such alternatives are used where appropriate. However, for a significant number of applications, no alternative materials with equivalent or superior qualities in respect to performance and safety have so far been developed.

Eucomed therefore concludes that

- DEHP-plasticized PVC has a long history of safe and effective use in medical products
- the opinions of the relevant European Commission Scientific Committee and of recent scientific literature suggest that DEHP-plasticized PVC is still a safe and useful medical material and that there are no scientific grounds, at present for restrictions on its use, although further scientific research is needed
- alternative materials may be available for some applications.
- as there have been many tens of millions of patient days of exposure to medical products containing DEHP-plasticized PVC in over 40 years without any reports of adverse effects, it can be concluded that the many benefits of the continued use of DEHP-plasticized PVC in medical products offset any perceived or actual risks following risk-benefit analysis
- the Commission should be asked to request further scientific research from both epidemiological and reproductive cell toxicity perspectives. It is suggested that this research could possibly be carried out, in the public interest, by the European Commission Joint Research Centre (JRC) in Ispra upon the request of DG Enterprise.