



EUROPEAN COMMISSION

Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs

Consumer, Environmental and Health Technologies
Health Technology and Cosmetics

SCIENTIFIC COMMITTEE ON HEALTH, ENVIRONMENTAL AND EMERGING RISKS (SCHEER)

Request for guidelines:

On the benefit-risk assessment of the presence of phthalates in certain medical devices covering phthalates which are carcinogenic, mutagenic, toxic to reproduction (CMR) or have endocrine-disrupting properties

Commission Department requesting the Opinion: Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs

1. Background

What are phthalates?

Phthalates are the esters of 1,2-benzenedicarboxylic acid (o-phthalic acid) and their chemical structure consists of one benzene ring and two ester functional groups linked with two consecutive carbons on the ring¹. The hydrocarbon chains of the ester groups are either straight or branching; they give each substance its name and they are responsible for the different properties among phthalates. Phthalate esters (PEs) are classified into three distinct groups according to the length of their carbon chain. High molecular weight (HMW) phthalates include those with 7–13 carbon atoms in their carbon chain and low molecular weight (LMW) those with 3–6 carbon atoms in their backbone. DEHP is classified as a LMW phthalate. A third group includes dimethyl phthalate (DMP) and diethyl phthalate (DEP).

What are they used for?

Phthalates are widely used in industry as plasticizers of polymers such as polyvinyl chloride (PVC). HMW phthalates are used in a variety of applications such as coated fabrics and roofing membranes. LMW phthalates are used in medical devices, adhesives, paints, inks and enteric-coated tablets. DEHP is the most widely used phthalate in medical devices. DMP and DEP are

¹ A global assessment of phthalates burden and related links to health effects. Katsikantami et al., Environ Int. 2016 Dec;97:212-236. <https://www.ncbi.nlm.nih.gov/pubmed/?term=katsikantami>

not used as plasticizers but e.g. as additives in cosmetics, medical devices, and household products.

Potential CMR or endocrine-disrupting properties

The interaction of phthalates with the polymers they are embedded in is weak, so they may migrate from the plastic product into the environment and into the human body if the product is in contact with it.

Correlation between exposure to a range of phthalates and adverse health effects has been documented in animals and humans (see for example tables in Mariana *et al.* 2016 and Katsikantami *et al.* 2016). A number of phthalates are suspected of and/or have been classified or identified as having CMR or endocrine-disrupting properties.

Previous work of Commission Scientific Committees on phthalates

Previous opinions on the most commonly used phthalate DEHP [di-(2-(ethylhexyl) phthalate] in medical devices were issued by EU Scientific Committees in 2002 (SCMPMD), 2008 and 2015 (SCENIHR). The 2008 Opinion concluded that *"So far, there is no conclusive scientific evidence that DEHP exposure via medical treatments has harmful effects in humans"*, but noted that *"newborn and pre-term born male infants are of special concern"*. In the 2015 Opinion, SCENIHR additionally identified that *"patients subject to haemodialysis procedure may be at risk of DEHP induced effects"*. The Committee noted that *"Food is the primary source of exposure to DEHP for the general population."*

In both opinions, the Committee emphasised that *"the benefit of the medical devices must also be considered"* and in the 2008 Opinion the Committee states that *"each alternative to DEHP, however, must also be evaluated with regard to their functionality in respect to medical devices. The risk and benefits of using alternative plasticizers should be evaluated case by case."* In the 2015 opinion, the Committee states that *"The potential for replacement of DEHP in these products should be considered against their efficiency in the treatment, as well as the toxicological profile and leaching properties of the alternative materials."*

The legal obligation

Article 5 paragraph 2 of the Regulation 2017/745 on medical devices stipulates: *"A device shall meet the general safety and performance requirements set out in Annex I which apply to it, taking into account its intended purpose."*

Accordingly, Section 10.4 of Annex I, which deals with substances in medical devices, states that *"Devices shall be designed and manufactured in such a way as to reduce as far as possible the risks posed by substances or particles, including wear debris, degradation products and processing residues, that may be released from the device."* Particular substances of concern are those which (a) are carcinogenic, mutagenic or toxic to reproduction (CMR), of category 1A or 1B,² or (b) have endocrine-disrupting properties (ED)³. The Regulation states that:

² in accordance with Part 3 of Annex VI to Regulation (EC) No 1272/2008

³ identified as such in accordance with the relevant provisions of Regulation (EC) No 1907/2006 or respectively of Regulation (EU) No 528/2012

"Devices, or those parts thereof or those materials used therein that:

- are invasive and come into direct contact with the human body,*
- (re)administer medicines, body liquids or other substances, including gases, to/from the body, or*
- transport or store such medicines, body fluids or substances, including gases, to be (re)administered to the body"*

shall only contain any such substance above the concentration of 0.1% weight by weight where justified pursuant to Section 10.4.2. The justification shall be based on several elements, including the latest relevant scientific committee guidelines on benefit-risk assessment of the presence of such substance in devices.

According to Section 10.4.3, the Commission shall provide a mandate to the relevant scientific committee to prepare such guidelines for phthalates which are subject to these provisions. These guidelines are explicitly requested by the Regulation to be available at the latest on the date of application of the Regulation, and are to be updated whenever appropriate on the basis of the latest scientific evidence, or at least every five years.

2. Terms of reference

The Scientific Committee is requested to provide guidelines on the benefit-risk assessment of the presence, in the medical devices specified below, of phthalates which have one or more of the following properties: carcinogenic, mutagenic, toxic to reproduction or endocrine-disrupting, according to the criteria outlined in the previous section.

The devices covered, or those parts thereof of those materials used therein, are those which:

- are invasive and come into direct contact with the human body,
- (re)administer medicines, body liquids or other substances, including gases, to/from the body, or
- transport or store such medicines, body fluids or substances, including gases, to be (re)administered to the body.

The guidelines shall include guidance on how, for an individual device, to:

- analyse and estimate potential patient or user exposure to the substance,
- analyse possible alternative substances, materials, designs, or medical treatments,
- to justify why possible substance and/or material substitutes, if available, or design changes, if feasible, are inappropriate in relation to maintaining the functionality, performance and the benefit-risk ratios of the product, including taking into account if the intended use of such devices includes treatment of children or treatment of pregnant or breastfeeding women or treatment of other patient groups considered particularly vulnerable to such substances and/or materials.

In addition, the Scientific Committee is requested to

- identify any relevant knowledge gap; and
- to give consideration to what extent of new evidence would be deemed appropriate to justify an update of these guidelines before the maximum period of five years.

In order to ensure the appropriateness of this guidance the Scientific Committee should *inter alia*:

- involve at the appropriate level the notified bodies active in the field of medical devices, or other relevant stakeholders such as Competent Authorities, professional and patient associations, industry associations, while maintaining scientific independence;
- involve to the necessary extent the relevant EU Agencies and Scientific Committees;

3. Deadline

31 March 2019

SCHEER approved this mandate at its plenary meeting on 28 September 2017.