**Scientific Committee on Health, Environmental and Emerging Risks**
**SCHEER**

# UPDATE of the 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 (ED) properties

The SCHEER adopted this document by written procedure on 14 June 2024

## ACKNOWLEDGMENTS

Members of the Working Group are acknowledged for their valuable contribution to these guidelines. The members of the Working Group are:

SCHEER members:

Teresa Borges
Rodica Mariana Ion
Wim H. de Jong (Chair and Rapporteur)
Renate Krätke
Demosthenes Panagiotakos
Emanuela Testai

SCCS member:

Ulrike Bernauer

External experts:

Pascal Amireault (Institut National de la Santé et de la Recherche Médicale, INSERM, Paris, France)
Maria Rosaria Milana (formerly Istituto Superiore di Sanità, Environment and Health Department, Roma, Italy)
Tanja Schmidt (Ansbach University of Applied Sciences, Ansbach, Germany)

Experts from EU Agencies:

Francesco Pignatti (European Medicines Agency)
Evgenia Stoyanova (European Chemicals Agency)
Katharina Volk (European Food Safety Authority)

Observer:
Hubert Chassaigne (European Commission, Joint Research Centre)

All Declarations of Working Group members are available at the following webpage:

Register of Commission expert groups and other similar entities (europa.eu)

**Keywords:** Update, guidelines, benefit-risk assessment, CMR/ED phthalates, medical devices, SCHEER.

**Guidelines to be cited as:** SCHEER (Scientific Committee on Health, Environmental and Emerging Risks), Update of the 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 (ED) properties, preliminary version adopted on 12 March 2024, final version adopted on 14 June 2024.

About the Scientific Committees (2022-2026)

Two independent non-food Scientific Committees provide the European Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

These committees are the Scientific Committee on Consumer Safety (SCCS) and the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER). The Scientific Committees review and evaluate relevant scientific data and assess potential risks. Each Committee has independent scientists from all over the world who are committed to work in the public interest.

In addition, the Commission relies upon the work of other Union bodies, such as the European Food Safety Authority (EFSA), the European Medicines Agency (EMA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCHEER

This Committee, on request of Commission services, provides Opinions on questions concerning health, environmental and emerging risks. The Committee addresses questions on:

- health and environmental risks related to pollutants in the environmental media and other biological and physical factors in relation to air quality, water, waste and soils.
- complex or multidisciplinary issues requiring a comprehensive assessment of risks to consumer safety or public health, for example antimicrobial resistance, nanotechnologies, medical devices and physical hazards such as noise and electromagnetic fields.

SCHEER members

Thomas Backhaus, Teresa Borges, Wim de Jong, Pim de Voogt, Raquel Duarte-Davidson, Peter Hoet, Rodica Mariana Ion, Renate Krätke, Demosthenes Panagiotakos, Ana Proykova, Theo Samaras, Marian Scott, Emanuela Testai, Marco Vighi, Sergey Zacharov

Contact

European Commission
DG Health and Food Safety
Directorate B: Public Health, Cancer and Health security
Unit B3: Health monitoring and cooperation, Health networks
L-2920 Luxembourg
SANTE-SCHEER@ec.europa.eu



PDF ISSN 2467-4559 ISBN 978-92-68-28232-8 doi:10.2875/3841716 EW-01-25-070-EN-N

The Opinions of the Scientific Committees present the views of the independent scientists who are members of the committees. They do not necessarily reflect the views of the European Commission. The Opinions are published by the European Commission in their original language only.

SCHEER - Opinions (europa.eu)

## Main changes in the first UPDATE of the guidelines

The 2019 "SCHEER guidelines on the benefit-risk assessment of phthalates in certain medical devices covering phthalates which are carcinogenic, mutagenic, toxic to reproduction (CMR) or have endocrine-disrupting (ED) properties" have been revised for the first time after five years. The update was based on experiences with the guidelines and a literature search over the last five years. Changes were included in the following sections:

- Scope: referring to information on the use of the guidelines.
- Introduction: regarding chemical description of substances of the group of phthalates as esters of phthalic acid, and recent regulatory developments.
- Methods: a section was included with the sources of evidence used and the use of the Weight of Evidence (WoE) approach of the SCHEER, and in view of the literature search performed.
- Framework: in the framework for the evaluation of alternatives in the non-phthalate scenario, the terminology of "potential relevant" candidates for assessment as alternatives for CMR/ED phthalates, has been changed into "most relevant" candidates (starting in Step 5 of the framework). While a number of alternatives might be available, the focus should be limited to the likely most relevant alternatives based on a preliminary evaluation of the suitability of the available alternatives. This is to avoid unnecessary extensive evaluation of many alternatives. For the evaluation of alternatives, a minimum number to be evaluated is suggested to be 3, while evaluation of less than 3 alternatives needs to be justified by additional information.
- Framework: Step 1 Description and characterisation of the composition of the medical device. Additional information with reference to (EN) ISO 10993-18 was included.
- New information on regulation regarding ED hazard classification was included (Category 1: known or presumed endocrine disruptors, and Category 2 suspected endocrine disruptors, both for human health and for the environment).
- Annexes: the number of Annexes was extended with Annex 8 that describes the exposure to currently used CMR/ED phthalate alternatives, Annex 9 that describes the health hazards of currently used CMR/ED phthalate alternatives, and Annex 10 that describes progress in the development of CMR/ED phthalate alternatives for use in blood bags.

## ABSTRACT

The SCHEER was requested to provide an update of the guidelines on the benefit-risk assessment (BRA) of the presence, in the medical devices specified in the regulation, of phthalates, which have one or more of the following properties: carcinogenic, mutagenic, toxic to reproduction (CMR) or endocrine-disrupting (ED), according to the criteria outlined in the mandate. Only minor changes were included in this update regarding terminology for selection of alternatives for the CMR/ED phthalates. The main text describing the selection and evaluation procedure remains essentially the same as presented in the guidelines as published in 2019. The update mainly concerns the progress made in the last five years regarding the application, exposure and toxicology of alternatives for the phthalate plasticisers in medical devices which is presented in additional Annexes.

Phthalates are widely used in industry as plasticisers of polymers, in a variety of applications such as coated fabrics and roofing membranes, as well as in medical devices, adhesives, paints, inks and enteric-coated tablets. Di-(2-(ethylhexyl) phthalate (DEHP) is the most widely used phthalate in medical devices. Dimethyl phthalate (DMP) and diethyl phthalate (DEP) are not used as plasticisers but for other purposes *e.g*. as additives in cosmetics, medical devices, and household products.

The interaction of phthalates with the polymers they are embedded is weak, so they may be released from the plastic product into the environment and into the human body when exposure occurs.

The Regulation (EU) 2017/745 ("Medical Device Regulation", MDR), allows the use of CMR 1A/1B and/or ED substances in certain medical devices above a concentration of 0.1% w/w when proper justification can be provided (Annex I, Chapter II Section 10.4). For such a justification, several steps need to be considered including the availability of alternative substances, materials, designs, and medical treatments. In addition, the risk associated with such alternatives should be weighed against the risk of the use of CMR 1A/1B and/or ED identified phthalates covered under the MDR Annex I, Chapter II Section 10.4.1. However, the risk by itself is not the only parameter to consider: the impact of the possible alternatives on the functionality, performance and the overall benefit-risk ratio of the medical device shall also be evaluated.

These guidelines describe the methodology on how to perform a BRA for the justification of the presence of CMR 1A or 1B and/or ED phthalates (CMR/ED phthalates) in medical devices and/or parts or materials used therein at percentages above 0.1% by weight (w/w).

They also describe the methodology for the evaluation of possible alternatives as replacement of CMR/ED phthalates currently used in medical devices, including alternative materials, designs or medical treatments.

They are intended to be used by the relevant stakeholders e.g., manufacturers, notified bodies and regulatory bodies.

The approach of these guidelines may also be used for a BRA of other CMR/ED substances present in medical devices.

For a number of plasticiser applications, alternative substances, including phthalates other than DEHP, were reported for use in medical devices. However, it can be foreseen that there may not be suitable alternatives for phthalate plasticisers available for all applications. During the preparation of the update of these guidelines for BRA of the use of CMR/ED phthalates in medical devices, the SCHEER noted that a number of BRA methodologies were theoretically available. However, there is often a lack of adequate data needed for the BRA of possible relevant alternatives to be used in medical devices. Therefore, the SCHEER again encourages manufacturers to generate high-quality data on such alternatives for CMR/ED phthalates in medical devices.

The current guidelines are an update of the guidelines on phthalates published in 2019, according to the MDR Annex I, Chapter II Section 10.4.3, stating that the guidelines need to be updated at least every five years, depending on the latest scientific evidence.

## TABLE OF CONTENTS

# A. UPDATE of the GUIDELINES on benefit-risk assessment for CMR and/or endocrine-disrupting phthalates used in medical devices

## Scope

The Regulation (EU) 2017/745 on medical devices (MDR), Annex I "General Safety and Performance Requirements", Chapter II "Requirements regarding design and manufacture", Section 10.4 deals with the presence of substances that may be released from a medical device. Annex I Chapter II Section 10.4.1 states that substances that are carcinogenic, mutagenic, or reprotoxic (CMR) of category 1A and 1B, or substances having endocrine-disrupting (ED) properties for which there is scientific evidence of probable serious effects on humans, shall only be present in devices, or parts thereof or those materials used therein, above 0.1% weight by weight (w/w) when justified according to a set of criteria listed under Section 10.4.2. The MDR Annex I, Chapter II Section 10.4.3, specifies a guideline for the use and evaluation of CMR/ED phthalates, whereas Annex I Chapter II Section 10.4.4 indicates to draft, when appropriate, such a guideline for other CMR/ED listed substances.

This is the first five-year update of the 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 (ED) properties as presented in the MDR Annex I, Chapter II Section 10.4.3.

A SCHEER call for information and experience with the 2019 published guidelines was published in 2023 and was open from 28 April 2023 until 17 July 2023. The results of this call indicated the usefulness of the guidelines, but also identified a need for more focus in specific areas of the guidelines. In addition, the call for information also revealed that the guidelines were also applied for other listed CMR/ED substances as indicated in Annex I Chapter II Section 10.4.4. For the update of these guidelines, the scientific literature was evaluated regarding new information on the toxicity of phthalates and their alternatives, as well as on the use of these alternatives in medical devices.

For the phthalates and their alternatives, as indicated in MDR Annex I, Chapter II Section 10.4.2, dedicated Annexes regarding recent scientific developments were included in this update of the guidelines. Considering the methodology for the Benefit Risk Assessment (BRA) and the reduction of hazardous substances in medical devices according to the MDR Annex I, Chapter II Section 10.4.1., the general principles of the evaluation of alternatives for phthalates may also be applicable for other CMR/ED listed substances. Indeed, the call for information also revealed that the guidelines were also applied for other listed CMR/ED substances as indicated in Annex I Chapter II Section 10.4.4, notably cobalt (Co).

These guidelines[1] describe the methodology on how to perform a BRA for the justification of the presence of CMR 1A or 1B and/or ED phthalates in medical devices at percentages above 0.1% by weight (w/w). They also describe the methodology for the evaluation of possible alternatives as replacement of CMR/ED phthalates currently used in medical devices, including alternative materials, designs or medical treatments. They are intended

[1] It should be noted that, in accordance with Regulation (EC) 2017/745, Annex I, Chapter II Section 10.4.3. and 10.4.4., updates of these guidelines might be available in the future, pending new scientific evidence, but the guidelines need to be updated at least every five years according to Annex I Chapter II Section 10.4.3.

to be used by the relevant stakeholders *e.g.* manufacturers, notified bodies and regulatory bodies.

These guidelines apply to those medical devices and components thereof indicated in Annex I, Chapter II Section 10.4.1. of the MDR. They do not provide information for the BRA of the use of a medical device itself. However, the BRA as described can be integrated within the risk management system for individual medical devices. For the BRA of medical devices in general, stakeholders are referred to Section A7.2. of MEDDEV 2.7/1, revision 4. Additional information may be found elsewhere, for example in the following documents FDA 2016, 2017, 2018, and 2019, (EN) ISO[2] 14971, and (EN) ISO/TR 24971. It should be noted that the acceptability of any risk is evaluated in relation to the benefit of the use of the medical device.

More specific information supporting the guidelines is presented in several Annexes. Annex 1 to these guidelines describes the mandate, Annex 2 describes the legal text as present in Annex I, Chapter II Section 10.4. of the MDR regarding the use of substances that could be released from the medical device and pose a risk to patients, and Annex 3 describes the definitions and abbreviations used in these guidelines. Annex 4 presents a description of CMR and/or ED substances and the classification thereof according to Regulation (EC) 1272/2008 ("Classification, Labelling and Packaging Regulation," CLP). Annex 5 describes the regulatory context on CMR/ED phthalates including specific migration limits for a number of phthalates authorised for use as additives in food contact materials (FCM). Annex 6 presents information on the use of phthalates in medical devices. Annex 7 presents additional information on various approaches for the risk benefit assessment.

Additional Annexes are included in this update of the guidelines. Annex 8 describes the exposure to a number of CMR/ED phthalate alternatives. Annex 9 describes information on the health hazards of a number of CMR/ED phthalate alternatives. Annex 10 describes progress in the development of CMR/ED phthalate alternatives for use in blood bags.

When the word "patient" is used in these guidelines, it covers professional users and other persons (*e.g.* donors in case of blood donation) exposed to the medical device, as well as patients themselves.

[2] the latest published version of the (EN) ISO standards/documents mentioned in these guidelines should be used.

## 1. Introduction

Placing medical devices on the market, making them available on the market and putting them into service are all activities governed by Regulation (EU) 2017/745 (MDR) that replaces Directives 90/385/EEC and 93/42/EEC. Medical devices are defined in the MDR as presented in the text box below:

> For the purposes of this Regulation, the following definitions apply
>
> (1) 'medical device' means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:
>
> — diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,
>
> — diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,
>
> — investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,
>
> — providing information by means of *in vitro* examination of specimens derived from the human body, including organ, blood and tissue donations, and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.
>
> The following products shall also be deemed to be medical devices:
>
> — devices for the control or support of conception;
>
> — products specifically intended for the cleaning, disinfection or sterilisation of devices as referred to in Article 1(4) and of those referred to in the first paragraph of this point.

As a general requirement, the medical device shall perform according to its intended purpose and be safe for patients, or where applicable, other persons (*e.g*. donors) on which the device is used. The conformity of medical devices shall be evaluated against the requirements of the MDR. They shall be presumed to be in conformity with this Regulation if they are in conformity with EU-harmonised standards or the relevant parts of those standards, the references of which have been published in the Official Journal of the European Union. Although not mandatory, these standards provide a route to comply with the MDR. In addition, the Medical Device Coordination Group (MDCG) document MDCG 2021-5 "Guidance on standardisation for medical devices", provides information on different aspects related to standards in the medical devices sector in support of the requirements laid down in the MDR. It describes the general framework for harmonised European standards and the relationship between harmonised European standards and EU legislation.

For medical devices, the horizontal standards (EN) ISO 14971 and (EN) ISO 10993-1 are especially relevant. (EN) ISO 14971 describes the application of a risk management

process for medical devices, whereas (EN) ISO 10993-1 deals with the biological evaluation and testing of medical devices within a risk management process. According to (EN) ISO 10993-1, evaluation of the biological safety of a medical device should be a strategy planned on a case-by-case basis to identify the hazards and estimate the risks of known hazards. In Annex A of (EN) ISO 10993-1, a series of endpoints is indicated from which a selection can be made for the biological evaluation of a medical device. The selection is based on the nature of the device's contact with the body (device category: surface device, external communicating device, or implant device; type of contact: skin, mucosal membrane, compromised surface, blood, tissues, organs; duration of the contact: limited ≤24 h, prolonged >24 h to 30 days, permanent >30 days). A systematic literature review is conducted as part of the biological evaluation of a medical device, in order to avoid unnecessary testing ((EN) ISO 10993-1). For this literature review all available information needs to be considered including peer reviewed publications and regulatory studies. This systematic literature review should also be performed for a CMR/ED phthalate or relevant potential alternatives identified for a given phthalate in a medical device. The FDA published a guidance to provide further clarification and update information on the use of ISO 10993-1 (FDA 2023).

In addition to (EN) ISO 10993-1, a series of (EN) ISO 10993 standards have been published describing various assays and approaches for the evaluation of the endpoints identified in (EN) ISO 10993-1 for the biological evaluation of medical devices. Assays described in the various standards address cytotoxicity, sensitisation, irritation, systemic toxicity, implantation, haemocompatibility, genotoxicity, and carcinogenicity endpoints. Additionally, immunotoxicity and organ-specific toxicities need to be considered, if appropriate. In addition, reproductive and developmental toxicity should be addressed for novel materials, materials containing substances with known reproductive or developmental toxicity, medical devices used in relevant target populations *(e.g*. pregnant women), and/or medical devices where there is the potential for local presence of device materials in the reproductive organs ((EN) ISO 10993-1). For the risk assessment, (EN) ISO 10993-17 describes the process and requirements for the toxicological risk assessment of medical device constituents, whereas (EN) ISO 10993-18 and (EN) ISO 10993-18:2020/Amd.1:2022 describe methods for chemical characterisation of materials used in medical devices. In addition to the horizontal standards, vertical *i.e*. device specific standards and standards for clinical investigation are available and can be applied (*e.g.* (EN) ISO 14155).

Furthermore, the EC also provides guidance documents in MEDDEV (*e.g*. MEDDEV 2.7/1 rev.4 "Clinical evaluation: A guide for manufacturers and notified bodies under directives 93/42/EEC and 90/385/EEC"), and MDCG documents, aligned with the MDR (MDCG 2020-5 "Guidance on clinical evaluation – Equivalence", and MDCG 2020-6 "Guidance on sufficient clinical evidence for legacy devices").

The MDR states that substances that are classified as carcinogenic, mutagenic, or toxic to reproduction (CMR) of category 1A or 1B, or substances identified at EU level as having endocrine-disrupting (ED) properties for which there is scientific evidence of probable serious effects on humans (CMR/ED substances, in this text), shall only be present in devices or parts thereof or those materials used therein above 0.1% weight by weight (w/w) when justified (MDR Annex I, Chapter II Section 10.4.1). Annex 4 of this document provides further information on the classification of CMR and on identification of ED substances. The justification for the use of CMR/ED substances in a medical device above 0.1% w/w shall be based on an analysis of potential patient exposure, availability of

possible alternatives, an argumentation why possible alternatives are appropriate or inappropriate, and on the most recent revision of these guidelines (MDR Annex I, Chapter II Section 10.4.3).

Phthalates are a group of substances widely used in medical devices as plasticisers. They are a family of chemicals with different chemical structures: phthalates are esters of the phthalic acid, *i.e.* benzene dicarboxylic acid. The position of the carboxylic groups on the benzene ring differentiates *ortho*-phthalates (esters of 1,2-benzendicarboxylic acid) from *meta*- and *para*-phthalates (esters of 1,3- and 1,4-benzendicarboxylic acid, respectively). Many *ortho*-phthalates have a long history of use as primary plasticisers for polyvinyl chloride (PVC) and with that function, they may comprise a substantial part of the medical device. A typical concentration of Bis(2-ethylhexyl) phthalate (DEHP; CAS 117-81-7) in plasticised polyvinyl chloride (PVC) can be around 30%-40%, based on weight (ECB 2008, SCENIHR 2015, European Pharmacopeia, 11$^{th}$ ed. 2022). Reproductive toxicity and the endocrine disrupting activity of a number of phthalates have been acknowledged and resulted in regulatory measures (*e.g.,* Classification, Labelling and Packaging (CLP) Regulation (Regulation (EC) 1272/2008); use restrictions *e.g.,* under Regulation (EC) 1907/2006 (Registration, Evaluation, Authorisation, and Restriction of Chemicals, REACH)), and Regulation (EU) 2017/745 (MDR)).

In the context of these guidelines, the term "phthalate" refers to *ortho*-phthalates, if not otherwise stated.

Phthalates currently classified as reproductive toxicants category 1B under the Classification, Labelling and Packaging (CLP) Regulation (Regulation (EC) 1272/2008) and identified as substances of very high concern (SVHC) under Article 57(c) of Regulation (EC) 1907/2006 (REACH) are listed in Annex 5 of this document. This list may continuously be updated, so it is recommended to consult the Annex VI of the CLP Regulation when using a CMR/ED phthalate as constituent in a medical device.

In addition, the Commission Implementing Decision (EU) 2017/1210 and Commission Implementing Decision (EU) 2018/636 identified some phthalates as substances of very high concern (SVHC) according to Article 57(f) of Regulation (EC) 1907/2006 (REACH), due to their endocrine disrupting properties with probable serious effects to humans, namely Bis(2-ethylhexyl) phthalate (DEHP), Benzyl butyl phthalate (BBP), Dibutyl phthalate (DBP), Diisobutyl phthalate (DIBP), and Dicyclohexylphthalate (DCHP).

The SCENIHR adopted an Opinion on the safety of medical devices containing DEHP-plasticised PVC in 2008, and a revision of that Opinion in 2015 (SCENIHR 2015). The main source for DEHP exposure of the general population was determined to be food after migration from food contact materials (FCM). In addition, the use of medical devices can increase the exposure considerably in the course of specific medical treatments, for example during massive blood transfusions, haemodialysis, and in neonatal intensive care units (NICU) for prematurely born neonates (SCENIHR 2015). Although quite a number of alternative substances were available for DEHP, serious data gaps were observed for some of them regarding hazard identification and exposure estimation (Bui *et al.*, 2016, SCENIHR 2015). The Danish EPA assessed different alternatives and concluded that, to various degrees, some substances can be considered to be relevant alternatives to DEHP in terms of human health hazards, especially regarding the endpoints reproductive and developmental toxicity (Nielsen *et al.* 2014). However, the data set was limited for a number of possible alternatives. Some alternatives showed a low migration rate and some

of them are already used as substitutes in medical devices for traditional DEHP-applications. For example, four additional plasticisers for PVC ((n-butyryl-tri-n-hexyl citrate) (BTHC), (di(2-ethylhexyl) terephthalate (DEHT), (1,2-cyclohexanedicarboxylic acid, diisononylester) (DINCH), and (trioctyltrimellitate, tris(2-ethylhexyl)trimellitate) (TOTM)) used in medical devices have been included in the updated chapters of the European Pharmacopoeia (EDQM 2019). More recently the 11th edition of the European Pharmacopoeia (2022) was published (see EDQM at European Pharmacopoeia (Ph. Eur.) 11th Edition - European Directorate for the Quality of Medicines & HealthCare (edqm.eu)

Phthalates classified as CMR of category 1A or 1B according to the procedure described in Annex 4 are listed in Annex VI of the CLP Regulation (classification, labelling and packaging of substances and mixtures) (Regulation (EC) 1272/2008). According to article 57(f) of Regulation (EC) 1907/2006 (REACH) or the Regulation (EC) 528/2012 (Biocides), phthalates can be identified as having ED-properties when there is scientific evidence of probable serious effects to human health. Recently, the Commission Delegated Regulation (EU) 2023/707 amended Regulation (EC) 1272/2008 (CLP), introducing two hazard categories for endocrine disruptors for human health with Category 1 considering known or presumed endocrine disruptors for human health, and Category 2 considering suspected endocrine disruptors for human health.

These guidelines provide a framework of how to perform a BRA for the presence of such CMR and/or ED phthalates in medical devices or parts or materials used therein at percentages above 0.1% weight by weight (% w/w), and shall be used by all relevant stakeholders, *e.g.,* manufacturers, notified bodies and regulatory bodies for the justification of the presence of CMR/ED phthalates. According to the guidelines, the evaluation should be performed by a multidisciplinary team, including amongst others *e.g.,* a material scientist, medical device specialist, toxicologist and clinician.

A justification for the use of a CMR/ED phthalate can also be based on an already available justification relating to a medical device for which equivalence with the device in question can be demonstrated according to the MDR Annex XIV Section 3. The MDR (MDR Annex XIV, Part A, point 3) requires that biological characteristics also be taken into consideration for the demonstration of equivalence (MDCG 2020-5). The existing justification can be used as a reference, and the data used for this justification should be available.

The approach described in these guidelines can also be used for the BRA of other CMR/ED substances present in medical devices.

Other descriptions for BRA may be "benefit-risk analysis" or "benefit-risk determination" as defined in the MDR. As Annex I, Chapter II Section 10.4.3 of the MDR indicates a benefit-risk assessment, this terminology is used in these guidelines.

## 2. Methods

In drafting an Opinion, the SCHEER relies on the SCHEER Memorandum on Weight of Evidence and Uncertainties (SCHEER, 2018). However, the Weight of Evidence (WoE) approach could not be applied for the drafting of these BRA guidelines as they do not provide a risk assessment and are mainly based on regulatory documents or documents published by international institutions.

The scientific data referring to plasticisers, plastics, medical device, and toxicity, were collected from the available scientific literature (through searches in relevant databases, *i.e.,* MEDLINE/PubMed, Scopus and Find-eR), websites and from documents of other Scientific Committees and International Organisations (*e.g.,* IARC (WHO), EPA (US), EFSA, SCCS, etc), as well as Government and Agency publications. As a number of substances are already known as possible alternative plasticisers for phthalates, the literature search included a dedicated search for these substances (see below). The terms used in the literature searches are presented in Table 1.

**Table 1: Terms used in literature search**

| Key words | Searches by combination of key words |
|---|---|
| 1. Alternative substances (see Table 3) | 1 |
| 2. Medical device | 1 AND 2 |
| 3. Health, safety (NOT environment, NOT ecotox) | 1 AND 3 |
| 4. Functionality, material properties | 1 AND 2 AND 4 |
| 5. Endocrine disruption | 1 AND 5 |
| | 1 AND 2 AND 5 |
| 6. CMR | 1 AND 6 |
| | 1 AND 2 AND 6 |
| 7. Risk-benefit analysis | 1 AND 2 AND 7 |
| 8. Toxic* | 1 AND 8 |
| | 1 AND 2 AND 8 |
| 9. Epidemiology | 1 AND 2 AND 9 |

The terms were searched in the: *Title, Abstract, Key Word(s) and, when accessible, text* of the relevant documents.

The types of documents used are:

- *peer-reviewed original research and review papers*
- *book chapters*
- *Government and Agency publications*

Additional literature provided by the WG members was included, when appropriate.

The Commission Library Service performed a literature search for publications released between January 1, 2017, and October 1, 2023. The search terms and results are listed in Tables 2, 3 and 4 as presented below, whereas Table 5 shows the overall results of the literature search. This search resulted in 381 published articles. In addition, the SCHEER

made use of reports by other organisations on this topic, as well as on information provided by the Commission. Additional literature that was provided by the Working Group members was also considered and evaluated. Each document was assessed for relevance according to the WoE document (SCHEER, 2018).

**Table 2: Results from the search using general terminology (period covered 01/2017 – 09/2023)**

| Key words including MeSH terms | No of entries | Duplicates |
|---|---|---|
| Medical device AND phthalate | 6 | 1 |
| Health, safety AND medical devices AND phthalate | 2 | 0 |
| Guidance, guideline AND medical device AND phthalate AND health | 0 | 0 |
| Functionality, material properties AND medical device AND phthalate AND guidance | 1 | 0 |
| Phthalate OR plasticiser OR Di(2-ethylhexyl) phthalate OR DEHP AND medical device | 6 | 1 |
| Endocrine disruption AND health, safety AND medical device | 8 | 0 |
| CMR AND medical device AND health, safety | 1 | 0 |
| Risk-benefit analysis AND phthalate AND medical device AND health, safety | 12 | 0 |
| Toxicity OR biomonitoring AND phthalate AND medical device | 3 | 0 |
| Alternative chemicals, alternative materials, alternative procedures, alternative methodologies, essential use, biomaterials, and medical devices | 4 | 0 |
| | | |
| **Total number of hits** | **43** | **2** |

**Table 3: Results from search by substance (period covered 01/2017 – 09/2023)**

| Key words including MeSH terms | No of entries | Duplicates |
|---|---|---|
| **Alternative substance** | | |
| ATBC (acetyl tri-n-butyl citrate) | 8 | 4 |
| BTHC (n-butyryl-tri-n-hexyl citrate) | 0 | 0 |
| COMGHA (glycerides, castor-oil-mono-, hydrogenated, acetates) | 21 | 1 |
| DEHA (di(2-ethylhexyl)adipate) | 17 | 16 |
| DINCH (1,2-cyclohexanedicarboxylic acid, diisononylester) | 8 | 2 |
| DINP (di-iso-nonyl phthalate) | 68 | 12 |
| DEHS (di-(2-ethylhexyl)sebacate, dioctylsebacate) | 2 | 0 |
| DEHT (di(2-ethylhexyl) terephthalate | 12 | 9 |

| | | |
|---|---|---|
| DBA (dibutyl adipate) | 0 | 0 |
| DIBA (diisobutyl adipate) | 0 | 0 |
| DBS (dibutylsebacate) | 0 | 0 |
| DIDA (diisodecyl adipate) | 5 | 5 |
| DINA (diisonanyl adipate) | 35 | 16 |
| TOTM (trioctyltrimellitate, tris(2-ethylhexyl)trimellitate) | 8 | 3 |
| Total hits | 184 | 68 |
| **Alternative substance AND medical device** | | |
| ATBC (acetyl tri-n-butyl citrate) | 8 | 4 |
| BTHC (n-butyryl-tri-n-hexyl citrate) | 4 | 3 |
| COMGHA (glycerides, castor-oil-mono-, hydrogenated, acetates) | 33 | 0 |
| DEHA (di(2-ethylhexyl)adipate) | 13 | 11 |
| DINCH (1,2-cyclohexanedicarboxylic acid, diisononylester) | 7 | 7 |
| DINP (di-iso-nonyl phthalate) | 13 | 10 |
| DEHS (di-(2-ethylhexyl)sebacate, dioctylsebacate) | 8 | 1 |
| DEHT (di(2-ethylhexyl) terephthalate | 11 | 10 |
| DBA (dibutyl adipate) | 0 | 0 |
| DIBA (diisobutyl adipate) | 3 | 1 |
| DBS (dibutylsebacate) | 1 | 0 |
| DIDA (diisodecyl adipate) | 1 | 1 |
| DINA (diisononyl adipate) | 29 | 6 |
| TOTM (trioctyltrimellitate, tris(2-ethylhexyl)trimellitate) | 23 | 17 |
| Total hits | 154 | 71 |

**Table 4: Results from other sources** (Scientific Committees, International Organisations, Government and Agencies)

| Key words including MeSH terms | No of entries | Duplicates |
|---|---|---|
| Phthalate | 4 | 0 |

**Table 5: Overall results literature search**

| Key words | No of entries | Duplicates |
|---|---|---|
| General terminology (medical device, safety, risk benefit analysis, toxicity, biomonitoring) | 43 | 2 |
| Search by substance | 338 | 139 |
| Other sources | 4 | 0 |

## 3. Framework for Benefit-Risk Assessment

The MDR allows the use of CMR 1A/1B and/or ED substances in medical devices above a concentration of 0.1% w/w when a proper justification can be provided (MDR Annex I, Chapter II Section 10.4). For such a justification, several steps need to be considered including the availability of alternative substances, materials, designs, and medical treatments. In addition, the risks associated with such alternatives shall be weighed against the risks of the use of CMR 1A/1B and/or ED identified phthalates covered under MDR Annex I, Chapter II Section 10.4.1. However, risk is not the only parameter to be considered. The impact of the possible alternatives on the functionality, performance and the overall benefit-risk ratio of the medical device should also be evaluated.

The justification for the presence of CMR 1A or 1B and/or ED phthalates for which there is scientific evidence of probable serious effects on humans should be based on a number of considerations as described below and in Figure 1.

In order to perform the BRA as indicated above, it is important to describe the terminology to compare the risks of the presence of the phthalates to be evaluated (see text box below). Annex 3 provides a selection of definitions as present in the MDR and/or the OECD Substitution and Alternatives Assessment Toolbox.
Alternatives assessment and substitution of harmful chemicals - OECD

For the purpose of these guidelines the following definition for "alternatives" is used:

"**alternatives** are defined as substances, materials, designs and medical treatments that can be used to replace the use of CMR and/or ED substances in medical devices"

The alternative therefore is not limited to a possible substitute substance or material but could also be another device design (*e.g.* coating/production process/ techniques/lower concentration of substances) or medical treatment (*e.g.* procedure, device) or a combination of technical and substance alternatives that can substitute or eliminate the use of the CMR/ED phthalate (modified from the REACH Guidance on the preparation of an application for authorisation).

The functionality and performance of the alternative should be comparable to the extent that there would be no clinically relevant difference foreseen in the performance of the device or in the outcome of the alternative medical procedure. Considerations of functionality and performance shall be based on proper scientific justification. In order to justify the use of a CMR 1A or 1B and/or ED phthalate, the manufacturer shall clearly demonstrate that the identified alternative(s) are not appropriate for maintaining the functionality, performance and benefit-risk ratios of the medical device.

A number of aspects need to be considered for the justification of the presence of a phthalate classified as CMR category 1A or 1B and/or identified as ED with a content > 0.1% w/w in a medical device, or parts thereof or those materials used therein, as intended to be used.

In summary, these aspects can be considered by a stepwise approach given below and presented in Figure 1. Further details and examples on the steps used in the guidelines are given in the following sections.

Assessment of the CMR/ED phthalate (CMR/ED phthalate scenario)

Step 1:

Description and characterisation of the composition of the medical device (or parts or materials thereof). Identification of the presence and concentration of CMR/ED phthalate(s) in weight by weight percentage (% w/w).

Step 2:

Description of the use and function of the CMR/ED phthalate used in the medical device.

2a. Description of functionality/performance provided by the presence of the CMR/ED phthalate.

2b. Description of the benefit in terms of material properties and/or clinical outcome of the presence of CMR/ED phthalate in the medical device.

Step 3:

Assessment of the risks of the CMR/ED phthalate.

3a. Determination of the patient exposure based on realistic worst-case[3] use scenarios in the intended use.

3b. Identification of biocompatibility, general toxicological and specific CMR/ED hazard characterisation associated with the phthalate.

3c. Determination of the toxicological risk based on tolerable/acceptable exposure for the patient, based on pre-clinical and clinical information (if available).

3d. Determination of the risks for various intended use scenarios and patient groups.

It should be noted that the information obtained in steps 1 to 3 needs to be provided for the risk assessment (and BRA) of the CMR/ED constituents of any medical device. For a medical device already on the market, this information should already be available. For the

[3] Realistic worst case is the situation where the exposure is estimated using a range of factors (*i.e.* duration, amount, exposure controls), where applicable, the ones that would be expected to lead to maximum amount of exposure (e.g. exposure might be assessed under realistic simulated-use scenarios by (EN) ISO 10993-12 and (EN) ISO 10993-18 or a non-volatile residue test (USP <661>)). The realistic worst case does not include deliberate misuse. (EU Biocides Regulation 528/2012).

risk assessment, all available information needs to be used including peer reviewed publications and regulatory studies. The SCHEER recommends using a WoE approach for performing the risk assessment.

Assessment of possible alternative(s) (non CMR/ED phthalate scenario)

Step 4:

Inventory of possible alternative(s).
4a. Substances.
4b. Materials.
4c. Designs and/or medical treatments[4].

Step 5:

Identification of the most relevant candidates for assessment as alternatives to CMR/ED phthalates and justification for the selection and exclusion of possible alternatives. This also includes assessment of the availability of the most relevant alternative(s).

Step 6:

Description of the most relevant alternative(s) identified.
6a. Description of functionality and performance of the most relevant alternative(s).
6b. Description of the benefit in terms of material properties and/or clinical outcome of the use of the most relevant alternative(s).

Step 7:

Assessment of the risks of the most relevant alternative(s) identified
7a. Determination of patient exposure of the alternative(s) based on a realistic worst-case use scenario of intended use.
7b. Determination, where available, of biocompatibility, toxicological and CMR/ED hazard characterisation associated with the alternative(s).
7c. Determination of toxicological risk to the patient, based on tolerable/acceptable exposure of the alternative(s) (if available).
7d. Determination of risk of the alternative(s) for various use scenarios and patient groups.

For the risk assessment all available information needs to be used including peer reviewed publications and regulatory studies. The SCHEER recommends using a WoE approach for performing the risk assessment.

Assessment of most relevant alternative(s) versus CMR/ED phthalate

Step 8:

Comparison of functionality and performance of CMR/ED phthalate as used in the medical device with functionality and performance of the most relevant alternative(s) identified

[4] It should be noted that for alternative designs and/or medical treatments, appropriate endpoints for risks and benefits shall be selected.

Step 9:

Comparison of hazard characterisation and exposure in the realistic worst-case scenario of original CMR/ED phthalate as used in the medical device with those identified for the most relevant alternative(s) identified.

Step 10:

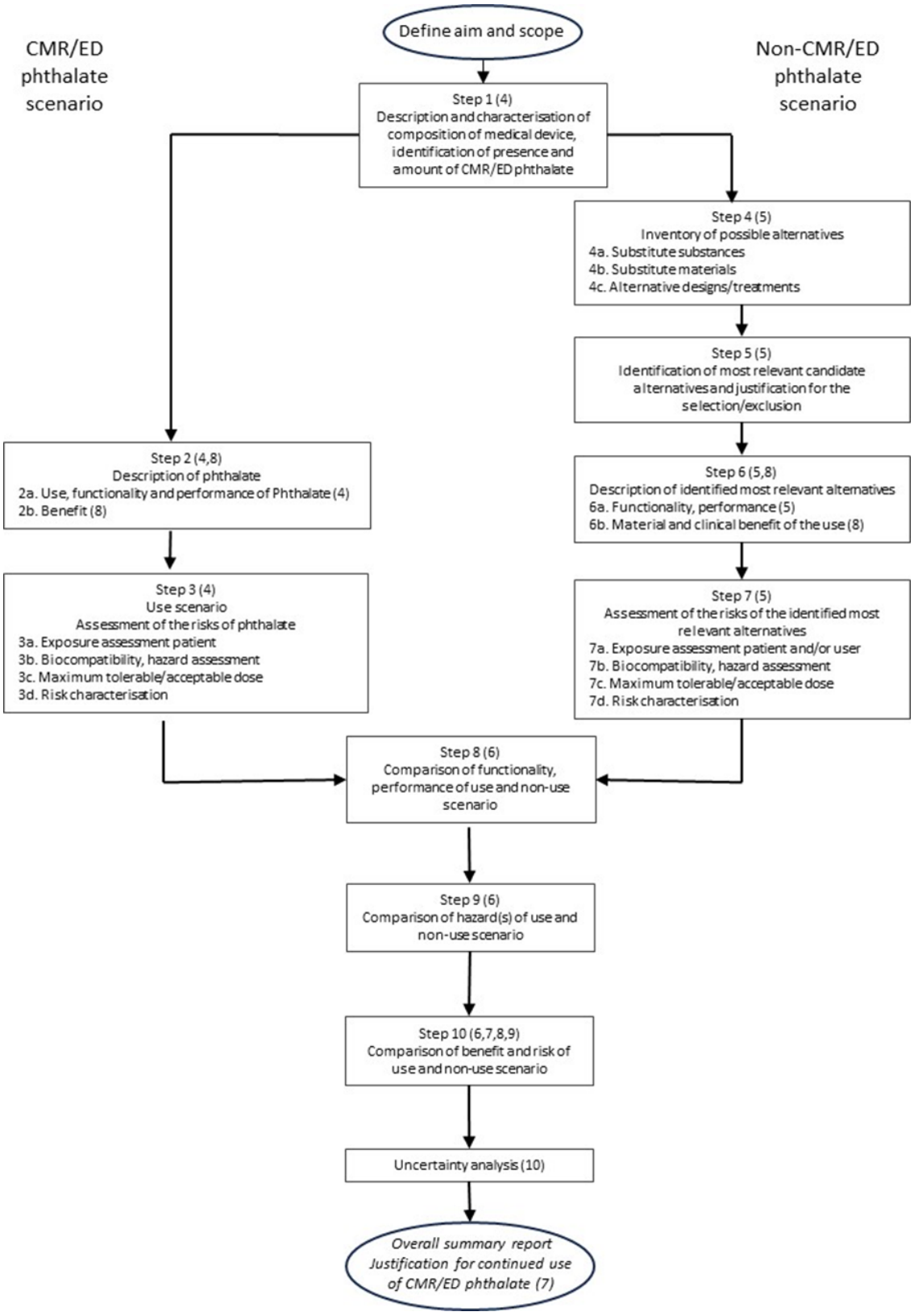
Comparison of benefit and risk of CMR/ED phthalate used in the medical device with the most relevant alternatives identified.

The same approach as used for assessing risks to patients shall be used for the justification of the presence of CMR/ED phthalates in medical devices to evaluate the risk for professional users and for other persons (*e.g.* donors) exposed to CMR/ED phthalates released from medical devices. When alternative designs or medical treatments were identified as potential alternatives in Step 5, adequately adopted endpoints for risks and benefits shall be chosen.

It should be noted that scientific information and/or technical developments may become available after the initial assessment regarding the use of alternatives for CMR/ED phthalates. Therefore, a revision of the BRA of the presence of the CMR and/or ED phthalate may be necessary. Revisions of the above indicated BRA shall occur as indicated in the relevant sections of MDR for the general risk assessment of the medical device.

Figure 1 illustrates the BRA and is based on Eliason and Morose (2011), EMA (2014), FDA (2016) and a critical selection from the OECD Substitution and Alternatives Assessment Toolbox (http://www.oecdsaatoolbox.org). It presents the stepwise approach described above, including a general description of factors to consider when performing a BRA. Figure 1 presents a use scenario in which the CMR/ED phthalate is used in a medical device versus a non-use scenario in which a relevant alternative is evaluated.

**Figure 1. BRA for evaluation of presence of CMR/ED phthalates and their potential alternatives in medical devices (relevant sections in the text between brackets).**



## 4. Assessment of the presence of phthalates in a medical device[5]

When evaluating the risk for the use of a medical device, it is necessary to identify the components and substances present in the medical device, in order to estimate any possible patient and user exposure. Therefore, it is necessary to provide most of the information as indicated for the use of CMR/ED phthalates, in order to prove compliance with the general safety and performance requirements (see MDR) for the phthalate-containing medical device.

When more than one CMR/ED phthalate is used simultaneously in the medical device, a justification shall be provided for each of the phthalates and their combination. Some risk assessment data regarding the combination of phthalates are available, as EFSA has recently proposed a Group Tolerable Daily Intake (TDI) for some of them, having a similar Mode of Action (MoA) *in vivo* (EFSA 2019, see Annex 5). Information on assessment of combined exposures to phthalates can be found, for example, in the report by the National Research Council (US) Committee on the Health Risk of Phthalates (2008) and the ECHA restriction of articles containing BBP, DEHP, DBP and DiBP for indoor environments and direct exposure (ECHA, 2014) (https://echa.europa.eu/registry-of-restriction-intentions/-/dislist/details/0b0236e180d73895), and EFSA guidance on cumulative exposure (EFSA, 2019, 2021). In addition, the US EPA has drafted a framework for cumulative risk assessment, which was made publicly available for comments in 2023 (see EPA website)

*Step 1: Description and characterisation of the composition of the medical device.*

Provide a description of the medical device and its composition including identification and the concentration of each CMR/ED phthalate in the device, and the type of chemical/physical binding of the phthalate in the formulation/device, when there is an impact on leakage.
Use available chemical information for identifying target phthalates (*e.g.* CAS Nº; EINECS Nº; IUPAC name). The chemical characterisation process can use various qualitative and quantitative techniques (*e.g.* see Annex F of (EN) ISO 10993-18). These techniques can provide detailed information regarding a material's characterisation, its purity, the chemical composition, and the presence of impurities and degradation products.
The chemical characterisation includes the determination of extractables (chemicals that can be extracted from a medical device using laboratory extraction conditions) and leachables (chemicals that are released from a medical device during its clinical use, under normal clinical conditions).
The chemical composition of a medical device can be evaluated by using, for example, (EN) ISO 10993-18. This standard covers the chemical characterisation of the medical device and the determination of leachables, and it provides information on the quality requirements of the analytical methods.

[5] The analysis presented in Section 4 (Steps 1-3) describes the current use scenario of the CMR/ED phthalate, *i.e.*, the scenario that would continue in the future if no additional action (other than, e.g., a planned regulatory action entering into force) is taken to limit, substitute or eliminate the presence of the CMR/ED phthalate in the medical device. The current scenario can also be referred to as baseline, business as usual or continued use scenario.

*Step 2: Use and function of CMR/ED phthalates in the medical device.*

Characterise the function and use of the CMR/ED phthalates in the medical device and the properties it imparts to the device.
Provide a description of the intended use, indications(s), functionality and performance of the medical device containing the CMR/ED phthalate and how the use of the phthalate is critical for its functionality and performance (MDCG 2019-9 rev.1 "Summary of safety and clinical performance"). For PVC, for example, consider the performance, maintenance, flexibility, and durability of the medical device, and for CMR/ED, consider phthalate viscosity and PVC compatibility. Provide a description of the patients targeted (*e.g.,* with respect to sex, age, probable vulnerable groups[6]).
Provide a description of use types of the medical device for which it is intended (*e.g.,* single versus repeated exposure).
Other factors that can be relevant include the critical properties (*e.g.,* flexibility), the conditions of use, critical quality criteria, process/treatment and performance constraints (*e.g.,* sterilisation, device/drug interactions), regulatory or clinical or other requirements that the CMR/ED phthalates and the phthalate-containing device need to deliver.
Key criteria for the function, performance and overall use should be outlined and applied as the basis for an identification and screening of possible alternatives and a more detailed assessment of the most relevant alternatives.
Justification for the selection of these criteria should be provided. It should be noted that CMR/ED phthalates may have different functions depending on the medical device in which they are used (*e.g.,* DEHP for flexibility in tubing and red blood cells (RBCs) quality for storage in blood bags).
Benefits of the device with CMR/ED phthalates should also be considered, *e.g.* some medical treatments require the use of a medical device with a high degree of flexibility for the patient's comfort and safety.
Present an inventory of the benefits of the CMR/ED phthalates in the medical device for the patients (separately for vulnerable groups). More detailed information on the benefit assessment is presented in Section 8.

*Step 3: Assessment of the risks of the CMR/ED phthalate.*

Perform a risk assessment of the CMR/ED phthalate present in the medical device by using all the available information, including peer reviewed publications and regulatory studies. The SCHEER recommends the application of WoE methodology. The risk assessment should contain:
1) a description of the potential phthalate exposure of various patient groups for which the medical device is intended (*e.g.* single vs repeated exposure). This should separately include vulnerable groups. (EN) ISO 10993-1 provides information on use type in terms of exposure potential (*e.g.* limited (≤24h), prolonged (>24h to 30d) and permanent (>30d)) that slightly differs from the duration of use as defined in the MDR (Annex VIII, 1, transient <60 minutes, short term 60 minutes to 30 days, long term >30 days);
2) a description of the hazard characterisation.

[6] Vulnerable Groups (in these guidelines): vulnerable groups of the population such as children and individuals with increased susceptibility due to pre-existing disease, medication, compromised immunity, pregnancy or breastfeeding, women and men in reproductive age. These vulnerable groups also include infants, elderly people or people with poor health conditions.

Exposure estimation

Estimate the release of the CMR/ED phthalate from the medical device, when used in various clinical modalities. This information should preferably be based on data from direct measurement or, when not available, on an estimation based on worst-case scenario or from high quality scientific literature. For a medical device as a whole, a leachable study is not practical due to challenges with reproducing actual clinical conditions. Therefore, simulated-use extraction studies using representative materials are often performed instead (as specified in (EN) ISO 10993-12 and (EN) ISO 10993-18). For data generation, analytical evaluations should include material contact conditions for the evaluation of leaching of substances from medical devices. These should consider, for example, temperature, contact duration and frequency, polarity of contact liquids, flow rates, contact surface, and volume of contact liquids ((EN) ISO 10993-1, (EN) ISO 10993-12, (EN) ISO 10993-18, USP 661). The contact conditions should be set to represent realistic worst-case conditions, taking into account the intended use of the medical device.
Estimate exposure to the phthalate(s) considering data on the release of the substance from the device in the conditions of use.
Consider repeated use scenarios (*e.g.* dialysis, apheresis donation, chronic treatment) and different population groups.
If a medical device contains several types of CMR/ED phthalates, the potential impact of this combined exposure must also be considered.

More details on the use of phthalates in medical devices are presented in Annex 6. Risk management measures in place and their effectiveness should be described and taken into account in the assessment ((EN) ISO 14971, (EN) ISO 10993-1). In addition, data from biomonitoring programmes may become available that could also provide information on exposure levels of phthalates in the general population and more specifically during medical treatment.
Information on human exposure to phthalates in general and currently used alternatives in medical devices is presented in Annex 8.

Hazard characterisation

Describe hazards associated with the CMR/ED phthalate by considering all relevant toxicological endpoints for acute as well as for repeated dose toxicity. (EN) ISO 10993-1 provides information on hazard endpoints to be considered depending on the exposure and use category of a medical device, whereas a tolerable intake (systemic toxicity) or tolerable contact level (local toxicity) can be determined according to (EN) ISO 10993-17. Possible hazardous effects of combined exposure should also be assessed. This information can be based on data from direct measurement or from any source of scientific literature analysed on the base of the WoE principles.
Identify an adequate Point of Departure (PoD) for risk assessment, meaning it should be representative of the route and duration of exposure associated to the actual use of the specific medical device under evaluation. In case of a threshold Mode of Action, such a PoD could be the most sensitive no-observed-adverse-effect-level (NOAEL) or lowest-observed-adverse-effect-levels (LOAEL), or a dose that causes a predefined response (Benchmark Dose – BMD or BMDL, the lower limit of the BMD confidence interval) obtained by benchmark dose modelling. In case of non-threshold effects (*e.g.* in the case of genotoxic

carcinogens), such a dose descriptor could be a T25[7] value or the benchmark dose associated with a 10% response (BMD10) (EFSA, 2022). Hazards should be evaluated by a relevant exposure route for the intended use of the assessed medical device.

Where a reference derived no effect level (DNEL) and/or a reference derived minimum effect level (DMEL) or a Tolerable Daily Intake (TDI) or any other reference value have already been derived in the context of other EU legislations, the analysis could refer to these derived figures without referring to detailed assessment how these data have been derived (*e.g.* under Regulation (EC) 1907/2006 (REACH), Regulation (EC) 1935/2004 (Food Contact Materials), and Commission Regulation (EU) 10/2011 (Plastic materials intended to come into contact with food)). However, as some of these data may have been derived in the past, relevant up-to-date scientific evidence (based upon a systematic literature review) and up-to-date risk assessment methodology for all relevant toxicological endpoints needs to be considered. If such already available reference values are not used in the assessment, a justification should be presented (*e.g.* new information/studies). Some of these other legislations for CMR/ED substances are presented in Annex 4. In addition, information on the hazard characterisation of DEHP is detailed in the SCENIHR Opinion on DEHP (2015).

The ED property of the phthalate, which is inherent part of the hazard characterisation, can be described according to the published EFSA/ECHA guidance document[8]. The current version of the document can be found here: https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5311
ED properties include impacts on fertility, birth defects (*e.g.,* cryptorchidism, hypospadias), developmental effects (*e.g.* effects on thyroid), and other effects associated with the CMR/ED phthalates.

The Commission Delegated Regulation (EU) 2023/707 of 19 December 2022 identifies, based on the level of evidence, two categories of endocrine disruptors: known or presumed endocrine disruptors (Category 1) and suspected endocrine disruptors (Category 2), both for human health and for the environment. (Publications Office (europa.eu)) However, Guidance on how to assign substances as EDs and to designate different ED categories is still under development (date: 26 Jan 2024) (https://echa.europa.eu/documents/10162/2324909/clp_ed_guidance_v6_draft_peg_en.pdf/c76d64b9-8d1c-e2e5-a0aa-d29cb20743b3?t=1694172505673). As the MDR was published in 2017, there is no reference to this ED categorisation. This ED categorisation is also not yet included in the Medical Device Coordination Group (MDCG) endorsed documents or other EU Guidance documents on medical devices.

Risk characterisation

Evaluate the risk by comparing exposure levels that are considered safe *(i.e.* health-based reference values) with the expected exposure (worst-case scenario) to obtain a Risk Characterisation Ratio (RCR). Alternatively, for obtaining a MoS, compare the expected exposure (worst-case scenario) with the relevant PoD. PoDs for this comparison could be the most relevant and lowest no-observed-adverse-effect-level (NOAEL) or lowest-

[7] Animal dose-descriptor; chronic dose rate that will give 25% of the animal's tumours at a specific tissue site after correction for spontaneous incidence (Dybing *et al.,* 1997)
[8] ECHA and EFSA are working on updating the Guidance on the application of CLP criteria for newly added hazard classes, e.g., ED for human health. For more information see: New hazard classes 2023 - ECHA (europa.eu)

observed-adverse-effect-levels (LOAEL), or a dose that causes a predefined response (Benchmark dose – BMD or BMDL, the lower limit of the BMD confidence interval) for threshold substances. For non-threshold substances (*e.g.* carcinogen acting with a genotoxic mechanism), a T25 value or the benchmark dose associated with a 10% response (BMD10) could be used.
Data (*i.e.* exposure level and PoD) on the relevant exposure route of the medical device application (*e.g.* intravenously) should be used (see also (EN) ISO 10993-1 Table A.1). A route-to-route extrapolation is only possible when the kinetic behaviour of the phthalates is known by using appropriate modelling. It has to be noted that patients are sometimes exposed to medical devices only for a limited period of time. According to (EN) ISO 10993-17 for medical devices a toxicological risk can be estimated based on tolerable intake (systemic toxicity) or tolerable contact level (local toxicity), using an estimated worst-case exposure for each constituent.

By dividing the PoD by appropriate uncertainty factors (also known as safety or assessment factors) reference values can be derived, such as "Derived No-Effect Level" (DNEL), "Derived Minimum Effect Level" (DMEL) or intakes over lifetime without presenting an appreciable risk to health (ADI or TDI/TWI)[9]. Specifically for ED effects, additional assessment factors have been suggested as proposed recently (Hass *et al.,* 2019).

The risks can be described by calculating the Margin of Exposure (MoE) or the Margin of Safety (MoS), which is the ratio between the lowest relevant PoD and the expected exposure (worst-case scenario). This ratio should be compared with an adequate MoS, which quantitatively corresponds to the uncertainty factors used to derive the reference values.
Alternatively, it is also possible to compare the reference values (*e.g.* the TDI) with the expected exposure (worst-case scenario): when the ratio, known as RCR, is <1 there is no concern, whereas values >1 represent a potential concern (and a refinement of the evaluation could be performed, for example not using the worst case scenarios).
If neither of these procedures is followed, a scientifically-based justification should be provided (*e.g.* new information/studies).
This evaluation must be performed for every group (patients/donors) for which the device is intended to be used.
Determine and describe any situations in which the risk could be acceptable for the use of the CMR/ED phthalate in the medical device. The benefit-risk assessment for the use of the CMR/ED phthalate can be performed using for example MEDDEV 2.7/1rev4 and (EN) ISO 14971 (see also Section 8). The MDR considers a risk acceptable when it is outweighed by the benefit of using the device in patients (MDR Chapter I and Chapter VI Article 61 and 62, Annex I Chapter I Sections 1 and 9).

In addition to potential CMR/ED effects, discuss any other potential hazards associated with the composition of the device (*e.g.* by using the EN ISO 10993 series of standards). Evaluate if such effects are associated with the use of the CMR/ED phthalates in the device.

The assessment of the risk should be accompanied by an estimation of the impact of uncertainties in the described outcomes (see Section 10).

[9] ADI (Acceptable Daily Intake and TDI (Tolerable Daily Intake) are defined as the dose to which an individual can be daily exposed lifetime, without experiencing significant adverse effects. The TWI (Tolerable Weekly Intake) is generally used for persistent bioaccumulating chemicals instead of TDI.

It is to be noted that most of this information as described for Step 1 to Step 3 should already be embedded in the BRA of the marketed medical device, and for high-risk devices, in the Summary of Safety and Clinical Performance (SSCP) as part of the dossier of the currently used medical device (see MDCG 2019-9 rev.1 "Summary of safety and clinical performance"). In this SSCP, a description of the device shall be presented, including, for example, key functional elements and any materials or substances in contact with the patient's tissues.

## 5. Assessment of possible alternative substances, materials, designs or medical treatments[10]

In general, a similar risk assessment as presented in Step 3 above has to be performed for the alternative (substances, materials, designs or medical treatment). An inventory should be prepared in order to be able to evaluate possible alternatives. An alternative could be another substance/material or device design modification, or it could be a clinical procedure (*e.g.,* a process, technique, treatment or modification) or a combination of technical and substance alternatives.

*Step 4: Inventory of possible alternatives*

Prepare a list of possible alternatives (such as substances, materials, designs or medical treatments)[11].

A description of the alternative scenario (CMR/ED phthalate "non-use scenario") needs to be presented including identification of alternative substances, materials, designs or medical treatment, *e.g.* by including consideration of all available information, such as alternative medical devices available on the market, information about independent research, published peer-reviewed studies, systematic literature reviews, risk assessment reports or scientific opinions from relevant scientific committees and the results of in-house research and development. The identification of possible alternatives should be properly documented.

*Step 5: Identification of the candidates for assessment as most relevant alternatives for phthalates*

The MDR indicates that an analysis of all possible alternatives shall be performed. However, when many alternatives are available it would not be feasible to do an extensive evaluation of all alternatives. It is therefore recommended to select a number of most relevant alternatives based on screening against key criteria for function, performance, toxicity, and overall use in the medical device in question (see below). In addition, analysis of availability and technical feasibility might affect choices for alternatives as well. Preferably a number of alternatives should be evaluated, and justification should be provided when fewer than three alternatives are evaluated.

A preliminary analysis of possible alternative substances, materials or designs or medical treatments should be performed. This preliminary analysis should include a description of their possible use as alternative substance, material, designs or medical treatments.

[10] The analysis presented in Section 5 constitutes the non-use scenario or the scenario that would transpire if the CMR/ED phthalates would no longer be used in the medical device.
[11] Information source for alternatives might be the European Pharmacopoeia.

Justification on how and why alternatives are rejected for further assessment by defining inclusion and exclusion criteria should be provided.

Information/data on functionality (*e.g.,* level of flexibility in tubes) as well as performance and/or chemical safety assessment (*e.g.,* hazard profile) may be used for rejection of the less likely alternatives (see below) and no further risk assessment for the alternative is required. The rejection of the less likely alternatives requires justification and documentation. The compliance to chemical requirements, according to the MDR, should be demonstrated after a positive outcome of the assessment of the functionality and performance.

In addition to the comparison in terms of functionality, technical performance and risks to patients and users, which are critical elements for the benefit-risk assessment, Annex I Section 10.4.2 of the MDR states that the justification for the presence of CMR/ED substances should also be based on an analysis of the availability of possible alternatives. Availability has several aspects, including, for example, the availability of necessary quantity (volumes) of the alternative on the market within a required timeframe and the ability to gain access to alternatives that may be proprietary (*e.g.* via licensing).

If potential alternatives can be identified, a shortlist of the most relevant alternatives can be established for further detailed assessment with regard to technical feasibility, health benefits, comparison of risks, existing legal requirements, availability, and technical performance. In the event that no alternative is identified, information should be presented on the actions undertaken to identify alternatives.

A compilation of resources and elements in support of chemical substitution and an assessment of alternatives can be found on the OECD webpage:
http://www.oecdsaatoolbox.org/

*Step 6: Description of identified most relevant alternative(s) and conclusion on their technical feasibility*

CMR/ED phthalates are present in medical devices for a specific purpose depending on the intended use of the medical device. For example, phthalates offer the possibility for fine-tuning the flexibility (*e.g.,* providing optimal flexibility of tubes without kinking) of a PVC-based medical device. In addition, DEHP has a stabilising effect on red blood cells in blood bags, reducing haemolysis during storage and improving transfusion efficacy (Klei *et al.,* 2022). Technical feasibility of an alternative is based on the alternative fulfilling the function of the CMR/ED phthalate. Therefore, it is essential to assess the functional properties in relation to the intended use of the medical device. Besides functionality, performance under intended use conditions should also be considered.

Argumentation shall be provided for justifying why possible substances and/or material substitutes, if available, or design or medical treatment changes, if feasible, are inappropriate in relation to maintaining the functionality and/or performance of the medical device. For example, it might be the case that replacement is possible for one specific functional use, whereas for another functionality the use of the CMR/ED phthalate remains necessary. Other aspects related to the performance of the alternatives also need to be considered, like material processing conditions (Crespo *et al.,* 2007), material quality after sterilisation (Burgos and Jiménez 2009), and possible interaction with drugs in therapeutic infusion systems (Treleano *et al.*, 2009, Salloum *et al.*, 2015, Tortolano *et al.,* 2018).

The benefit(s) should also be considered. An inventory of the benefit(s) of the most relevant alternative substances, materials, designs or medical treatments for patient populations (separately for vulnerable patient groups) should be presented (see Section 8).

The evaluation of the most relevant alternatives identified can be done in a tiered way to avoid full assessments for each candidate alternative. For example, based on the outcome of the functionality evaluation, the choice of the most relevant candidates might be reconsidered, and some might be discarded before performing the risk assessment (see Step 7).

The ECHA guidance on the preparation of an application for authorisation and ECHA formats for Analysis of Alternatives provide more detailed information on how to conduct an initial screening of possible alternatives and how to assess the technical feasibility of potential alternatives. Submitted applications for authorisations contain a number of examples (https://echa.europa.eu/applications-for-authorisation-previous-consultations) of technical feasibility assessments for uses of substances of very high concern.

*Step 7: Assessment of the risk of the most relevant alternatives*

The risk assessment of alternatives is comparative in nature. Its aim is to assist in determining whether the transition to the alternatives would lead to lower/higher benefit and/or risk to human health for patients when compared to the current use of the CMR/ED phthalates in the medical device. The methodology of the assessment in this step is similar to that in Step 3, as performed for the phthalate to be evaluated with reference to the alternative. For the risk assessment, all available information needs to be used including peer-reviewed publications and regulatory studies. The SCHEER recommends using a WoE approach for performing the risk assessment.

If a number of most relevant alternatives were identified under Steps 1-6, a risk assessment of these most relevant alternative substance/material or designs or medical treatments should be performed. The risk assessment should contain a description of the substance/material (alternative design or medical procedure) exposure of various person groups (*e.g.,* including patients, donors, professional users) for which the medical device is intended to be used (considering single or repeated use). The assessment for vulnerable groups should be included as a separate section. For each subgroup, a different level of risk may be accepted based on the potential benefit of the medical device for that particular group. Risk management measures ((EN) ISO 14971, (EN) ISO 10993-1) and their effectiveness to reduce exposure should be described and taken into account in the assessment.

Exposure estimation

Estimate the possible release of the most relevant alternative substance(s) when used in various treatment modalities. The rate of leaching should be considered when estimating the potential exposure to the alternative substance. Multiple use scenarios (including various types of possible contact) should be considered for estimating exposure of the alternative substance also considering repeated use scenarios (*e.g.* frequent use of dialyzer) and different population groups. This information should preferably be based on data from direct measurement or on an estimation based on worst-case scenario. The

leaching tests should be performed using similar conditions as for the original medical device ((EN) ISO 10993-12, (EN) ISO 10993-18). Scientific argumentation should be provided in case of deviation from these conditions. Some information on the exposure to possible alternative substances for DEHP is presented in Annex 8.

Hazard identification

Identify hazards based on literature, supplier documentation and other information (such as risk assessments performed by regulatory bodies). Describe hazards associated with the most relevant alternative substance/material by considering all relevant toxicological endpoints for acute as well as for repeated dose toxicity including human data.
Identify an adequate point of departure (PoD) for risk assessment, meaning that it should be representative of the route and duration of exposure for the specific medical device under evaluation. In case of a threshold Mode of Action, such a PoD could be the most sensitive no-observed-adverse-effect-level (NOAEL) or lowest-observed-adverse-effect-levels (LOAEL), or a dose that causes a predefined response (Benchmark dose – BMD or BMDL, the lower limit of the BMD confidence interval) obtained by benchmark dose modelling. When there are non-threshold effects (*e.g.* in the case of genotoxic carcinogens), such a dose descriptor could be a T25 value or the benchmark dose associated with a 10% response (BMD10) (EFSA, 2022). Hazards should be evaluated by a relevant exposure route for the intended use of the assessed medical device.

For the hazard identification, special attention should be on the determination of any potential CMR and/or ED property of the alternative substance used. For further information, consider the ECHA Guidance on the application of the CLP criteria (https://echa.europa.eu/documents/10162/23036412/clp_en.pdf/58b5dc6d-ac2a-4910-9702-e9e1f5051cc5)
or see Annex VI of the CLP Regulation. ED properties of the alternative substance/material can be described according to the recently published EFSA/ECHA guidance document (ECHA 2018)[12].

These effects may include impacts on fertility, birth defects (*e.g.,* cryptorchidism, hypospadias), developmental effects, and other potential toxic effects associated with phthalates with ED properties and reprotoxic effects category 1A/B. It needs also to be considered that the potential alternative (substances, materials, designs or medical treatments) could also have other hazards than those of the CMR/ED activity. These other hazards and their possible associated risks should be discussed for example by using the EN ISO 14971 and the EN ISO 10993 series. See also (EN) ISO 10993-1 Table A.1. Some information on the health hazards of possible alternative substances for DEHP are presented in Annex 9.

[12] ECHA and EFSA are working on updating the Guidance on the application of CLP criteria for newly added hazard classes, e.g., ED for human health. For more information see: New hazard classes 2023 - ECHA (europa.eu)

Risk characterisation

Evaluate the risk by comparing exposure levels that are considered safe (*i.e.* health-based reference values), with the expected exposure (realistic worst-case use scenario) to obtain a Risk Characterisation Ratio (RCR). For obtaining a MoS, compare the expected exposure (worst-case scenario) with the relevant PoD in relation to route and duration of exposure. PoD could be the most relevant and lowest NOAEL, LOAEL, BMDL for threshold substances, or T25 or BMD10 for non-threshold substances. Data on the relevant exposure route of the medical device application (*e.g.* intravenously) should be used (see also (EN) ISO 10993-1 Table A.1).
It has to be noted that patients may be exposed to medical devices only for a limited period of time. (EN) ISO 10993-17 provides information for estimating a toxicological risk based on tolerable intake or tolerable contact level, using a worst-case estimated exposure for each of the constituents. For medical devices, a tolerable contact level *(e.g.* for irritation) or tolerable intake (*e.g.* for systemic toxicity) can be determined by (EN) ISO 10993-17.

By dividing the point of departure for risk assessment by appropriate assessment or uncertainty factors, reference values can be derived, such as DNELs, ADI, TDI or TWI for threshold substances, or DMELs for non-threshold substances. Specifically for ED effects, additional assessment factors have been suggested as proposed recently (Hass *et al.,* 2019). Where a reference DNEL and/or a reference DMEL have already been derived in the context of other EU legislations, the assessment could refer to these derived figures without referring to a detailed assessment of how these data have been derived (*e.g.* under REACH legislation, Food Contact Material legislation).

The risks can be described by calculation of the Margin of Exposure (MoE) or the Margin of Safety (MoS) for the substances present in a medical device, which is the ratio between the lowest relevant PoD and the expected exposure (*e.g.* realistic worst-case use scenario) and comparison with an adequate MoS, which quantitatively corresponds to the uncertainty factors used to derive the reference values.
Alternatively, it is also possible to compare the reference values (*e.g*. the TDI) with the expected exposure (worst-case scenario): when the ratio, known as RCR, is <1 there is no concern, whereas values >1 represent a potential concern (and a refinement of the evaluation could be performed, for example not using the worst case scenarios).
If neither of these procedures is followed, a scientifically-based justification should be provided (*e.g.* new information/studies).

Perform this evaluation for every patient and other groups for which the device is intended to be used.

Determine and describe acceptability of the risk for the use of the most relevant alternatives. Risks may be acceptable when they are outweighed by the benefits for the patient.

Consider any known adverse events associated with the operation of the device using the phthalate, and whether the potential alternatives might affect these adverse events. These considerations can be based upon a systematic literature review (see MEDDEV 2.7/1rev4).

This exercise has to be performed for each of the most relevant alternative substances identified and/or materials.

There are a large number of phthalates, and some, not yet classified/identified as CMR/ED, may be potentially relevant alternatives for the CMR/ED phthalate used in medical devices. However, these phthalates may have CMR or ED hazardous properties and some are already classified/designated for these properties (see above). Such phthalates might be identified as alternatives when their CMR/ED risk is reduced compared to the phthalate intended to be used. In addition, different non-ortho-phthalate substances have also been proposed as alternative plasticisers. The SCENIHR published an updated DEHP Opinion, including some information on potential alternative plasticisers for DEHP (SCENIHR, 2015). Although many alternatives were potentially available, it was also observed that for many of them, the information on potential risks and the necessary risk assessment was rather limited, precluding their use as alternatives. Some information on the exposure and health hazards of possible alternative substances for DEHP are presented in Annex 8 and Annex 9, respectively.

In the event that the risk assessment of a most relevant alternative cannot be performed when PoD or reference values for the alternative are lacking, documentation should be presented on the actions undertaken to obtain information to characterise the risk, including the outcome (for example, QSAR /read-across could be performed).

Note shall be taken that alternative designs or medical treatments might lead to the adaptation of endpoints for the benefit-risk assessment when compared to the toxicological endpoints of CMR/ED phthalates.

The assessment of the risk should be accompanied by an estimation of the uncertainties in the described outcomes, which might be quantitative (*e.g.,* confidence interval, standard deviation) or qualitative (see Section 10).

Conclude the analysis of the most relevant alternative(s) with a summary describing the possible scenario(s) (see Figure 1).

## 6. Assessment of most relevant alternative substances, materials, designs or medical treatments

Based on the information obtained above, a decision can be made on the appropriateness of the most relevant alternatives (substance, material, design or medical treatment. Several factors need to be included in the evaluation, such as weighing of technical feasibility, benefits and risks and, if possible, quantification of benefits and risks. These steps entail a comparison of the CMR/ED phthalate "use-scenario" (summarised in Step 3) with the "Non-use scenario" (summarised in Step 4) as shown in Figure 1.

*Step 8: Comparison of functionality and performance of CMR/ED phthalate as used in the medical device with functionality and performance of identified most relevant alternative(s).*

Compare the functionality and performance of CMR/ED phthalate in the medical device and the potential relevant alternative substance/material (or designs or medical treatments by choosing adequate endpoints). Perform Step 8 for each candidate identified as the most relevant alternative in Section 5.

If several potential alternatives have a similar functionality and hazard profile, exposure conditions and possibilities for Risk Management Measures (RMM) resulting in risk reduction should be considered (see below). Risk management is described in (EN) ISO 14971.

In this comparison, additional issues, not directly related to the functionality and performance of the alternative itself, like availabilities and technical possibilities, sterilisation effects and interactions with infusion liquids, are also important for the application of the alternative and the comparison with the CMR/ED phthalates, and thus should be considered.

*Step 9: Comparison of risk(s) of CMR/ED phthalate as used in the medical device with risk(s) of identified most relevant alternatives.*

Compare the risk of both CMR/ED phthalate and alternative substance/material (or designs or medical treatments by choosing adequate endpoints).
Perform Step 9 for each potential alternative.

If several potential alternatives have a similar functionality and hazard profile, exposure conditions and possibilities for Risk Management Measures (RMM) resulting in risk reduction should be considered. Risk management is described in (EN) ISO 14971.

There may be difficulties in comparing the risks of a substance *e.g.* a phthalate, and the risks of a technical alternative such as medical design or medical treatment. For example, there may be risks associated with alternative technologies, but these may not be of the same nature of the risk presented by the use of phthalates. However, the potential alternative must represent a reduction in the overall risks to human health (Step 10). Therefore, a comparison of risks must be conducted, and the applicant will need to consider how these different risks might be compared in terms of risks to human health. Note that an alternative medical design or medical treatment may also result in exposure to other risks previously not present in the treatment modality. Possible additional risks of these alternatives will also need to be considered in the overall assessment. The comparison with technological alternatives such as a medical design or medical treatment can normally not be fully quantitative (*i.e.* with directly comparable numeric values), as the hazards and associated risks will not be expressed in similar terms, but will in most cases be qualitative or semi-quantitative. Nevertheless, a clear and transparent description can provide a good basis to conclude whether overall risks are reduced or not (Step 10).

*Step 10: Comparison of benefit and risk of CMR/ED phthalate used in the medical device with identified most relevant alternatives.*

A summary/overview of a benefit/risk comparison between using CMR/ED phthalate in the medical device and the most relevant alternatives should be provided, including uncertainties about the estimates or reliability of the data, assumptions, etc. for the parameters presented. The summary should contain various aspects of functionality, performance, risk and benefit of the use of the original CMR/ED phthalate used in the medical device and the potentially relevant alternative(s). In Section 7 below, the justification of the use of a CMR/ED phthalate is described based on the summary presented in Table 6 comparing an alternative with the CMR/ED phthalate.
Perform Step 10 for all of the most relevant alternatives identified.

Each of the assessments performed in steps 1 to 10 will have some degree of uncertainty. Some of them can be described by the use of standard deviation or confidence interval. For other uncertainties, a description may be necessary to explain the extent of the uncertainty and its impact on the final outcome.

Benefit and risks should be described and weighted against each other in the use of the potential alternative substance/material in the medical device (or designs or medical treatments by choosing adequate endpoints) similar to the procedure for the CMR/ED phthalate (see Step 2).

## 7. Justification for the use of CMR/ED phthalate

Based on the comparison of functionality, performance, availability, risk and benefit, an argument could be made as to why a possible substance and/or material alternative, if available, or changes in designs or medical treatment, if feasible, are inappropriate in relation to maintaining the functionality, performance and the benefit-risk ratio or profile (quantitative/semi-quantitative or qualitative) of the medical device containing a CMR/ED phthalate.

Explain the importance of any difference in terms of benefits and risks between the CMR/ED phthalate to be used in the medical device and the most relevant alternatives using value judgements and explain how the use of the CMR/ED phthalate can be justified over the alternatives by describing the acceptability of trade-offs in the achievement of some criteria against others. Any advantage in benefits needs to be weighed against possible disadvantages in terms of functionality and risks. Both differences in benefits and risks need to be considered jointly.

In building the argumentation for the use of a CMR/ED phthalate, note can be taken of the Memorandum on Weight of Evidence and Uncertainties of the SCHEER (SCHEER 2018). This Memorandum describes a methodology that classifies the strength of evidence in the human health risk assessment based on integration of different lines of evidence into strong, moderate, weak, uncertain and inconclusive (no suitable evidence available). Any WoE evaluation needs to show the overall confidence in the assessment. By the term "confidence in the assessment" it is meant any measure of uncertainty related to the effect size of the association, *e.g.,* its related statistical uncertainty indicated by the confidence intervals of the effect estimates, as well as the internal consistency of the results. Methods for assessing confidence in the assessment may also include resampling procedures *(e.g.* bootstrap), Bayesian inference, probability bounds analysis, and Monte Carlo simulations.

The argumentation should specifically take into account the intended use of such devices. This should include consideration and discussion of possible high-risk groups such as children or pregnant or breastfeeding women, and other patient groups considered particularly vulnerable to such substances and/or materials. In addition, where applicable and available, any future update of these guidelines shall be considered. A table with the most relevant information and values should be used to present an overview of the performed assessment comparing the CMR/ED phthalate with potential alternative(s). A non-exhaustive example of such a table is presented below. Table 6 should be extended depending on the number of criteria evaluated and the number of potential alternatives identified.

**Table 6:** Non exhaustive example for a comparison of CMR/ED phthalate with the most relevant alternative(s) identified.

| Assessment criteria | Description (examples) | Reference phthalate | Alternative I | Alternative II etc. |
|---|---|---|---|---|
| Identification of substances/material etc Name and CAS number | Chemical information | CAS<br><br>117-81-7 | | |
| Functionality/performance | Used as plasticiser | *e.g.* DEHP | | |
| Clinical benefit/performance | Treatment possibility | *e.g.* Flexibility of tubing / red blood cells storage | | |
| Material benefit | | | | |
| Concentration (% w/w) | | | | |
| Leaching from medical device for relevant conditions *e.g.* media, temperature, etc ((EN) ISO 10993-12) | | | | |
| Exposure estimation (realistic worst-case use scenario) for relevant route of exposure | | | | |
| Hazard identification | Local and systemic acute and repeat-dose toxicity, ED-properties, organ toxicity, CMR properties, biocompatibility, and others | | | |
| Identification of a point of departure for risk assessment (LOAEL, NOAEL, BMD, T25, BMD10) | | | | |
| Identification of dose levels associated with minimal or negligible risk (*e.g.* DNEL, DMEL, TDI, TE, TI) | | | | |
| Risk characterisation (MoE, MoS, RCR) | | | | |
| Confidence estimation (see Table 7) | | | | |
| Technical feasibility | | | | |
| Other | | | | |

This Table 6 shall be completed for every component of the medical device that contains CMR/ED phthalate(s) above the 0.1% w/w level. For some medical devices used as a system (*e.g.,* blood bag system) the whole system might be evaluated. Note that in case of alternative designs or medical treatments, adequate hazard endpoints for the

comparison shall be chosen. These hazard endpoints may represent risks that may be of a different nature than that of the risk of the phthalate.

When the outcome of the comparison shows that the alternative fulfils a comparable or better intended functionality as well as performance and shows a reduced risk, use of a CMR/ED phthalate is not acceptable. The risk assessment should also indicate whether there would be a reduced hazard concerning CMR and/or ED properties, and/or reduced exposure overall resulting in reduced risk. In this evaluation, a full toxicological profile of the most relevant alternatives shall be taken into account, including other toxicities (*e.g.,* target specific toxicity for any other organ or system).

A balanced weighing of the benefit versus the risk has to be performed. For example, it is possible to use a combination of a CMR/ED phthalate and PVC/material with intrinsic toxicological hazards, thus accepting a risk from a toxicological perspective, if the clinical benefit is very high. In contrast, a minor loss in medical functionality might be acceptable if there is a large reduction or even absence of risk. Each comparison of a potential alternative for the use of a phthalate should be based on the combination of functionality, risks and benefits for patients.

In this final evaluation, the assessment of uncertainties associated with the alternatives (*e.g.,* on the nature of the risks; assumptions made) should also be considered (see Table 7 below in Section 10). Therefore, where possible, quantitative results should be collected and compared (*e.g.,* NOAEL, estimated exposure in mg/kg) and their uncertainties should be reported. A qualitative description of the uncertainties may also be useful (see Table 7 below in Section 10). Their impact on the conclusions should also be discussed.

Although not the main subject of these guidelines, it should be noted that availability and accessibility on the market might be a limitation for the introduction of an alternative substance/material. Some chemicals proposed as alternatives are widely available, however, this may not be the case for other alternatives. The unavailability of a potential alternative for a medical device might lead to the conclusion that replacement is not feasible and that the continued use of a phthalate with CMR and/or ED property is acceptable in order to keep the device available for patients. In addition to considering the technical feasibility in terms of functionality and risk reduction (risk assessment of the phthalate versus the alternative), the availability and accessibility on the market needs to be taken into consideration.

The BRA of the CMR/ED phthalate should be updated when new scientific information becomes available on alternatives for the use of phthalates, when new guidelines are released, or as the "overall" benefit-risk determination of the medical device is updated. A plan to perform an update of the relevant part of the technical file of the device needs to be submitted during the certification process (post-market surveillance plan referred to in Article 84, the requirements are set out in Section 1.1 of Annex III MDR) and this should also cover updates needed on the justification for the presence of CMR/ED phthalates.

## 8. Benefit assessment

Both benefits and risks should be specified considering their nature, likelihood of occurrence, extent and duration, as well as frequency. However, these guidelines do not provide information for the benefit-risk assessment of the use of a medical device itself

but are limited to the methodology on how to perform a BRA for the justification of the presence of CMR 1A or 1B and/or ED phthalates in a medical device above 0.1% (w/w). A detailed evaluation of the overall benefit-risk assessment of a medical device is presented in other documents *(e.g.,* MEDDEV 2.7/1 rev.4, MDCG 2020-5, and MDCG 2020-6, (EN) ISO 14971, FDA 2017, 2019), and it is currently based on a Multiple Criteria Decision Analysis (MCDA) approach (https://doi.org/10.1007/978-1-4615-1495-4), which is defined as a systematic and theory-based approach to perform a comparative analysis of various competing options, based on their functioning on multiple and complicated criteria. MCDA involves a clear definition of the studied problem, the selection of the appropriate evaluation criteria, the assessment of the performance of each alternative on each criterion, the determination of the criteria's weights and uncertainty and, finally, the aggregation of performance scores in an overall value. Information on BRA approaches is presented in Annex 7.

The benefits of the CMR/ED phthalate used in a medical device need to be compared to the benefits of the most relevant alternatives, with the focus of the analysis being on the net or incremental benefits of use of the CMR/ED phthalate in comparison to the alternatives. These benefits may include material or clinical benefits. Uncertainties about the estimates or reliability of the data, assumptions, etc. for the parameters need to be presented.

### 8.1 Material benefit

A medical device does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but may be assisted in its function by such means. For the use of phthalates in medical devices, additional functionalities need to be considered. One of the functionalities is the fine-tuning of the flexibility of PVC when used as plasticisers, *e.g.,* in intubation devices. For blood bag set materials other requirements are, for example, resistance to heat and chemicals, especially during sterilisation, and permeability of gases to assure that pH and oxygen levels remain stable. In addition, DEHP has an additional property namely the stabilising effect on red blood cells (RBCs) (Klei *et al.,* 2022). A number of alternatives were evaluated as alternative for DEHP during RBC storage and some of these are already in use (see Annex 10). Platelets are extremely sensitive to changes in the pH of the medium in which they are suspended, so sufficient gas permeability to $O_2$ and $CO_2$ has to be assured in the containers devoted to their storage (Simmchen *et al.*, 2012). For this reason, DEHP, although still present in connecting tubes and ports of blood bag sets, has been almost fully replaced with BTHC, DINCH, and/or Trioctyltrimellitate (TOTM or Tri(2-ethyl hexyl)trimellitate (TEHTM)) in platelet storage bags (Simmchen *et al.,* 2012; Prowse *et al.,* 2014). A better gas exchange has been found in bags plasticised with these chemicals. Also, other materials, like polyolefins, are used for platelet storage bags (Prowse *et al.,* 2014).

It should be noted that the benefit of CMR/ED phthalates in terms of material functionality and performance may differ from device to device. An alternative may be available for one application, but not for another, due to added or specific demands on the functionality of the CMR/ED phthalate.

### 8.2 Clinical benefits

Clinical benefit of medical devices is defined in the MDR as follows:

- "Clinical benefit" means the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health (MDR, Article 2 Definitions: (53))

This "clinical benefit" has to be substantiated by the manufacturers in the "clinical evaluation" of the medical device, which includes a number of considerations. These comprise a discussion and overall conclusions covering safety and performance results, assessment of risks and clinical benefits, discussion of clinical relevance in accordance with clinical state of the art, any specific precautions for specific patient populations, implications for the investigational device and limitations of the investigation.

A "clinical benefit" could include any meaningful, measurable, patient-relevant outcome as presented below. The SCHEER identified the following examples that may be relevant for the use of phthalates (list not exclusive):

- Improved survival rates
- Improved quality of life
- Reduced length of hospital stay
- Improved placement times (among others in tubes and catheters)
- Improved product quality/clinical performance (among others in tubes and catheters) in terms of, for example:
    - leakage rates
    - breakage rates
    - knotting rates
    - blockage rates
    - bending performance rates
    - release rates of toxic substances
    - release rates of (nano-)particles
- Improved displacement rates
- Improved possibilities for sterilisation procedure
- Reduction of diameters in relation to performance
- Possibility to produce a "multi-functional" device (*e.g.,* inclusion of additional sensors), and therefore reduction of over-all stress and impact on the patient
- Improved observability (safety) in terms of translucence, printability, radiopaque lines included, identifiability, traceability, etc. (among others in tubes and catheters)
- Fewer adverse events, *e.g.,* reduced mucosal or endothelial irritation or injury rates (among others in tubes and catheters)
- Fewer serious adverse events and serious incidents

The benefit of the use of the CMR/ED phthalate should always be judged with respect to the "intended use" of the medical device and the exposed patient-group to the medical device and weighed in its clinical impact *(i.e.*, "clinically relevant difference"). These aspects should be judged by clinical experts.

Quantitative information on the benefits should be provided where possible or at a minimum qualitative description of their magnitude. Information on the probability of the benefit to occur and/or the duration of the benefit should also be included.

## 9. Methodologies for Benefit –Risk Assessment

In general, a Benefit - Risk Assessment (BRA) aims to evaluate the desired effects of therapeutic means, medicines or devices, against their undesired effects, *i.e.* risks for human health. An appropriate BRA can contribute to a more objective analysis and provide a more objective and transparent decision-making process for conformity verification bodies and authorities. Weighing the benefits and risks can be a complex task. It may involve the evaluation of a large amount of data that should be as accurate as possible, without methodological weaknesses and biases. There is always some uncertainty around the actual benefits and risks, because they can only be determined by looking at the information that is available at a given point in time which may contain various sources of uncertainty.

For the BRA of medical devices in general, guidance is available in Section A7.2. of MEDDEV 2.7/1 rev. 4, and in MDCG 2020-5 and MDCG 2020-6 guidance documents. (EN) ISO 14971 and the accompanying ISO/TR 24971 provide information on the risk benefit analysis to be performed within a risk management process. Additional information may be found elsewhere, for example in the documents of the FDA 2017 and FDA 2019. It should be noted that the acceptability of any risk is weighted against the benefit of the use of the medical device.

Several methodologies for BRA have been proposed (Guo *et al.,* 2010; Mt-Isa *et al.,* 2014), mainly, so far, those are used for pharmaceutical products. However, it should be underlined that for medical devices, it may prove difficult to make the quantitative determination of a benefit-risk ratio and express it numerically. In such cases, a qualitative approach of weighing the benefit based on expert judgement might be used. One methodology, namely the multi criteria decision analysis (MCDA), can be generally applied to various areas of BRA. The Multiple Criteria Decision Analysis (MCDA) approach (https://doi.org/10.1007/978-1-4615-1495-4) is defined as a systematic and theory-based approach to perform a comparative analysis of various competing options, based on their functioning on multiple and complicated criteria (Belton and Stewart, 2002). Therefore, this methodology might also be suitable for performing the BRA of medical devices (see Annex 7). The MCDA methodology originates from a decision-making process that evaluates multiple conflicting criteria. These criteria can include the benefits and risks of the use of a medical device on human health.

The final BRA of both the used CMR/ED phthalate and most relevant alternatives should contain all aspects as indicated in the framework above. A quantitative or semi-quantitative description of the risks (*e.g.,* MoS, RCR) and of the benefits of a medical device containing a CMR/ED phthalate or alternative should be the basis for a BRA. However, although quantitative approaches for a BRA are preferable, presenting a qualitative description of the value judgements about the balance of benefits and risks might also be an acceptable approach when justified (see Step 10).

## 10. Uncertainty analysis

Uncertainty analysis aims to identify and, when possible, to quantify uncertainties in measurements involved in medical and technical data modelling. Medical uncertainty has been considered an inherent feature of medicine, especially in clinical practice. Especially when considering the clinical prognosis and life expectancy of patients, the uncertainty related to the expressed prognosis remains difficult to estimate (Smith *et al.*, 2013). Based on a scoping review, a framework for decision making in medicine was suggested, taking into consideration various aspects of uncertainty (Helou *et al.,* 2020). Understanding and measuring medical uncertainty has been regarded to be a core competency for good and quality health and plays an important role in medical decision making. It is widely accepted that, despite the methodological and technological improvements that were achieved in the past decades, there is never absolute certainty regarding the safety, effectiveness, or performance of a medical treatment or use of a device. Therefore, the degree of certainty and thus, uncertainty of the benefits and risks of a medical device is a factor that should always be considered when making a BRA.

There are various sources of uncertainty in bio-medical studies; a major source of uncertainty is the biological difference among individuals. Another source of uncertainty is the intra- and inter- variability of the laboratories, with respect to equipment, reagents, and methods used. It is also accepted that diagnostic tools, which evaluate benefit and risk, share several limitations, giving false negative and false positive results in a variety of cases. Observer variation occurs quite often and should always be taken into account. Other factors that may influence the degree of uncertainty include: the type of clinical information available (*e.g.*, clinical investigation data, observational studies, evidence derived from registries or use experience), the representativeness of the information (*e.g.*, sample size, relevance of the sample to the referent population exposed to the device), and the statistical inferences derived from the information. For medical devices, the determination of an uncertainty factor for the analytical evaluation of constituents is described in ISO 10993-18 as amended in ISO 10993-18:2020/Amd.1:2022(E).

Another source of uncertainty could be the data set of the pre-clinical studies used for risk assessment.

A number of techniques for uncertainty analysis are described in the Guidance for Socio-Economic Analysis on authorisation from ECHA (ECHA 2011). The aim is to determine whether uncertainties in the estimation of impacts could affect the overall conclusions. More accurately, the techniques shown can be used to either reduce the variability of estimates, or to help test whether uncertainties affect the conclusions drawn. The only way to actually reduce uncertainty is through better data, better understanding and knowledge of the uncertainties and through further analysis. However, in most cases residual uncertainties will remain.

EFSA published a guidance on uncertainty analysis (EFSA 2018a) and a description of the principles and methods behind the guidance for uncertainty analysis (EFSA 2018b). The EFSA Guidance recognises that the form and extent of uncertainty analysis, and how the conclusions should be reported, vary widely depending on the nature and context of each analysis and the degree of uncertainty that is present. Therefore, it is important to identify appropriate options for each BRA. The EFSA documents provide a flexible framework for uncertainty analysis within which different methods may be selected, according to the

needs of each BRA. It seems likely that similar flexibility is needed for medical devices too, in view of the broad range of medical devices used.

EFSA describes a number of main elements of uncertainty that need to be considered in the uncertainty analysis:

- Identifying uncertainties affecting the assessment. This is necessary in every assessment and should be done in a structured way to minimise the chance of overlooking relevant uncertainties. In assessments that follow standardised procedures, it is only necessary to identify nonstandard uncertainties.
- Prioritising uncertainties within the assessment plays an important role in planning the uncertainty analysis, enabling the assessor to focus detailed analysis on the most important uncertainties and address others collectively when evaluating overall uncertainty. Often prioritisation will be done by expert judgement during the planning process, but in more complex assessments it may be done explicitly using influence analysis or sensitivity analysis.
- Dividing the uncertainty analysis into parts. In some assessments, it may be sufficient to characterise overall uncertainty for the whole assessment directly, by expert judgement. In other cases, it may be preferable to evaluate uncertainty for some or all parts of the assessment separately and then combine them, either by calculation or expert judgement.
- Ensuring the questions or quantities of interest are well-defined. Each question or quantity of interest must be well-defined so that the true answer or value could be determined, at least in principle. This is necessary to make the question or quantity a proper subject for scientific assessment, and to make it possible to express uncertainty about the true answer or value clearly and unambiguously. Some assessments follow standardised procedures, within which the questions and/or quantities of interest should be predefined. In other assessments, the assessors will need to identify and define the questions and/or quantities of interest case by case.
- Characterising uncertainty for parts of the uncertainty analysis. This is needed for assessments where assessors choose to divide the uncertainty analysis into parts but only for some of the parts, with the other parts being considered when characterising overall uncertainty.
- Combining uncertainty from different parts of the uncertainty analysis. This is needed for assessments where the assessors quantify uncertainty separately for two or more parts of the uncertainty analysis.
- Characterising overall uncertainty. Expressing quantitatively the overall impact of as many as possible of the identified uncertainties and describing qualitatively any that remain unquantified. This is necessary in all assessments except those standardised assessments where only standard uncertainties are identified (*e.g.* inter-and intra-species uncertainty factors).
- Prioritising uncertainties for future investigation. This is implicit or explicit in any assessment where recommendations are made for future data collection or research and may be informed by influence or sensitivity analysis.
- Reporting uncertainty analysis. Required for all assessments, but extremely briefly in standardised assessments where only standard uncertainties are identified.

A number of methods that can be used in the uncertainty analysis include:

- Sensitivity analysis
- Scenario analysis

- Expert judgement
- Monte Carlo Simulations

Some of these techniques can be used in combination (*e.g.,* scenario analysis together with expert judgement to establish ranges for key variables) but also together with less commonly used techniques such as risk-risk analysis, Delphi techniques and portfolio analysis, which can be used to help reduce the variability of estimates but are not discussed in these guidelines.

After performing the uncertainty analysis, the observed overall confidence associated with a BRA can be expressed as a probability score. This score gives the risk assessor an indication of what the uncertainty is in the BRA.

In situations where sufficient data are available, a quantitative categorisation of probability levels is preferred. If this is not possible, the manufacturer should give a qualitative description. A good qualitative description is preferable to an inaccurate quantitative description ((EN) ISO 14971).

EFSA (EFSA, 2018b) and SCHEER (2018) use a rather detailed probability scale of 9 and 7 probability levels, respectively. EFSA stresses that this scale may be used as an aid to support the development of judgements and that other ranges or qualitative descriptions can be used as well. EFSA (2018b) also argues that presenting the numerical probabilities alongside verbal expressions of probability, *e.g.*, 'Likely (> 66% probability)', increases the consistency of interpretation.

A detailed scale does not seem to be applicable for the uncertainties that can be obtained during a BRA evaluation of medical devices. For medical devices, a probability scale as indicated in Table 7 may be used showing a 5-level scale recommended by ISO for semi-quantitative assessments (ISO TR 24971, Tables 3 and 4). Table 7 further shows the verbal terms and subjective probability ranges that are based on a simplification of the EFSA/SCHEER scales (EFSA 2018a, 2018b; SCHEER 2018).

**Table 7: Probability scale for (semi-)quantitative description of the overall confidence in the uncertainty of the BRA of the CMR/ED phthalate and the identified most relevant alternatives.**

| ISO probability term | Subjective probability range | Probability term |
|---|---|---|
| Frequent | > 90% | very likely |
| Probable | 66-90% | likely |
| Occasional | 33-66% | as likely as not |
| Remote | 10-33% | unlikely |
| Improbable | <10% | very unlikely |

The US FDA published a guidance document specifically on how to consider uncertainty in a BRA for medical devices (FDA 2019).

## 11. Conclusions

These guidelines are intended to be used for a BRA of the presence of phthalates in certain medical devices covering phthalates which are carcinogenic, mutagenic, toxic to reproduction (CMR) or have endocrine-disrupting (ED) properties. The guidelines can be used for the justification of the use of CMR/ED phthalates in a medical device according to the MDR (EU 2017/745). They also provide a framework on how to assess and compare possible alternative substances, materials, designs or medical treatments to the use of CMR/ED phthalates in medical devices. Major aspects include the functionality of CMR/ED phthalates, the performance of the medical device using the CMR/ED phthalate or the identified most relevant alternatives for the CMR/ED phthalate, as well as the risk assessment of the CMR/ED phthalate or the most relevant alternatives. In the end, the benefit(s) shall be weighed against the possible risks of the use of the CMR/ED phthalate and of the most relevant alternatives*, i.e.*, substance, materials, designs or medical treatments. This overall analysis will determine whether or not it is justified to use a CMR/ED phthalate in a medical device.
In view of the concern about the CMR/ED properties of phthalates, further research to replace these phthalates in medical devices is highly encouraged by the SCHEER. In this update of these guidelines, progress regarding the replacement of CMR/ED phthalates is presented in some of the annexes, notably Annexes 8, 9, and 10.

During the preparation of these guidelines for BRA of the use of CMR/ED phthalates in medical devices, the SCHEER noticed that a number of BRA methodologies are theoretically available. However, there is a considerable lack of data for the BRA for potentially relevant alternatives to be used in medical devices. Therefore, the SCHEER encourages manufacturers to generate high-quality data for such alternatives to CMR/ED phthalates in medical devices.

As the BRA of the presence of phthalates may have an impact on the conclusions of the "overall" benefit-risk determination of the medical device, a periodic update of the BRA of the medical device may be needed. The BRA of the presence of the CMR/ED phthalate should be updated when new scientific information becomes available on phthalates and/or alternatives for the use of phthalates, when new guidelines are released, or as the "overall" benefit-risk determination of the medical device is updated. A plan to perform an update of the general BRA for the medical device should be included in the dossier before marketing the device, and this should also include a plan regarding the necessary updates on the evaluation of alternatives for CMR/ED phthalates.

## 12. Results of the public consultation

After the adoption (12 March 2024) and publication of the preliminary "UPDATE of the 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 (ED) properties", a public consultation period was held from 21 March 2024 to 28 April 2024.

A total of 49 comments were received. Eight organisations (four companies, three trade-associations, and one scientific society) commented on the preliminary document. Based on the comments, the final text was adapted in several locations where appropriate, particularly in Annex 10 on the current use of alternative plasticisers to DEHP for red blood cell storage.

## B. REFERENCES

Belton V, Stewart TJ. (2002). Multiple Criteria Decision Analysis. An Integrated Approach. Springer-Science+Business Media B.V. Dordrecht, The Netherlands. ISBN 978-1-4613-5582-3.

Bui TT, Giovanoulis G, Cousins AP, Magnér J, Cousins IT, de Wit CA. (2016). Human exposure, hazard and risk of alternative plasticizers to phthalate esters. Sci Total Environ. 541:451-467.

Burgos N, Jiménez A. (2009). Degradation of poly(vinyl chloride) plasticized with non-phthalate plasticizers under sterilization conditions. Polymer Degradation and Stability 94, 1473–1478.

Commission Delegated Regulation (EU) No 2023/707 of 19 December 2022 amending Regulation (EC) No 1272/2008 as regards hazard classes and criteria for the classification, labelling and packaging of substances and mixtures (OJ L 93, 31.3.2023). https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32023R0707

Commission Implementing Decision (EU) No 2017/1210 of 4 July 2017 on the identification of bis(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), benzyl butyl phthalate (BBP) and diisobutyl phthalate (DIBP) as substances of very high concern according to Article 57(f) of Regulation (EC) No 1907/2006 of the European Parliament and of the Council. Official Journal of the European Commission, L173/35, 6.7.2017.
https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A32017D1210

Commission Implementing Decision (EU) No 2018/636 of 17 April 2018 on the identification of dicyclohexyl phthalate (DCHP) as a substance of very high concern according to Article 57(c) and (f) of Regulation (EC) No 1907/2006 of the European Parliament and of the Council
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32018D0636#:~:text=Commission%20Implementing%20Decision%20(EU)%202018,2018)%202167)%20(Text%20with

Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food. https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ%3AL%3A2011%3A012%3A0001%3A0089%3Aen%3APDF

Crespo JR, Balart R, Sanchez L, López J. (2007). Substitution of Di(2-ethylhexyl) Phthalate by Di(isononyl) Cyclohexane-1,2-Dicarboxylate as a Plasticizer for Industrial Vinyl Plastisol Formulations. Journal of Applied Polymer Science, 104, 1215–1220.

Dybing E, Sanner T, Roelfzema H, Kroese D, Tennant RW. (1997). T25: a simplified carcinogenic potency index: description of the system and study of correlations between carcinogenic potency and species/site specificity and mutagenicity. Pharmacol Toxicol. 80, 272-279.

ECB (European Chemical Bureau). (2008). European Union Risk Assessment Report for Bis(2-ethylhexyl) phthalate (Consolidated Final Report) 2008. file:///C:/Users/whmde/Downloads/european%20union%20risk%20assessment%20report%20bis2-ethylhexylphthalate-LBNA23384ENC%20(1).pdf

ECHA (2011). Guidance on the preparation of socio-economic analysis as part of an application for authorisation, European Chemicals Agency 2011. https://www.echa.europa.eu/documents/10162/2324906/sea_authorisation_en.pdf/aadf96ec-fbfa-4bc7-9740-a3f6ceb68e6e

ECHA (2018). European Chemical Agency (ECHA) and European Food Safety Authority (EFSA) with the technical support of the Joint Research Centre (JRC). Andersson N, Arena M, Auteri D, Barmaz S, Grignard E, Kienzler A, Lepper P, Lostia AM, Munn S, Parra Morte JM, Pellizzato F, Tarazona J, Terron A, Van der Linden S. Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. EFSA Journal 2018;16(6):5311.

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5311

EFSA (2018a). (European Food Safety Authority) Scientific Committee, Benford D, Halldorsson T, Jeger MJ, Knutsen HK, More S, Naegeli H, Noteborn H, Ockleford C, Ricci A, Rychen G, Schlatter JR, Silano V, Solecki R, Turck D, Younes M, Craig P, Hart A, Von Goetz N, Koutsoumanis K, Mortensen A, Ossendorp B, Martino L, Merten C, Mosbach-Schulz O and Hardy A, 2018. Guidance on Uncertainty Analysis in Scientific Assessments. EFSA Journal 2018;16(1):5123, 39 pp. (https://doi.org/10.2903/j.efsa.2018.5123.)

EFSA (2018b). Scientific Committee, Benford D, Halldorsson T, Jeger MJ, Knutsen HK,More S, Naegeli H, Noteborn H, Ockleford C, Ricci A, Rychen G, Schlatter JR, Silano V, Solecki R, Turck D, Younes M, Craig P, Hart A, Von Goetz N, Koutsoumanis K, Mortensen A, Ossendorp B, Germini A, Martino L, Merten C, Mosbach-Schulz O, Smith A and Hardy A, 2018. Scientific Opinion on the principles and methods behind EFSA's Guidance on Uncertainty Analysis in Scientific Assessment. EFSA Journal 2018;16(1):5122,235 pp.
https://doi.org/10.2903/j.efsa.2018.5122

EFSA (2019). Scientific Committee, More SJ, Bampidis V, Benford D, Bennekou SH,Bragard C, Halldorsson TI, Hernandez-Jerez AF, Koutsoumanis K, Naegeli H, Schlatter JR, Silano V,Nielsen SS, Schrenk D, Turck D, Younes M, Benfenati E, Castle L, Cedergreen N, Hardy A, Laskowski R,Leblanc JC, Kortenkamp A, Ragas A, Posthuma L, Svendsen C, Solecki R, Testai E, Dujardin B, Kass GEN,Manini P, Jeddi MZ , Dorne J-LCM and Hogstrand C, 2019. Guidance on harmonised method ologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals.EFSA Journal 2019;17(3):5634, 77 pp.
https://doi.org/10.2903/j.efsa.2019.5634

EFSA (2022). Scientific Committee, More SJ, Bampidis V, Benford D, Bragard C, TI Halldorsson, Hernandez-Jerez AF, Hougaard Bennekou S, Koutsoumanis K, Lambre C, Machera K, Mennes W, Mullins E, Nielsen SS, Schrenk D, Turck D, Younes M, Aerts M, Edler L, Sand S, Wright M, Binaglia M, Bottex B, Cortinas Abrahantes, Schlatter J. EFSA. Guidance on the use of the benchmark dose approach in risk assessment. EFSA Journal 2022;20(10):7584. https://doi.org/10.2903/j.efsa.2022.7584

Eliason P, Morose G. (2011). Safer alternatives assessment: the Massachusetts process as a model for state governments. Journal of Cleaner Production 19, 517-526

European Directorate for the Quality of Medicines and Healthcare (EDQM), European Pharmacopoeia (Ph. Eur.) 9th Edition 2019, Council of Europe, Strasbourg, France.

European Directorate for the Quality of Medicines and Healthcare (EDQM), European Pharmacopoeia (Ph. Eur.) 11th Edition 2022, Council of Europe, Strasbourg, France

EMA (2014). European Medicines Agency. Benefit-risk methodology project (https://www.ema.europa.eu/documents/report/benefit-risk-methodology-project-update-work-package-5-effects-table-pilot-phase-i_en.pdf)

FDA (2016). US Food and Drug Administration. Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions. Guidance for Industry and Food and Drug Administration Staff. December 27, 2016. Washington, USA. https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM506679.pdf

FDA (2017). US Food and Drug Administration. Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions. Guidance for Investigational Device Exemption Sponsors, Sponsor-Investigators and Food and Drug Administration Staff. Document issued on January 13, 2017. https://www.fda.gov/media/92427/download

FDA (2018). US Food and Drug Administration. Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics. Guidance for Industry and Food and Drug Administration Staff. September 25, 2018. Washington, USA. https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM404773.pdf

FDA (2019). US Food and Drug Administration. Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications Guidance for Industry and Food and Drug Administration Staff Document issued on August 30, 2019. https://www.fda.gov/media/99769/download

FDA (2023). US Food and Drug Administration. Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process". Guidance for Industry and Food and Drug Administration Staff. September 8, 2023. Washington, USA. https://www.fda.gov/media/142959/download

Guo JJ, Pandey S, Doyle J, Bian B, Lis Y, Raisch DW. (2010). A review of quantitative risk-benefit methodologies for assessing drug safety and efficacy-report of the ISPOR risk-benefit management working group. Value Health. 13, 657-666.

Hass U, Christiansen S, Andersson A-M, Holbech H, Bjerregaard P. (2019). Report on interpretation of knowledge on endocrine disrupting substances (EDs) – what is the risk? Danish Centre on Endocrine Disruptors, Denmark. http://www.cend.dk/files/ED_Risk_report-final-2019.pdf

Helou MA, DiazGranados D, Ryan MS, Cyrus JW. (2020). Uncertainty in Decision Making in Medicine: A Scoping Review and Thematic Analysis of Conceptual Models. Acad Med. 95:157-165.

ISO 10993-1. Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process. 2018. ISO, Geneva, Switzerland.

ISO 10993-12. Biological evaluation of medical devices - Part 12: Sample preparation and reference materials. 2021. ISO, Geneva, Switzerland.

ISO 10993-17. Biological evaluation of medical devices - Part 1: Toxicological risk assessment of medical device constituents. 2023. ISO, Geneva, Switzerland.

ISO 10993-18. Biological evaluation of medical devices - Part 18: Chemical characterization of medical device materials within a risk management process. 2020. ISO, Geneva, Switzerland.

ISO 10993-18 :2020/Amd.1 :2022(E). Biological evaluation of medical devices - Part 18: Chemical characterization of medical device materials within a risk management process. Amendment 1: Determination of the uncertainty factor. 2022. ISO, Geneva, Switzerland.

ISO 14155. Clinical investigation of medical devices for human subjects. Good clinical practice. 2020. ISO, Geneva, Switzerland.

ISO 14971. Medical Devices - Application of risk management to medical devices. 2019. ISO, Geneva, Switzerland.

ISO/TR 24971. Medical Devices - Guidance on the application of ISO 14971. 2020. ISO, Geneva, Switzerland

Klei TRL, Begue S, Lotens A, Sigurjonsson ÓE, Wiltshire MD, George C, Van Den Burg PJM, Evans R, Larsson L, Thomas S, Najdovski T, Handke W, Eronen J, Mallas B, De Korte D. (2023). Recommendations for in vitro evaluation of blood components collected, prepared and stored in non-DEHP medical devices. Vox Sanguinis. 118, 165-177.

MDCG 2019-9 Rev.1 Summary of safety and clinical performance. A guide for manufacturers and notified bodies. Medical Device Coordination Group Document, March 2022. https://health.ec.europa.eu/document/download/5f082b2f-8d51-495c-9ab9-985a9f39ece4_en?filename=md_mdcg_2019_9_sscp_en.pdf

MDCG 2020-5. Clinical Evaluation - Equivalence A guide for manufacturers and notified bodies, Medical Device Coordination Group Document, April 2020. https://health.ec.europa.eu/system/files/2020-09/md_mdcg_2020_5_guidance_clinical_evaluation_equivalence_en_0.pdf

MDCG 2020-6. Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC A guide for manufacturers and notified bodies, Medical Device Coordination Group Document, April 2020.
https://health.ec.europa.eu/system/files/2020-09/md_mdcg_2020_6_guidance_sufficient_clinical_evidence_en_0.pdf

MDCG 2021-5. Guidance on standardisation for medical devices, Medical Device Coordination Group Document, April 2021.

https://health.ec.europa.eu/system/files/2021-04/md_mdcg_2021_5_en_0.pdf

MDCG 2023-7. Guidance on exemptions from the requirement to perform clinical investigations pursuant to Article 61(4)-(6) MDR and on 'sufficient levels of access' to data needed to justify claims of equivalence, Medical Device Coordination Group Document, December 2023.
https://health.ec.europa.eu/document/download/1b5f9cc0-cea0-4459-921f-eaf4b4f80983_en?filename=mdcg_2023-7_en.pdf.

MEDDEV 2.7/1 rev. 4. Clinical evaluation: a guide for manufacturers and notified bodies under directives 93/42/EEC and 90/385/EEC, European Commission, June 2016.
https://www.medical-device-regulation.eu/wp-content/uploads/2019/05/2_7_1_rev4_en.pdf

Mt-Isa S, Hallgreen C.E., Wang N., Callréus T., Genov G., Hirsch I., Hobbiger S., Hockley S., Luciani D., Phillips L.D., Quartey G., Sarac S.B., Stoeckert I., Tzoulaki I., Micaleff A., Ashby D. (2014). IMI-PROTECT benefit-risk participants. Balancing benefit and risk of medicines a systematic review and classification of available methodologies, Pharmacoepidemiol Drug Saf. 23, 667-678.

National Research Council (US) (2008). Committee on the Health Risks of Phthalates. Phthalates and Cumulative Risk Assessment. The Tasks Ahead. Washington (DC): National Academies Press (US); ISBN-13: 978-0-309-12841-4ISBN-10: 0-309-12841-2. https://www.ncbi.nlm.nih.gov/books/NBK215040

Nielsen BS, Andersen BN, Giovalle E, Bjergstrom M, Larsen PB. (2014). Alternatives to classified phthalates in medical devices. The Danish Environmental Protection Agency, Copenhagen, Denmark. https://www2.mst.dk/Udgiv/publications/2014/03/978-87-93178-27-4.pdf

Prowse CV, de Korte D, Hess JR, van der Meer PF. (2014). Biomedical Excellence for Safer Transfusion (BEST) Collaborative. Commercially available blood storage containers. Vox Sang. 106, 1-13. doi: 10.1111/vox.12084.

Regulation (EC) No 1935/2004 of the European Parliament and of the Council of 27 October 2004 on materials and articles intended to come into contact with food and repealing Directives 80/590/EEC and 89/109/EEC (OJ L 338, 13.11.2004).
https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02004R1935-20210327

Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC (OJ L 396, 30.12.2006).
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02006R1907-20140410

Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures,

amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 (OJ L 353, 31.12.2008).
https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32008R1272

Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products (OJ L 167, 27.6.2012).
https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32012R0528

Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (OJ L 117 5.5.2017).
https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:L:2017:117:FULL

Commission Delegated Regulation (EU) 2023/707 of 19 December 2022 amending Regulation (EC) No 1272/2008 as regards hazard classes and criteria for the classification, labelling and packaging of substances and mixtures (OJ L 93, 31.3.2023)
https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32023R0707

Salloum HA, Saunier J, Aymes-Chodur C, Barakat H, Yagoubi N. (2015). Impact of the nature and concentration of plasticizers on the ability of PVC to sorb drug. International Journal of Pharmaceutics 496, 664–675.

SCCS 1647/22 The SCCS Notes of guidance for the testing of cosmetic ingredients and their safety evaluation 12th revision. 2023. https://health.ec.europa.eu/document/download/32a999f7-d820-496a-b659-d8c296cc99c1_en?filename=sccs_o_273_final.pdf

SCCS 1655/23 Guidance on the safety assessment of nanomaterials in cosmetics. 2nd revision. https://health.ec.europa.eu/document/download/f0987165-c2e1-41a6-8655-6fb3d52b728c_en?filename=sccs_o_278.pdf

SCHEER (2018). Memorandum on weight of evidence and uncertainties. Revision 2018.
https://ec.europa.eu/health/sites/health/files/scientific_committees/scheer/docs/scheer_o_014.pdf

SCENIHR (2015). Opinion on the safety of medical devices containing DEHP plasticized PVC or other plasticizers on neonates and other groups possibly at risk (2015 update).
https://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_047.pdf

Simmchen J, Ventura R, Segura J. (2011). Progress in the removal of di-[2-ethylhexyl]-phthalate as plasticizer in blood bags. Transfus Med Rev. 26, 27-37. doi: 10.1016/j.tmrv.2011.06.001. Epub 2011 Aug 5.

Smith AK, White DB, Arnold RM. (2013). Uncertainty--the other side of prognosis. N Engl J Med. 368, 2448-2450.

Tortolano L, Matmati H, Bourhis M,Manerlax K, Lemare F, Saunier J,Yagoubi N. (2018). DinCH and ESBO actual migration from PVC infusion tubings used in an oncopediatric unit. J. Appl. Polym. Sci. 135, 46649.

Treleano A,Wolz G,Brandsch R, Welle F. (2009). Investigation into the sorption of nitroglycerin and diazepam intoPVC tubes and alternative tube materials during application. Intl JPharmac 369, 30–37.

USP, United States Pharmacopeia (2024). General Chapter, ?661? Plastic Packaging Systems and Their Materials of Construction. 2024. USP-NF. Rockville, MD: United States Pharmacopeia. DOI:https://doi.org/10.31003/USPNF_M99420_04_01

## C. ANNEXES

**Annex 1:** SCHEER mandate on benefit-risk assessment on the use of CMR/ED phthalates

### 1. Background

Regulation (EU) 2017/745 on medical devices (MDR) ([13]) establishes a legal obligation on the Commission([14]) to provide the relevant scientific committee with a mandate to prepare guidelines on the benefit-risk assessment of the presence of phthalates, which belong to either of the groups of substances that are carcinogenic, mutagenic or toxic to reproduction of category 1A or 1B, in accordance with Part 3 of Annex VI to Regulation (EC) 1272/2008, or that have endocrine-disrupting properties.
The benefit-risk assessment has to take into account the intended purpose and context of the use of the device, as well as any available alternative substances and alternative materials, designs or medical treatments.

The obligation to have the guidance available was set on 26 May 2020 and the document was adopted by the SCHEER at plenary meeting on 18 June 2019.

The MDR sets also a legal obligation for the update of the guidance, on the basis of the latest scientific evidence. Such update can be made when appropriate and, at least, every five years.

### 2. Terms of reference

The SCHEER is requested to update the guidelines on the benefit-risk assessment of the presence of phthalates in certain medical devices that was adopted by that committee at the plenary meeting on 18 June 2019.

The update has to take into consideration and be based on the latest scientific evidence.

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 continue to 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,
- 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

[13] Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC http://data.europa.eu/eli/reg/2017/745/2020-04-24.
[14] MDR, Annex I, Section 10.4.3.

pregnant or breastfeeding women or treatment of other patient groups considered particularly vulnerable to such substances and/or materials.

Where the SCHEER committee will consider, during its assessment, that the current version of the guidance is still fit for purpose in the light of the latest scientific evidence, the committee will issue a new version of the document including such confirmation.

## **Annex 2:** CMR and/or ED substances under the Medical Device Regulation (Regulation (EU) 2017/745)

The requirement for justification of the presence of CMR 1A or 1B and/or ED hazardous substances is described in Annex I 10.4.2 as presented in the text box below.

10.4. Substances

10.4.1. Design and manufacture of devices

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.

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 the following substances in a concentration that is above 0,1 % weight by weight (w/w) where justified pursuant to Section 10.4.2:

(a) substances which are carcinogenic, mutagenic or toxic to reproduction ('CMR'), of category 1A or 1B, in accordance with Part 3 of Annex VI to Regulation (EC) No 1272/2008 of the European Parliament and of the Council (1), or

(b) substances having endocrine-disrupting properties for which there is scientific evidence of probable serious effects to human health and which are identified either in accordance with the procedure set out in Article 59 of Regulation (EC) No 1907/2006 of the European Parliament and of the Council (2) or, once a delegated act has been adopted by the Commission pursuant to the first subparagraph of Article 5(3) of Regulation (EU) No 528/2012 of the European Parliament and the Council (3), in accordance with the criteria that are relevant to human health amongst the criteria established therein.

10.4.2. Justification regarding the presence of CMR and/or endocrine-disrupting substances

The justification for the presence of such substances shall be based upon:

(a) an analysis and estimation of potential patient or user exposure to the substance;

(b) an analysis of possible alternative substances, materials or designs, including, where available, information about independent research, peer-reviewed studies, scientific opinions from relevant scientific committees and an analysis of the availability of such alternatives;

(c) argumentation as to 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; and

(d) where applicable and available, the latest relevant scientific committee guidelines in accordance with Sections 10.4.3 and 10.4.4.

**Annex 3:** Definitions/descriptions – References - Glossary

## ***Definitions (Regulation (EU) 2017/745)***

**Adverse event:** means any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.

**Benefit-risk determination:** means the analysis of all assessments of benefit and risk of possible relevance for the use of the device for the intended purpose, when used in accordance with the intended purpose given by the manufacturer.

**Clinical benefit:** means the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health.

**Clinical performance:** means the ability of a device, resulting from any direct or indirect medical effects which stem from its technical or functional characteristics, including diagnostic characteristics, to achieve its intended purpose as claimed by the manufacturer, thereby leading to a clinical benefit for patients, when used as intended by the manufacturer.

**Device deficiency:** means any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

**Incident:** means any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect.

**Performance:** means the ability of a device to achieve its intended purpose as stated by the manufacturer.

**Risk:** means the combination of the probability of occurrence of harm and the severity of that harm.

**Serious adverse event:** means any adverse event that led to any of the following:

(a) death,

(b) serious deterioration in the health of the subject, that resulted in any of the following:

(i) life-threatening illness or injury,

(ii) permanent impairment of a body structure or a body function,

(iii) hospitalisation or prolongation of patient hospitalisation,

(iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

(v) chronic disease,

(c) fetal distress, fetal death or a congenital physical or mental impairment or birth defect.

**Serious incident:** means any incident that directly or indirectly led, might have led or might lead to any of the following:

(a) the death of a patient, user or other person,

(b) the temporary or permanent serious deterioration of a patient's, user's or other person's state of health,

(c) a serious public health threat.

**Serious public health threat**: means an event which could result in imminent risk of death, serious deterioration in a person's state of health, or serious illness, that may require prompt remedial action, and that may cause significant morbidity or mortality in humans, or that is unusual or unexpected for the given place and time.

**Regulation (EU) 2017/745 Annex XIV Clinical evaluation and post-market clinical follow-up. Part A "Clinical evaluation" Section 3 describes the characteristics that shall be considered for demonstration of equivalence**.

A clinical evaluation may be based on clinical data relating to a device for which equivalence to the device in question can be demonstrated (see also MDCG 2020-5 and MDCG 2023-7). The following technical, biological and clinical characteristics shall be taken into consideration for the demonstration of equivalence:

**Biological characteristics**: the device uses the same materials or substances in contact with the same human tissues or body fluids for a similar kind and duration of contact and similar release characteristics of substances, including degradation products and leachables.

Leachables may include degradation products or other substances from the materials or substances that the device is made of, but also other constituents for example residuals from the manufacturing process or sterilisation, any contaminations etc.

**Clinical characteristics**: the device is used for the same clinical condition or purpose, including similar severity and stage of disease, at the same site in the body, in a similar population, including as regards age, anatomy and physiology; has the same kind of user; has similar relevant critical performance in view of the expected clinical effect for a specific intended purpose.

The characteristics shall be similar to the extent that there would be no clinically significant difference in the safety and clinical performance of the device. Considerations of equivalence shall be based on proper scientific justification. It shall be clearly demonstrated that manufacturers have sufficient levels of access to the data relating to devices with which they are claiming equivalence in order to justify their claims of equivalence."

**Technical characteristics**: the device is of similar design; is used under similar conditions of use; has similar specifications and properties including physicochemical properties such

as intensity of energy, tensile strength, viscosity, surface characteristics, wavelength and software algorithms; uses similar deployment methods, where relevant; has similar principles of operation and critical performance requirements.

**Some definitions on assessment of alternatives**

Note: The term "chemical" is used synonymously with "substance"

**Alternatives assessment**: A process for identifying and comparing potential chemical and non-chemical alternatives that can be used as substitutes to replace chemicals or technologies of high concern [1]

**Chemical substitution**: The process of replacing a chemical of concern with a safer chemical, material or product, or technology/process that eliminates the need to use that chemical

**Cost/benefits and availability**: The negative (cost) and positive (benefit) implications, direct and indirect, resulting from some action. This includes both financial and non-financial information. Availability refers to the production of an alternative and its market accessibility [2]

**Functional use approach**: This approach starts with identifying the function that is desired. The concept is applied in two ways: first and foremost, to characterise the purpose a chemical or mixture serves, or the properties it imparts in a product or process (functional use), and second, to evaluate the function of the product and how its use may influence the assessment of alternatives [2-4]

**Material substitution**: The process of replacing a material containing a chemical of concern with a safer chemical, material, product or technology/process that eliminates the need to use that chemical

**Mixture**: A composition of at least two chemicals in which they do not react [5], or any combination of two or more chemicals that may contribute to effects regardless of source and spatial or temporal proximity [6]

**Process modification**: Changes in manufacturing processes to eliminate, reduce or substitute chemicals of concern. Such changes may include synthesis pathways, waste reduction, and manufacturing procedures where chemicals are used.

**Product performance**: The ability of a product to meet identified performance requirements. The boundaries of performance characteristics are defined by the user [2]

**Product substitution**: The process of replacing a product containing a chemical of concern with a chemical, material or product or technology/process that eliminates, reduces or substitutes the need to use that chemical.

**Technical feasibility**: The determination as to whether the performance or functional requirements of a chemical, material or product could be fulfilled or replaced by eliminating or using an alternative chemical, material, product, process or technology, while considering any need for process adaptations and changes [2]

In addition, information on definitions related to alternative substances can also be found in the OECD Toolbox[15]

[1] Adapted from *Alternatives Assessment Guide, version 1.1*. 2017. Interstate Chemicals Clearinghouse. https://www.theic2.org/wp-content/uploads/2022/09/IC2_AA_Guide_Version_1.1.pdf

[2] Current Landscape of Alternatives Assessment Practice: A Meta-Review. Organisation for Economic Cooperation and Development. 2013. https://www.oecd.org/chemicalsafety/risk-management/substitution-of-hazardous-chemicals/#3

[3] U.S. EPA. 2006. National Pollution Prevention and Toxics Advisory Committee (NPPTAC) Recommendation to the EPA Administrator and Deputy Administrator on Incorporating the Functional Use Approach into OPPT Activities.

[4] Lavoie, E. T., *et al.* 2010. "Chemical Alternatives Assessment: Enabling Substitution to Safer Chemicals." Environmental Science & Technology 44(24): 9244-9249.

[5] Adapted from *U.N. Globally Harmonized System of Classification and Labelling of Chemicals*. GHS Rev. 10, 2023. https://unece.org/transport/dangerous-goods/ghs-rev10-2023

[6] EFSA 2019 Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals EFSA Journal;17:5634, 77 pp. https://doi.org/10.2903/j.efsa.2019.5634

[15] https://www.oecd.org/chemicalsafety/risk-management/substitution-of-hazardous-chemicals/

**List of abbreviations**

| | |
|---|---|
| ADI | Acceptable daily intake |
| ATBC | Acetyl tri-n-butyl citrate |
| BBP | Benzylbutylphthalate (also BzBP, synonym, Butyl benzylphthalate BBzP) |
| BBzP | Butyl benzylphthalate (synonym Benzyl butylphthalate, BBP) |
| BMD | Bench Mark Dose |
| BMDL | Bench Mark Dose Low, the lower limit of the BMD confidence interval |
| BMD10 | Bench Mark Dose associated with a 10% response |
| BRA | Benefit-Risk Assessment |
| BTHC | Butyryl-tri-n-hexylcitrate |
| CAS | Chemical Abstracts Service |
| CEN | European Committee for Standardization |
| CLH | Harmonised classification and labelling |
| CLP | Classification Labelling and Packaging Regulation (Regulation (EC) 1272/2008) |
| CMR | Carcinogenic, Mutagenic, toxic to Reproduction (Reprotoxic) |
| COMGHA | Glycerides, castor-oil-mono-, hydrogenated, acetates |
| DBA | Dibutyl adipate |
| DBP | Dibutylphthalate, |
| DBS | Dibutylsebacate |
| DCHP | Dicyclohexylphthalate |
| DEHA | Di(2-ethylhexyl)adipate |
| DEHP | Diethylhexylphthalate |
| DEHS | Di-(2-ethylhexyl)sebacate, dioctylsabasate |
| DEHT | Di-2-ethylhexyl terephthalate (also DEHTP or DOTP) |
| DEHTP | Di-2-ethylhexyl terephthalate (also DEHT or DOTP) |
| DEP | Diethylphthalate |
| DIBA | Diisobutyl adipate |
| DIBP | Diisobutylphthalate |
| DIDA | Diisodecyl adipate |
| DIDP | Diisodecyl phthalate |
| DINA | Diisononyl adipate |
| DINCH | 1,2- cyclohexanedicarboxylic acid, diisononyl ester) |
| DINP | Di isononyl phthalate) |
| DIPP | Diisopentylphthalate |

| | |
|---|---|
| DMP | Dimethylphthalate |
| DMEL | Derived Minimum Effect Level |
| DnBP | di-n-butyl phthalate |
| DNEL | Derived No Effect Level |
| DNOP | Di-n-octyl phthalate |
| DOTP | Di-2-ethylhexyl terephthalate (also DEHT or DEHTP) |
| DPHP | Bis(2-propylheptyl) phthalate |
| EC | European Commission |
| ECB | European Chemicals Bureau (now ECHA) |
| ECDC | European Centre for Disease prevention and Control |
| ECHA | European Chemicals Agency (formerly ECB) |
| ECMO | Extracorporal Membrane Oxygenation |
| ED | Endocrine Disrupting |
| EDQM | European Directorate for the Quality of Medicines and Health Care (Council of Europe, Strasbourg, France) |
| EEC | European Economic Community |
| EINECS | European INventory of Existing Commercial chemical Substances |
| EFSA | European Food Safety Authority |
| EPA | Environmental Protection Agency (Denmark or USA) |
| EMA | European Medicines Agency (previously abbreviated as EMEA) |
| EN-ISO | also (C)EN-ISO, ISO document endorsed by CEN (European Committee for Standardization) |
| EU | European Union |
| FCM | Food Contact Material(s) |
| FDA | Food and Drug Administration (USA) |
| IARC | International Agency for Research on Cancer, Lyon, France |
| ISO | International Organization for Standardization |
| IUPAC | International Union of Pure and Applied Chemistry |
| LOAEL | Lowest Observed Adverse Effect Level |
| MEDDEV | MEDDEV guidance documents are published by the European Commission to support the Medical Device Regulation (MDR) |
| MCDA | Multi Criteria Decision Analysis |
| MD | Medical Device |
| MDCG | Medical Device Coordination Group established according to MDR art. 103, and which tasks are described in the MDR art. 105. |
| MDR | Medical Device Regulation (Regulation (EU) 2017/745) |

| | |
|---|---|
| MoA | Mode of Action |
| MoE | Margin of Exposure |
| MoS | Margin of Safety |
| NICU | Neonatal Intensive Care Unit |
| NOAEL | No Observed Adverse Effect Level |
| OECD | Organization for Economic Cooperation and Development |
| PoD | Point of departure |
| PVC | Polyvinyl chloride |
| RAC | Committee for Risk Assessment (ECHA) |
| RBC | Red Blood Cell |
| RCR | Risk Characterisation Ratio |
| REACH | Registration, Evaluation, Authorisation and restriction of CHemicals.(EC 1907/2006) |
| RMM | Risk management Measures |
| SCCS | Scientific Committee on Consumer Safety |
| SCHEER | Scientific Committee on Health, Environmental and Emerging Risks |
| SCENIHR | Scientific Committee on Emerging and Newly Identified Health Risks |
| SEAC | Committee for Socio-economic Analysis (ECHA) |
| SML | Specific Migration Limit |
| SSCP | Summary of Safety and Clinical Performance |
| SVHC | Substances of Very High Concern (Regulation (EC) 1907/2006) |
| T25 | 25 % increase of the tumour rate over controls |
| TDI | Tolerable Daily IntakeTE Tolerable Exposure (EN ISO 10993-17:2002 in mg/day) |
| TEHTM | Tri( 2-ethyl hexyl)trimellitate also TOTM Trioctyltrimellitate |
| TE | Tolerable Exposure (EN ISO 10993-17:2002 in mg/day) |
| TI | Tolerable Intake |
| TOTM | Trioctyltrimellitate also TEHTM Tri( 2-ethyl hexyl)trimellitate |
| TWI | Tolerable Weekly Intake |
| US | United States |
| USP | US Pharmacopeia |
| WHO | World Health Organization, Geneva, Switzerland |
| WoE | Weight of Evidence |
| w/w | weight by weight |

**Table 3.1 Chemical identifiers of substances frequently used as plasticisers**

| Acronym | Chemical name | IUPAC NAME | CAS n. | Notes or other indicators |
|---|---|---|---|---|
| ATBC | Acetyl tri-n-butyl citrate | tributyl 2-acetoxypropane-1,2,3-tricarboxylate | 77-90-7 | |
| BBP | Benzylbutylphthalate | 1-benzyl 2-butyl benzene-1,2-dicarboxylate | 85-68-7 | |
| BTHC | Butyryl-tri-n-hexylcitrate | trihexyl 2-butanoyloxypropane-1,2,3-tricarboxylate | 82469-79-2 | |
| COMGHA | Glycerides, castor-oil-mono-, hydrogenated, acetates | not available | 736150-63-3 | Listed in Reg EU n 10/2011"Reaction mass of 1,3-diacetoxypropan-2-yl 12-acetoxyoctadecanoate and 2,3-diacetoxypropyl 12-acetoxyoctadecanoate" |
| DBA | Dibutyl adipate | 1,6-dibutyl hexanedioate | 105-99-7 | |
| DBP | Dibutylphthalate, | 1,2-dibutyl benzene-1,2-dicarboxylate | 84-74-2 | |
| DBS | Dibutylsebacate | 1,10-dibutyl decanedioate | 109-43-3 | |
| DCHP | Dicyclohexylphthalate | 1,2-dicyclohexyl benzene-1,2-dicarboxylate | 84-61-7 | |
| DEHA | Di(2-ethylhexyl)adipate | 1,6-bis(2-ethylhexyl) hexanedioate | 103-23-1 | |
| DEHP | Di(2-ethylhexyl)phthalate | Bis(2-ethylhexyl) phthalate | 117-81-7 | |
| DEHS | Di(2-ethylhexyl)sebacate | Bis(2-ethylhexyl) sebacate | 122-62-3 | |
| DEHT | Di(2-ethylhexyl)terephthalate | Bis(2-ethylhexyl) benzene-1,4-dicarboxylate or Bis(2-ethylhexyl)terephthalate | 6422-86-2 | The same as DOTP, also DEHTP |
| DEP | Diethylphthalate | 1,2-diethyl benzene-1,2-dicarboxylate | 84-66-2 | |
| DIBA | Diisobutyl adipate | 1,6-bis(2-methylpropyl) hexanedioate | 141-04-8 | |
| DIBP | Diisobutylphthalate | 1,2-bis(2-methylpropyl) benzene-1,2-dicarboxylate | 84-69-5 | |
| DIDA | Diisodecyl adipate | 1,6-bis(2-methylnonyl) hexanedioate | 27178-16-1 | |

| | | | | |
|---|---|---|---|---|
| DIDP | Diisodecyl phthalate | bis(8-methylnonyl) benzene-1,2-dicarboxylate | 26761-40-0 | |
| DINA | Diisononyl adipate | 1,6-bis(7-methyloctyl) hexanedioate | 33703-08-1 | |
| DINCH | 1,2-cyclohexanedicarboxylic acid, diisononyl ester | 1,2-bis(7-methyloctyl) (1R,2S)-cyclohexane-1,2-dicarboxylate | 166412-78-8 | |
| DINP | Diisononyl phthalate | 1,2-bis(7-methyloctyl) benzene-1,2-dicarboxylate | 28553-12-0 | |
| DIPP | Diisopentylphthalate | 1,2-bis(3-methylbutyl) benzene-1,2-dicarboxylate | 605-50-5 | |
| DIDP* | | 1,2-Benzenedicarboxylic acid, di-C9-11-branched alkyl esters, C10-rich | 68515-49-1 | *a mixture of esters, mainly based on diisoodecyl ester |
| DINP* | | 1,2-Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich | 68515-48-0 | *a mixture of esters, mainly based on diisononyl ester |
| DL9TH | 4-cyclohexene-1,2-dicarboxylic acid dinonyl ester | | 1609185-22-9 | |
| DMEP | Bis(2-methoxyethyl)phthalate | Bis(2-methoxyethyl) phthalate | 117-82-8 | |
| DMP | Dimethylphthalate | 1,2-dimethyl benzene-1,2-dicarboxylate | 131-11-3 | |
| DOTH | di(2-ethylhexyl)4-cyclohexene-1,2-dicarboxylate | Bis (2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate | 2915-49-3 | |
| DOTP | Di-(2-ethylhexyl) terephthalate | Bis(2-ethylhexyl) benzene-1,4-dicarboxylate or Bis(2-ethylhexyl)terephthalate | 6422-86-2 | The same as DEHT |
| DOS | Dioctylsebacate | 1,10-dioctyl decanedioate | 2432-87-3 | sometimes confused with DEHS |
| DPHP | Bis(2-propylheptyl) phthalate | 1,2-bis(2-propylheptyl) benzene-1,2-dicarboxylate | 53306-54-0 | |
| TEHTM | Tri(2-ethylhexyl)trimellitate | 1,2,4-tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate | 3319-31-1 | The same as TOTM |
| TOTM | Trioctyltrimellitate | 1,2,4-tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate | 3319-31-1 | The same as TEHTM |

## **Annex 4:** CMR and/or ED substances

CMR substances are substances identified and classified as carcinogenic, mutagenic or toxic for reproduction of different categories based on the intrinsic toxic properties of a substance for which categories 1A and 1B apply to these guidelines. In Europe, classification for these endpoints is harmonised through harmonised classification and labelling (CLH). Details can be found at https://echa.europa.eu/regulations/clp/understanding-clp. For a specific substance to be classified as CMR 1A, 1B or 2 an ECHA RAC Opinion is developed based on the CLH dossier. If the Commission agrees on the proposed hazard classification, it submits a draft decision concerning the inclusion of that substance in Part 3 of Annex VI of Regulation (EC) 1272/2008 (CLP Regulation, (R classification, labelling and packaging of substances and mixtures).

- Category 1A means that the substance is a known human carcinogen, mutagen or reproductive toxicant based on human evidence.
- Category 1B means that the substance is a presumed human carcinogen, mutagen or reproductive toxicant based on animal studies.
- Category 2 means that a substance is considered as suspected carcinogen, mutagen or reproductive toxicant based on limited evidence from animal studies or humans (not part of these guidelines).

Documents on the classification and labelling are publicly available, and information on the C&L Inventory to search for notified and registered substances is given here:

https://echa.europa.eu/information-on-chemicals/cl-inventory-database

For endocrine disruptor activity, Commission Delegated Regulation (EU) 2023/707 was recently published including an amendment on the classification of ED substances. It is indicated that the level of evidence as regards endocrine disrupting properties may be of different scientific strength. It is therefore considered appropriate to create two categories of endocrine disruptors based on the available level of evidence. According to the Commission Delegated Regulation (EU) 2023/707 of 19 December 2022 amending Regulation (EC) 1272/2008, based on the level of evidence, there are two categories of endocrine disruptors: known or presumed endocrine disruptors (Category 1) and suspected endocrine disruptors (Category 2), both for human health and for the environment. The criteria to meet these two hazard categories are described in Annex I, Table 3.11.1. of Commission Delegated Regulation (EU) 2023/707 (see Table below).

*Table 3.11.1.*

**Hazard categories for endocrine disruptors for human health**

| Categories | Criteria |
|---|---|
| CATEGORY 1 | Known or presumed endocrine disruptors for human health<br><br>The classification in Category 1 shall be largely based on evidence from at least one of the following:<br><br>a) human data;<br>b) animal data;<br>c) non-animal data providing an equivalent predictive capacity as data in points a or b.<br>Such data shall provide evidence that the substance meets all the following criteria:<br>(a) endocrine activity;<br>(b) an adverse effect in an intact organism or its offspring or future generations;<br>(c) a biologically plausible link between the endocrine activity and the adverse effect.<br><br>However, where there is information that raises serious doubt about the relevance of the adverse effects to humans, classification in Category 2 may be more appropriate. |
| CATEGORY 2 | Suspected endocrine disruptors for human health<br><br>A substance shall be classified in Category 2 where all the following criteria are fulfilled:<br><br>(a) there is evidence of:<br>i. an endocrine activity; and<br>ii. an adverse effect in an intact organism or its offspring or future generations;<br>(b) the evidence referred to in point (a) is not sufficiently convincing to classify the substance in Category 1;<br>(c) there is evidence of a biologically plausible link between the endocrine activity and the adverse effect. |

Guidance for the identification of endocrine disruptors (ED) in the context of Regulations (EU) 528/2012 and (EC) 1107/2009 has been published on 7 June 2018 by ECHA and EFSA (doi: 10.2903/j.efsa.2018.5311; EFSA Journal 2018;16(6):5311) and can be accessed via:https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2018.5311

EDs identified with the procedure set out in Article 59 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), will finally be placed on the REACH candidate list of substances of very high concern for potential inclusion in REACH Annex XIV. This information can be found in the respective decision document accessible via: https://echa.europa.eu/candidate-list-table.

For substances having endocrine-disrupting properties as indicated above, there is currently no information concerning whether it is foreseen to publish them in central lists or annexed to a Regulation.

EDs identified by the delegated act pursuant to the first subparagraph of Article 5(3) of Regulation (EU) 528/2012 concerning the market availability and use of biocidal products can be accessed through the Biocidal Products Committee Opinions on active substance approval, which can be found on ECHA's website: https://echa.europa.eu/regulations/biocidal-products-regulation/approval-of-active-substances/bpc-opinions-on-active-substance-approval.

Substances undergoing an ED assessment under the REACH or Biocidal Products regulations that have been brought for discussion to ECHA's ED Expert Group are included in ECHA's endocrine disruptor (ED) assessment list that can be accessed at: https://echa.europa.eu/ed-assessment. For each substance, the list shows the assessing or evaluating Member State (submitter), the outcome and the suggested follow-up for the assessment, and the date of the latest update to the list entry.

The Commission Implementing Decision (EU) 2017/1210 identified a number of phthalates (Bis(2-ethylhexyl) phthalate (DEHP), Benzyl butyl phthalate (BBP), Dibutyl phthalate (DBP) and Diisobutyl phthalate (DIBP)) as substances of very high concern due to their endocrine disrupting properties with probable serious effects to humans (European Commission 2017), and was followed by restrictions of use set by Commission Regulation (EU) 2018/2005.

https://publications.europa.eu/en/publication-detail/-/publication/357b3d45-620f-11e7-9dbe-01aa75ed71a1/language-en/format-PDF

https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018R2005

For completeness, even if not relevant for the purpose of these guidelines, Bis(2-ethylhexyl) phthalate (DEHP) was also identified in 2014 as a substance of very high concern due to its endocrine-disrupting properties with probable serious effects to the environment.

In addition, Commission Implementing Decision (EU) 2018/636 identified Dicyclohexylphthalate (DCHP) as substance of very high concern (SVHC), according to Article 57(f) of Regulation (EC) 1907/2006 (REACH), due to its endocrine-disrupting properties with probable serious effects to humans.

https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018D0636&from=EN

## **Annex 5:** Regulatory context on CMR and/or ED phthalates

A number of phthalates are identified as substances of very high concern (SVHC) due to their reprotoxic and endocrine disrupting properties and are included in the REACH Candidate List (see https://echa.europa.eu/de/candidate-list-table). Several are also included on the REACH Authorisation List (REACH Annex XIV) to ensure that the risks of these SVHC are properly controlled and they are progressively replaced by suitable alternative substances or technologies. When risks cannot be adequately controlled, the use of those substances may only be authorised where the socio-economic benefit exceeds the risk of continued use and there are no suitable alternatives. The Authorisation List (available at https://echa.europa.eu/de/authorisation-list) contains substances which cannot be used within the European Union without an authorisation. However, imported articles do not come under the authorisation requirement. Of all phthalates on the Authorisation list, to date, applications for authorisation have been submitted for DEHP and DBP only. For the purpose of evaluating applications for authorisation, the ECHA Committee for Risk Assessment (RAC) has developed reference DNELs regarding reprotoxicity for several substances, including DEHP, BBP, DBP, and DIPP. (See Evaluating Applications Table/Reference DNELs on ECHA's website:
https://echa.europa.eu/applying-for-authorisation/evaluating-applications

Risks to human health arising from the use of an Annex XIV substance in medical devices regulated by Directives 90/385/EEC, 93/42/EEC or 98/79/EC were exempted from authorisation requirements under Title VII of the REACH Regulation[16] if the substance is listed on Annex XIV based on hazards to human health only. Regulation (EU) 2017/745 (MDR) repealing Council Directives 90/385/EEC (active implantable medical devices) and 93/42/EEC (medical devices) contains specific provisions on reducing the risk of substances released from the device. More specifically, for substances present above 0.1% weight by weight that are carcinogenic, mutagenic or toxic to reproduction (CMR), or which have endocrine-disrupting (ED) properties, justification for their use in certain medical device must be presented. The MDR contained the requirement for the Commission to mandate the relevant scientific committee to draft a guideline for the benefit-risk assessment of phthalates with CMR/ED properties that was published by the SCHEER in 2019.

REACH Annex XVII (entry 51) restricts the placing on the market of articles containing DEHP, BBP, DBP, and DIBP in concentration greater than 0.1% weight by weight of the plasticised material, individually or in combination in a range of articles. These articles include toys[17] and childcare articles, as well as other primarily consumer and professional use articles which lead to dermal or inhalation exposure. Medical devices (or parts thereof) within the scope of Directives 90/385/EEC, 93/42/EEC or 98/79/EC are exempted from the scope of the restriction. For risk assessment conclusions, including derivation of a DNEL

[16] See generic_exemptions_authorisation_en.pdf (europa.eu). The exemption for uses in medical devices within the scope of Directives 90/385/EEC, 93/42/EEC and 98/79/EC EC will expire on 27 May 2025 (COMMISSION REGULATION (EU) 2021/2045 of 23 November 2021). More recently the exemption for medical devices was prolonged to 2030: Commission Regulation (EU) 2023/2482 of 13 November 2023 amending Regulation (EC) No 1907/2006 of the European Parliament and of the Council as regards the substance bis(2-ethylhexyl) phthalate (DEHP) in medical devices (europa.eu)

[17] The Toy Safety Directive (2009/48/EC) stipulates that chemicals that are susceptible to cause cancer, change genetic information, harm fertility or harm an unborn child (CMR substances) are no longer allowed in accessible parts of toys beyond the concentration limits set in the CLP Regulation ((EC) No 1272/2008).

for DIBP, see Compiled RAC & SEAC Opinion and background document on ECHA's website: Substance Information - ECHA (europa.eu)

REACH Annex XVII (entry 52) restricts the placing on the market and the use of DINP, DIDP, or DNOP as a substance or in mixture, in concentrations greater than 0.1% weight by weight of the plasticised material in toys and childcare articles which can be mouthed by children. Information on the restrictions of use for these phthalates can be found on ECHA's website: Search for chemicals - ECHA (europa.eu)

Regarding the exemption of medical devices from the REACH restriction requirements several changes have been published recently. Regulation (EU) 2021/2045 (amending Annex XIV of REACH (Regulation (EC) No 1907/2006) authorisation list Annex XIV REACH) extended the scope of use of several phthalates in the EU, including that of DEHP. Since this modification of entry n°4 of the REACH authorisation list to include DEHP's endocrine disrupting (ED) properties, use of DEHP in medical devices (previously exempt from the REACH authorisation) will be subject to an authorisation requirement.

Originally, for medical devices, the use of DEHP was to be subject to authorisation requirements after May 2025, but the new Regulation (EU) 2023/2482, issued in November 2023, postpones this deadline. This amendment aligns with the extended transitional periods for medical device Regulation (EU) 2017/745 (MDR) reflecting the need for a gradual shift to DEHP-free medical devices.

Under the new Regulation (EU) 2023/2482, users of DEHP in medical devices will no longer be able to use DEHP from July 2030, unless they apply for authorisation before January 2029. After 2030, this authorisation will add an authorisation process to the current requirements in the MDR that includes for the use of DEHP above 0.1% in a medical device a justification and comparison with potential alternatives for which the revised guidelines can be used.

In addition to the REACH legislation, there is also product-specific legislation which regulates certain phthalates, *i.e.* the Cosmetic Products' Regulation (EC/1223/2009) and the Regulation on materials and articles intended to come into contact with food (Food Contact Materials (FCM), Regulation (EC) 1935/2004, as general framework regulation and Regulation (EU) 10/2011 specific for plastic materials and articles destined to be in contact with foodstuffs. The latter also includes provisions for the use of phthalates in plastic food contact materials and articles with respect to migration limits.

In 2019, EFSA published an update of the risk assessment of di-butylphthalate (DBP), butyl-benzyl-phthalate (BBP), bis(2-ethylhexyl)phthalate (DEHP), di-isononylphthalate (DINP) and diisodecylphthalate (DIDP) for use in food contact materials.[18] As a follow-up to this work, the European Commission requested EFSA to carry out a re-evaluation of the risks to public health related to the presence of plasticisers (such as phthalates, structurally similar substances, and substances used to replace phthalates) in food contact materials (FCMs).

The EFSA re-evaluation has been divided into two parts, with part 1 relating to preparatory work, and part 2 encompassing the actual risk assessment(s). Part 1 has been completed and the following related outputs have been published:

[18] Although not authorised for use in plastic FCM, some considerations on DIBP were also included in the Opinion as the Panel noted a similar potency with regards to reproductive toxic effects and intake estimates compared to DBP.

- Identification and prioritisation of phthalates, structurally similar substances and replacement substances potentially used as plasticisers in materials and articles intended to come into contact with food
- Protocol for exposure assessment
- Protocol for hazard assessment
- Extensive literature review on plasticisers

Discussions on the scope of part 2 of the EFSA re-evaluation are ongoing.

Plastic FCM show similarity regarding migration (and thus potential internal exposure) of phthalates as present in plastics used for medical device manufacturing. In Annex I of Regulation (EU) 10/2011 (recently amended by Regulation (EU) 2023/1442) all substances are listed, which are authorised for the use as starting material or additive for plastic layers in plastic materials and articles. Each substance must not exceed its specific migration limit (SML).

The following phthalates and other plasticisers[19] are authorised for use as additives in FCM:

DBP (FCM No 157): SML = 0.12 mg/kg food

only to be used as:

(a) plasticiser in repeated use materials and articles in contact with non-fatty foods;

(b) technical support agent in polyolefins in concentrations up to 0.05% (w/w) in the final product

BBP (FCM No 159): SML = 6 mg/kg food

Only to be used as:

(a) plasticiser in repeated use materials and articles;

(b) plasticiser in single-use materials and articles in contact with non-fatty foods, except for infant formula and follow-on formula;

(c) technical support agent in concentrations up to 0.1% (w/w) in the final product.

DEHP (FCM No 283): SML = 0.6 mg/kg food

Only to be used as:

(a) plasticiser in repeated use materials and articles in contact with non-fatty foods;

(b) technical support agent in concentrations up to 0.1% (w/w) in the final product.

DINP (FCM No 728): SML(T) = 1.8 mg/kg food (group-SML with DIDP, expressed as sum of the two substances)

only to be used as

[19] Not exhaustive examples for other than phthalates

(a) plasticiser in repeated use materials and articles

(b) plasticiser in single-use materials and articles in contact with non-fatty foods except for infant formula and follow-on formula

(c) technical support agent in concentrations up to 0.1% (w/w) in the final product

Not to be used in combination with FCM substances 157, 159, 283, or 1085.

DIDP (FCM No 729): SML(T) = 1.8 mg/kg food (group-SML with DINP, expressed as sum of the two substances)

Only to be used as

(a) plasticiser in repeated use materials and articles

(b) plasticiser in single-use materials and articles in contact with non-fatty foods except for infant formulae and follow-on formulae (as defined by Directive 2006/141/EC) or processed cereal-based foods and baby foods for infants and young children (as defined by Directive 2006/125/EC)

(c) technical support agent in concentrations up to 0.1% in the final product

Furthermore, for certain plasticisers listed in Regulation (EU) 10/2011, including a number of phthalates, a group restriction (Group restriction number 32) applies, namely that the sum of these substances must not exceed an SML of 60 mg/kg foodstuff.

An additional group restriction (Group restriction number 36) applies for DBP, BBP, DEHP and DIBP*, i.e.* 0.6 mg/kg food expressed as the sum of DBP, DIBP[20], BBP and DEHP expressed as DEHP equivalents using the following equation: DBP*5 + DIBP*4 + BBP*0,1 + DEHP*1.

DEHP, BBP, DBP and DIBP have not been permissible in homogenous materials above the concentration of 0.1% w/w since July 2019 in accordance with the Restriction of Hazardous Substances Directive in electrical and electronic equipment RoHS2 (2011/65/EC). For medical devices and *in vitro* diagnostic products, this restriction came into effect in July 2021.

ECHA has published an assessment of regulatory needs dealing with ortho phthalates for future considerations on regulatory risk management action at EU level (ECHA, 2021). It should be noted that a limited number of the *ortho*-phthalates as indicated in ECHA 2021 are currently used for the manufacturing of the medical devices.

[20] Diisobutyl phthalate, FCM No 1085, with synonyms 1,2-bis(2-methylpropyl) benzene-1,2-dicarboxylate or 'DIBP' and CAS number 84-69-5 is not listed as an authorised substance. However, it may co-occur with other phthalates as a consequence of its use as an aid to polymerisation and is included in group restrictions with the assignment FCM No 1085.'

## **Annex 6:** Use of phthalates in medical devices

Besides being used as plasticiser in a multitude of polyvinyl chloride (PVC) based consumer products, phthalates are also abundantly used in polyvinyl chloride (PVC) medical devices such as blood bag sets, bags storing liquids for intravenous administration, nutrition pockets, tubing, catheters, respiratory masks or disposable gloves (Luis *et al.,* 2021; Šimunović *et al.,* 2022). More than 40% of all plastic-based disposable medical devices are made from PVC. Di-2-ethylhexyl phthalate (DEHP), which has been for many years the most commonly used phthalate ester plasticiser in medical devices. A survey among the Danish Medical Device Industry found that 95% of the products contained DEHP (Huntley 2014).

Safety concerns have been expressed for several high-risk patient groups, such as neonates, infants, pregnant and breast-feeding women exposed to DEHP. The SCENIHR in its Opinion of 2015 indicated that "a lack of evidence of causation between DEHP-PVC and any disease or adverse effect does not mean that there are no risks". This lack of evidence applies to all phthalates classified as CMR and/or identified as ED. The requirement of patient subgroup analysis for the target patient groups as defined in the "Intended Use" of a medical device is included in Regulation (EU) 2017/745.

For the use of DEHP, high-risk groups were identified including patients undergoing haemodialysis, extracorporeal membrane oxygenation (ECMO), and prematurely born infants in Neonatal Intensive Care Units (NICU), (SCENIHR 2015). Especially in NICU, DEHP is abundantly present, in addition to a number of other plasticisers in the medical devices used for neonatal intensive care (Malarvannan *et al*., 2019; Bernard *et al*., 2023; Cleys *et al*., 2023; Paneel *et al*., 2023, Wang and Kannan, 2023). That preterm neonates are at risk was confirmed by Al-Saleh (Al-Saleh *et al.,* 2023), reporting high NICU exposures above reference doses for anti-androgenicity by several phthalate isomers (di-n-butyl phthalate (DnBP), diisobutyl phthalate (DIBP), butylbenzyl phthalate (BBzP), and DEHP. In a laboratory study on migration profiles of phthalates (extracted in ethanol/water 1:1 mixture) from single-use medical devices present in intensive care units, including NICU, in 99% of the medical devices DEHP was demonstrated including those labelled DEHP-free (Wang and Kannan, 2023). Exposure doses to DEHP from medical devices was estimated in the range of 0.005−730 µg/kg bw/day, with the highest exposure doses from cannulas for newborns.

The actual exposure of such patient groups relative to the toxicity, including CMR/ED property, needs to be determined. However, even if the remaining risk is high, the benefit of the treatment should be considered as well. It might be useful to evaluate the patient subgroups separately:

- Paediatric Population (see subgroups)
- Peripubertal individuals
- Pregnant women
- Breast-feeding women
- Any other patient group considered particularly vulnerable or exposed to high levels of phthalates.

For purposes of these guidelines, the following ranges of paediatric subpopulations are proposed to be used as a guide for manufacturers in medical devices as described by EMEA in 2001 and confirmed by EMA in 2017 (EMA/CPMP/ICH/2711/1999).

Definition of Paediatric Population Subgroups (EMA)

| Paediatric Subgroup | Approximate Age Range |
|---|---|
| Preterm newborn infants | |
| Newborn infants | 0 to 27 days |
| Infants/toddler | 28 days to 23 months |
| Children | 2 to 11 years |
| Adolescents | 12 to 16-18 years (dependent on region) |

In view of ED activity, additional (paediatric) subpopulations may need to be considered including:

- extremely low birth weight (ELBW) newborns, weighing less than 1.0 kg (WHO-ICD-11)
- very low birth weight (VLBW) describes newborns less than 1.5 kg (WHO-ICD-11)
- low birth weight (LBW) describes newborns less than 2.5 kg (WHO-ICD-11)
- prepubertal age group typically ranges from 9 to 12 years.
- peripubertal males or females

It should be realised that the benefit of medical devices including the use of phthalates must also be considered: The survival of prematurely born infants often depends on the availability of the same medical devices that result in a relatively high phthalate content exposure due to treatment. Whenever possible, material with low release potential should be used (SCENIHR 2015).

Besides the direct patient benefits of the treatment with a medical device containing phthalates, other functionalities may also need to be considered. For example, DEHP is incorporated into RBCs, stabilising their membrane and reducing storage hemolysis. This results in a prolonged shelf life and thus patient availability of RBCs stored in DEHP containing blood bags (SCENIHR 2015). In addition, RBCs have increased post-transfusion survival rates when stored in DEHP-containing blood bags. A maximum limit of extractable DEHP of 15 mg/100 mL for flexible PVC containing DEHP is indicated in EN ISO 3826-1 on containers for the collection of human blood and blood components.

The plasticiser industry has been investing in and developing alternatives to DEHP in medical devices. Today, other plasticisers such as Di-isononyl cyclohexanoate (DINCH, CAS 166412-78-8), Tri-2-ethylhexyl trimellitate (TEHTM (TOTM), CAS 3319-31-1), butyryl tri-n-hexyl citrate (BTHC, CAS 102818-95-1) and Dioctyl Terephthalate (DOTP (DEHT, DEHTP), CAS 6422-86-2) are being proposed in medical applications such as medical tubing and blood bag sets. (Home - European plasticisers) For any BRA on the use of phthalates and the development of alternatives in medical devices, careful consideration

should be used for the appropriate patient subgroup analysis regarding medical device use and the resulting potential exposure.

**References**

Al-Saleh I, Elkhatib R, Alnuwaysir H, Aldhalaan H, Binmanee A, Hawari A, Alhazzani F, Bin Jabr M. (2023). The cumulative risk assessment of phthalates exposure in preterm neonates.Int J Hyg Environ Health. 248:114112.

Bernard L, Masse M, Boeuf B, Chennell P, Decaudin B, Durand N, Genay S, Lambert C, Le Basle Y, Moreau E, Pinguet J, Ponsonnaille V, Richard D, Saturnin N, Storme L, Sautou V (2023). Medical devices used in NICU: The main source of plasticisers' exposure of newborns. The Science of the Total Environment, 858(Pt 3), 159994.

Cleys P, Panneel L, Bombeke J, Dumitrascu C, Malarvannan G, Poma G, Mulder A, Jorens PG, Covaci A. (2023). Hair as an alternative matrix to assess exposure of premature neonates to phthalate and alternative plasticizers in the neonatal intensive care unit. Environmental Research, 116712.

Huntley P, (2014). The classified phthalates should be phased out of medical devices. Presented at Meeting on Alternatives to Classified Phthalates in PVC Medical Devices. 2014 Mar 27; Copenhagen, Denmark.
https://pvc.dk/wp-content/uploads/2016/02/pvc-alternativer-til-klassificerede-ftalater-program.pdf

Luís C, Algarra M, Câmara JS, Perestrelo R. (2021). Comprehensive Insight from Phthalates Occurrence: From Health Outcomes to Emerging Analytical Approaches. Toxics 2021, 9, 157.

Malarvannan G, Onghena M, Verstraete S, Van Puffelen E, Jacobs A, Vanhorebeek I, Verbruggen SCAT, Joosten KFM, Van den Berghe G, Jorens PG, Covaci A. (2019). Phthalate and alternative plasticizers in indwelling medical devices in pediatric intensive care units. J Hazard Mat, 363, 64–72.

Panneel L, Cleys P, Breugelmans C, Christia C, Malarvannan G, Poma G, Jorens PG, Mulder A, Covaci A. (2023). Neonatal exposure to phthalate and alternative plasticizers via parenteral nutrition. International Journal of Pharmaceutics, 631.

SCENIHR (2015). Opinion on The safety of medical devices containing DEHPplasticized PVC or other plasticizers on neonates and other groups possibly at risk (2015 update). https://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_047.pdf

Šimunović A, Tomić S, Kranjčec K. (2022). Medical devices as a source of phthalate exposure: a review of current knowledge and alternative solutions. Arh Hig Rada Toksikol 73:179-190.

Wang W, Kannan K. (2023). Leaching of phthalates from medical supplies and their implications for exposure. Environ. Sci. Technol. 57, 7675−7683.

## **Annex 7:** Approaches for Benefit-Risk Assessment

Several approaches and frameworks for Benefit-Risk Assessment (BRA) have been proposed, especially in the context of medicinal products. Many approaches were identified and classified as descriptive (qualitative or semi-qualitative) or quantitative frameworks (relying on quantitative methods of trading risks and benefits following mathematical principles), metrics (measures for benefits and risks that are usually endpoint specific), estimation techniques *(i.e.* simulation techniques and meta-analysis), and utility survey techniques (to elicit stakeholders' preferences) (Guo *et al.,* 2010, Mt-Isa *et al.,* 2014). A detailed review of approaches used for BRA was published by Mt-Isa *et al*. (Mt-Isa *et al.,* 2014).

Concerning quantitative frameworks, according to the European Medicines Agency (EMA) Project Report (EMA/227124/2011), there is no agreement on any approach to be used in regulatory submissions on the benefits and risks of medicines. However, the EMA has encouraged the use of quantitative frameworks in regulatory submissions of applications for marketing authorisation of medicinal products. Although there is little experience with quantitative frameworks in the area of medical devices, some of the BRA approaches used for pharmaceuticals or veterinary medicinal products may also be relevant for medical devices and particularly regarding the use of CMR/ED phthalates.

| Step-by-step<br>Description and relation to framework for Benefit-Risk Assessment described in Section A of the guidelines | |
|---|---|
| Problem | Describe the medical device, its intended use, and the therapeutic context; frame the decision problem in terms of potential alternatives to CMR/ED phthalate. See Step 1: Description and characterisation of the composition of the medical device; and Step 2: Use and function of the phthalates in the medical device. |
| Objectives | Identify the full set of criteria to evaluate different alternatives. See Step 2: Use and function of the phthalates in the medical device; and Step 3: Assessment of the risks of the CMR/ED phthalate. See 7 Benefit assessment. |
| Alternatives | Identify alternatives that are being evaluated in comparison with each other. See Step 4: Inventory of possible alternatives; and Step 5: Identification of the candidates for assessment as most relevant alternatives for phthalates. |
| Consequences | Describe how the alternatives perform for each of the criteria, *i.e.* the magnitudes of all effects in terms of the different benefits and risks. See Step 2: Use and function of the phthalates in the medical device; Step 3: Assessment of the risks of the CMR/ED phthalate; Step 6: Description of identified potential alternative(s); Step 7: Assessment of the risk of identified most relevant alternatives. For a summary see Table 6. Example for a comparison of CMR/ED phthalate with most relevant alternative(s). |
| Trade-offs | Assess the balance between benefits and risks using criteria and weights to judge the value associated with the benefits and risks of every alternative. MCDA techniques commonly achieve this through numerical analysis. A number of different weighing methods can be used. Conduct sensitivity analyses to explore uncertainties using different scenarios and assess how different weights affect the overall ordering of the alternatives.<br>See also Step 8: Comparison of functionality and performance of CMR/ED phthalate as used in the medical device with functionality and performance of identified most relevant alternatives; Step 9: Comparison of risk(s) of original |

| | |
|---|---|
| | CMR/ED phthalate as used in the medical device with risk(s) of identified most relevant alternatives; and Step 10: Comparison of benefit and risk of CMR/ED phthalate used in the medical device with identified most relevant alternatives. |
| Uncertainty | Report the uncertainty associated with the benefits and risks. Consider how the balance between benefits and risks is affected by uncertainty. A quantitative model will explore in sensitivity analyses and scenario analyses (or by explicitly incorporating probability distributions in the model) the effects on the overall benefit-risk balance of all sources of uncertainty. See Section 10 covering uncertainty analysis. |
| Risk tolerance | Describe any considerations that could or should affect the decision maker's attitude toward risks (*e.g.* special population, unmet medical need). |
| Linked-decisions | Discuss how the value judgements and data are consistent with similar decisions on medical devices. |

Approaches based on multicriteria decision analysis (MCDA) have attracted much attention during the past years, particularly in the field of medical decisions. For an introduction to MCDA, see Dodgson et al., (2009), and for more detailed information, see Gongora-Salazar et al., (2023) and Khan et al., (2022). In brief, MCDA is based on decision theory and belongs to the general class of multi-criteria analysis models that accommodate decision making with multiple objectives. The main purpose of MCDA is to bring together evaluations of options on different criteria into one overall evaluation. The starting point for MCDA approaches includes identification of the alternatives and the criteria against which the alternatives are appraised. MCDA includes weighing, which ensures that the units of value on all the criteria are comparable so that benefits and risks can be compared by using a common unit of value. In this way, the added value of benefits can be compared to the loss of value from the risks. A number of different weighing methods can be used, ranging from precise elicitation of weights to weights based on qualitative judgements or including uncertainty. A generic framework for conducting an MCDA can be based on the steps of the PROACT-URL framework (Hammond *et al.,* 2015), as presented below. A detailed description of the different implementations of MCDA techniques is beyond the scope of these guidelines. The chosen techniques and analyses should be presented and justified on the basis of internal consistency, logical soundness and transparency, among other considerations.

In 2016 the US FDA developed a Guidance Document to provide clarity regarding the benefit and risk factors in prioritising resources for compliance and enforcement efforts to maximize medical device quality and patient safety (FDA, 2016). This guidance describes a framework for medical device decision-making in the product availability, compliance, and enforcement field. A common understanding of how FDA considers benefit and risk may better align industries and FDA on actions that maximize benefit to patients, improve medical device quality, and reduce risk to patients. In January 2017, a guidance document was published by the FDA explaining the principal factors that the FDA considers when assessing benefits and risks of investigational device exemption (IDE) applications, or amendments and supplements for human clinical investigations of medical devices to determine safety and effectiveness (FDA, 2017). In addition, in 2019, the US FDA published a guidance document that explains the main factors that should be considered when making benefit-risk determinations in the premarket review of certain medical devices (FDA, 2019).

In December 2023, the EMA released for public consultation guidelines on the evaluation of the benefit-risk balance of veterinary medicinal products (EMA/CVMP/248499/2007 Rev.

1, 2023). This guideline aims to replace the "Recommendation on the evaluation of the benefit-risk balance of veterinary medicinal products". The guideline provides methodological details on the conduct of the BRA, provides guidance on when and how to perform a BRA, and can be the basis for the elaboration of all assessment documents that include a section on the evaluation of the benefit-risk balance. The principles of the methodology provided in this guideline regarding the BRA factually describe the observed effects and uncertainties in terms of important benefits and risks, as well as of their impact. It is suggested that the identified benefits and risks should be evaluated separately, the direct benefit(s) of the product must be clearly established for each target species and each indication, and each risk should be assessed considering all the elements present in the different parts of the dossier, which should be accompanied, if appropriate, by proposals for risk mitigation measures. The goal is to objectively bring to light and critically discuss the benefits and risks described. This guideline suggests a structured approach for the BRA to ensure that the reasoning leads to a clear conclusion, comprising the following elements: (a) the conclusion of the BRA should include an introduction summarising the main characteristics of the product and outlining the legal basis of the marketing authorisation application which forms the framework of the assessment; (b) the direct benefits of the product should be clearly described for each target species and each indication. Any additional benefits should be identified separately; (c) the BRA should consider potential dose-effect relationships if relevant. A balance between the benefit(s) and the risks for the target can often be done directly; (d) the risk assessments should be performed for all relevant risks and information about each risk should be stated; and (e) for each risk, risk mitigation options should be considered, and the potential residual risk discussed. An overall conclusion should be drawn on the BRA, recognising that zero risk does not exist and considering potential risk mitigation measures. The evaluation of the overall BRA should clearly describe why it is considered as favourable (positive) or unfavourable (negative), explaining the reasoning which led to the conclusion. After the analysis of benefits and risks, a clear discussion and conclusion should be written, following the benefit-risk evaluation principles mentioned above.

Consistency in the use of data requirements and risk assessment methodologies applied within the regulatory frameworks is of crucial importance when performing a BRA. The European Food Safety Authority (EFSA) commissioned RPA Europe and FoBiG (Forschungs- und Beratunsinstitut Gefarhstoffe GmbH) to carry out the study "Mapping of data requirements and assessment methodologies linked to the regulatory frameworks and remits of the relevant EU Agencies (ECHA, EFSA and EMA) and EC Scientific Committees (Scientific Committee on Consumer Safety, SCCS, and Scientific Committee on Health, Environmental and Emerging Risks, SCHEER)" (Oltmanns *et al.,* 2023). The objective was to collect and analyse data requirements and risk assessment methodologies applied within regulatory frameworks, *i.e.*, EFSA, ECHA, EMA, as well as the EC Scientific Committees, SCCS and SCHEER. These data requirements and risk assessment methodologies can also be used for a formal BRA framework. Based on a comparative analysis methodology, the database of data requirements and risk assessment methodologies across different regulatory frameworks was created by extracting information on various data requirements (*e.g.* substance identity, physico-chemical and environmental fate properties as well as ecotoxicity and toxicity and target organism safety) and risk assessment methodologies for the environment, human health, and target organisms. The study identified inconsistencies within regulatory areas, *e.g.* between legal acts and guidance documents. Differences were also found between regulatory frameworks with respect to terminology, the quality standards for experimental studies, and other issues. Based on the identified differences

and the potential for harmonisation across the regulatory frameworks, several recommendations were outlined in the study that involve addressing specific as well as more principal and structural differences that could also be considered for a formal BRA analysis.

Although not specifically addressing medical devices, the guideline documents mentioned above from the FDA, ECHA, EFSA and EMA provide information that can be considered and can be useful when performing a BRA for the use of CMR/ED phthalate alternatives.

Drug and medical device life science companies (n=20) were interviewed for their use of BRA methodology. They were reported to use both qualitative and semi-quantitative benefit risk assessment approaches, which was limited to a small number of assets primarily for internal decision making or regulatory submissions (Smith *et al.,* 2021).

**References**

Dodgson J, Spackman M, Pearman A, Phillips LD. (2009). Multi-criteria analysis: A manual. Department for Communities and Local Government, First published in 2000 by the Department for Environment, Transport and the Regions; London, United Kingdom 2009. ISBN 9781409810230. https://assets.publishing.service.gov.uk/media/5a790545e5274a2acd18b975/1132618.pdf

EMA/CVMP/248499/2007 Rev. 1. Guideline on the evaluation of the benefit-risk balance of 4 veterinary medicinal products, 2023. Guideline on the evaluation of the benefit-risk balance of veterinary medicinal products (europa.eu)

FDA (2016). Factors to Consider Regarding BenefitRisk in Medical Device Product Availability, Compliance, and Enforcement Decisions. Guidance for Industry and Food and Drug Administration Staff. Center for Devices and Radiological Health (CDRH), Food and Drug Administration (FDA), U.S. Department of Health and Human Services, Silver Spring, MD, USA. https://www.fda.gov/media/98657/download

FDA (2017). Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions. Guidance for Industry and Food and Drug Administration Staff. Center for Devices and Radiological Health (CDRH), Food and Drug Administration (FDA), U.S. Department of Health and Human Services, Silver Spring, MD, USA. https://www.fda.gov/media/92427/download

FDA (2019). Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications. Guidance for Industry and Food and Drug Administration Staff. Center for Devices and Radiological Health (CDRH), Food and Drug Administration (FDA), U.S. Department of Health and Human Services, Silver Spring, MD, USA. https://www.fda.gov/media/99769/download

Gongora-Salazar P, Rocks S, Fahr P, Rivero-Arias O, Tsiachristas A. (2023). The Use of Multicriteria Decision Analysis to Support Decision Making in Healthcare: An Updated Systematic Literature Review. Value Health. 26, 780-790.

Guo JJ, Pandey S, Doyle J, Bian B, Lis Y, Raisch DW.(2010). A review of quantitative risk-benefit methodologies for assessing drug safety and efficacy-report of the ISPOR risk-benefit management working group. Value Health. 13, 657-666.

Hammond JS, Keeney RL, Raiffa H. (2015). Smart Choices: A Practical Guide to making Better Decisions. Harvard Business School Press, Boston, MA, USA.

Khan I, Pintelon L, Martin H. (2022). The Application of Multicriteria Decision Analysis Methods in Health Care: A Literature Review. Med Decis Making. 42, 262-274.

Mt-Isa S, Hallgreen C.E., Wang N., Callréus T., Genov G., Hirsch I., Hobbiger S., Hockley .S., Luciani D., Phillips L.D., Quartey G., Sarac S.B., Stoeckert I., Tzoulaki I., Micaleff A., Ashby D. (2014). Balancing benefit and risk of medicines a systematic review and classification of available methodologies, Pharmacoepidemiol Drug Saf. 23, 667-678.

Oltmanns J, Macherey M, Schwarz M, Manžuch Z, Hayleck M, Heine K. (2023). Mapping of Data Requirements and Assessment Methodologies Linked to the Regulatory Frameworks and Remits of the Relevant EU Agencies (ECHA, EFSA and EMA) and EC Scientific Committees (SCCS and SCHEER). Final Report. EFSA supporting publication 2023: EN-8540, 264. https://efsa.onlinelibrary.wiley.com/doi/abs/10.2903/sp.efsa.2023.EN-8540

Smith MY, Van Til J, DiSantostefano RL, Hauber AB, Marsh K. (2021). Quantitative Benefit–Risk Assessment: State of the Practice Within Industry. Therapeutic Innovation & Regulatory Science 55:415–425.

## **Annex 8:** Exposure identified for currently used alternatives

### 8.1 Leaching and extractable properties

In the (EN) ISO 10993 series for the biological and clinical evaluation of medical devices (MDs), both determination of the chemical composition of the device and the possibility for migration/leakage of potentially harmful substances from the device are key issues in the safety evaluation of MDs. Potential human exposure to plasticisers leaching from MDs is basically dependent on the structure of the plasticiser, the plastic of which the MD is made of, and the fluid in contact with the MD. The factors that influence the degree of leaching, in addition to the concentration in the MD, are lipophilicity/hydrophobicity of the plasticiser (*e.g.,* octanol/water partition coefficient), physicochemical affinity for the plastic of the MD, vapour pressure, molecular weight, and steric hindrance. The overall exposure is determined by the actual conditions of use of the MD (*e.g.,* temperature, duration of storage or infusion, contact duration and area, type and flow of the fluid, mechanical stress in peristaltic pumps).

When medical devices need to be flexible (*e.g.,* tubings, bags, circuits), they are generally made of PVC with the addition of varying amounts of plasticisers that can add up to 50% w/w (Bernard *et al.,* 2023). The plastic formulation may be composed of either a unique plasticiser or, more commonly, by a mixture of different plasticisers, altogether contributing to the desired performance. In a study on 97 samples of indwelling medical devices in pediatric intensive care unit (PICU), Malarvannan *et al.* (2019) showed that DEHP was the most used plasticiser (60/97 samples), while non ortho-phthalate alternatives were bis(2-ethylhexyl) adipate (DEHA, 32/97), bis(2-ethylhexyl) terephthalate (DEHT, 24/ 97), tris(2-ethylhexyl) trimellitate (TOTM, 20/97), and tributyl-O-acetyl citrate (ATBC, 10/ 97). Other plasticisers detected, although less frequently, were di-isononyl-cyclohexane-1,2-dicarboxylate (DINCH, 2/97), di-isononyl phthalate (DiNP, 4/97), di(2-propylheptyl) phthalate (DPHP, 4/97) and di-isodecyl phthalate (DiDP, 2/97). It was observed that in most cases a mixture of plasticisers was used (TOTM in combination with DEHP and DEHT).

Similarly to phthalates, alternative plasticisers may be potentially released from the MD and their behavior with respect to leaching needs to be characterised. When alternatives are used as a replacement for DEHP in medical devices, the use conditions of the MD with these alternatives are the same as the original DEHP-containing device. Indeed, in terms of quantitative exposure (mg/kg bw), differences may occur depending on the actual amount of a plasticiser or a mixture of plasticisers present in the medical devices and the leaching properties of these alternatives in the actual intended use of the medical device. Faessler *et al.* (2017) measured the leakage of DEHP and alternative plasticisers in lipid emulsion from seven perfusion lines, containing a range of plasticisers from 22 to 44% (*i.e*. DEHP, DEHT, TOTM and DINCH). DEHP was the plasticiser with the greatest leaching, while lower release was measured for DINCH (8 times smaller), DEHT (18 times) and TOTM (more than 100 times smaller than DEHP). In an *in vitro* model system, both DEHP and TOTM were found to be leaking from PVC infusion lines (Fernandez-Canal *et al.,* 2018).

Regarding fluid transport, lipidic fluids showed higher levels of leached plasticisers than non-lipidic ones due to the hydrophobic character of the plasticisers (Panneel *et al.,* 2023). The detected plasticisers, in addition to DEHP, were ATBC, TOTM, DEHT and DEHA. The higher molecular weight and/or higher steric hindrance of the alternatives in comparison with DEHP was related to their lower release from the tested MD.

Labile blood products (LBPs) were evaluated using a PVC blood bag plasticised with DEHP, DINCH or DEHT and leaching was evaluated after storage (Thelliez *et al.,* 2023). At the end of the 49-day storage period, the DEHP equivalent concentration in RBC concentrates was statistically higher when compared to DINCH and DEHT.

### 8.2 Analytical methods

Various analytical methods for detecting and measuring phthalates and alternative plasticisers are available, as already reviewed by Bernard *et al*. back in 2014 (Bernard *et al.,* 2014). The differences in the applicable methods depend on the matrix to be analysed (*i.e.* the plastic device itself or the fluid in contact with it), the chemical structure of the plasticiser, the concentration to be analysed, and/or the presence of a mixture of plasticisers. For direct analysis of a plastic medical device, the sample preparation is carried out with a solvent dissolution step of the plastic (*e.g.* Tetrahydrofuran for PVC) or with a liquid/solid extraction of the plasticisers (*e.g.,* Soxhlet or Accelerated Solvent Extraction). The supercritical $CO_2$ extraction technique is also used. For analysis of the fluid in which the plasticisers are potentially leached, the sample preparation is done by means of liquid-liquid extraction (LLE), solid-phase extraction (SPE), solid-phase microextraction (SPME), liquid-phase microextraction (LPME).

There is a certain similarity in the release or leakage of material components between medical biomaterials, food packaging/food contact materials and other consumer products. For these types of applications, similar methodologies might be used to determine plasticiser presence and/or release. Chromatographic techniques are the most suitable for separation, identification and detection of the constituents of the device: gas-chromatography with different detectors such as flame ionization detection (GC-FID) and mass spectrometry (GC-MS), high-performance liquid chromatography (HPLC), coupled with a diode array detector (UV- DAD) or with Mass Spectrometry detectors (*e.g.,* tandem mass spectrometry and time-of-flight mass spectrometry). Suitable tests should be chosen depending on the device ((EN) ISO 10993-18; Thelliez *et al.,* 2023; Min *et al.,* 2023; Weng *et al.,* 2023). A method using $^{1}H$ NMR was reported by Genay (Genay *et al.,* 2017). The International Electrotechnical Commission (IEC) has adopted GC–MS for the analysis of seven phthalates (BBP, DBP, DEHP, DIBP, DIDP, DINP, and DnOP) in polymers with the range as low as 100–2000 mg/kg (corresponding to 0.01 to 0.2 % w/w) as a standard test method (IEC 2017).

Desorption Corona Beam Ionization (DCBI) MS/MS was reported as a quick method for screening face masks for the presence of phthalates originating from the packaging material (Min *et al.,* 2021). Phthalate di-esters dibutyl phthalate (DBP), di(2-ethylhexyl)phthalate (DEHP), di-iso-butyl phthalate (DIBP), and butyl benzyl phthalate (BBP) were also found in face masks used during the COVID-19 pandemic, resulting in inhalation exposure (Vimalkumar *et al.*, 2022; Kisielinski *et al*., 2024; Shende *et al.,* 2024) and potential dermal absorption (Shende *et al.*, 2024). Screening of gloves prepared from different materials (vinyl, nitrile, neoprene, and latex) showed a variation in plasticiser content depending on the glove material used, with relative high amounts in vinyl gloves of the three main plasticisers DEHP, DEHT and DINP (Poitou *et al.,* 2021). Currently, a number of alternative non-ortho phthalate plasticisers are used in flexible PVC food contact materials as reviewed by Harmon and Otter (2022).

For biological samples (*e.g.,* tissue, blood or urine), similar methods as those described above can be applied. It should be noted that to estimate the exposure to the plasticisers,

it is important to determine not only the parent compound, but also its metabolites. A HPLC-MS/MS method was developed for simultaneous determination in urine of 22 metabolites of DEHP and alternative plasticisers present in medical devices used in a NICU (Pinguet *et al.,* 2019). Simultaneous determination of DEHP and DINCH and their metabolites was also reported using a tandem LC-MS/MS method (Descat *et al.,* 2020). Been *et al.* (2019) developed a method using solid phase extraction (SPE) and liquid-chromatography coupled to tandem mass spectrometry (LC-MS/MS) to evaluate multiple exposure biomarkers for alternative plasticisers determining metabolites of amongst others DINCH, DEHTP, and DEHA, in urine and blood samples (Been *et al.,* 2019).

### 8.3 Human exposure to DEHP and alternative plasticisers

The general population is exposed to DEHP through a variety of routes, with food being the primary source of exposure. Matrices for biomonitoring human exposure to phthalates or their alternatives can be urine, blood serum, fingernails and hair (Alves *et al.,* 2017; Been *et al.,* 2019; Yin *et al.,* 2019; Bernard *et al.,* 2021, 2023). Several biomonitoring studies, measuring primary and secondary excreted DEHP metabolites, that were analysed in detail in the SCENIHR Opinion in 2015, indicate widespread exposure to DEHP (SCENIHR, 2015). Since all DEHP metabolites have been demonstrated to have a short half-life, it is essential to measure the time between exposure and urine sampling in order to characterise DEHP exposure and to be able to discriminate between short- and long-term exposure, which can be estimated by using the ratio between primary and secondary metabolites. The median background exposure for the general population reported in the 2015 Opinion was 2-5 µg/kg bw/day, whereas the 95$^{th}$ percentile is estimated to be between 6 and 17 µg/kg bw/day. Children may have a somewhat higher body burden of DEHP than adults, with a median exposure of around 4 to 8 µg/kg/day. A decreasing trend was noted over time, although medical procedures using PVC medical devices can lead to DEHP exposures much higher than the background levels, and even similar or above NOAEL concentrations (SCENIHR 2015).

After the SCENIHR Opinion on DEHP (SCENIHR 2015) and the SCHEER publication on the guidelines for a BRA of phthalates (SCHEER 2019) considerable progress has been made on the replacement of DEHP by other phthalates and/or alternative substances in various applications. The use of these alternatives in a variety of products, including medical devices, is shown in the reports indicating human exposure to these alternatives. Even for the replacements though, multiple plasticisers could be detected in medical devices used at a paediatric intensive care unit (PICU) (Malarvannan *et al.,* 2019). See Table 8.1 for some (non-exhaustive) examples of the demonstrated presence of phthalates in these medical products and human exposure to phthalates through these replacements. It should be noted that there is also a widespread exposure to the classical phthalates (DEHP, DEP, DBP) and alternative plasticisers (DINCH, DINP, DIDA, DEHA) from other sources as well, including food and potable water, personal care products, toys and other children's products (Kim *et al.,* 2020; Praveena *et al.,* 2021, Wu *et al.,* 2021; Struzina *et al.,* 2022; Stuchlík Fišerová *et al.,* 2022). In a recent review by Kisielinski *et al*. (2024) also face masks used during the SARS-CoV-2 (COVID-19) pandemic were observed to induce exposure to a number of substances including DEHP (Kisielinski *et al*., 2024). In addition, it was noted that in some medical devices the amount of DEHP reported was higher than the 0.1% content as indicated in the MDR (EU 2017/745).

**Table 8.1. Examples of biomonitoring data of human exposure to DEHP and other plasticisers in different products**

| Substance[21] | Detection techniques | Test sample | References |
|---|---|---|---|
| DEHP | SPE-LC-MS/MS[ab], TurboFlow-LC-MS/MS[c], LC-MS/MS[d] | Urine[abcd] | a) Bernard 2021<br>b) Bernard 2023<br>c) Frederiksen 2020<br>d) Vogel 2023 |
| DEHA | LC/ESI-Orbitrap-MS[a] | Urine[ab],finger nail[a] | a) Alves 2017<br>b) Ketema 2023 |
| DEHT/ DEHTP | LC/ESI-Orbitrap-MS[a] , SPE-LC-MS/MS[bc], TurboFlow-LC-MS/MS[d] | Urine[abcde],finger nail[a] | a) Alves 2017<br>b) Bernard 2021<br>c) Bernard 2023<br>d) Frederiksen 2020<br>e) Ketema 2023 |
| ATBC | LC/ESI-Orbitrap-MS[a] | Urine[a], finger nail[a] | a) Alves 2017 |
| DINCH | LC-MS/MS[ac] | Urine[abc] | a) Fredriksen 2020<br>b) Ketema 2023<br>c) Vogel 2023 |
| DiNP | SPE-LC-MS/MS[a], LC-MS/MS[b] | Urine[ab] | a) Bernard 2021<br>b) Vogel 2023 |
| DPHP | LC/ESI-Orbitrap-MS[a] | Urine[ab],finger nail[a] | a) Alves 2017<br>b) Been 2019 |
| DiDP | LC-MS/MS[a] | Urine[a] | a) Vogel 2023 |
| TEHTM | SPE-LC-MS/MS[a] | Urine[a] | a) Bernard 2023 |

## References

Alves, A., Giovanoulis, G., Nilsson, U., Erratico, C., Lucattini, L., Haug, L. S., Jacobs, G., de Wit, C. A., Leonards, P. E. G., Covaci, A., Magner, J., Voorspoels, S. (2017). Case Study on Screening Emerging Pollutants in Urine and Nails. Environmental Science & Technology, 51(7), 4046–4053.

Been F, Malarvannan G, Bastiaensen M, Yin S, Van Nuijs ALN, Covaci A. (2019). Development and validation of a bioanalytical assay based on liquid chromatography-tandem mass spectrometry for measuring biomarkers of exposure of alternative plasticizers in human urine and serum. Talanta 198, 230–236.

[21] In most cases, the exposure to the substances was identified by detection of their metabolites.

Bernard L, Bouattour Y, Masse M, Boeuf B, Decaudin B, Genay S, Lambert C, Moreau E, Pereira B, Pinguet J, Richard D, Sautou V, and for the ARMED Study Group. (2021). Association between Urinary Metabolites and the Exposure of Intensive Care Newborns to Plasticizers of Medical Devices Used for Their Care Management. Metabolites 11, 252.

Bernard L, Décaudin B, Lecoeur M, Richard D, Bourdeaux D, Cueff R, Sautou V; Armed Study Group. (2014). Analytical methods for the determination of DEHP plasticizer alternatives present in medical devices: a review. Talanta, 129, 39-54.

Bernard l., Masse M., Boeuf B., Chennell P., Decaudin B., Durand N., Genay S., Lambert C., Le Basle Y., Moreau E., Pinguet J., Ponsonnaille V., Richard D., Saturnin N., Stormeh L., Sautou V., for the ARMED Study Group. (2023). Medical devices used in NICU: The main source of plasticisers' exposure of newborns. Science of the Total Environment 858 (2023) 159994.

Descat, A., Lecoeur, M., Kouach, M., Goossens, L., Thelliez, A., Odou, P., Decaudin, B., Goossens, J.-F. (2020). Simultaneous determination of di(2-ethylhexyl) phthalate and diisononylcyclohexane-1,2-dicarboxylate and their monoester metabolites in four labile blood products by liquid chromatography tandem mass spectrometry. Journal of Pharmaceutical and Biomedical Analysis, 181.

ISO 10993-18:2020. Biological evaluation of medical devices - Part 18: Chemical characterization of medical device materials within a risk management process. 2020. ISO, Geneva, Switzerland.

Faessler D, Gregor McCombie, Maurus Biedermann, Florian Felder, Ulrike Subotic. (2017). Leaching of plasticizers from polyvinylchloride perfusion lines by different lipid emulsions for premature infants under clinical conditions, International Journal of Pharmaceutics 520, 119–125.

Fernandez-Canal C, Pinta P-G, Eljezi T, Larbre V, Kauffmann S, Camilleri L, Cosserant B, Bernard L, Pereira B, Constantin J-M, Grimandi G, Sautou V, and for Armed Study Group. (2018). Patients' exposure to PVC plasticizers from ECMO circuits, Expert Review of Medical Devices, 15:5, 377-383.

Frederiksen H, Nielsen O, Koch HM, Skakkebaek NE, Juul A, Jørgensen N, Andersson A-M. (2020). Changes in urinary excretion of phthalates, phthalate substitutes, bisphenols and other polychlorinated and phenolic substances in young Danish men; 2009–2017. Int J Hyg Environm Health. 223, 93-105.

Genay, S., Feutry, F., Masse, M., Barthélémy, C., Sautou, V., Odou, P., Décaudin, B., & Azaroual, N. (2017). Identification and quantification by 1H nuclear magnetic resonance spectroscopy of seven plasticizers in PVC medical devices. Analytical and Bioanalytical Chemistry, 409(5), 1271–1280.

Harmon P, Otter R. (2022). A review of common non-ortho-phthalate plasticizers for use in food contact materials. Food and Chemical Toxicology 164, 112984.

IEC 62321-8:2017. Determination of certain substances in electrotechnical products - Part 8: Phthalates in polymers by gas chromatography-mass spectrometry (GC-MS), gas chromatography-mass spectrometry using a pyrolyzer/thermal desorption accessory (Py-TD-GC-MS). IEC, International Electrotechnical Commission, Geneva, Switzerland.

Ketema, R. M., Kasper-Sonnenberg, M., Ait Bamai, Y., Miyashita, C., Koch, H. M., Pälmke, C., Kishi, R., Ikeda, A. (2023). Exposure Trends to the Non-phthalate Plasticizers DEHTP, DINCH, and DEHA in Children from 2012 to 2017: The Hokkaido Study. Environmental Science & Technology.

Kisielinski K, Hockertz S, Hirsch O, Korupp S, Klosterhalfen B, Schnepf A, Dyker G. (2024). Wearing face masks as a potential source for inhalation and oral uptake of inanimate toxins – A scoping review. Ecotoxicology and Environmental Safety 275 (2024) 115858.

Kim DY, Chun S-H, Jung Y, Mohamed DFMS, Kim H-S, Kang D-Y, An J-W, Park S-Y, Kwon H-W, Kwon J-H. (2020). Phthalate Plasticizers in Children's Products and Estimation of Exposure: Importance of Migration Rate. Int J Environ Res Public Health. 17:8582.

Malarvannan, G., Onghena, M., Verstraete, S., van Puffelen, E., Jacobs, A., Vanhorebeek, I., Verbruggen, S. C. A. T., Joosten, K. F. M., Van den Berghe, G., Jorens, P. G., Covaci, A. (2019). Phthalate and alternative plasticizers in indwelling medical devices in pediatric intensive care units. Journal of Hazardous Materials, 363, 64–72.

Min, K., Weng, X., Long, P., Ma, M., Chen, B., Yao, S. (2021). Rapid in-situ analysis of phthalates in face masks by desorption corona beam ionization tandem mass spectrometry. Talanta, 231, 122359.

Min S-W, Lim DK, Lee S, Kim J, Baek S-Y. (2023). Accurate determination of 11 representative phthalates and di(2-ethylhexyl) terephthalate in polyvinyl chloride using isotope dilution-gas chromatography/mass spectrometry, J Chromatography A, 1711, 464454.

Panneel, L., Cleys, P., Breugelmans, C., Christia, C., Malarvannan, G., Poma, G., Jorens, P. G., Mulder, A., Covaci, A. (2023). Neonatal exposure to phthalate and alternative plasticizers via parenteral nutrition. International Journal of Pharmaceutics, 631.

Pinguet J, Kerckhove N, Eljezi T, Lambert C, Moreau E, Bernard L, Boeuf B, Decaudin B, Genay S, Masse M, Storme L, Sautou V, Richard D; ARMED Study Group. (2019). New SPE-LC-MS/MS method for the simultaneous determination in urine of 22 metabolites of DEHP and alternative plasticizers from PVC medical devices. Talanta. 198, 377-389.

Poitou, K., Rogez-Florent, T., Lecoeur, M., Danel, C., Regnault, R., Vérité, P., Monteil, C., Foulon, C. (2021). Analysis of phthalates and alternative plasticizers in gloves by gas chromatography–mass spectrometry and liquid chromatography–uv detection: A comparative study. Toxics, 9(9).

Praveena, S. M., Siok Fong, C., Amaruddin, A. F. (2021). Phthalates in children toys available in Malaysian market: Quantification and potential human health risk. The Journal of Steroid Biochemistry and Molecular Biology, 213, 105955.

SCENIHR (Scientific Committee on Emerging and Newly-Identified Health Risks) (2015). Scientific Opinion on the safety of medical devices containing DEHP-plasticized PVC or other plasticizers on neonates and other groups possibly at risk. (2015 update). https://health.ec.europa.eu/document/download/d17de743-1077-4654-81a7-b4148667f20c_en?filename=scenihr_o_047.pdf

SCHEER (Scientific Committee on Health, Environmental and Emerging Risks) (2019). 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 (ED) properties, final version adopted at SCHEER plenary on 18 June 2019. https://health.ec.europa.eu/publications/guidelines-benefit-risk-assessment-presence-phthalates-certain-medical-devices_en

Shende N, Hippargi G, Gurjar S, Kumar AR, Rayalu S. (2024). Occurrence of phthalates in facemasks used in India and its implications for human exposure. Int J Environm Health Res. 34, 166–182.

Struzina, L., Pineda Castro, M. A., Kubwabo, C., Siddique, S., Zhang, G., Fan, X., Tian, L., Bayen, S., Aneck-Hahn, N., Bornman, R., Chevrier, J., Misunis, M., Yargeau, V. (2022). Occurrence of legacy and replacement plasticizers, bisphenols, and flame retardants in potable water in Montreal and South Africa. Science of the Total Environment, 840, 156581.

Stuchlík Fišerová, P., Melymuk, L., Komprdová, K., Domínguez-Romero, E., Scheringer, M., Kohoutek, J., Přibylová, P., Andrýsková, L., Piler, P., Koch, H. M., Zvonař, M., Esteban-López, M., Castaño, A., Klánová, J. (2022). Personal care product use and lifestyle affect phthalate and DINCH metabolite levels in teenagers and young adults. Environmental Research, 213, 113675.

Thelliez A, Sumian C, Chazard E, Reichenberg S, Lecoeur M, Decaudin B. (2023). Migration of di(2-ethylhexyl) phthalate, diisononylcyclohexane-1,2-dicarboxylate and di(2-ethylhexyl) terephthalate from transfusion medical devices in labile blood products: A comparative study. Vox Sang.118, 533-542.

Vimalkumar, K., Zhu, H., Kannan, K. (2022). Widespread occurrence of phthalate and non-phthalate plasticizers in single-use facemasks collected in the United States. Environment International, 158, 106967.

Vogel, N., Schmidt, P., Lange, R., Gerofke, A., Sakhi, A. K., Haug, L. S., Jensen, T. K., Frederiksen, H., Szigeti, T., Csákó, Z., Murinova, L. P., Sidlovska, M., Janasik, B., Wasowicz, W., Tratnik, J. S., Mazej, D., Gabriel, C., Karakitsios, S., Barbone, F., … Kolossa-Gehring, M. (2023). Current exposure to phthalates and DINCH in European children and adolescents - Results from the HBM4EU Aligned Studies 2014 to 2021. International Journal of Hygiene and Environmental Health, 249, 114101.

Weng X, Zhu Q, Liao C, Jiang G. (2023). Cumulative Exposure to Phthalates and Their Alternatives and Associated Female Reproductive Health: Body Burdens, Adverse Outcomes, and Underlying Mechanisms, Environ. Sci. Technol. 57, 22, 8189–8212.

Wu, Y., Song, Z., Little, J. C., Zhong, M., Li, H., Xu, Y. (2021). An integrated exposure and pharmacokinetic modeling framework for assessing population-scale risks of phthalates and their substitutes. Environment International, 156, 106748.

Yin, S., Been, F., Liu, W., Covaci, A. (2019). Hair as an alternative matrix to monitor human exposure to plasticisers – Development of a liquid chromatography - tandem mass spectrometry method. Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences, 1104, 94–101.

## **Annex 9**: Health hazards of CMR/ED phthalate alternatives

After the publication of the guidelines for the benefit risk assessment (BRA) for the justification on the use of CMR/ED phthalates in medical devices (SCHEER 2019), some progress has been made in the development and use of alternatives for phthalate plasticisers. With increasing use, more studies have emerged describing the actual exposure risks presented by these alternatives (see Annex 8) and investigating the potential hazards associated with these CMR/ED phthalate alternatives. However, compared to DEHP, information on toxicology is less exhaustive for the alternative plasticisers.
It is of note that aggregate exposure from other sources of alternative plasticisers different from medical devices should be taken into account for the general risk assessment, because they are used in many other consumer products. In addition, since several different plasticisers are used not as a single plasticiser but in plasticiser mixtures, possible combined exposure and risk should also be evaluated, as it was suggested for male developmental toxicity risk assessment caused by exposure to phthalate mixtures (Kortenkamp and Koch, 2020).

This Annex is not intended to provide any systematic review nor any exhaustive hazard characterisation for the potential phthalates alternatives, which is out of the scope of these guidelines (see Annex 1). Rather, it provides a brief compilation of toxicological information for a number of alternatives that can be used as plasticisers to replace the CMR/ED phthalates. Although the actual replacement of the CMR/ED phthalates depends also on the functionality and performance of the proposed alternatives, alternatives demonstrating a lower net risk due to a reduction of exposure (*e.g.* due to lower leaching properties from the plastic) and/or having a lower toxicity may serve as suitable replacements.

The main hazard characteristics of a number of the currently known alternatives are summarised in Table 9.1. The hazard characteristics are presented by showing the critical endpoint on the basis of which the NOAEL and or the BMDL has been derived for oral repeated dose toxicity, which sometimes differs from the reproductive properties characterising the action of DEHP. None of them has been reported to be genotoxic, therefore any carcinogenic effect is generally assumed to be associated with a non-genotoxic mechanism for which a threshold can be determined.

Some alternatives can cause reproductive toxicity, in analogy with DEHP, but so far, higher doses were reported to be needed to cause reproductive toxicity for the alternatives, indicating a lower potential of inducing such an outcome. However, in many instances, critical effects driving NOAEL derivations were other than reproductive effects. The doses for these critical effects (other than reproductive toxicity) may also be lower than the doses noted for reproductive effects identified for CMR/ED phthalates.

A recent evaluation of the toxicity of various alternatives confirmed the critical NOAELS as reported by the Danish EPA and the SCENIHR (2015) and identified DINCH and TOTM as having a more favourable migration and/or toxicity profile compared to DEHP (Den Braver-Sewradj *et al.,* 2020). In a review on six phthalates, DEHP, DINP, DBP, DIBP, BBP, and DEP, it was concluded based on robust evidence that DEHP and DBP phthalate exposure affects male reproductive outcomes, while there was moderate evidence for the same outcome from DINP and BBP exposure, and slight evidence for similar effects from DIBP and DEP exposure (Radke *et al.,* 2018). In rats a comparison between DBP and DINP

indicated that the latter does not cause the adverse reproductive effects known to occur with DBP, a well-established ED (van den Driesche *et al.,* 2020).

Based on a plausible common mode of action *(i.e.* reduction in fetal testosterone) underlying the reproductive effects of DEHP, DBP and BBP, the EFSA CEP Panel (EFSA CEP Panel, 2019) considered it appropriate to establish a group-TDI for these phthalates, taking DEHP as index compound as a basis for introducing relative potency factors. The CEP Panel noted that DINP also affected fetal testosterone levels at doses around three-fold higher than liver effects and therefore considered it prudent to include it within the group-TDI, which was established to be 50 µg/kg bw per day, expressed as DEHP equivalents.

The combined exposure to different plasticisers with the same mode of action is therefore important also considering that different plasticisers may be used in mixtures.

**Table 9.1. Non-exhaustive examples of hazards of some CMR/ED phthalate alternatives**

| **Plasticisers (CAS n°)** | **NOAEL mg/kg bw per day** (oral) | **Critical toxicological endpoint for NOAEL derivation** | **Developmental and/or Reproductive Toxicity** | **Carcinogenicity** | **References** |
|---|---|---|---|---|---|
| DEHP (117-81-7) | 4.8 | Reproduction | Yes | Liver * | SCENIHR 2015 |
| ATBC (77-90-7) | 100 (90 days in male rats, 2 years rat) | Decreased bw ; haematological and biochemical changes, increased liver weight | No NOAEL for Decreased bw in F1 male rats identical to maternal toxicity NOAEL = 100 mg/kg bw/day (rat) | Negative | ECHA 2016a; Sung et al., 2020; Bernauer and Fromme 2022 |
| COMGHA (736150-63-3) | 1333 (highest dose tested) | None | No (up to 1333 mg/kg/day) | No data | Bernauer and Fromme 2022 |
| BTHC (82469-79-2) | 250 (i.v. 50 ) | Liver weight; haematological changes | No (up to 500 mg/kg bw/day) | No data | Bernauer and Fromme 2022 |
| DEHA (103-23-1) | 40 | Increased kidney weight reduction (male rat-28 day study) | Yes Foetotoxicity in rat at 200 mg/kg bw/day (with maternal toxicity at 400 mg/kg bw/day) | Negative in rats Positive in mice (hepatocellular carcinomas and adenomas)* | CPSC 2018a; Bernauer and Fromme 2022 |
| DINCH (166412-78-8) | 40 (chronic toxicity study)<br><br>100 -107 (2-gen reproductive and 90 days rat) | Thyroid toxicity<br><br>Kidney (Liver) | No (up to 1,000 mg/kg bw/day) | Positive (Thyroid: follicular cell hyperplasia and adenomas with NOAEL at 40 mg/kg bw/day)* | EFSA 2006; ECHA 2016b; Bernauer and Fromme 2022 |
| DINP (28553-12-0) | 15 | Liver | Yes | Positive (liver and Kidney)* | EFSA 2019; Dekant 2020 |

| | | | | | |
|---|---|---|---|---|---|
| | | | but NOAEL >> than the critical hepatic toxicity | | |
| DEHT (6422-86-2) | 277 (90 days rat)<br><br>79-142 (2 year rat) | Liver weight and haematological changes<br><br>Eye toxicity and turbinate changes | Yes<br>Developmental effects with NOAEL 100 mg/kg bw/day (the same set for the systemic maternal toxicity) for pup decreased body weight | Negative in rats (2 studies) | CPSC 2018b |
| TOTM (3319-31-1) | 225 (90 days rat)<br><br>100 | Hepatocellular hypertrophy + increased hematopoiesis<br><br>Liver toxicity | No<br>(up to 1000 mg/kg bw/day in rat) | No data | CPSC 2018c<br>Bernauer and Fromme 2022 |
| DiNA Diisononyl adipate (33703-08-1) | 500 (90 days rat highest dose tested) | No relevant effects | No data available | | Bernauer and Fromme 2022 |
| DBA (105-99-7) | 300 (reproductive/dev toxicity study rat) | Kidney weight increased & Decreased pup viability | Yes (Developmental NOAEL =300 mg/kg bw/day in rat) | | CPSC 2019 |
| DBS Dibutyl sebacate (109-43-3) | 1000 (26 weeks dog; highest dose tested) | No effects | No (up to 1000 mg/kg bw/day in rat) | | Bernauer and Fromme 2022 |

* The human relevance of the mechanism of tumor development (liver, kidney and thyroid) has been questioned.

It is evident from Table 9.1 that besides the relevant endocrine disrupting activity, the overall toxicity of the alternatives needs to be considered.

Recently some publications showed possible effects *in vivo* for a number of CMR/ED phthalate alternatives *e.g.*:

For ATBC

- changes in fat metabolism and disruption of antral follicle function following ATBC oral exposure (Zhang *et al.*, 2023; Rasmussen *et al.,* 2017)

For DINP

- induction of apoptosis, autophagy and oxidative stress of the ovary tissue caused by DINP (Chen *et al.,* 2022);
- long term alteration of estrous cycle, reduction in pregnancy, decreased fertility (Chiang and Flaws 2019; Chiang *et al.,* 2020)
- effects on colon morphology and physiology in adult female mice (Chiu *et al.,* 2020);
- alteration of inflammatory cytokines in the kidney (Gu *et al.,* 2021);
- alteration of lipid metabolism (Yang *et al.,* 2021).

*In vitro* findings have also been reported, including the cytotoxic effects of DEHP and several alternatives and/or their metabolites, suggesting that metabolites can also display some biological activity in fibroblasts (Eljezi *et al.,* 2017, 2019), in kidney cells (Vasconcelos *et al.*, 2019) or adipocytes (Zhang *et al.,* 2019). More recently other models were reported, including the use of fetal testis samples (Tardif *et al.,* 2023) or zebrafish (Tsai *et al.,* 2023) to further study the reproductive effects of DEHP and some alternatives.

Regarding the possibility for screening of ED activity, many *in vitro* studies have been published recently. They were carried out using many different cell lines and models, some of which have been adopted as OECD test guidelines suitable for the identification of specific hazards, such as steroidogenesis testing, binding to estrogen receptors or thyroxine-binding globulin (Boccard *et al.,* 2019; Sheikh and Beg, 2022; Langsch *et al.,* 2018; Engel *et al.,* 2018; Lee *et al.,* 2019; Moche *et al.,* 2021; Rajkumar *et al.,* 2022).

Outcomes related to ED-mediated activity varied, depending on the chemical, dose and cell lines used: this implies that *in vitro* data should always be interpreted with caution. Indeed, the *in vitro* test is only one of the first steps within the OECD framework for the testing and assessment of ED activity (OECD 2018) and does not take into consideration the kinetic behaviour of the chemical or the interplay of different organs and system characterising the endocrine system.

This is relevant in view of the definition "An ED is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse effects in an intact organism, or its progeny, or (sub)populations." (WHO/IPCS, 2002) and considering that endocrine disruption should not be seen as an adverse effect *per se*, but rather as a mode or mechanism of action potentially leading to other outcomes, for example carcinogenic, reproductive, or developmental effects, routinely considered in reaching regulatory decisions. In addition, many cell lines are not representative of the *in vivo* situation (*e.g.,* many immortalised cells have lost the ability of biologically transforming exogenous chemicals). This can lead to discrepancies between *in vitro* and *in vivo* responses.

Therefore, although relevant for the understanding of the mode of action, these *in vitro* studies cannot be used at present to derive or change the reference values reported for the risk assessment procedure.

Table 9.2 presents a non-exhaustive overview of abbreviations, chemical names and CAS numbers for substances as potential alternatives for DEHP.

**Table 9.2. Non-exhaustive overview of possible CMR/ED phthalate alternatives**

| Acronym | Chemical name | IUPAC NAME | CAS n. | Notes or other indicators |
|---|---|---|---|---|
| ATBC | Acetyl tri-n-butyl citrate | tributyl 2-acetoxypropane-1,2,3-tricarboxylate | 77-90-7 | |
| BBP | Benzylbutylphthalate | 1-benzyl 2-butyl benzene-1,2-dicarboxylate | 85-68-7 | |
| BTHC | Butyryl-tri-n-hexylcitrate | trihexyl 2-butanoyloxypropane-1,2,3-tricarboxylate | 82469-79-2 | |
| COMGHA | Glycerides, castor-oil-mono-, hydrogenated, acetates | 1,3-bis(acetyloxy)propan-2-yl 12-(carboxyoxy)octadecanoate; 2,3-bis(acetyloxy)propyl 12-(acetyloxy)octadecenoate | 736150-63-3 | |
| DBA | Dibutyl adipate | 1,6-dibutyl hexanedioate | 105-99-7 | |
| DBP | Dibutylphthalate, | 1,2-dibutyl benzene-1,2-dicarboxylate | 84-74-2 | |
| DBS | Dibutylsebacate | 1,10-dibutyl decanedioate | 109-43-3 | |
| DCHP | Dicyclohexylphthalate | 1,2-dicyclohexyl benzene-1,2-dicarboxylate | 84-61-7 | |
| DEHA | Di(2-ethylhexyl)adipate | 1,6-bis(2-ethylhexyl) hexanedioate | 103-23-1 | |
| DEHP | Di(2-ethylhexyl)phthalate | Bis(2-ethylhexyl) phthalate | 117-81-7 | |
| DEHS | Di(2-ethylhexyl)sebacate | Bis(2-ethylhexyl) sebacate | 122-62-3 | |
| DEHT | Di(2-ethylhexyl)terephthalate | Bis(2-ethylhexyl) benzene-1,4-dicarboxylate or Bis(2-ethylhexyl)terephthalate | 6422-86-2 | The same as DOTP, also DEHTP |
| DEP | Diethylphthalate | 1,2-diethyl benzene-1,2-dicarboxylate | 84-66-2 | |
| DIBA | Diisobutyl adipate | 1,6-bis(2-methylpropyl) hexanedioate | 141-04-8 | |
| DIBP | Diisobutylphthalate | 1,2-bis(2-methylpropyl) benzene-1,2-dicarboxylate | 84-69-5 | |
| DIDA | Diisodecyl adipate | 1,6-bis(2-methylnonyl) hexanedioate | 27178-16-1 | |
| DIDP | Diisodecyl phthalate | bis(8-methylnonyl) benzene-1,2-dicarboxylate | 26761-40-0 | |
| DIDP* | | 1,2-Benzenedicarboxylic acid, di-C9-11-branched alkyl esters, C10-rich | 68515-49-1 | *a mixture of esters, mainly based on diisoodecyl ester |
| DINA | Diisononyl adipate | 1,6-bis(7-methyloctyl) hexanedioate | 33703-08-1 | |
| DINCH | 1,2-cyclohexanedicarboxylic acid, diisononyl ester | 1,2-bis(7-methyloctyl) (1R,2S)-cyclohexane-1,2-dicarboxylate | 166412-78-8 | |

| | | | | |
|---|---|---|---|---|
| DINP | Diisononyl phthalate | 1,2-bis(7-methyloctyl) benzene-1,2-dicarboxylate | 28553-12-0 | |
| DINP* | | 1,2-Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich | 68515-48-0 | *a mixture of esters, mainly based on diisononyl ester |
| DIPP | Diisopentylphthalate | 1,2-bis(3-methylbutyl) benzene-1,2-dicarboxylate | 605-50-5 | |
| DL9TH | 4-cyclohexene-1,2-dicarboxylic acid dinonyl ester | | 1609185-22-9 | |
| DMEP | Bis(2-methoxyethyl)phthalate | Bis(2-methoxyethyl) phthalate | 117-82-8 | |
| DMP | Dimethylphthalate | 1,2-dimethyl benzene-1,2-dicarboxylate | 131-11-3 | |
| DOTH | di(2-ethylhexyl)4-cyclohexene-1,2-dicarboxylate | Bis (2-ethylhexan-1-yl) cyclohex-4-ene-1,2-dicarboxylate | 2915-49-3 | |
| DOTP | Di-(2-ethylhexyl) terephthalate | Bis(2-ethylhexyl) benzene-1,4-dicarboxylate or Bis(2-ethylhexyl)terephthalate | 6422-86-2 | The same as DEHT |
| DOS | Dioctylsebacate | 1,10-dioctyl decanedioate | 2432-87-3 | sometimes confused with DEHS |
| DPHP | Bis(2-propylheptyl) phthalate | 1,2-bis(2-propylheptyl) benzene-1,2-dicarboxylate | 53306-54-0 | |
| TEHTM | Tri(2-ethylhexyl)trimellitate | 1,2,4-tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate | 3319-31-1 | The same as TOTM |
| TOTM | Trioctyltrimellitate | 1,2,4-tris(2-ethylhexyl)benzene-1,2,4-tricarboxylate | 3319-31-1 | The same as TEHTM |

## References

Bernauer U, Fromme H. (2022). VI – 4. Organische Verbindungen/Phthalat-Alternativen als Weichmacher. Eds. Wichmann HE, Fromme H. Handbuch Umweltmedizin -72 Erg-Lfg 4/22. Verlag CH Beck, Germany. ISBN 978-3-609-71181-2.

Boccard J, Tonoli D, Strajhar P, Jeanneret F, Odermatt A, Rudaz S. (2019). Removal of batch effects using stratified subsampling of metabolomic data for in vitro endocrine disruptors screening. Talanta, 195, 77–86.

Chen J, Yang S, Ma B, Wang J, Chen J. (2022). Di-isononyl phthalate induces apoptosis and autophagy of mouse ovarian granulosa cells via oxidative stress. Ecotoxicology and Environmental Safety, 242, 113898.

Chiang C, Flaws JA. (2019). Subchronic Exposure to Di(2-ethylhexyl) Phthalate and Diisononyl Phthalate During Adulthood Has Immediate and Long-Term Reproductive Consequences in Female Mice. Toxicological Sciences : An Official Journal of the Society of Toxicology, 168, 620–631.

Chiang C, Lewis LR, Borkowski G, Flaws JA. (2020). Late-life consequences of short-term exposure to di(2-ethylhexyl) phthalate and diisononyl phthalate during adulthood in female mice. Reproductive Toxicology (Elmsford, N.Y.), 93, 28–42.

Chiu K, Bashir ST, Nowak RA, Mei W, Flaws JA. (2020). Subacute exposure to di-isononyl phthalate alters the morphology, endocrine function, and immune system in the colon of adult female mice. Scientific Reports, 10(1), 18788.

CPSC Consumer Product Safety Commission (2018a). Toxicity Review for Bis(2-Ethylhexyl)Adipate (DEHA). https://www.cpsc.gov/s3fs-public/Toxicity%20Review%20of%20DEHA.pdf?TSiSSb20aUy68dV0qk1AllBUrIaPFSaE (accessed 22.3.2021).

CPSC Consumer Product Safety Commission (2018b). Toxicity Review for Di-2-Ethylhexylterephthalate (DEHT). https://www.cpsc.gov/s3fs-public/Toxicity%20Review%20of%20DEHT.pdf?FObpuBBqgypVtw7gIEGMFXHN5H7vbeEz. accessed 17.3.2021

CPSC Consumer Product Safety Commission (2018c). Toxicity Review for Trioctyltrimellitate (TOTM). https://www.cpsc.gov/s3fs-public/Toxicity%20Review%20of%20TOTM.pdf?Yjo0hEI05eJsEziyutApCzEobdUITWhX. accessed: 17.3.2021

CPSC Consumer Product Safety Commission (2019) Toxicity Review for Dibutyl and Diisobutyl Adipate (DBA , DiBA) available at: ToxicityReviewforDBAandDiBA062019.pdf (cpsc.gov) last accessed 04.03.2024

Dekant W. (2020). Grouping of phthalates for risk characterization of human exposures. Toxicology Letters 330, 1-6.

Den Braver-Sewradj SP, Piersma A, Hessel EVS. (2020). An update on the hazard of and exposure to diethyl hexyl phthalate (DEHP) alternatives used in medical devices. Crit Rev Toxicol. 50, 650-672.

ECHA (2016a). Risk Management Analysis Conclusion Document: tributyl O-acetylcitrate (ATBC). Authority: France. Online (accessed 7 February 2024). https://echa.europa.eu/documents/10162/2068f4bc-5264-1e22-e9cb-032a7b7e419d

ECHA (2016b). Risk Management Analysis Conclusion Document: 1,2-CYCLOHEXANEDICARBOXYLIC ACID, DIISONONYL ESTER (DINCH®). Authority: France. On line (accessed 29 February 2024). https://echa.europa.eu/documents/10162/c06d1a56-dd6a-ab7c-ec71-282e7623aad3

EFSA (European Food Safety Authority) (2006). Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) related to the 12th list of substances for food contact materials. EFSA Journal 2006;4(10):395, 21 pp. https://doi:10.2903/j.efsa.2006.395

EFSA (2019). Panel on Food Contact Materials, Enzymes and Processing Aids (CEP), Silano V, Barat Baviera JM, Bolognesi C, Chesson A, Cocconcelli PS, Crebelli R, Gott DM, Grob K,

Lampi E, Mortensen A, Riviere G, Steffensen I-L, Tlustos C, Van Loveren H, Vernis L, Zorn H, Cravedi J-P, Fortes C, De Fatima Tavares Pocas M, Waalkens-Berendsen I, Wolfle D, Arcella D, Cascio C, Castoldi AF, Volk K and Castle L. Update of the risk assessment of di-butylphthalate (DBP), butyl-benzyl-phthalate (BBP, bis(2-ethylhexyl)phthalate (DEHP), di-isononylphthalate (DINP) and diisodecylphthalate (DIDP) for use in food contact materials. EFSA Journal 2019;17(12):5838, 85 pp. https://doi.org/10.2903/j.efsa.2019.5838

Eljezi T, Pinta P, Nativel F, Richard D, Pinguet J, Roy O, Sautou V, Grimandi G, Moreau E. (2019). In vitro cytotoxic effects of secondary metabolites of DEHP and its alternative plasticizers DINCH and DINP on a L929 cell line. International Journal of Hygiene and Environmental Health, 222(3), 583–589.

Eljezi T, Pinta P, Richard D, Pinguet J, Chezal J-M, Chagnon M-C, Sautou V, Grimandi G, Moreau E. (2017). In vitro cytotoxic effects of DEHP-alternative plasticizers and their primary metabolites on a L929 cell line. Chemosphere, 173, 452–459.

Engel A, Buhrke T, Kasper S, Behr A-C, Braeuning A, Jessel S, Seidel A, Völkel W, Lampen A. (2018). The urinary metabolites of DINCH® have an impact on the activities of the human nuclear receptors Erα Erβ AR, PPARα and PPARγ. Toxicology Letters, 287, 83–91.

Gu Y, Gao M, Zhang W, Yan L, Shao F, Zhou J. (2021). Exposure to phthalates DEHP and DINP May lead to oxidative damage and lipidomic disruptions in mouse kidney. Chemosphere, 271, 129740.

Kortenkamp A, Koch HM. (2020). Refined reference doses and new procedures for phthalate mixture risk assessment focused on male developmental toxicity. Int J Hyg Environm Health 224, 113428.

Langsch A, David RM, Schneider S, Sperber S, Haake V, Kamp H, Leibold E, Ravenzwaay BV, Otter R. (2018). Hexamoll® DINCH: Lack of in vivo evidence for obesogenic properties. Toxicology Letters, 288, 99–110.

Lee H, Lee J, Choi K, Kim K-T. (2019). Comparative analysis of endocrine disrupting effects of major phthalates in employed two cell lines (MVLN and H295R) and embryonic zebrafish assay. Environmental Research, 172, 319–325.

Moche H, Chentouf A, Neves S, Corpart J-M, Nesslany F. (2021). Comparison of in Vitro Endocrine Activity of Phthalates and Alternative Plasticizers. Journal of Toxicology, 2021.

OECD (2018), Revised Guidance Document 150 on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption, OECD Series on Testing and Assessment, OECD Publishing, Paris, France. https://doi.org/10.1787/9789264304741-en

Radke EG, Braun JM, Meeker JD, Cooper GS. (2018). Phthalate exposure and male reproductive outcomes: A systematic review of the human epidemiological evidence. Environment International 121, 764-793.

Rajkumar A, Luu T, Beal MA, Barton-Maclaren TS, Hales BF, Robaire B. (2022). Phthalates and alternative plasticizers differentially affect phenotypic parameters in gonadal somatic and germ cell lines. Biology of Reproduction, 106(3), 613–627.

Rasmussen LM, Sen N, Vera JC, Liu X, Craig ZR. 2017. Effects of in vitro exposure to dibutyl phthalate, mono-butyl phthalate, and acetyl tributyl citrate on ovarian antral follicle growth and viability. Biology of Reproduction, 96(5), 1105–1117.

SCENIHR (Scientific Committee on Emerging and Newly-Identified Health Risks). (2015). Opinion on the safety of medical devices containing DEHP plasticized PVC or other plasticizers on neonates and other groups possibly at risk (2015 update). European Commission, Luxembourg, Luxembourg.
https://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_047.pdf

SCHEER (Scientific Committee on Health, Environmental and Emerging Risks) (2019). 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 (ED) properties, final version adopted at SCHEER plenary on 18 June 2019.
https://health.ec.europa.eu/publications/guidelines-benefit-risk-assessment-presence-phthalates-certain-medical-devices_en

Sheikh IA, Beg MA. (2022). Structural binding perspectives of common plasticizers and a flame retardant, BDE-153, against thyroxine-binding globulin: potential for endocrine disruption. Journal of Applied Toxicology, 42(5), 841–851.

Sung CR, Kang HG, Hong JY, Kwack SJ. (2020). Citrate ester substitutes for di-2-ethylhexyl phthalate: In vivo reproductive and in vitro cytotoxicity assessments. J Toxicol Environ Health A 83, 589-595.

Tardif S, Rwigemera A, Letourneau N, Robaire B, Delbes G. (2023). Reproductive toxicity of emerging plasticizers, flame retardants, and bisphenols, using culture of the rat fetal testis†. Biology of Reproduction, 108(5), 837–848.

Tsai SC, Tseng Y-J, Wu SM. (2023). Reproductive and Developmental Alterations on Zebrafish (Danio rerio) Upon Long-Term Exposure of Di-ethyl phthalate (DEP), Di-isononyl phthalate (DINP) and Di (2-ethylhexyl) phthalate (DEHP). Bulletin of Environmental Contamination and Toxicology, 110(2), 49.

Van Den Driesche S, Shoker S, Inglis F, Palermo C, Langsch A, Otter R. (2020). Systematic comparison of the male reproductive tract in fetal and adult Wistar rats exposed to DBP and DINP in utero during the masculinisation programming window. Toxicology Letters, 335, 37–50.

Vasconcelos AL, Silva MJ, Louro H. (2019). In vitro exposure to the next-generation plasticizer diisononyl cyclohexane-1,2-dicarboxylate (DINCH): cytotoxicity and genotoxicity assessment in human cells. Journal of Toxicology and Environmental Health - Part A: Current Issues, 82(9), 526–536.

WHO/IPCS (International Programme on Chemical Safety) (2002). Global assessment of the state-of-the-science of Endocrine Disruptors. Eds. Damstra T, Barlow S, Bergman A, Kavlock R, Van Der Kraak G. World Health Organization, Geneva, Switzerland.

https://iris.who.int/bitstream/handle/10665/67357/WHO_PCS_EDC_02.2.pdf?sequence=1

WHO/IPCS (International Programme on Chemical Safety) (2012). State of the science of Endocrine Disruptors 2012. Eds. Bergman A, Hendel JJ, Jobling S, Kidd KA, Zoeller RT. World Health Organization, Geneva, Switzerland. https://iris.who.int/bitstream/handle/10665/78102/WHO_HSE_PHE_IHE_2013.1_eng.pdf?sequence=1

Yang Y, Sun F, Chen H, Tan H, Yang L, Zhang L, Xie J, Sun J, Huang X, Huang Y. (2021). Postnatal exposure to DINP was associated with greater alterations of lipidomic markers for hepatic steatosis than DEHP in postweaning mice. The Science of the Total Environment, 758, 143631.

Zhang W, Jie J, Xu Q, Wei R, Liao X, Zhang D, Zhang Y, Zhang J, Su G, Chen Y, Weng D. (2023). Characterizing the obesogenic and fatty liver-inducing effects of Acetyl tributyl citrate (ATBC) plasticizer using both in vivo and in vitro models. Journal of Hazardous Materials, 445, 130548.

Zhang L, Sun W, Duan X, Duan Y, Sun H. (2019). Promoting differentiation and lipid metabolism are the primary effects for DINP exposure on 3T3-L1 preadipocytes. Environmental Pollution (Barking, Essex: 1987), 255(Pt 1), 113154.

## **Annex 10:** Recent progress in the use of alternative plasticisers to DEHP for red blood cell storage

Polyvinyl chloride (PVC) plasticised with di(2-ethylhexyl) phthalate (DEHP) has been the material of choice for blood bag sets used for the collection, processing and storage of red blood cell concentrates since the mid-20th century. DEHP is important for material flexibility; facilitating centrifugation, sealing, transport and general handling of blood bag sets without risk of breakage and product loss (Walter 1984). In addition, leached DEHP incorporates in the red blood cell membrane and has a stabilising effect, which helps to maintain cell integrity, reducing hemolysis and thus permitting longer storage duration of red blood cell concentrates (Horowitz *et al.*, 1985; Rock *et al.*, 1984). As per European legislation (Directive 2004/33/EC, Annex V), hemolysis of red cell must be below 0.8% at the end of shelf life (usually between 5-7 weeks, depending on the Member State). In the EDQM guide (2023) it is indicated that at least 90% of the hemolysis tests should meet the required values. In addition, specific requirements for blood bag sets are also presented in ISO 3826-1:2019 and ISO 3826-1:2023 Amendment 1. Furthermore, some Member States may have additional quality requirements.
At least five independent Phase I studies compared red blood cell storage in DEHP-PVC bags with the plasticiser alternatives diisononyl-cyclohexane-1,2-dicarboxylate (DINCH), di(2-ethylhexyl) terephthalate (DEHT), n-Butyryl-tri-n-hexyl citrate (BTHC), DINCH and di (2-ethylhexyl) 4-cyclohexene-1,2-dicarboxylate (DOTH, CAS 2915-49-3) or DOTH and 4-cyclohexene-1,2-dicarboxylic acid dinonyl ester (DL9TH, CAS 1609185-22-9).

For red blood cells stored in DINCH bags in the storage solution SAGM, end of storage hemolysis was increased in DINCH when compared to DEHP but remained below the European limit of 0.8%. (Lagerberg *et al*., 2015). This study also showed that two second generation storage solutions (phosphate–adenine–glucose–guanosine–saline–mannitol (PAGGSM) and AS-3) or an experimental storage solution (phosphate–adenine–glucose–guanosine–gluconate–mannitol PAGGGM) reduced hemolysis associated with the usage of DINCH-PVC bags to a level similar to DEHP bags/SAGM solution.

The plasticisers alternatives DINCH+DOTH or DL9TH+DOTH associated with the mannitol-adenine-phosphate storage solution (MAP) showed a tendency to increased hemolysis that did not reach statistical significance when compared to DEHP-PVC bags/MAP solution at 42 days of storage (Morishita *et al.* 2017).

For red blood cells stored in DEHT bags in the storage solution SAGM, although end of storage hemolysis was slightly higher in DEHT when compared to DEHP, it remained below the European limit of 0.8%. (Larsson *et al.*, 2021). Similarly, for red blood cells stored in DEHT-PVC in the storage medium AS-1, increased hemolysis rates at the end of storage were observed when compared to DEHP-PVC but also remained below the European limit of 0.8% (Graminske *et al.*, 2018). Interestingly, both studies showed that the PAGGSM storage solution reduced hemolysis associated with the usage of DEHT-PVC bags, when compared to AS-1 and SAGM. Lastly, a recent Phase I study by Vermeulen *et al.* showed that BTHC bags/PAGGSM solution had hemolysis levels comparable to DEHP bags/SAGM solution (Vermeulen *et al.*, 2022).

In the same report, a Phase III hemovigilance surveillance was performed to track adverse event frequency in patients transfused with red blood cells stored in BTHC bags/PAGGSM solution (652 patients) or in standard of care DEHP/SAGM solution (1633 patients). Transfusion of red blood cell concentrates stored in BTHC/PAGGSM solution did not result in an increased rate of transfusion reactions (Vermeulen *et al.*, 2022).

One Phase I study compared DEHP/DEHT and SAGM/PAGGSM solution combinations for storage of irradiated red blood cells, a blood product used to transfuse

immunocompromised patients (Larsson *et al.*, 2022). The hemolysis level was slightly increased at the end of storage in DEHT bags conditions but remained below the European limit of 0.8%. As for standard red blood cell storage, the PAGGSM solution reduced hemolysis associated with the usage of DEHT bags.

In all of these studies, the plasticiser alternatives for DEHP did not show a negative impact on the end of storage ATP level, suggesting that red cell metabolism is not negatively impacted by DEHP removal (Lagerberg *et al*., 2015; Morishita *et al.*, 2017; Larsson *et al.*, 2021; Graminske *et al.*, 2018; Vermeulen *et al.*, 2022).

These studies show that it may be possible to replace DEHP by an alternative plasticiser that does not affect the storage capacity of the red blood cells in these blood bags. However, a careful benefit risk assessment extending beyond hemolysis needs to be performed before replacing DEHP by any alternative in blood bag sets. These guidelines are intended to provide information how to perform such BRA.

It should be noted that the sunset date for the continued use of DEHP in medical devices has recently been extended to 1 July 2030 (Commission Regulation (EU) 2023/2482) as described in Annex 5 of these guidelines. After this date authorisation according to REACH (Regulation (EC) 1907/2006) is required, in addition to justification for the use of CMR/ED phthalates according to the MDR (Regulation (EU) 2017/745).

**References**

EDQM (European Directorate for the Quality of Medicines and Health Care). (2023). Guide to the preparation, use and quality assurance of blood components. 21st Edition. EDQM, Council of Europe, Strasbourg, France. https://www.edqm.eu/en/d/1692268?p_l_back_url=%2Fen%2Fsearch%3Fq%3DGuide%2Bto%2Bthe%2Bpreparation%252C%2Buse%2Band%2Bquality%2Bassurance%2Bof%2Bblood%2Bcomponents.%2B21st%2BEdition.

Graminske S, Puca K, Schmidt A, Brooks S, Boerner A, Heldke S, De Arruda Indig M, Brucks M, Kossor D. (2018). *In vitro* evaluation of di(2-ethylhexyl)terephthalate-plasticized polyvinyl chloride blood bags for red blood cell storage in AS-1 and PAGGSM additive solutions. Transfusion. 58:1100–1107.

Horowitz B, Stryker MH, Waldman AA, Woods KR, Gass JD, Drago J. (1985). Stabilization of red cells by the plasticizer diethylhexylphthalate. Vox Sang. 48:150-155.

ISO 3826-1:2019. Plastic collapsible containers for human blood and blood components - Part 1: Conventional containers. ISO, Geneva, Switzerland.

ISO 3826-1:2023. Amendment 1. Plastic collapsible containers for human blood and blood components - Part 1: Conventional containers. Amendment 1. ISO, Geneva, Switzerland.

Lagerberg JW, Gouwerok E, Vlaar R, Go M, de Korte D. (2015). In vitro evaluation of the quality of blood products collected and stored in systems completely free of di(2-ethylhexyl)phthalate–plasticized materials. Transfusion 55: 522-531.

Larsson L, Sandgren P, Ohlsson S, Derving J, Friis-Christensen T, Daggert F, Frizi N, Reichenberg S, Chatellier S, Diedrich B, Antovic J, Larsson S, Uhlin M. (2021). Non-phthalate plasticizer DEHT preserves adequate blood component quality during storage in PVC blood bags. Vox Sang. 116:60–70.

Larsson L, Ohlsson S, Derving J, Diedrich B, Sandgren P, Larsson S, Uhlin M. (2022). DEHT is a suitable plasticizer option for phthalate-free storage of irradiated red blood cells. Vox Sang. 117:193–200.

Morishita Y, Nomura Y, Fukui C, Kawakami T, Ikeda T, Mukai T, Yuba T, Inamura K, Yamaoka H, Miyazaki K, Okazaki H. Haishima Y. (2017). Pilot study on novel blood containers with alternative plasticizers for red cell concentrate storage. PLoS One. 12:e0185737.

Rock G, Tocchi M, Ganz PR, Tackaberry ES. (1984). Incorporation of plasticizer into red cells during storage. Transfusion 24: 493-498.

Vermeulen C, den Besten G, van den Bos AG, Go M, Gouwerok E, Vlaar R, Schipperus MR, Spelmink SE, Janssen M, Lagerberg JW, De Korte D, Klei TRL. (2022). Clinical and *in vitro* evaluation of red blood cells collected and stored in a non-DEHP plasticized bag system. Vox Sang. 117:1163–1170.

Walter CW. (1984). Invention and development of the blood bag. Vox Sang. 47:318-324.

---