

DEHP IN BLOOD BAG SYSTEMS

TERUMOBCT

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Agenda

❖ Regulatory Environment:

- Background
- Safety of DEHP in Medical Devices

❖ Blood Bag Systems

- Definition
- Unique Properties of DEHP
- DEHP Alternatives
- Evidence needed to Phase out DEHP

❖ Terumo BCT's recommendation

Regulatory Environment

Background

- ❖ **Europe** – DEHP is classified as a CMR 1b and an endocrine disruptor^[1,2,3] As such, it is on the candidate list as a substance of very high concern (SVHC). Already there are restrictions on the use of DEHP for most applications. Currently, **medical devices are exempt** from the requirement to substitute DEHP for another substance.
- ❖ **European Chemicals Agency Consultation (ECHA)^[4]** - As DEHP is now considered an endocrine disruptor **for the environment**, ECHA had launched a consultation as to whether the exemption for medical devices on the use of DEHP and 3 other phthalates are still justified.
- ❖ **EU Medical Device Regulation (EU MDR, 2017/745)**: MDR requires a justification for the continued use of materials such as DEHP above 0.1% w/w (cfr. Annex 1, Chapter 2, Section 10.4 on Substances) as well as appropriate labeling.

1. EU Regulation (EC) No 1272/2008 (CLP) Annex VI

2. Inclusion of DEHP on SVHC candidate list (REACH XIV) Based on toxicity to reproduction (57c) and endocrine disruption (Art 59) but exemption for medical devices regarding human health per REACH Art.2,6(c).

3. Inclusion of DEHP on SVHC candidate list concerning probable effects to mammals in the environment (REACH Art 57f) in December 2014

4. Reclassification of DEHP and 3 other phthalates as endocrine disruptions an amendment to REACH, Annex IV amendment Art 57f Medical devices would no longer fall under the generic exemptions

Regulatory Environment

Safety of DEHP in Medical Devices

- ❖ SCENIHR (Scientific Committee of Emerging and Newly-Identified Health Risks, 2015 update):
 - Benefits of DEHP in medical devices outweigh the risks for the vast majority of applications.
 - Viable alternatives to DEHP having such a protective effect on red blood cells remain to be identified and validated.
 - The complete toxicity profile of the alternatives to DEHP is not conclusive
 - Clinical data on the long-term effect of the use of non-DEHP products still have to be established.
 - Collection of data on exposure in the actual conditions of use are strongly recommended to define the knowledge on their toxicological profile for humans and environment.

Blood Bag Systems

Definition

- ❖ Closed systems composed of one or more sterile containers made from plastic materials, commonly referred to as the “blood bag”, and one or more tubes and attachments. Blood Bag Systems are intended to collect, store, process and administer blood and blood components.
- ❖ A blood bag system may also contain or be coated with an anticoagulant, preservative solutions and other substances, which will assist on ensuring good storage conditions of blood and blood components and one or more tubes and attachments
- ❖ European Pharmacopoeia, section 3.2.3.
 - *“The containers may contain anticoagulant solutions, depending on their intended use, and are supplied sterile” and “The container may be in the form of a single unit or the collecting container may be connected by one or more tubes to one or more secondary containers to allow separation of the blood components to be effected within a closed system”.*

Blood Bag Systems

Unique Properties of DEHP

- ❖ Well-defined and tested plasticizer:
 - Introduced in all markets in early 1960 to facilitate separation and storage of blood components. A plasticizer is necessary to prevent PVC from fracturing during processing and handling.
- ❖ Improved blood safety and blood banking efficiency:
 - Increased durability and flexibility prevents container breakage and bacterial contamination
 - Allows for steam sterilization, heat welding, centrifugation/componentization
- ❖ Due to the lipophilic nature of DEHP, it leaches from PVC blood bag systems into blood products and intercalates into the lipid bilayer of RBCs^[1].
- ❖ Improved RBC quality^[1,2]
 - Improved morphology, deformability, osmotic fragility
 - Decreased hemolysis
 - Increased in vivo Survival & Recovery of the cells in vivo
 - Storage for up to 49 days
- ❖ Improved Plasma storage:
 - Resistance to breakage
- ❖ DEHP has no effect on Platelet quality:
 - Platelet storage requires gas permeability of the bags. DEHP has low permeability.
 - All TBCT's platelet storage containers are DEHP-free
- ❖ Lack of clinical evidence of significant adverse consequences in patients

1. Horowitz B, et al. Stabilisation of red blood cells by the plasticizer, diethylhexylphthalate. Vox Sang, Volume 48, pp.150-155.

2. AuBuchon JP, et al. The effect of the plasticizer di-2-ethylhexylphthalate on the survival of stored RBC's. Blood, 1988.71(2): pp 448-452.

Blood Bag Systems

DEHP Alternatives*

❖ BTHC (butyryl tri-n-hexyl citrate):

- Less leaching than DEHP
- Low toxicity
- RBC storage limited to approx. 35 days

❖ DINCH (cyclohexane 1,2-dicarboxylic acid):


- Less leaching than DEHP
- Adverse effects of DINCH metabolites on human reproductive health^[1]
- Toxicity data (GreenScreen): classification of Moderate is warranted for the endpoint of endocrine activity
- RBC storage limited to approx. 35 days

❖ DEHT (bis(2-ethylhexyl) terephthalate):

- Less leaching than DEHP
- Toxicity data (GreenScreen): classification of Low
- RBC storage limited to approx. 35 days

❖ TOTM or TEHTM (tris(2-ethylhexyl) trimellitate):

- Less leaching than DEHP
- Sufficient gas permeability for platelet storage
- RBC storage limited for 21 days

 Limited in vitro data for RBCs storage in Blood Bag Systems plasticized with alternatives has been generated, and data indicates that alternatives do not achieve the same characteristics as DEHP

GreenScreen Benchmark Score and Hazard Summary Table:^{6,6,7,8} Hexamoll® DINCH® (166412-78-8, 474919-59-0) was assigned a Benchmark Score of 3 based on criteria 3a moderate persistence (P) and 3c moderate skin irritation (IrS) in CPA 2016.

GreenScreen™ Hazard Ratings: Diisononyl cyclohexanedicarboxylate (CAS #166412-78-8, 474919-59-0)																			
Group I Human					Group II and II* Human								Ecotox		Fate		Physical		
C	M	R	D	E	AT	ST		N		Sn S*	Sn R*	IrS	IrE	A A	C A	P	B	R X	F
						ding le	Rep eate d*	ding le	Rep eate d*										
L	L	L	L	L	L	L	L	L	L	L	L	M	L	L	L	M	L	L	L

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated values, authoritative B lists, screening lists, weak analogues, and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analog data.

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): M

Hexamoll® DINCH® was assigned a score of Moderate (high confidence) for persistence based on a half-life between 16 and 60 days for both water and soil, following GLP compliant OECD 301 biodegradation Study, and a OECD 307 transformation study, respectively. Confidence is high because the persistence rating is based on data.

GreenScreen Benchmark Score and Hazard Summary Table:^{4,6,8,7} DEHT (6422-86-2) was assigned a Benchmark Score of 4.

GreenScreen™ Hazard Ratings: Bis(2-ethylhexyl) terephthalate																			
Group I Human					Group II and II* Human								Ecotox		Fate		Physical		
C	M	R	D	E	AT	ST		N		Sn S*	Sn R*	IrS	IrE	A A	C A	P	B	R X	F
						ding le	Rep eate d*	ding le	Rep eate d*										
L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	vL	L	L	L

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated values, authoritative B lists, screening lists, weak analogues, and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogs.

1. Minguez-Alarcon L B, et al. Urinary concentrations of cyclohexane-1,2-dicarboxylic acid monohydroxy isononyl ester, a metabolite of the non-phthalate plasticizer di(isononyl)cyclohexane-1,2-dicarboxylate (DINCH), and markers of ovarian response among women attending a fertility center. Environ Res 2016 Nov;151:595-600.

*Plasticizers proposed by the European Pharmacopoeia

Blood Bag Systems

DEHP Alternatives

- ❖ Less characterized toxicity:
 - SCENIHR (2015): ...*most considered plasticizers can cause reproductive toxicity, although this occurs at doses several folds higher than DEHP.*
- ❖ GreenScreen^[1]:
 - Carcinogenic potential exists for some alternate plasticizers that are being considered
- ❖ Potential adverse effects of plasticizer metabolites on human reproductive health^[2]
- ❖ Lack of adequate leaching data:
 - No standardized and validated assay methods to measure plasticizers in solution and cellular membranes
- ❖ In vitro data:
 - No alternative plasticizer reaches the same in vitro RBC storage characteristics as DEHP
- ❖ Lack of human exposure data:
 - Impact on clinical effectiveness and patient safety
 - Long term toxicological effect
 - Synergistic role of new plasticizer and new storage solutions needs to be carefully evaluated
- ❖ Impact on shelf life may result in increase wastage of blood products and need for more blood donations

1. <http://www.greenchemistryandcommerce.org>

2. Minguez-Alarcon L B, et al. Urinary concentrations of cyclohexane-1,2-dicarboxylic acid monohydroxy isononyl ester, a metabolite of the non-phthalate plasticizer di(isononyl)cyclohexane-1,2-dicarboxylate (DINCH), and markers of ovarian response among women attending a fertility center. Environ Res 2016 Nov;151:595-600.

Blood Bag Systems

Evidence needed before DEHP can be phased out

❖ Validations and verifications required:

- Physical/technical properties
- Biocompatibility
- Toxicology assessments
- In vitro testing
- In vivo/clinical testing in various patient populations
- Risk-benefit assessments
- Long term follow-up (post-market surveillance)
- Environmental impact

❖ Application for licensing by the Blood Center

- Validations
- New contracts



This is a multi-year development effort: development, validation and clinical trials are estimated to take a at least 5 years, followed by application for authorization estimated to take up to 2 years

Guidelines on the benefit-risk assessment of the presence of phthalates in certain medical devices

Framework of the benefit-risk assessment

- ❖ Step 1: Identification of the presence and concentration of phthalates
- ❖ Step 2+3: Use scenario
 - Description of the use and function of the phthalate
 - Assessment of the risks of the phthalate
- ❖ Step 4-7: Non-use scenario
 - Assessment of the risks of possible alternatives
- ❖ Step 8-10: Assessment of potential alternatives versus phthalates
 - Comparison of benefit-risk of phthalate and possible alternatives
 - Uncertainty analysis
- ❖ Justification for continued use of phthalates

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- ❖ Justification for continued use of phthalates

TBCT's recommendation

Assessment of the risks of possible alternatives

- ❖ DEHP alternatives need to demonstrate:
 - no loss in clinical performance
 - acceptable safety profile
 - no loss of product quality or safety
 - to meet current manufacturing and storage requirements
 - to have equal or superior risk-benefit ratio compared to DEHP

- ❖ Until all functionality, performance and risk factors of potential alternatives in relation to the intended use of the medical device are established, a proper comparison of benefits and risks of DEHP and alternatives is not feasible

- ❖ The benefit-risk assessment should focus on the description of the use and function of DEHP, the benefits and the patient exposure based on realistic worst-case use scenario in the intended use.

**THANK
YOU**



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