SCHEER
- Hearing on the preliminary Guidelines on benefit - risk assessment of Phthalates in Medical Devices

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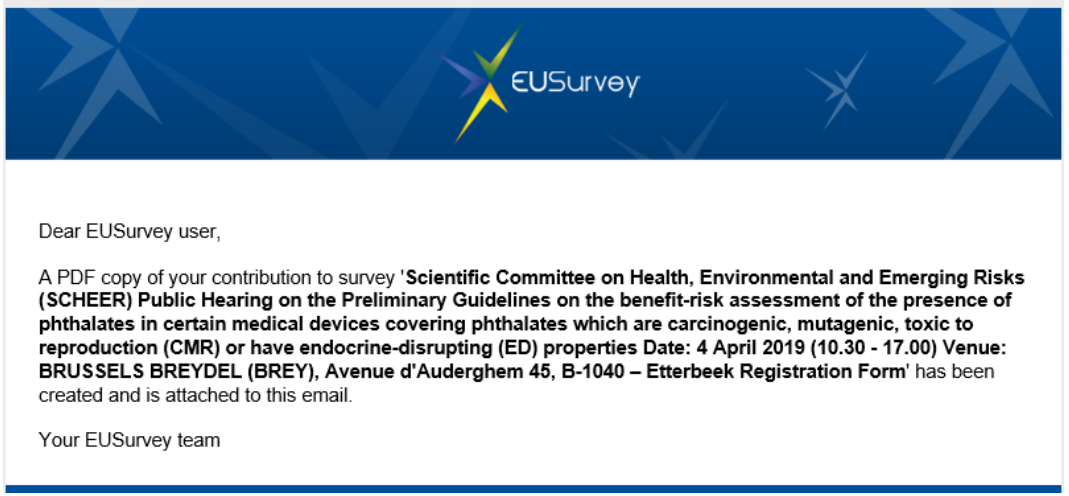
Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) – Medical Devices: New Guidelines

Please note:

Phthalates and all the alternative plasticisers in this document are neither mutagenic nor carcinogenic!



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Preliminary Version - Guidelines by SCHEER, March 15, 2019
General comments

- Missing references need to be added to the final document
- „Serious data gaps (e.g. page 9)“ for alternatives needs to be specified
  - Alternatives like e.g. Hexamoll® DINCH provide a complete toxicological database – in some aspects even more specific data as compared to DEHP are available
  - For some of the alternatives exposure data are available using state of the art methods
    - DEHP data were in parallel established for comparison
- SCHEER needs to take note of the updated EU Pharmacopoeia
  - 4 further plasticisers are now listed
  - Use of DEHP needs to be critically evaluated as specified in the guidelines
- Associations are no proof of adverse effects in humans
  - Mariana (2016) and Katsikantami (2016) do provide robust conclusions
    - page 33, lines 32-33, page 34, line 1-2 need to be checked

Preliminary Version of the Guidelines by SCHEER, March 15, 2019

- Annex 5, page 48:
- 20 Furthermore, for DBP, BBP, DEHP, DINP, DIDP and DINCH (the latter not being a
- 21 phthalate) applies a group restriction, that is, the sum of these substances must not
- 22 exceed an SML of 60 mg/kg foodstuff.

- Please note that (32) is a group restriction that refers to several plasticizers
  - further: **this is the overall migration limit**

32	8 72 73 138 140 157 159 207 242 283 532 670 728 729 775 783 797 798 810 815	60	expressed as the sum of the substances

Regulatory: DEHP – SVHC Listing

Substance name	EC / List no	CAS no	Status	Expected date of submission	Submitter	Scope	Latest update	
Bis(2-ethylhexyl) phthalate	204-211-0	117-81-7	Submitted	04/08/2014	Denmark	Endocrine disrupting properties (Article 57 (f) - environment) Endocrine disrupting properties (Article 57 (f) - human health)	28/02/2018	
Bis(2-ethylhexyl) phthalate	204-211-0	117-81-7	Submitted	27/06/2008	Sweden	Toxic for reproduction (Article 57c)	28/02/2018	

- Regulation (EC) No 1907/2006
  - Annex XIV for toxicity to reproduction (57c)
  - SVHC Candidate listing for probable effects to animals in the environment (Equivalent level of concern, **57f**)
    - For medical devices and food contact applications REACH will apply
- Regulation (EU) 2018/2005: Restrictions on DEHP, BBP, DBP and DIBP
  - Starting from July 7, 2020: articles < 0.1 % by weight

European Pharmacopoeia – Chapters on Plasticized PVC

- Inclusion of four additional plasticizers
  - DINCH
  - BTHC
  - TOTM
  - DEHT

https://www.edqm.eu/en/news/ph-eur-revised-its-general-chapters-plasticised-pvc-materials

The Ph. Eur. revised its general chapters on plasticised PVC materials

Back

EUROPEAN PHARMACOPOEIA GENERAL TEXT/CHAPTER | NEWS | 18 JANUARY 2018 | STRASBOURG, FRANCE

At its 159th Commission session (November 2017) the Ph. Eur. Commission adopted the following revised general chapters:

- 3.1.1.1/90001. Materials based on plasticised poly(vinyl chloride) for containers for human blood and blood components;
- 3.1.1.2/90002. Materials based on plasticised poly(vinyl chloride) for tubing used in sets for the transfusion of blood and blood components;
- 3.2.4. Empty sterile containers of plasticised poly(vinyl chloride) for human blood and blood components;
- 3.2.5. Sterile containers of plasticised poly(vinyl chloride) for human blood containing anticoagulant solution.

These chapters had been revised to include four new PVC plasticisers:

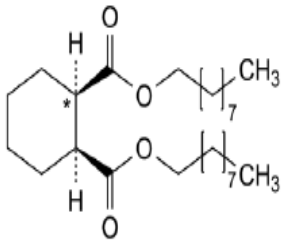
- cyclohexane 1,2-dicarboxylic acid, diisononyl ester;
- butyryl tri-n-hexyl citrate;
- tris(2-ethylhexyl) trimellitate;
- bis(2-ethylhexyl) terephthalate.

Another 2 general chapters were also indirectly impacted by the revision:

- 3.1.13. Plastic additives: the list of additives has been updated with the 4 additives mentioned above;
- 3.1.14. Materials based on plasticised poly(vinyl chloride) for containers for aqueous solutions for intravenous infusion: the quantification of plasticisers (including DEHP) is now performed by gas chromatography/mass spectrometry.

European Pharmacopoeia – 2019

plastic additive 24. $C_{26}H_{48}O_4$. [166412-78-8].



and epimer at C*

mixture of 90 ± 10 per cent of the *cis*-isomer and 10 ± 10 per cent of the *trans*-isomer of:

dinonyl (1*RS*,2*S*)-cyclohexane-1,2-dicarboxylate

synonyms: – **cyclohexane 1,2-dicarboxylic acid, diisononyl ester,**

– 1,2-cyclohexanedicarboxylic acid, 1,2-diisononyl ester.

3.1.14. MATERIALS BASED ON PLASTICISED POLY(VINYL CHLORIDE) FOR CONTAINERS FOR AQUEOUS SOLUTIONS FOR INTRAVENOUS INFUSION

DEFINITION

Materials based on plasticised poly(vinyl chloride) contain not less than 55 per cent of poly(vinyl chloride) and contain various additives, in addition to the high-molecular-mass polymer obtained by polymerisation of vinyl chloride.

Materials based on plasticised poly(vinyl chloride) for containers for aqueous solutions for intravenous infusion are defined by the nature and the proportions of the substances used in their manufacture.

PRODUCTION

Blood bags

- Blood bags based on Hexamoll® DINCH approved by notified body CE 0123
- Compared to DEHP migration into the blood product is ~10 times lower
- Hexamoll® DINCH stabilizes red blood cells as good as DEHP
  - 2nd generation additives necessary
- Pediatric platelet bag based on Hexamoll® DINCH in use since 2012 at the Dutch National Blood bank Sanquin

Medical Device Awards 2013

Sanquin Blood Supply

SolVin Award 2013

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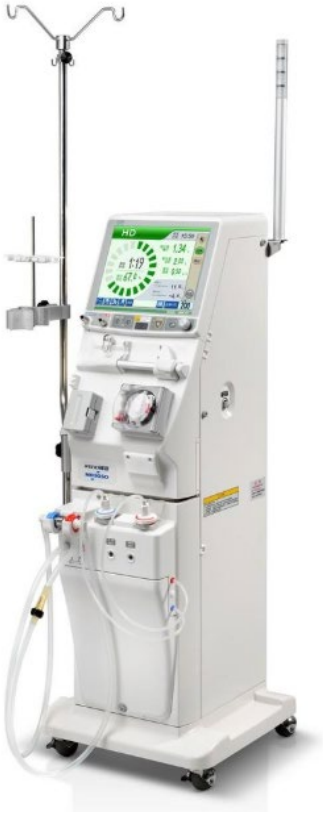
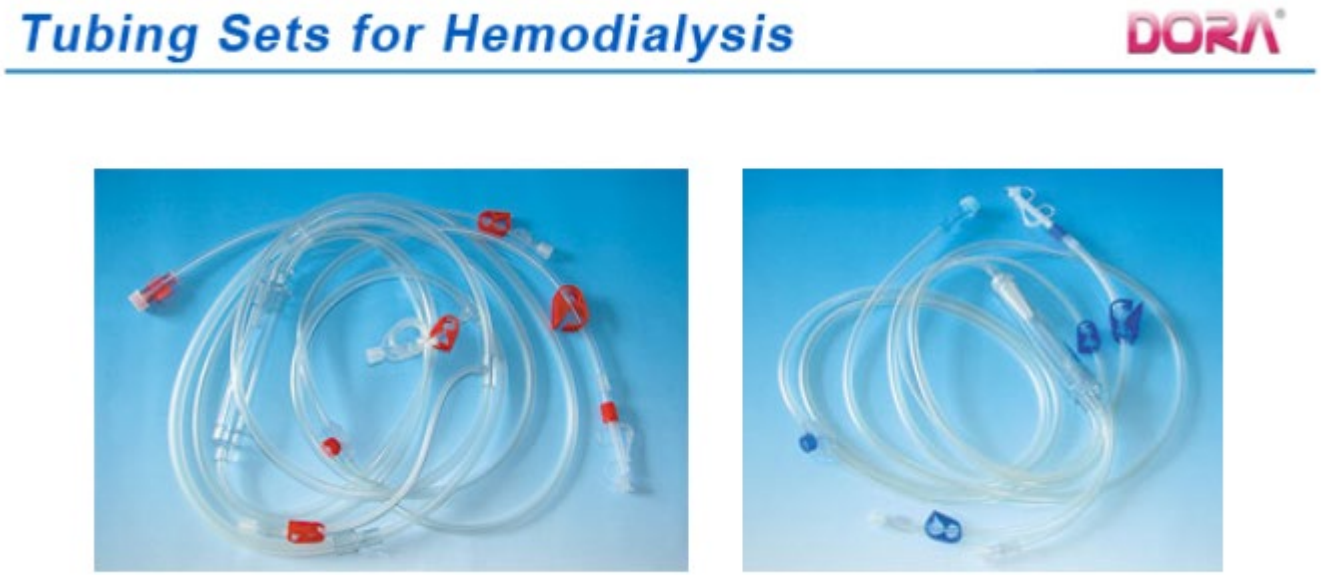
Wego Healthcare

- Infusion-/transfusion equipment
- Extracorporeal blood circuit for hemodialysis
- Heart-lung machine

Extracorpeal Blood Circuit For Hemodialysis



Bain Medical Guangzhou Co. Ltd. – Medical Tubing



Scientific Publications

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Drug Device Interactions

- Treleano A. et al., Int. Journal. Pharmac. 369 (2009), 30–37
  - Nitroglycerin and Diazepam
- Tortolano L. et al., J. Appl. Polym. Sci. (2018), 46649 1-8, DOI: 10.1002/APP.46649
  - DINCH, TOTM, ESBO and drugs used in oncopediatric unit

Open Issues from Comparison with Mandate (Terms of Reference)

- “In addition, the Scientific Committee is requested to
  - identify any relevant knowledge gap; and
  - to give consideration to what extent of new evidence would be deemed appropriate to justify an update of these guidelines before the maximum period of five years.”

- Are the guidelines suitable as guidance for medical device producers?
  - What is missing?

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