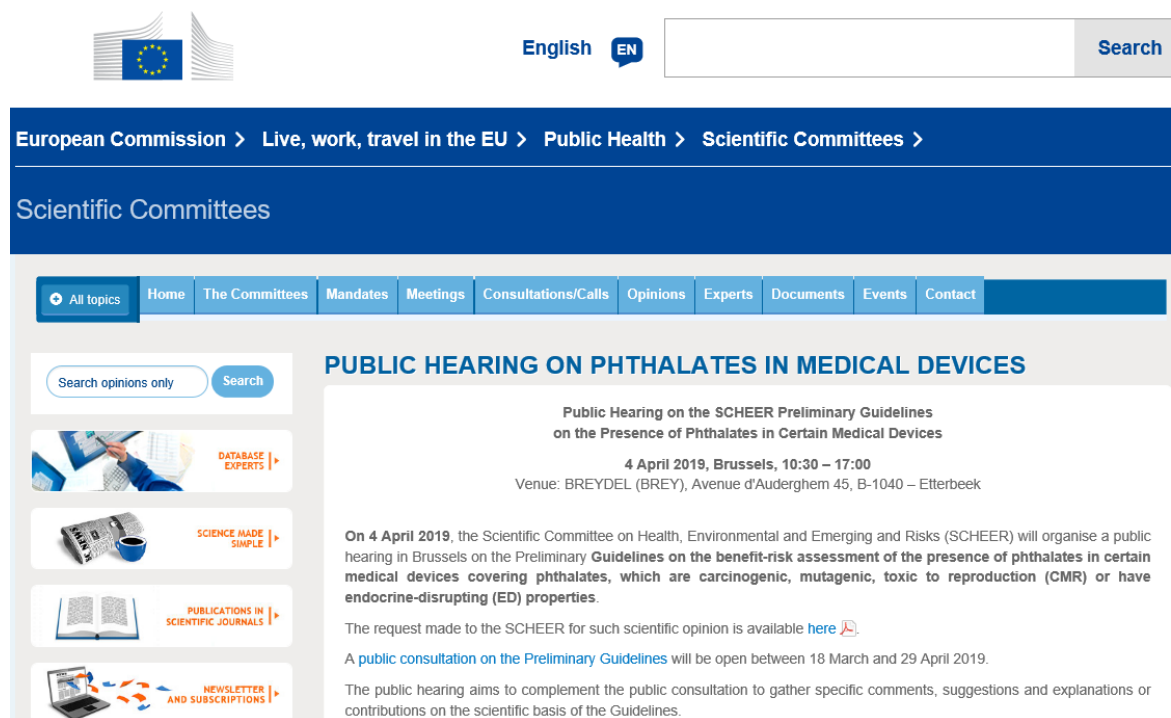


SCHEER

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

Dr. Rainer Otter

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



The screenshot shows the SCHEER website interface. At the top, there is a navigation bar with the European Commission logo, the text "European Commission > Live, work, travel in the EU > Public Health > Scientific Committees >", and a search bar. Below this is a secondary navigation bar with "Scientific Committees". A third navigation bar contains menu items: "All topics", "Home", "The Committees", "Mandates", "Meetings", "Consultations/Calls", "Opinions", "Experts", "Documents", "Events", and "Contact".

The main content area features a search box labeled "Search opinions only" and a "Search" button. Below the search box are four promotional tiles: "DATABASE EXPERTS" with a magnifying glass icon, "SCIENCE MADE SIMPLE" with a newspaper icon, "PUBLICATIONS IN SCIENTIFIC JOURNALS" with an open book icon, and "NEWSLETTER AND SUBSCRIPTIONS" with a laptop icon.

PUBLIC HEARING ON PHTHALATES IN MEDICAL DEVICES

Public Hearing on the SCHEER Preliminary Guidelines on the Presence of Phthalates in Certain Medical Devices

4 April 2019, Brussels, 10:30 – 17:00
Venue: BREYDEL (BREY), Avenue d'Auderghem 45, B-1040 – Etterbeek

On 4 April 2019, the Scientific Committee on Health, Environmental and Emerging and Risks (SCHEER) will organise a public hearing in Brussels on the Preliminary 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.

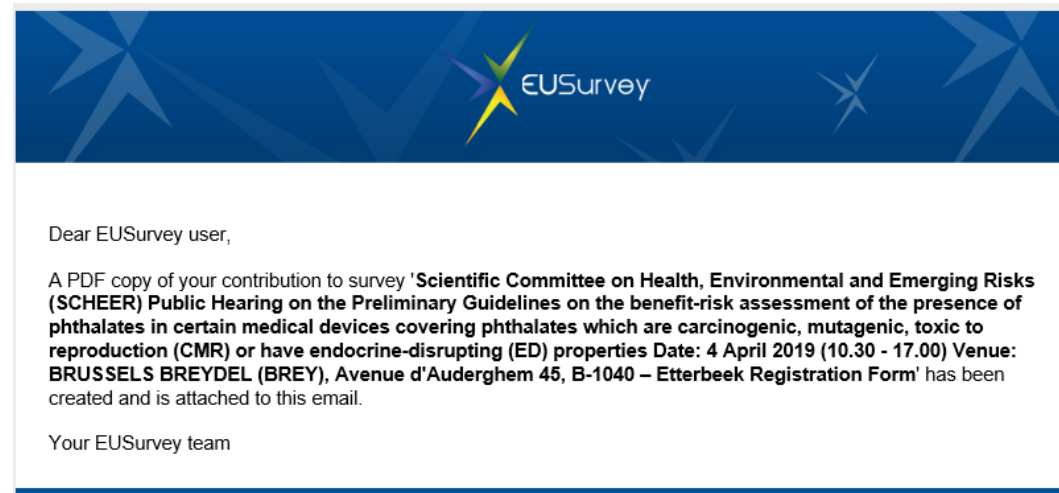
The request made to the SCHEER for such scientific opinion is available [here](#).

A public consultation on the Preliminary Guidelines will be open between 18 March and 29 April 2019.

The public hearing aims to complement the public consultation to gather specific comments, suggestions and explanations or contributions on the scientific basis of the Guidelines.

Please note:

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



The screenshot shows an email from the EUSurvey team. The header features the EUSurvey logo, which consists of a stylized starburst icon and the text "EUSurvey".

Dear EUSurvey user,

A PDF copy of your contribution to survey '**Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) Public Hearing on the Preliminary 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** Date: 4 April 2019 (10.30 - 17.00) Venue: BRUSSELS BREYDEL (BREY), Avenue d'Auderghem 45, B-1040 – Etterbeek Registration Form' has been created and is attached to this email.

Your EUSurvey team

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	<ul style="list-style-type: none">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.

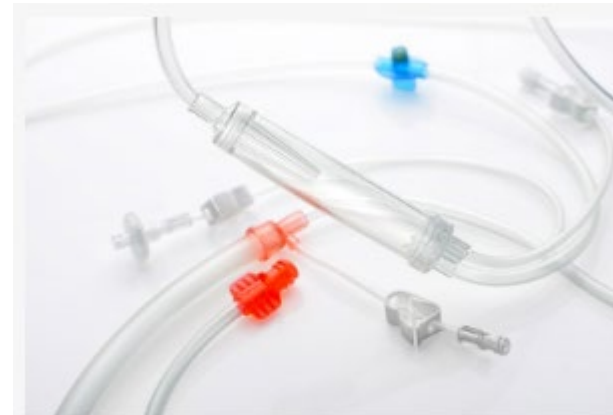
Blood bags

- Blood bags based on Hexamoll® DINCH approved by notified body 
- 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



Wego Healthcare

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



Extracorporeal Blood Circuit For Hemodialysis



Bain Medical Guangzhou Co. Ltd. – Medical Tubing



Tubing Sets for Hemodialysis

DORA[®]



Scientific Publications

ELSEVIER

Determination of met (DEHP) in human urine

Frederik Lessmann, André Schüttrötter*
Institute for Prevention and Occupational Medicine
Büro de-la Camp-Platz 4 44789 Bochum, Ger

ARTICLE INFO

Article history:
Received 11 August 2015
Received in revised form 7 December 2015
Accepted 19 December 2015
Available online 24 December 2015

Keywords:
Di-(2-ethylhexyl)terephthalate
DEHP
Plasticizer
Exposure assessment
Urinary metabolites
Human toxicokinetics

1. Introduction

Di-(2-ethylhexyl)terephthalate (DEHP) is a substitute for some high plasticizers like di-(2-ethylhexyl)phthalate and endocrine disrupting substances (EC) No. 1007/2006 [1]. It is restricted in the use of DEHP both in toy food contact materials. In the U.S., DEHP profiles differ considerably, can neither be regarded as a reproductive toxicant [5]. Compared to DEHP, DEHP did not show a significant

* Corresponding author. Fax: +49 234 302 4 628; e-mail address: lessmann@ipm.uni-bochum.de (F. Lessmann).

Published online: 26 April 2016

ELSEVIER

Metabolism and urinary excretion of di-(2-ethylhexyl)terephthalate (DEHP)

Frederik Lessmann*, André Schüttrötter*, Thomas Brüning

Received: 11 February 2016 / Accepted: 10 September 2016 / Available online: 26 April 2016

Abstract Di-(2-ethylhexyl)terephthalate (DEHP) is used as a substitute for di-(2-ethylhexyl)phthalate (DEHP) in ortho-phthalate-based plasticizers labeled due to its toxicity to reproductive metabolism and urinary excretion. We quantified specific metabolites of DEHP: mono-(2-ethylhexyl)terephthalate (MEHTP), bis-(2-ethylhexyl)terephthalate (BMEHTP), and mono-(2-ethylhexyl)terephthalate (MEHTP). Six MEHTP and two BMEHTP samples were consecutively collected over 48 h. The predominant, specific metabolite was MEHTP (mean: 26.3 μg/L, range: 0.2–0.4 μg/L). In total, 1.5 μg of MEHTP was recovered in urine as the metabolite within 48 h after the intake of DEHP.

Electronic supplementary material The online version of this article (doi:10.1007/s00204-016-1715-x) contains supplementary material, which is available to authorized users.

© Springer-Verlag Berlin Heidelberg 2016

ELSEVIER

Toxicity of Hexamol® DINCH

Raymond M. David*, Randy D. White, D. Klein^{a,b}, W. Kessler^c, R. Pütz^d, A.K.E. Gallien^e, S. Wurzenberger^f

Letter to the Editor

The publication "Cyclohexane-1,4-dicarboxylic acid diisomers (Hexamol® DINCH)" promotes the authors have over-interpreted their in vivo data.

ABSTRACT

In vivo, the authors report MINCH, a branched Hexamol® DINCH, promotes in vivo effects more than 10-fold compared to the linear Hexamol® DINCH. The authors have over-interpreted their in vivo data.

1. MINCH

According to Section 22, MINCH is a di-(2-cyclohexyl)terephthalate alcohol. The monoester (MINCH) results of the genotoxicity studies were consistent in a specific rat and the C30-alcohol (NCS, 2012). Structural properties of ligand for receptor-ligand interactions. Substituted by the authors is insufficient as a MS or di-trans-isomer ratio are substances may have been tested. The major metabolite in blood, but in contrast glucuronidated in human blood.

2. PPAR-α agonist

The authors suggest MINCH could be based on the following information: C inhibited the effect of MINCH while C (PPAR-α agonist) did not prevent differentiation. However, their conclusion "potent contrast with the results of animal studies" is not supported. The authors' conclusion "potent effect of MINCH in rat liver. The specific proliferating activity (yields-increased) of MINCH was not significantly different from the control" is not supported. Information about how PPAR-α in rat differs from PPAR-α in liver is missing. It is not clear from the authors' text how they understand the claims made by the authors.

Archives of Toxicology

ISSN 0340-5761
Volume 90
Number 7
Arch Toxicol (2016) 90:1659–1660
DOI 10.1007/s00204-016-1715-x

ELSEVIER

Metabolism and urinary excretion of di-(2-ethylhexyl)terephthalate (DEHP) in three male volunteers

Frederik Lessmann, Tobias Weis, Otter, Thomas, M. Koch

Archives of Toxicology

ISSN 0340-5761
Volume 90
Number 7
Arch Toxicol (2016) 90:1659–1660
DOI 10.1007/s00204-016-1715-x

ELSEVIER

Additional breakdown of DINCH in urine of human volunteers

André Schüttrötter, Modick, Ang, Brüning & H.

Archives of Toxicology

ISSN 0340-5761
Volume 90
Number 7
Arch Toxicol (2016) 90:1659–1660
DOI 10.1007/s00204-016-1715-x

ELSEVIER

Reproducibility of diisomer reanalysis of raw data study on diisomer

Min Chen^a, Rebecca Ahyia, Jessica Kemmerling^b, C.

Archives of Toxicology

ISSN 0340-5761
Volume 90
Number 7
Arch Toxicol (2016) 90:1659–1660
DOI 10.1007/s00204-016-1715-x

ELSEVIER

Single ingestion of di-(2-ethylhexyl)terephthalate (DEHP) in blood of volunteers: DPHP in blood

D. Klein^{a,b}, W. Kessler^c, C. Pütz^d, A.K.E. Gallien^e, S. Wurzenberger^f

Archives of Toxicology

ISSN 0340-5761
Volume 90
Number 7
Arch Toxicol (2016) 90:1659–1660
DOI 10.1007/s00204-016-1715-x

ELSEVIER

Metabolism and urinary excretion of di-(2-ethylhexyl)terephthalate (DEHP)

Frederik Lessmann*, André Schüttrötter*, Thomas Brüning

Received: 11 February 2016 / Accepted: 10 September 2016 / Available online: 26 April 2016

Abstract Di-(2-ethylhexyl)terephthalate (DEHP) is used as a substitute for di-(2-ethylhexyl)phthalate (DEHP) in ortho-phthalate-based plasticizers labeled due to its toxicity to reproductive metabolism and urinary excretion. We quantified specific metabolites of DEHP: mono-(2-ethylhexyl)terephthalate (MEHTP), bis-(2-ethylhexyl)terephthalate (BMEHTP), and mono-(2-ethylhexyl)terephthalate (MEHTP). Six MEHTP and two BMEHTP samples were consecutively collected over 48 h. The predominant, specific metabolite was MEHTP (mean: 26.3 μg/L, range: 0.2–0.4 μg/L). In total, 1.5 μg of MEHTP was recovered in urine as the metabolite within 48 h after the intake of DEHP.

Electronic supplementary material The online version of this article (doi:10.1007/s00204-016-1715-x) contains supplementary material, which is available to authorized users.

© Springer-Verlag Berlin Heidelberg 2016

ELSEVIER

Toxicity of Hexamol® DINCH

Raymond M. David*, Randy D. White, D. Klein^{a,b}, W. Kessler^c, R. Pütz^d, A.K.E. Gallien^e, S. Wurzenberger^f

Letter to the Editor

The publication "Cyclohexane-1,4-dicarboxylic acid diisomers (Hexamol® DINCH)" promotes the authors have over-interpreted their in vivo data.

ABSTRACT

In vivo, the authors report MINCH, a branched Hexamol® DINCH, promotes in vivo effects more than 10-fold compared to the linear Hexamol® DINCH. The authors have over-interpreted their in vivo data.

1. MINCH

According to Section 22, MINCH is a di-(2-cyclohexyl)terephthalate alcohol. The monoester (MINCH) results of the genotoxicity studies were consistent in a specific rat and the C30-alcohol (NCS, 2012). Structural properties of ligand for receptor-ligand interactions. Substituted by the authors is insufficient as a MS or di-trans-isomer ratio are substances may have been tested. The major metabolite in blood, but in contrast glucuronidated in human blood.

2. PPAR-α agonist

The authors suggest MINCH could be based on the following information: C inhibited the effect of MINCH while C (PPAR-α agonist) did not prevent differentiation. However, their conclusion "potent contrast with the results of animal studies" is not supported. The authors' conclusion "potent effect of MINCH in rat liver. The specific proliferating activity (yields-increased) of MINCH was not significantly different from the control" is not supported. Information about how PPAR-α in rat differs from PPAR-α in liver is missing. It is not clear from the authors' text how they understand the claims made by the authors.

Archives of Toxicology

ISSN 0340-5761
Volume 90
Number 7
Arch Toxicol (2016) 90:1659–1660
DOI 10.1007/s00204-016-1715-x

ELSEVIER

Metabolism and urinary excretion of di-(2-ethylhexyl)terephthalate (DEHP) in three male volunteers

Frederik Lessmann, Tobias Weis, Otter, Thomas, M. Koch

Archives of Toxicology

ISSN 0340-5761
Volume 90
Number 7
Arch Toxicol (2016) 90:1659–1660
DOI 10.1007/s00204-016-1715-x

ELSEVIER

Additional breakdown of DINCH in urine of human volunteers

André Schüttrötter, Modick, Ang, Brüning & H.

Archives of Toxicology

ISSN 0340-5761
Volume 90
Number 7
Arch Toxicol (2016) 90:1659–1660
DOI 10.1007/s00204-016-1715-x

ELSEVIER

Reproducibility of diisomer reanalysis of raw data study on diisomer

Min Chen^a, Rebecca Ahyia, Jessica Kemmerling^b, C.

Archives of Toxicology

ISSN 0340-5761
Volume 90
Number 7
Arch Toxicol (2016) 90:1659–1660
DOI 10.1007/s00204-016-1715-x

ELSEVIER

Single ingestion of di-(2-ethylhexyl)terephthalate (DEHP) in blood of volunteers: DPHP in blood

D. Klein^{a,b}, W. Kessler^c, C. Pütz^d, A.K.E. Gallien^e, S. Wurzenberger^f

Archives of Toxicology

ISSN 0340-5761
Volume 90
Number 7
Arch Toxicol (2016) 90:1659–1660
DOI 10.1007/s00204-016-1715-x

ELSEVIER

Hexamol® DINCH: Lack of in vivo evidence for obesogenic properties*

Angelika Langsch^a, Raymond M. David^{b,1}, Steffen Schneider^c, Saskia Sperber^d, Volker Haake^e, Henrike Kamp^f, Edgar Leibold^g, Bennard van Ravenzwaay^h, Rainer Otterⁱ

Archives of Toxicology

ISSN 0340-5761
Volume 90
Number 7
Arch Toxicol (2016) 90:1659–1660
DOI 10.1007/s00204-016-1715-x

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?



We create chemistry