FREQUENTLY ASKED QUESTIONS

1. For which medical applications is Hexamoll® DINCH used?

Medical device manufacturers using Hexamoll® DINCH are located worldwide covering a broad range of applications, for example:

- Intravenous applications, e.g. infusion, transfusion, cardiopulmonary bypass and dialysis sets
- Artificial nutrition
- Respiratory treatment
- Catheters, Gloves, Medical training dolls …. and more.

2. What is the difference between Hexamoll® DINCH and phthalates?

Hexamoll® DINCH is not a phthalate but a cyclohexanoate. As a non-aromatic plasticizer with a three-dimensional ring structure it belongs to a different structural class. The maximum residual concentration of phthalates in the current product specification is 0.01% and BASF conducts constant lab analytics and pre-loading inspections to deliver high quality products to our customers.

3. How is Hexamoll® DINCH's performance in medical device manufacturing?

Hexamoll® DINCH shows excellent high frequency weldability and low melt viscosity in extrusion processes (e.g. calendering, tube extrusion). Since plastisol viscosities of Hexamoll® DINCH and DEHP are similar, substitution of DEHP is feasible on existing equipment. It is compatible with the commonly used sterilization methods:

- Autoclave
- Ethylene oxide
- Radiation

4. What makes Hexamoll® DINCH preferable to other plasticizers?

The excellent toxicological profile is backed by a full regulatory database and acute and repeat dose i.v. studies. These confirm suitability for sensitive medical applications, including those used for treatment of the identified high-risk patient groups. The stabilizing properties of Hexamoll® DINCH enable substitution of DEHP for blood bags without compromising on technical specifications or storage requirements.

5. Do Hexamoll® DINCH-based medical devices comply with regulations globally?

CE-marked devices have been available on the market for years. The toxicological profile and extensive risk assessments have led to worldwide approvals. Medical devices made with Hexamoll® DINCH can fulfill the requirements of the following regulations:

- DIN EN ISO 10993
- Medical Device Regulation (EU) 2017/745 (formerly Directive 93/42/EEC)
- European Pharmacopoeia
- US FDA Masterfiles No. 16323 and 1484
- US Pharmacopoeia (Monograph 88, Class VI)
- Several approvals by the relevant Asian competent authorities, e.g. Chinese Food and Drug Administration (CFDA), Japanese Ministry of Health, Labor and Welfare (JHPA)

6. Where is Hexamoll® DINCH manufactured?

Hexamoll® DINCH is produced in Ludwigshafen, Germany, in two separately operating plants with a total capacity of 200,000 metric tons per year. It is available globally and the technical centers in Europe, Asia and North America are ready to support in any technical question.

BASF SE
Regional Business Unit
Industrial Petrochemicals Europe
Carl-Bosch-Str. 38
67056 Ludwigshafen, Germany
Email: hexamolldinch@basf.com

For further information:
www.hexamoll-dinch.com

Hexamoll® DINCH

The trusted non-phthalate plasticizer for sensitive applications

PVC IN HEALTHCARE

PVC is the preferred polymer for disposable medical applications, especially attributed to a long history of safe use, affordability, flexibility and chemical stability. Recycling schemes for PVC-based medical devices generate savings in the waste management of hospitals. PVC is used in various applications such as transfusion and infusion, artificial nutrition, dialysis, respiratory therapy and many more. It is the material of choice not only for devices but also for floorings, ceilings and surface coverings and therefore contributes substantially to the architecture of healthcare facilities and to the wellbeing of patients.

DEHP: FROM EXEMPTION TO FINAL SUNSET

DEHP has been the dominating plasticizer for the medical industry. However, its excellent plasticizing and processing properties are offset by toxicological concerns. DEHP has been classified for its reproductive toxicity (Cat. 1B) per CLP-Regulation[1]. As substance of very high concern (SVHC), DEHP has been subject to authorization, except for its use in medical devices[2]. However, once the final decision is taken to list DEHP in REACH Annex XIV regarding probable effects to the environment, DEHP-based medical devices would require authorization under the Scope of REACH[3]. In addition to this, the new Medical Device Regulation (EU) 2017/745 (published 5th of May 2017) includes a 0.1% concentration limit for substances that are carcinogenic, mutagenic and toxic to reproduction (CMRs Cat. 1A and 1B) - thus also applies for DEHP. A justification of use would require argumentation why any possible substitutes cannot be used and need to be in line with the guidelines (on phthalates) that are provided by the mandated scientific committee.

THE SUBSTITUTE: HEXAMOLL® DINCH

The European Pharmacopoeia (Ph. Eur.) introduced four alternative plasticizers that can be added to PVC for the manufacturing of medical devices. Hexamoll® DINCH is listed in the European Pharmacopoeia as Additive 24 for uses like e.g. blood bags and medical tubing.[4] Out of the four newly added plasticizers, only for DEHTP (bis-(2-ethylhexyl) terephthalate and Hexamoll® DINCH (cyclohexane 1,2-dicarboxylic acid, diisononyl ester) a Regulatory Management Option Analysis (RMOA) was performed. The RMOA for Hexamoll® DINCH was undertaken by France and published on the ECHA website. The conclusion is “No need to initiate further regulatory risk management action at this time” (published by ECHA in Jan 2016)[5]. BASF has invested more than € 7 million in toxicological testing for Hexamoll® DINCH, exceeding REACH requirements: A complete regulatory database is available including acute and repeat dose studies on the intravenous route that indicate no substance-related systemic toxicity[6]. The results of the toxicological studies have been evaluated by competent authorities worldwide, confirming that Hexamoll® DINCH is safe for its intended use, including highly sensitive applications[7]. The Danish[8] and Swedish[9] competent authority confirm Hexamoll® DINCH“(…) as one of the most promising alternatives to DEHP for medical devices”.

HEXAMOLL® DINCH: SUITABLE FOR INTENSIVE CARE

In general, manufacturers are responsible for the safety of their products and compliance with regulations. CE-marked Hexamoll® DINCH-based medical devices have been on the market for several years. Unlike for DEHP, there are no labelling or justification requirements. The new medical device regulation requires justification and several competent authorities have already identified high-risk groups to DEHP exposure[10]. DEHP may reach critical levels for highly exposed patients, such as premature babies (neonates) receiving a multitude of treatments in neonatal intensive care units (NICUs). Due to their low bodyweight, DEHP exposure in neonates may exceed levels known to cause adverse health effects in relevant animal studies[11]. Against this background, the use of DEHP-containing devices is problematic. In contrast, no risks were identified for Hexamoll® DINCH. Different manufacturers offer Hexamoll® DINCH-based medical devices in a wide range of applications, including those used for treatment of the identified high-risk patient groups. For example, neonates in NICUs commonly depend on artificial nutrition. Due to the favorable migration rate and excellent toxicological profile, the use of Hexamoll® DINCH reduces exposure and eliminates hazard. Unlike BTHC and TOTM[12], Hexamoll® DINCH is approved for use in food contact materials by the European Food Safety Authority (EFSA)[13]. Moreover, Hexamoll® DINCH can be used for life-saving disposable devices such as dialysis, extra-corporeal membrane oxygenation and transfusions.

HEXAMOLL® DINCH FOR BLOOD TRANSFUSION MEDICINE

Hexamoll® DINCH is an effective and toxicologically advanced substitute for DEHP in blood contact applications, as it was shown to be capable of stabilizing red blood cells, storing platelets and fresh frozen plasma.

A whole blood collection system made with Hexamoll® DINCH can fulfill all relevant technical specifications (storage at 2-6°C for 42 days) with comparable hemolysis rates to DEHP[14]: Excellent results were shown when replacing SAG-M with next-generation additive solutions, e.g. PAGGS-M, PAGGG-M and AS-3. This effect allows storage of red blood cells for up to 42 days – by that meeting the respective EU regulations, i.e. hemolysis does not exceed 0.8% of total hemoglobin content by the end of storage. A strong body of literature confirms those stabilization capabilities[15]. A main benefit lies in the reduction of the health risks for the patient. Zhong et al. (2013) and Lagerberg et al. (2015) showed that migration of Hexamoll® DINCH is significantly reduced compared to DEHP-based medical devices. Pediatric platelet bags based on Hexamoll® DINCH are in use for four years at the Dutch National Blood Bank Sanquin. This application was awarded the SolVin Award Innovation Special Prize in 2013.

REFERENCES

[1] **EU Regulation (EC) No 1272/2008 (CLP) Annex VI**
DEHP is classified for reproductive toxicity (Cat. 1B): may damage fertility and may cause harm to the unborn child (H360 FD).

[2] **Inclusion of DEHP on SVHC candidate list concerning human health in October 2008 (REACH Annex XIV)**
based on toxicity to reproduction (57c) but exemption for medical devices regarding human health per REACH Art.2, 6(c).
Medical devices have been regulated under the Medical Device Directive 93/42/EEC, now Medical Device Regulation (EU) 2017/745.

[3] **Inclusion of DEHP on SVHC candidate list concerning probable effects to mammals in the environment (REACH Art. 57f)**
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[6] **David R. et al. (2015).**
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[11] **SCENIHR (2015 Update).**
Opinion on the safety of medical devices containing DEHP-plasticized PVC or other plasticizers on neonates and other groups possibly at risk.

[12] **Reference to noted plasticizers:**
BTHC, butyryl tri-n-hexyl citrate (Ph. Eur. plastic additive 25) and TOTM, tris(2-ethylhexyl) trimellitate (Ph. Eur. plastic additive 26).

[13] **EFSA Regulation (EU) No 10/2011**
on substances in contact with food: Hexamoll® DINCH is listed as FCM 775: The overall migration limit applies, i.e. 60 mg/ kg food.

[14] **Lagerberg et al. (2015).**
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[15a] **Prowse et al. (2014).**
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[15b] **Zhong et al. (2013).**
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[15c] **Bicalho et al. (2016).**
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