EUROPEAN BLOOD ALLIANCE

Reclassification of DEHP: Impact on BEs

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Membership organization with expertise

Representing Non-Profit Blood Services across Europe

26 members, 2 observers

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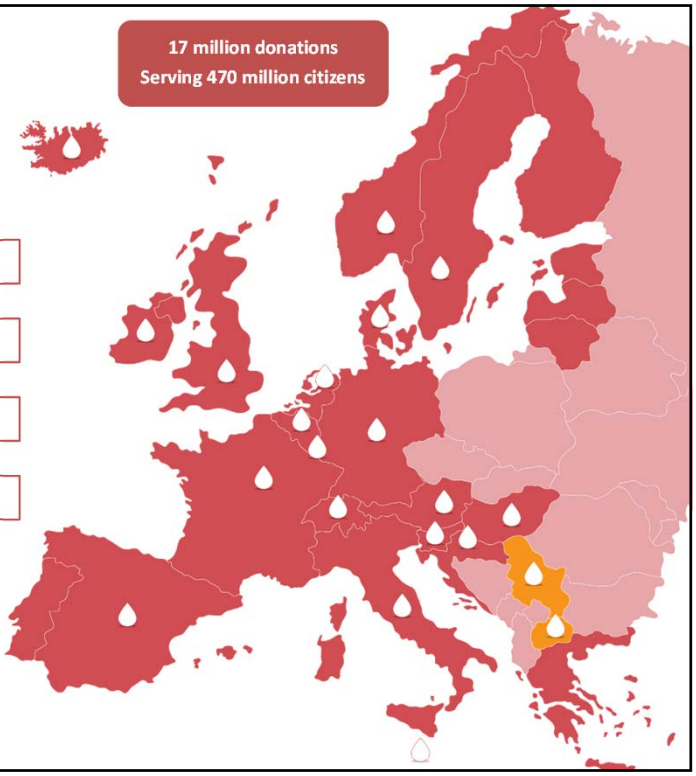
Germany, Finland, Switzerland, Spain
Ireland, Greece, Denmark, Croatia
Luxembourg, Italy, Hungary, France
Portugal, Malta, Latvia, Iceland
Sweden, Serbia, Netherlands



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Background I

- **Since introduction safety concerns regarding plasticizers, in particular Di (2 ethyl hexyl) phthalate (DEHP).**
- **?Carcinogenic, Mutagenic, Reprotoxic?**
- ***Carcinogenic*: Claim withdrawn, was based on differences between metabolism of animals used for tests and humans.**
- ***Mutagenic*: No**
- ***Reprotoxic*: Animal studies indicating endocrine disrupting properties with negative effect on male fertility. Not yet supported by evidence in human studies, but according to precautionary principle: to be avoided if possible.**
- **In Europe step by step towards a ban, but till now exemption for medical devices in Medical Device Directive.**
- **Complication:**

  EU Commission and ECHA (European Chemicals Agency) both working on reclassification of DEHP (in MDR and in REACH: Registration, Evaluation, Authorisation and restriction of Chemicals).

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Background II

- **Changes in MDR (Medical Device Regulation, replaces MDD) per May 2021 (originally May 2020, delay due to COVID-19):**

  No longer exemption for any use of DEHP, **authorisation needed,** based on risk assessment.

  Blood bags probably move from class IIb to class III (clinical studies needed; not completely clear what is required).
- **ECHA (meeting 26 June 2019):**

  Amendment Annex XIV: ban on DEHP **related to environment**, overruling possible DEHP exemption in MDR for medical reasons.

  Authorization needed to prolong DEHP use for specific applications

  Awaiting draft delegated act (for coming into force)

What did we learn from the past?

1) DEHP allows flexibility and stretching of collecting systems, combination with PVC in use since 1955 and has resulted in reliable products with known performance.
2) DEHP-containing PVC materials are used in whole blood collections and blood component collection via apheresis (but also for haematopoietic stem cell collection).
3) DEHP is lipophylic, non-covalently bound to PVC and can leach into blood bag content.
4) Beneficial effects of DEHP on stability of red blood cell membrane are both 'in vitro' and 'in vivo', compared to alternatives (10% better recovery/survival).
5) Toxic effects not from DEHP itself, but degradation product MEHP. MEHP not accumulating in body, rapid excretion

What did we learn from the past?

6) Current DEHP devices present very low levels of critical defects (e.g. leakage) and are stable (e.g. temperature, G-force, humidity).
7) Alternatives under development have yet to prove non-inferiority with respect to both device (critical defects) and blood product quality characteristics (hemolysis) and long-term safety data.

Ref: DEHP-plasticised PVC: relevance to blood services. J. Sampson & D. de Korte. Transfusion medicine, 2011, 21, 73-83.

Is DEHP a concern for transfusion activities ?

SCENIHR Report 2008 + 2018; specifically about DEHP in medical devices

Tolerable Daily Intake (TDI) 48 µg/kg/day
100x lower than *No Observed Adverse Effects Level* (NOAEL) in rats

Daily exposure (mainly food/water/air)
Adults 2-5 µg/kg/day
Children 4-8 µg/kg/day
For comparison, DEHP from *one* transfusion: 40 – 160 µg/kg

Decrease in exposure over period 1986 – 2006 (due to ban on use in other applications)

Is DEHP a concern for transfusion activities ?

SCENIHR Report 2008+2018; specifically about DEHP in medical devices

Concern about fertility when exposed during gestation

Peak load, sometimes long lasting, especially caused by medical interventions

Risk groups:

Neonates exchange transfusions and/or intensive treatment
Patients on hemodialysis (young boys and pregnant women)
Patients receiving massive and/or frequent transfusions
Frequent plasma or platelet apheresis donors

Conclusion: risk of ban is higher than continuation of exemption, but if possible: avoid use

Is DEHP a concern for transfusion activities ?

1. **EBA is concerned by potential hazard and endocrine disrupting properties of DEHP contained in medical devices for transfusion (whole blood and apheresis).**
2. **EBA members will strive to use any available alternative to prevent exposure of recipients and donors to DEHP and to avoid environmental exposure.**
3. **The main efforts in the development of alternative DEHP-free blood bag systems falls on the manufacturers.**
4. **EBA is working together with BTA (Terumo, Macopharma, Fresenius & Haemonetics) on plans to evaluate new products in such a way to be in line with EU and different national requirements, in order to avoid replication by every BE.**

What is needed to change to DEHP-free blood bags?

1) **The whole transfusion chain (highly regulated) must be validated;**
   - **manufacturers e.g. material properties, sterilisation and toxicity,**
   - **blood establishments, e.g. collecting, processing and storage,**
   - **clinical application, e.g. in vivo recovery and effectivity.**

2) **Transition time is dependent on:**
   A. **Development and validation of DEHP-free products by manufacturers.**
   B. **Validation of available DEHP-free products by blood establishments and hospitals.**
   C. **Tenders and legal requirements.**
   D. **MDR requirements for clinical evaluation (if Class III)**

3) **To safeguard the blood supply, the DEHP-free products should be 'not significantly inferior' (e.g. shelf life, critical defect rate) compared to DEHP-containing products.**

Current Status

All manufacturers are working on alternatives
- Various plasticizers under development:
  - DINCH
  - DEHT
  - TOTM
  - BTHC

Alternatives (much) higher TDI and mostly less leaching into blood products

How to prove low critical defect rate of 10 per million in development stage?

Apheresis equipment has to be calibrated again (different stretching of tubing)

Current Status

Degree of hemolyis critical, can we accept slightly higher average or shorter shelf-life?
- Current average for most BEs < 0.4 ± 0.2% at day 42 (maximal shelf life 35 – 42 days)
- Maximum 0.8% according to EDQM guide (90% of units)
  - not clear on which (clinical?) data this is based
  - hospitals are used to current level of hemolysis
  - prolongation of shelf-life is discussed to safeguard blood supply in Corona time

Effect of additive solution
- SAGM has relatively high hemolysis, most prominent DEHP effect
- (combination SAGM and PVC/DEHP happened by chance)

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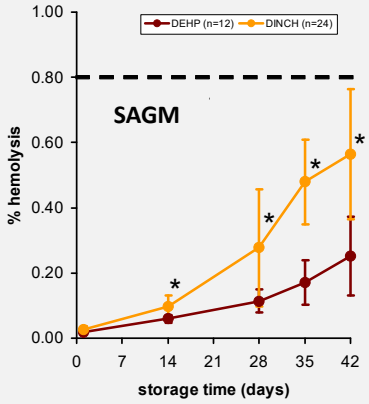
Current Status



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Other additive solutions lower hemolysis

- **Can we change to other additive solution?**

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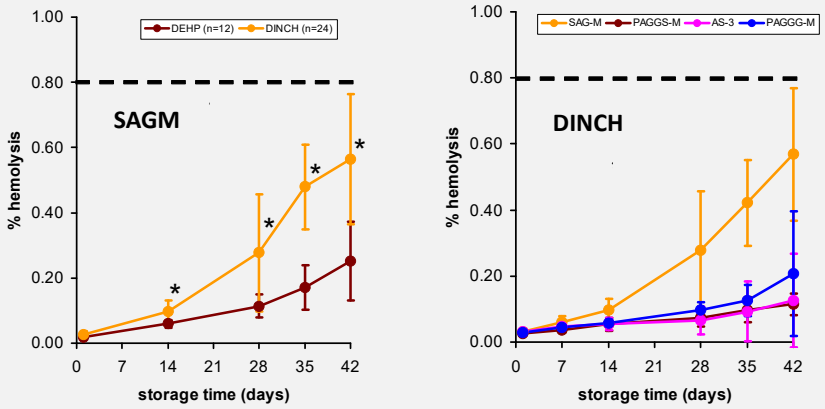

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Can we change to other additive solution?

Several publications about combination of PAGGS-M and/or AS-3 with one of the alternative plasticizers with very limited increase of hemolysis.

Most promising: DINCH and DEHT

Final Remarks

Platelet products are not stored in DEHP containers, contain only limited amount of DEHP from collection/processing

Plasma products are kept frozen, only limited amount of DEHP from collection/processing

- **Attention point when kept thawed at 4°C for 5 days (DEHP increase)**
- **No transfer of DEHP in fractionated plasma products**

Hospitals are mainly using DEHP-free transfusion sets, huge reduction of exposure

Transition requires money and time

Final Remarks

Concerns about proposed change from Class IIb to Class III for blood bags

- **Extra costs for registration (clinical studies)**
- **Hurdle for innovation, any significant change needs new clinical studies**
- **Why difference between much more complicated apheresis sets (both donor and recipient; class IIb) and blood bag systems (class III)**
- **Solutions in blood bags (anticoagulant and additive solution) are not meant to have pharmaceutical effects in recipients (not a medicinal product it self)**
- **Request to reconsider up-classification, as blood bags are already strictly regulated by EU Blood Directives**

Proposals for the transition to DEHP-free blood bags

For an orderly transition to DEHP-free blood collecting systems without threatening the blood and blood product supply we need:

1) **A concerted action between manufacturers, blood establishments, users and EC to reduce wastage of efforts and resources: Cooperation, Standardization and Recognition.**

2) **Non-inferiority criteria, risk-benefit (SCHEER) for validation and acceptance for DEHP-free products must be made and agreed upon to prevent a threat to the blood supply.**

3) **Time is needed for the blood establishments to perform validation of available DEHP-free products: 1-3 years dependent on the requirements for clinical evaluation.**

4) **The main efforts in the development of alternative DEHP-free blood bag systems falls on the manufacturers. EBA calls upon all concerned manufacturers to move diligently on this issue.**

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