Sanquin

Non-DEHP studie

Achtergrond & Status

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For Life.

Disclosure

Disclosure belangen spreker Onderwijsbijeenkomst Transfusiegeneeskunde ZO van 17 november 2022	
Naam: Christie Vermeulen	
Geen (potentiële) belangenverstrengeling	
• Voor bijeenkomst mogelijk relevante relaties[1] • Sponsoring of onderzoeksgeld[2] • Honorarium of andere (financiële) vergoeding[3] • Aandeelhouder[4] • Andere relatie, namelijk …[5]	Bedrijfsnamen

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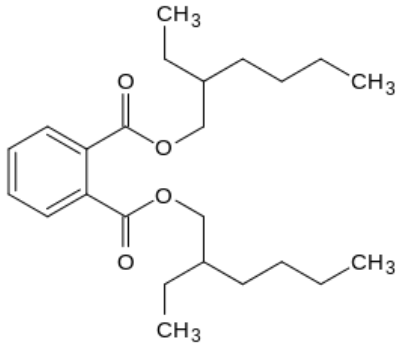
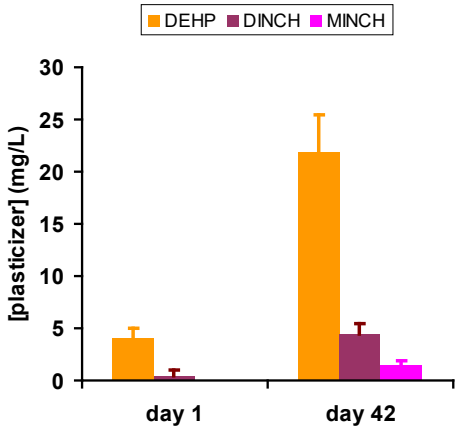
DEHP weekmaker

di(2-ethylhexyl) ftalaat



- Bloedzaksystemen zijn gemaakt van PVC
- Een weekmaker wordt toegevoegd om het PVC flexibel te maken
- DEHP-PVC is:
    - Makkelijk te steriliseren en bewerken
    - Chemisch stabiel
    - Veerkrachtig
    - Goedkoop
    - Etc.



- DEHP “lekt” vanuit het PVC het bloedproduct in
- Blijkt membraan van rode bloedcellen te stabiliseren en onderdrukt daarmee hemolyse
- Geen indicatie dat kwaliteit van plasma en trombocyten component wordt beïnvloed door weekmaker

DEHP weekmaker

Toxiciteit

- DEHP toxisch in verschillende diermodellen - reprotoxisch (onderzoek in ratten)
- Schadelijk voor milieu

- Geen bewijst voor toxiciteit in de mens

Regelgeving (Europa)

- MDR (Medical Device Regulation): ban op het gebruik van DEHP in MD boven 0.1% (w/w) per mei 2021 wegens toxiciteit in diermodellen
- REACH (Registration Evaluation Authorisation and Restriction of Chemicals): endocrine disruptor to the environment
- Productie van DEHP-PVC bloedzaksystemen tot mei 2024; sunset date mei 2025
- Sanquin wil voorkomen dat een inferieur rode bloedcel product wordt geïntroduceerd
- Uitgebreid in vitro en in vivo onderzoek
- Welk DEHP alternatief en van welke fabrikant?

Alternatieve non-DEHP weekmakers

Table 1: DEHP alternatives				
Plasticizer short name	**Full name**	**Leaching potential**	**Toxicity**	**Comments**
ATBC	Acetyl Tri-N-Butyl Citrate	Higher leaching observed compared to DEHP in medical devices.	Rapidly metabolised. No obvious toxic effects noted in animal models, no human studies available.	Used in cosmetics and as a plasticiser for PVC. Used in food applications. Has been used in medical devices, including blood bags and tubing.
BTHC	N-Butyryl-Tri-N-Hexyl Citrate	Slightly lower leaching rates than DEHP (limited data)	Rapidly metabolised. Low toxicity in animal models, no human studies available.	Uses similar to ATBC, in use in commercially available platelet storage bags.
COMGHA	Castor-oil-mono-, glycerides, hydrogenated, acetates	Slightly lower leaching rates than DEHP	Not completely metabolised, possibly due to limited absorption in GI tract. Low toxicity in animal models, no human studies available.	Similar use as DEHP. Approved in EU for food packaging. Listed in the European List of Notified Substances (ELINCS) as no. 451-530-8
DEHA	Di (2-ethylhexyl) Adipate	Slightly higher leaching rates than DEHP (limited data)	Reproductive toxicity noted	Has been put on the Community rolling action plan by REACH based on concerns of toxicity
DINCH	1, 2-Cylcohexanedicarboxylic acid, Diisononylester	Lower than DEHP	Low toxicity in animal models, limited human studies available. Adverse effects of DINCH metabolites on Human reproductive health. GreenScreen classification is Moderate due to endocrine activity	Shows good potential. Similar use as DEHP. Approved in EU for food packaging. Currently in use in commercially available RCC and platelet storage bags. CE certified medical devices for paediatric use
DINP	Di-Iso-Nonyl Phthalate	No data	Similar to DEHP toxicity in animal models, no human studies available.	Not used in medical devices. Listed in Regulation (EU) No 1907/2006 Annex XVII, 52 and 10/2011. Restrictions on use in toys.
DEHT	Di (2-ethylhexyl) Terephtalate	Lower than DEHP	Possibly lower than DEHP in animal models. Only 2 skin irritation and sensitisation studies in humans with no evidence found. GreenScreen classification is Low	Shows good potential. Similar use as DEHP. Used in toys and other consumer products. No information on use in medical devices, other than some explorative studies
TOTM / TEHTM	Trioctyltrimellitate	Unclear leaching rates compared to DEHP (limited data)	Poorly absorbed and metabolised. Low toxicity in animal models. Some skin sensitisation in human skin studies.	Used as plasticiser in electrical wires but also on commercially available platelet and plasma blood bags. Not approved in Europe for food contact.

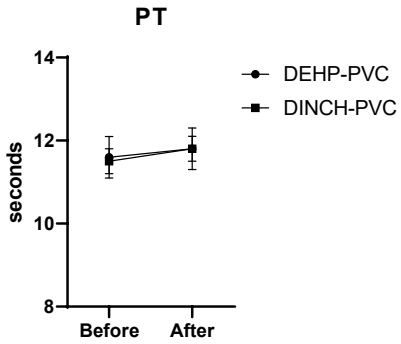
DINCH/BTHC-PVC hybride systeem

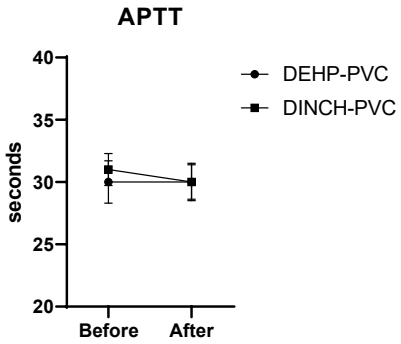
diisononyl-1,2-cyclohexaan-dicarbonzuur/butyryl-trihexylcitraat

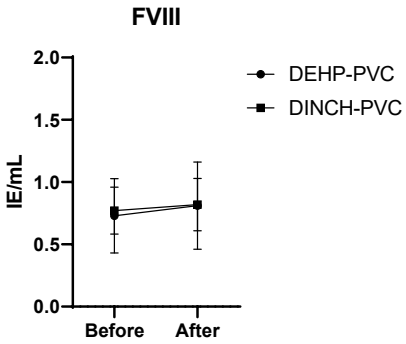
- DINCH/BTHC-PVC hybride systeem van Fresenius Kabi
- Alle onderdelen van DINCH-PVC, behalve RCC bewaarzak is BTHC-PVC
- In vitro kwaliteit van de plasma, plaatjes en rode bloedcel componenten is onderzocht
- Hemovigilantie surveillance is uitgevoerd om “differentiële transfusie reactie frequentie” te bepalen, met hartelijke dank aan de medewerkers van het Isala ziekenhuis en Radboud UMC

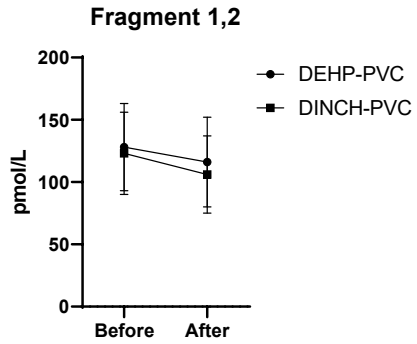
DINCH/BTHC-PVC hybride systeem

Plasma afgenomen en bewaard in DINCH-PVC









DINCH/BTHC-PVC

Trombocyten component

Outcome variable	WB collected in DEHP-PVC	WB collected in DINCH-PVC
Day 1		
Plt x 10^9/L	990 ± 72	919 ± 118
MPV (fL)	8.4 ± 0.2	8.5 ± 0.5
pH (at 37°C)	7.13 ± 0.02	7.13 ± 0.03
Glucose (mmol/L)	6.8 ± 0.1	8.1 ± 0.3*
Lactate (mmol/L)	4.5 ± 0.4	3.4 ± 0.6*
Morphology score	302 ± 11	280 ± 19
% Discoid cells	60 ± 5	58 ± 4
Swirling	3 ± 0	3 ± 0
% CD62P pos cells	7.4 ± 2.5	2.3 ± 1.0*
% Ann V pos cells	5.4 ± 1.3	3.6 ± 0.7
Day 8		
Plt x 10^9/L	887 ± 64	831 ± 104
MPV (fL)	9.0 ± 0.2	9.2 ± 0.4
pH (at 37°C)	7.18 ± 0.03	7.24 ± 0.02
Glucose (mmol/L)	3.8 ± 0.4	5.0 ± 0.2*
Lactate (mmol/L)	9.6 ± 0.3	9.4 ± 0.4
Morphology score	240 ± 9	236 ± 23
% Discoid cells	42 ± 3	46 ± 5
Swirling	3 ± 0	3 ± 0
% CD62P pos cells	13 ± 1.5	12 ± 2.8
% Ann V pos cells	16 ± 0.9	15 ± 2.5

DINCH/BTHC-PVC hybride systeem

RCC component

Whole blood collection bag	DEHP-PVC	DINCH-PVC	DINCH-PVC	DINCH-PVC
RBC storage bag	**DEHP-PVC**	**BTHC-PVC**	**BTHC-PVC**	**DINCH-PVC**
Storage solution	**SAGM (*n* = 30)**	**SAGM (*n* = 20)**	**PAGGSM (*n* = 88)**	**PAGGSM (*n* = 37)**
Day 1				
Hb (g/L)	193 ± 10	198 ± 6.5	194 ± 5.9	192 ± 7.5
Hct (L/L)	0.61 ± 0.03	0.64 ± 0.01[a]	0.63 ± 0.02[a]	0.61 ± 0.01[b]
MCV (fL)	95 ± 6.0	101 ± 3.3[a]	99 ± 4.0	96 ± 3.3[b]
ATP (µmol/g Hb)	5.7 ± 0.6	5.9 ± 0.5	5.1 ± 0.5	5.3 ± 0.5
Day 42				
Hct (L/L)	0.65 ± 0.02	0.65 ± 0.01	0.64 ± 0.02	0.62 ± 0.02
MCV (fL)	103 ± 5.4	106 ± 3.5[a]	101 ± 4.2[a]	98 ± 2.6[ab]
Hemolysis (%)	0.36 ± 0.17	0.66 ± 0.18	0.38 ± 0.12	0.48 ± 0.17[b]
ATP (µmol/g Hb)	3.3 ± 0.5	3.5 ± 0.5	3.9 ± 0.5[a]	4.0 ± 0.5[a]
DEHP (mg/L)	27.6 ± 7.9	<0.1	<0.1	<0.1
BTHC (mg/L)	Not determined	11.0 ± 2.6	9.6 ± 1.8	Not determined
DINCH (mg/L)	Not determined	Not determined	2.9 ± 1.2	7.5 ± 2.9

Data shown as mean ± SD. ap<0.05 as compared to SAGM/DEHP-PVC (Student's unpaired t-test). bp<0.05 as compared to PAGGSM/BTHC (Student's unpaired t-test).

Non-DEHP hemovigilantie surveillance

- Primaire uitkomst: frequentie transfusiereacties na transfusie van RCC afgenomen in DINCH-PVC en bewaard in PAGGSM/BTHC-PVC
- Dit is vergeleken met het huidige SAGM/DEHP-PVC RCC product afgenomen in DEHP-PVC
- Secundaire uitkomst: gebruiker ervaring (lekkage, geur, spiking issues etc.)

Non-DEHP hemovigilantie surveillance

Primaire uitkomst

Product	Number of products issued	Number of patients received RCC transfusion	Number of transfusion reactions	Transfusion reaction rate per 100 transfusions (95% CI)
Total number of RCC	7312	2285	30	0.41 [0.0026–0.0056]
RCC in PAGGSM/BTHC-PVC	1650	652	4	0.24 [0.0000–0.0048]
RCC in SAGM/DEHP-PVC	5662	1633	25	0.44 [0.0027–0.0061]
Combination group[a]			1	
Isala Hospital				
Total number of RCC	3971	1264	20	0.50 [0.0028–0.0072]
RCC in PAGGSM/BTHC-PVC	798	327	2	0.25 [-0.0010 to 0.0060]
RCC in SAGM/DEHP-PVC	3173	937	17	0.54 [0.0029–0.0079]
Combination group[a]			1	
Radboud University Medical Center				
Total number of RCC	3341	1021	10	0.30 [0.2845–0.3155]
RCC in PAGGSM/BTHC-PVC	852	325	2	0.23 [0.2017–0.2583]
RCC in SAGM/DEHP-PVC	2489	696	8	0.32 [0.0010–0.0054]

aTwo patients developed a transfusion reaction after receiving both types of RCC within 24 h. For one patient the reaction developed after administration of the first product (RCC in PAGGSM/BTHC), therefore included in the RCC/BTHC-PVC group. The second one was a delayed haemolytic transfusion reaction which could not be linked to one product type, therefore included in the combination group.

Non-DEHP hemovigilantie surveillance

Primaire uitkomst

Product	Category	Seriousness	Imputability[b]			
			Certainly not	Probably not	Possibly	Probably
RCC in PAGGSM/BTHC-PVC	Non-haemolytic transfusion reaction	Grade 1		1	2	
	Other	Grade 2		1		
RCC in SAGM/DEHP-PVC	Non-haemolytic transfusion reaction	Grade 1		1		
		Grade 2		1	8	4
	Other	Grade 1			2	3
		Grade 2	1	1		1
	Post transfusion bacteraemia/sepsis	Grade 1		1	1	
	Transfusion associated dyspnoea	Grade 1			1	
Combination group[a]	Haemolytic transfusion reaction	Grade 2				1

[a]Patient received both types of RCC. [b]None of the transfusion reactions had an imputability of certainly.

Non-DEHP hemovigilantie surveillance

Secundaire uitkomst

- Geen verhoogde lekkage
- Geen klachten over de geur
- Geen spiking problemen vanuit de kliniek
- Gemiddeld langere filtratietijd, maar geen impact op bewerking

Conclusie & vervolg

- In vitro kwaliteit non-DEHP plasma, bloedplaatjes en rode bloedcel componenten gelijkwaardig met huidige producten

- Vooralsnog geen indicatie verhoogde frequentie transfusiereacties

- Vervolg hemovigilantie surveillance (in samenwerking met TRIP en ziekenhuizen):
    - Vervolgen van de klinische evaluatie waarbij het aantal transfusies wordt uitgebreid om het betrouwbaarheidsinterval van de melding van transfusiereacties te verkleinen
    - Primaire uitkomst: frequentie transfusiereacties na transfusie van RCC afgenomen in DINCH-PVC en bewaard in PAGGSM/BTHC-PVC
    - Secundaire uitkomst: gebruiker ervaring (lekkage, geur, spiking issues etc.)

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For Life.