

presentation (WG9) . 25th Meeting of ISO/TC
194 (2014. 4, Mishima, Japan).

H. 知的財産権の出願・登録状況

特になし

参考文献

- 1)FDA : Safety Assessment of Di (2-ethylhexyl) phthalate (DEHP), Released from PVC Medical Devices. 2002.
- 2)ISO 3826-1 (2013): Plastics collapsible containers for human blood and blood components.
- 3) JIS T 3217 (2011):血液成分分離バッグ
- 4)ASTM F 756-08 (2008): Standard Practice for Assessment of Hemolytic Properties of Materials.
- 5)日比谷信 他：体外循環用血液回路からの可塑剤溶出の基礎的検討— DEHP と TOTM の溶出の比較—。体外循環技術。 Vol. 33, No. 12, p16-19, 2006.
- 6)Miyamoto M et al. :Effects of autoclave sterilization on the physical properties of storage bags and granulocyte function. Vox Sang. Vol. 54, p74-7, 1988.
- 7)橋本周郎 他：ポリ塩化ビニル樹脂用可塑剤 TOTM の安全性 (DEHP との比較)。第 25 回日本バイオマテリアル学会大会予稿集, p375, 2003.
- 8)伊藤好文 他：新規ポリ塩化ビニル樹脂用可塑剤 TOTM の簡易生殖発生毒性評価。第 25 回日本バイオマテリアル学会大会予稿集, p376, 2003.

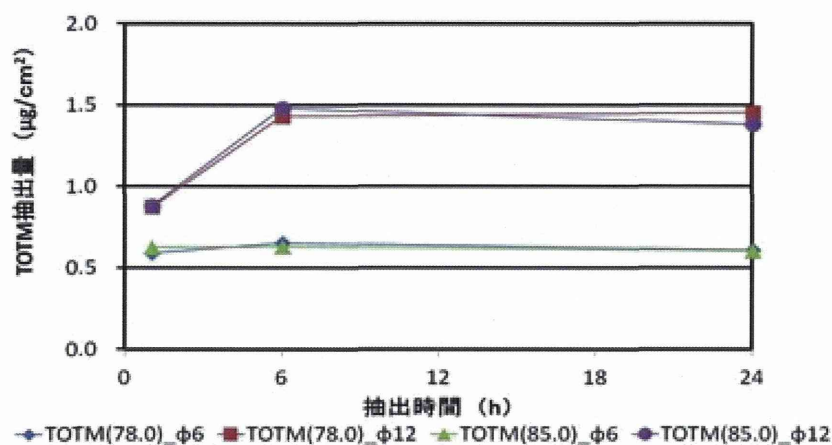


図1. 体外循環用TOTM-PVC製チューブからのTOTM溶出量
(内表面積あたり)

表1. TOTM溶出量測定サンプル—体外循環用血液回路チューブ

No.	材質、組成、製造日、滅菌条件等
1	塩化ビニル樹脂 (TOTM 78 パーツ)、φ6 mm、EOG 滅菌品
2	塩化ビニル樹脂 (TOTM 78 パーツ)、φ12 mm、EOG 滅菌品
3	塩化ビニル樹脂 (TOTM 85 パーツ)、φ6 mm、EOG 滅菌品
4	塩化ビニル樹脂 (TOTM 85 パーツ)、φ12 mm、EOG 滅菌品

表2. MS分析条件

プローブ	APCI
ネブライズガス流量	2.5 L/min
APCI インターフェイス温度	400 °C
CDI 温度	250 °C
ヒートブロック温度	200 °C
検出器電圧	1.5 kV
CDL 電圧	5.0 V

表3. 血液適合性評価サンプル(体外循環用血液回路チューブ)

No.	材質、組成、製造日、滅菌条件等
1	塩化ビニル樹脂 (TOTM 68.5 パーツ)、φ3 mm、γ 滅菌品
2	塩化ビニル樹脂 (TOTM 68.5 パーツ)、φ3 mm、EOG 滅菌品
3	塩化ビニル樹脂 (TOTM 68.5 パーツ)、φ3 mm、電子放射線滅菌品
4	塩化ビニル樹脂 (TOTM 85.0 パーツ)、φ3 mm、EOG 滅菌品

表4. TOTM-PVC 製チューブの溶血毒性試験結果

PVC tube (parts)	Sterilization	ASTM Hemolytic Index (%)	
		Extraction Method	Direct contact method
TOTM (68.5)	Gamma-ray	0.8	2.4
	EOG	0.0	0.0
	Electron Beam	0.4	0.9
TOTM (85.0)	EOG	0.0	0.2

II. 学会等発表実績

成果報告一覧

学 会 等 発 表 実 績

委託業務題目「医薬品・医療機器の実用化促進のための評価技術手法の戦略的開発」

機関名 国立医薬品食品衛生研究所 医療機器部

1. 学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
新規血液バッグ用代替可塑剤DOTHのラット亜慢性毒性試験・ポスター発表	齧島由二 福井千恵 山崎佳世 野村祐介 小園 知 熊田秀文 藤澤彩乃 井上 薫 森川朋美 市村亮平 前田 潤 高橋美和 河上強志 伊佐間和郎 柚場俊康 鄭 雄一 小川久美子 新見伸吾 吉田 緑	第36回 日本バイオマテリアル学会大会 (船堀)	2014. 11	国内
新規血液バッグ素材DOTH/DINCH配合PVCシートの性能評価・ポスター発表	齧島由二 河上強志 福井千恵 田上昭人 柚場俊康 向井智和 野村祐介 伊佐間和郎 新見伸吾	第36回 日本バイオマテリアル学会大会 (船堀)	2014. 11	国内
簡易溶血性試験法の性能評価と公定法との比較検証・ポスター発表	野村祐介 福井千恵 柚場俊康 新藤智子 坂口圭介 谷川隆洋 杉山知子 竹ノ内美香 新見伸吾 齧島由二	第36回 日本バイオマテリアル学会大会 (船堀)	2014. 11	国内
PVC製血液バッグに適用可能な新規可塑剤NJC-NPの毒性評価・ポスター発表	齧島由二 福井千恵 野村祐介 藤澤彩乃 山崎佳世 熊田秀文 井上 薫 森川朋美 高橋美和 河上強志 伊佐間和郎 柚場俊康 宮崎謙一 鄭 雄一 小川久美子 新見伸吾 吉田 緑	日本薬学会第135年会 (神戸)	2015. 3	国内

2. 学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所 （学会誌・雑誌等名）	発表した時期	国内・外の別
Characterization of alternative plasticizers in polyvinyl chloride sheets for blood containers	Haishima Y, Kawakami T, Fukui C, Tanoue A, Yuba T, Ozono S, Kumada H, Inoue K, Morikawa T, Takahashi M, Fujisawa A, Yamasaki K, Nomura Y, Isama K, Chung U, Ogawa K, Niimi S, Yoshida M.	J. Vinyl Add. Technol. (in press)	2015	国外

Ⅲ. 研究成果の刊行物・別刷

本研究の成果として、以下の論文が平成 27 年 2 月 16 日付けで *J. Vinyl Add. Technol.* に採択されたが、平成 27 年 3 月現在、発刊に向けた準備中であり、別冊が届いていない。なお、採択通知を次ページに添付した。

Haishima Y, Kawakami T, Fukui C, Tanoue A, Yuba T, Ozono S, Kumada H, Inoue K, Morikawa T, Takahashi M, Fujisawa A, Yamasaki K, Nomura Y, Isama K, Chung U, Ogawa K, Niimi S, Yoshida M.: Characterization of alternative plasticizers in polyvinyl chloride sheets for blood containers. *J. Vinyl Add. Technol.*, 2015, in press.

16-Feb-2015

Dear Dr. Haishima:

It is a pleasure to accept your manuscript titled "Characterization of alternative plasticizers in polyvinyl chloride sheets for blood containers", in its current form, for publication in the Journal of Vinyl and Additive Technology. The comments of the referee(s) who reviewed your manuscript are included at the bottom of this letter.

Your article cannot be published until the publisher has received the appropriate signed license agreement. Within the next few days the corresponding author will receive an email from Wiley's Author Services system which will ask them to log in and will present them with the appropriate license for completion.

Thank you for your fine contribution.

Sincerely,

Dr. James Summers
Editor-in-Chief
Journal of Vinyl and Additive Technology
jws1966@ameritech.net

Referee(s)' Comments to Author:

Reviewing: 1

Comments to the Author

The authors are to be commented for undertaking this important work. I think the paper will be an important contribution to the literature when published; however, I would like to make the strong recommendation to publish the information on the extent to which the plasticizers are released from the polymer and the ability of these plasticizers to inhibit hemolysis separately from the results of the oral toxicity study of DOTH. This would be a much better paper if the authors restricted the scope of the manuscript to address plasticizer release and hemolysis inhibition. The oral toxicity of DOTH is a separate topic that should be the subject of a separate manuscript.

Any statement in the manuscript to support the claim that DOTH is safe to use as a alternative to DEHP as a plasticizer in blood bags should point out that the results of this oral toxicity study may not be directly relevant to the adverse effects produced by DOTH after IV administration (i.e., following infusion of blood products) and that the potency of DOTH may differ depending on the route of administration.

Ideally, it would have been useful to examine other endpoints of RBC function in addition to hemolysis rate. Although hemolysis is an important endpoint, it would be helpful to also examine levels of oxidative stress, ATP, deformability, etc., in RBCs over time following incubation of dilute blood with the polymers containing various levels of the plasticizers. Although this information would have been very useful for the paper, the lack of this information on these endpoints should not serve as a barrier to the publication of the manuscript.

The authors should note that higher release of a new plasticizer compared to one that is commonly used is not necessarily an adverse event if the toxicity of the new plasticizer is less than the existing one. Perhaps this can be explained in the manuscript.

The hemolysis study was conducted using blood from one human donor. The sample size of 1 limits the broad interpretation and applicability of the results. RBCs from other donors may be more or less susceptible to hemolysis following incubation than RBCs from this single donor. This limitation should not prevent the publication of the manuscript, but perhaps some language can be added to underscore the preliminary nature of this work because the hemolysis data represents results from only one individual.

Reviewing: 2

Comments to the Author

For the Reader it could be helpful to add an Explanation why the authors changed from DOTP (Dioctyltetrahydrophthalate) as used in Posters to the Name DOTH(Di-octyl-4-cyclohexene-1,2-dicarboxylate; also a short remark like "formerly DOTP was used) could help.

Suggest to consider adding "women in childbearing Age" to the list of Groups where precautions have to be taken.

This is a very nice paper which describes first results with T-die Sheets. I would like to congratulate the authors to These results and would like to motivate them to continue as they proposed in the conclusions, i.e. to Show feasibility with real blood bags.

Please note the Header line of table 2 should be corrected. It should read "DINCH" and not "DINCHI"

Just for precautionary reasons, I would suggest to add a Statement that based on the results of the Pilot blood bag studies, toxicological testing of DOTH on the most likely route of exposure, i.e. the intravenous route is envisaged.

Comments:

The comments from the first reviewers have been successfully addressed by the authors. The second set of reviewers have offered a few new suggestions, but I see these more as differing opinions about how data should be interpreted and presented and not a requirement for publication. There was one type-o noted, of the use of DINCHI in Table 2 instead of DINCH. It is a very nice paper and I look forward to reading about future testing of blood containers prepared with your plasticizer blend recommendation.

