

The situation in Transfusion Medicine

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Transfusion Medicine.

- ◆ Transfusion of blood is one of the most important life-saving medical treatments in modern medical service.
- ◆ Due to this significant role, blood transfusion is regulated in detail, in Europe based on Commission directives of the European Union.
- ◆ Blood is always split into blood components before being used for transfusion.
- ◆ Systems of sterile blood containers are used for collection of whole blood and preparation of blood components. Some of those blood bags contain sterile additive solutions.
- ◆ Technical requirements for blood containers are comprehensive, i.e.
 - ◆ The plastic material in the blood container systems must not affect the blood components stored in such containers.
 - ◆ The plastic material must allow sterilization (generally steam sterilization), be stable and transparent.
 - ◆ Blood containers must allow handling at temperatures between 40°C down to -70°C and must allow centrifugation at up to 5000xg.
 - ◆ Plastic tubing must allow welding for sealing as well as sterile connection.

Historical perspective.

- 🔴 Blood bags were described in literature for the first time in 1952, manufactured from "polyvinyl resin". From the time of introduction of plastic blood containers in the 1950s until the early 1980s, essentially all blood bags were produced from PVC plastics plasticized with di-2-ethylhexyl-phthalate (DEHP).
- 🔴 PVC/DEHP meets all the requirements regarding stability, transparency, durability and sealing for the storage of blood components.

What quantities of plastic material are used for the production of our blood containers in Sweden?

- 🔴 In Sweden, we annually use about 500 000 blood containers/kits for blood collection and preparation of blood components.
- 🔴 This corresponds to approximately 80 000 kg of plastics, including about 50 000 kg of PVC and about 30 000 kg of phthalates (DEHP, plasticizer).
- 🔴 The situation is similar in the Western world.

The PVC/DEHP blood container:

- ◆ DEHP is classified as toxic to reproduction, Category 2; R60-61. Index Number (Annex I of Directive 67/548/EEC: 607-317-00-9).
- ◆ European Commission: Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR): PRELIMINARY REPORT ON THE SAFETY OF MEDICAL DEVICES CONTAINING DEHP, PLASTICIZED PVC OR OTHER PLASTICIZERS ON NEONATES AND OTHER GROUPS POSSIBLY AT RISK.
- ◆ There is limited evidence indicating a relation between DEHP exposures and certain effects in humans.
- ◆ “However, it is recognized that especially the potentially high exposure during medical treatments raise concern, even in the absence of clinical or epidemiological evidence for harmful effects in humans”.



MACONYTT

Ny information etikett samt bipacksedel SSP/SSP⁺

Macopharmas trombocytförvaringslösningar SSP och SSP+ förvaras i icke PVC påsar (polyolefin), men slangarna innehåller till viss del ftalater (DEHP). Även of ftalatinnehållet är mycket lågt måste vi enligt EU direktiv (Directive 2007/47/EC) ange detta. Produktetiketter och bipacksedlar kommer således märkas upp med en DEHP symbol. En förklarande text kommer även införas i bipacksedeln. Införande kommer ske på samtliga SSP och SSP⁺ produkter i mars månad 2010. Samtidigt jobbar Macopharmas utvecklingsavdelning med att försöka ta bort ftalaterna i slangarna en gång för alla.



Enligt ett annat EU direktiv (Directive 93/42/CEE) så måste även risker vid återanvändning av produkter anges i bipacksedel. När det gäller SSP/SSP+ så är riskerna kontaminering samt otillräcklig funktion. Införande kommer ske på samtliga SSP och SSP⁺ produkter i mars månad 2010.

macopharma.se

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How do we consider this issue from a Transfusion Medicine point of view?

- We are not very pleased about infusing plasticizer together with the transfusion blood components.
- Transfusion of blood is a transfer of living blood cells (or plasma) involving potentially immunological effects and effects associated with physiologically active substances. Those effects are considered to pose a significantly higher risk to the patient.
- Again transfusion of blood components may be the difference between life and death for a patient although it may also involve certain risks.

Blood components - four main components:

- 🔴 Red blood cells (erythrocytes).
- 🔴 Platelets
- 🔴 Plasma
- 🔴 Special components (e.g. for pediatric use)

Why don't we use other plastics?

- 🔥 Already mentioned physical and transfusion-medicine requirements

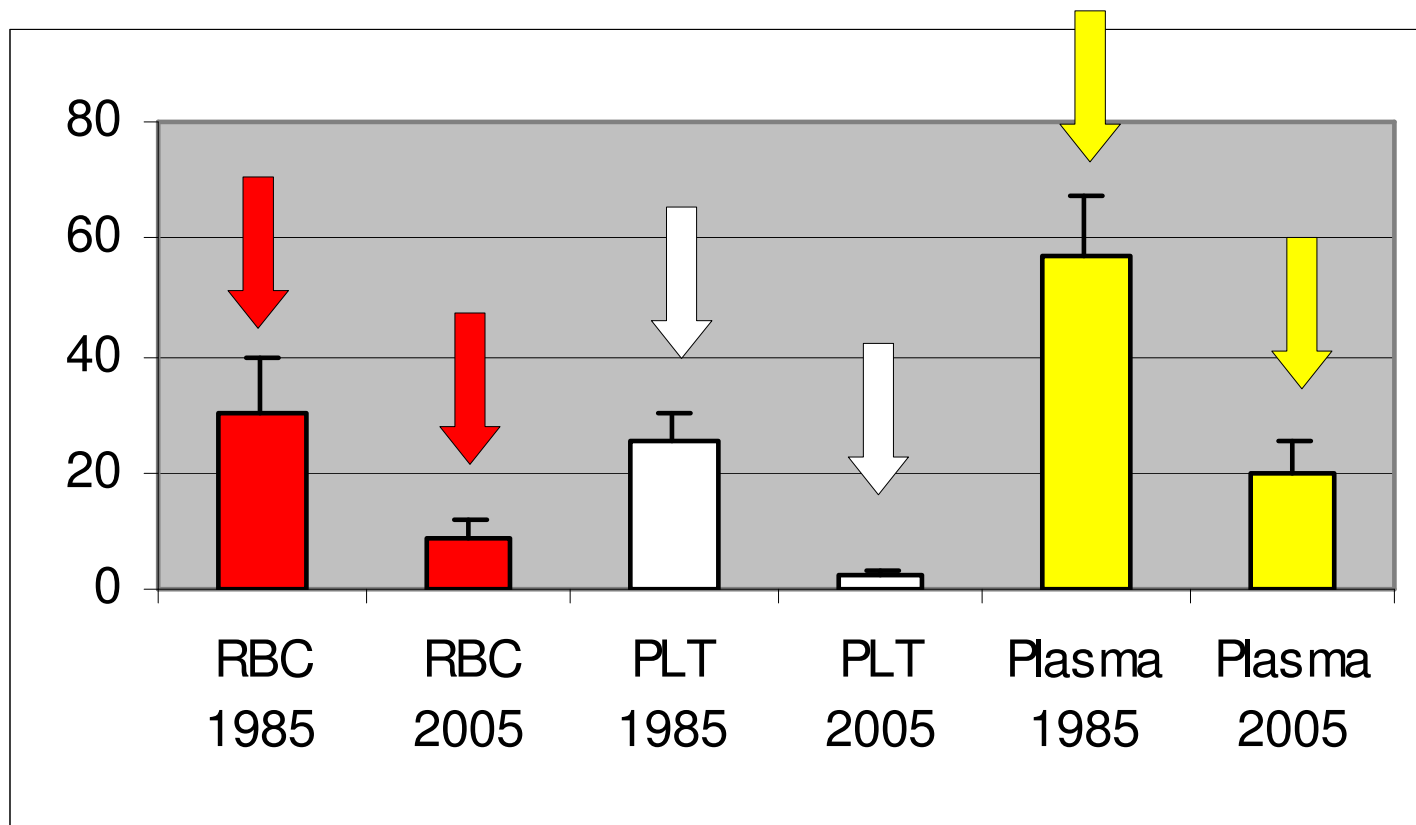
But

- 🔥 DEHP migrates into stored blood components since DEHP is lipophilic.
- 🔥 DEHP has a stabilizing effect on the erythrocyte membrane.
- 🔥 DEHP is incorporated into the interior and membrane fractions of erythrocytes and reduces osmotic fragility and hemolysis.
- 🔥 Hemolysis by the end of storage must not exceed 0,8% of total hemoglobin content according to EU directives.
- 🔥 This situation makes it difficult to replace PVC/DEHP by other plastic material.

Why does DEHP migrate from the plastic in blood containers into stored blood components?

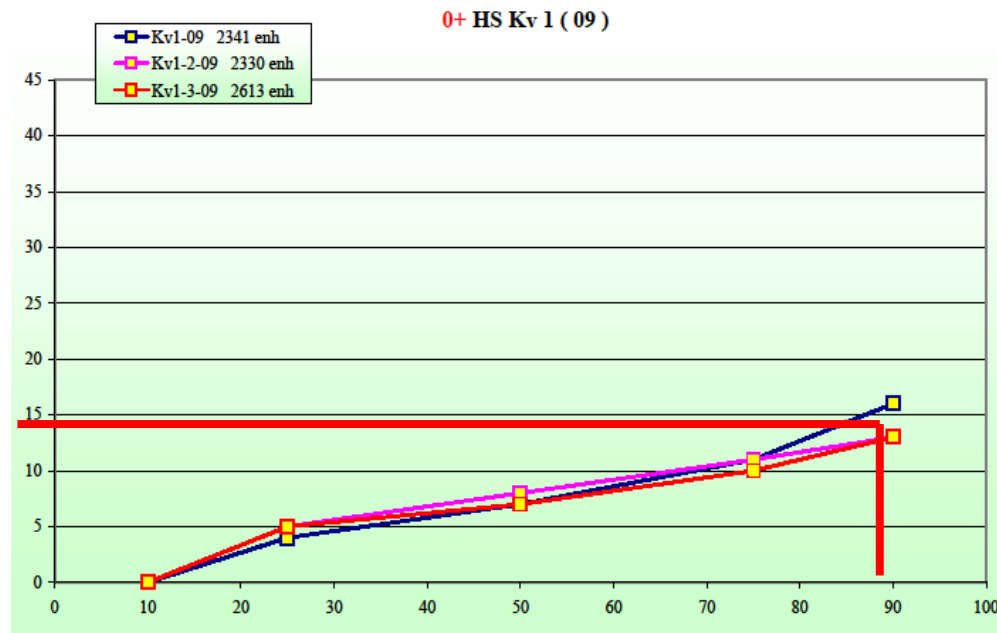
- 🔥 Lipids present in plasma are chemically related to DEHP and cause extraction of DEHP from the plastic into the blood.
- 🔥 The quantity of DEHP extracted may vary between blood from different donors.
- 🔥 The migration of DEHP is linear over time.
- 🔥 It is also temperature dependent. Migration will increase at higher temperature.
- 🔥 Most studies on DEHP migration and related consequences were performed in the 1980s, also the study from Stockholm (Gulliksson et al: Vox Sanguinis 1986; 50:16-20).

What has happened in Stockholm over the last 20 years?
Amount of DEHP in different blood components by the end of storage (mg/unit; mean \pm SD).



O Rh+, Karolinska, Huddinge

Days of storage

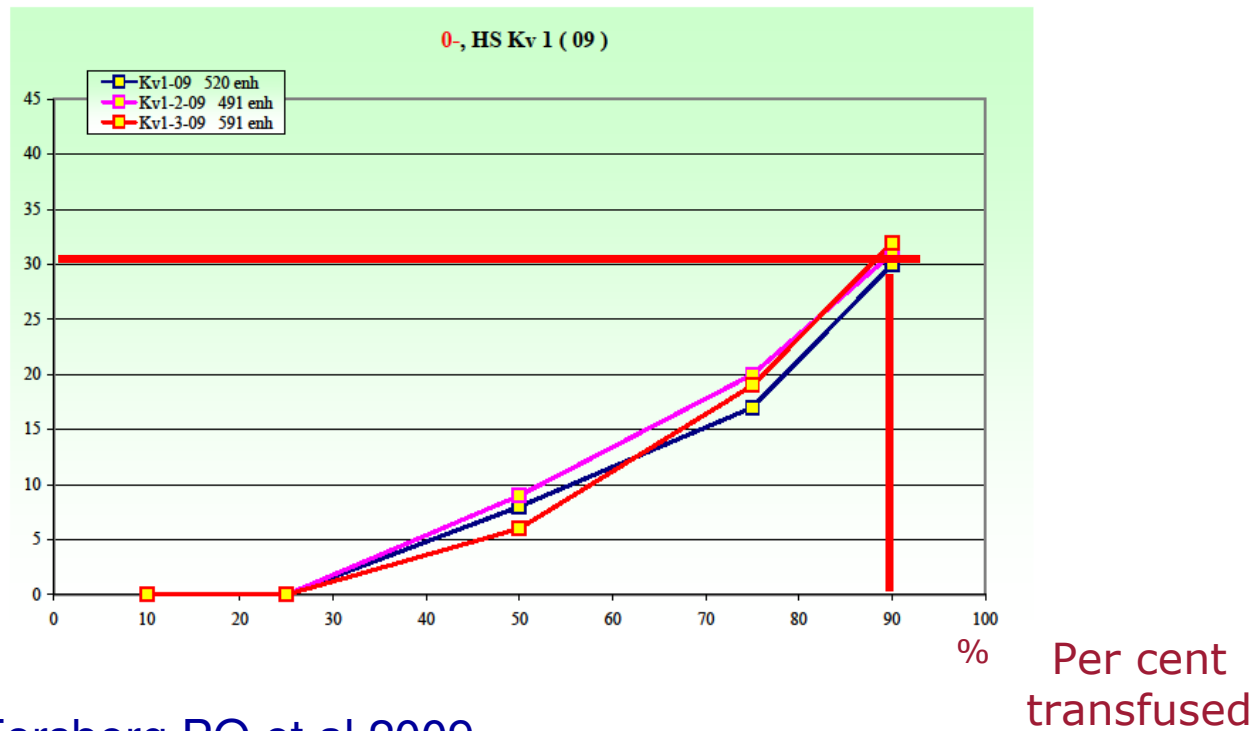


% Per cent transfused

Forsberg PO et al 2009.

O Rh-, Karolinska, Huddinge

Days of storage



Forsberg PO et al 2009.

Other plastics.

- 🔥 In the 1980s, new plastics that did not contain DEHP were introduced, mainly for the storage of platelets with increased gas permeability to facilitate the supply of oxygen through the plastic material for platelet aerobic metabolism and to allow increased diffusion of carbon dioxide produced by platelet metabolism.
- 🔥 Examples are:
 - (1) PVC plasticized with tri-(2-ethylhexyl)trimellitate (TEHTM, TOTM), Fenwal and others
 - (2) PL732, PL2410, polyolefin-based plastics lacking plasticizer, Fenwal.
 - (3) PVC med di-n-decyl phthalate (DnDP), Terumo
 - (4) PVC med n-butyryl-tri-n-hexyl citrate (BTHC), several manufacturers.
- 🔥 PVC/BTHC may be used for the storage of Red Blood Cells in the same way as PVC/DEHP.

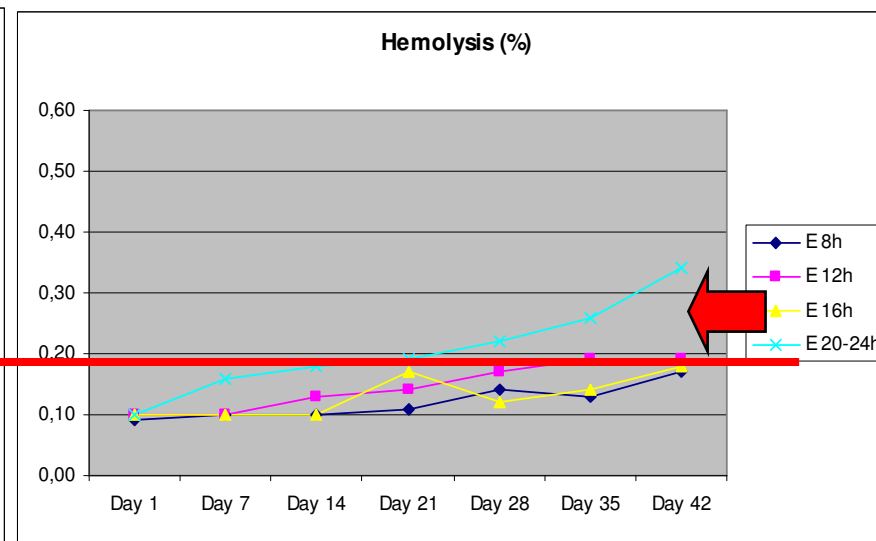
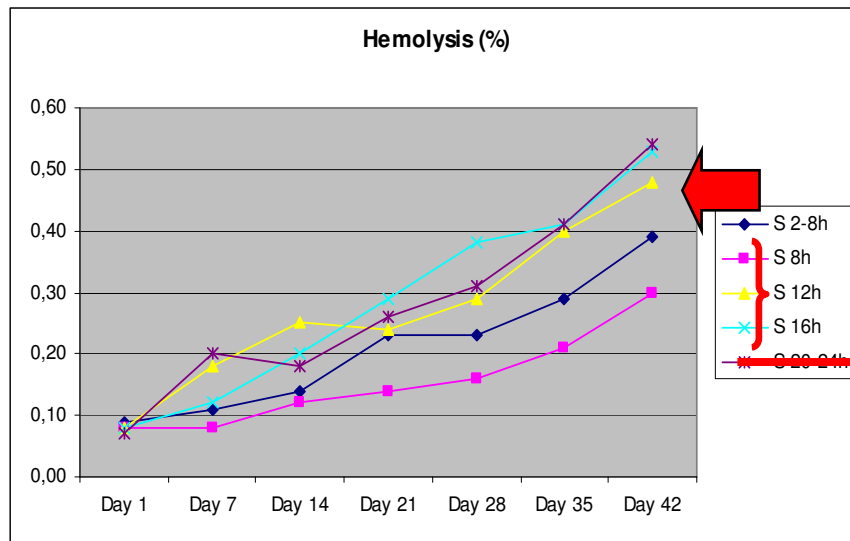
Alternatives to PVC/DEHP:

1. PVC in combination with a different plasticizer. PVC/BTHC or PVC-DINCH (1,2-Cyclohexane dicarboxylic acid diisononyl ester) may be used for the storage of Red Blood Cells in the same way as PVC/DEHP.
2. A combination of a non-PVC plastic material and one of the new Red Cell Additive Solutions with potentially lower level of hemolysis.

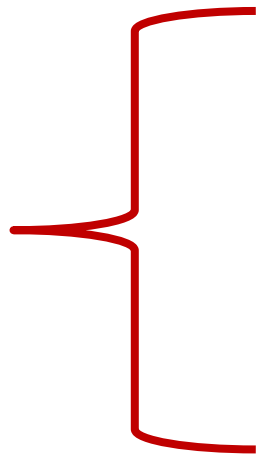
Hemolysis (%)

SAG-M

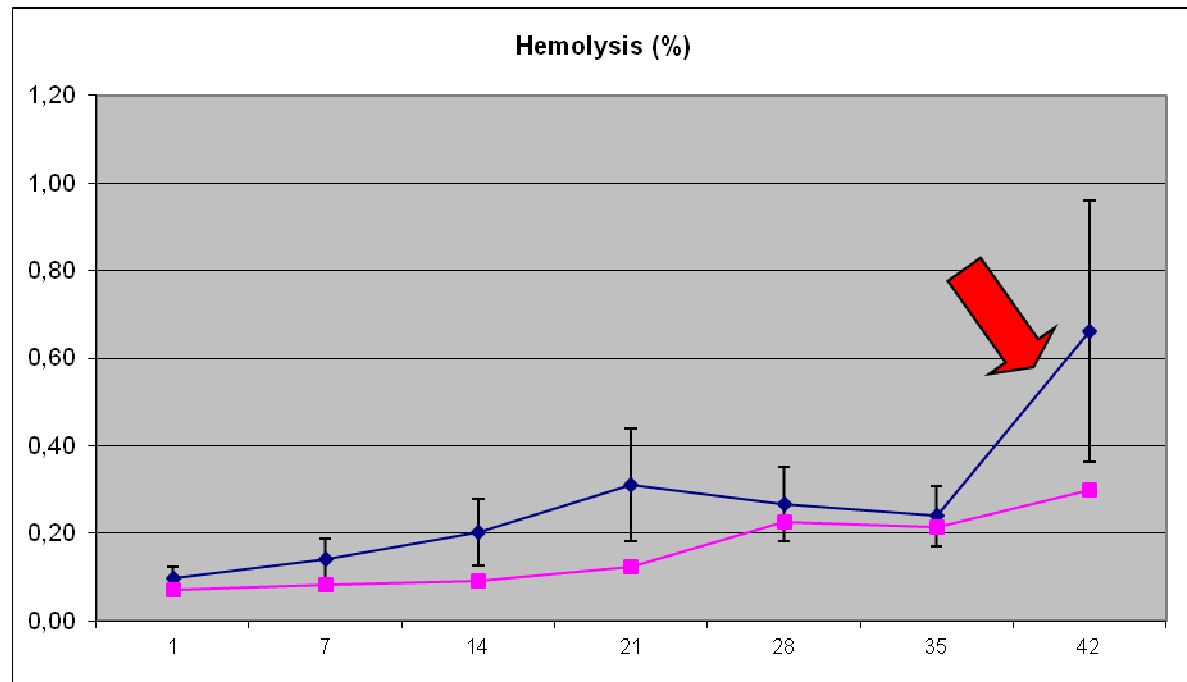
ErythroSol



New hypotonic additive solutions for the storage of Red Blood cells such as ErythroSol from Fenwal.



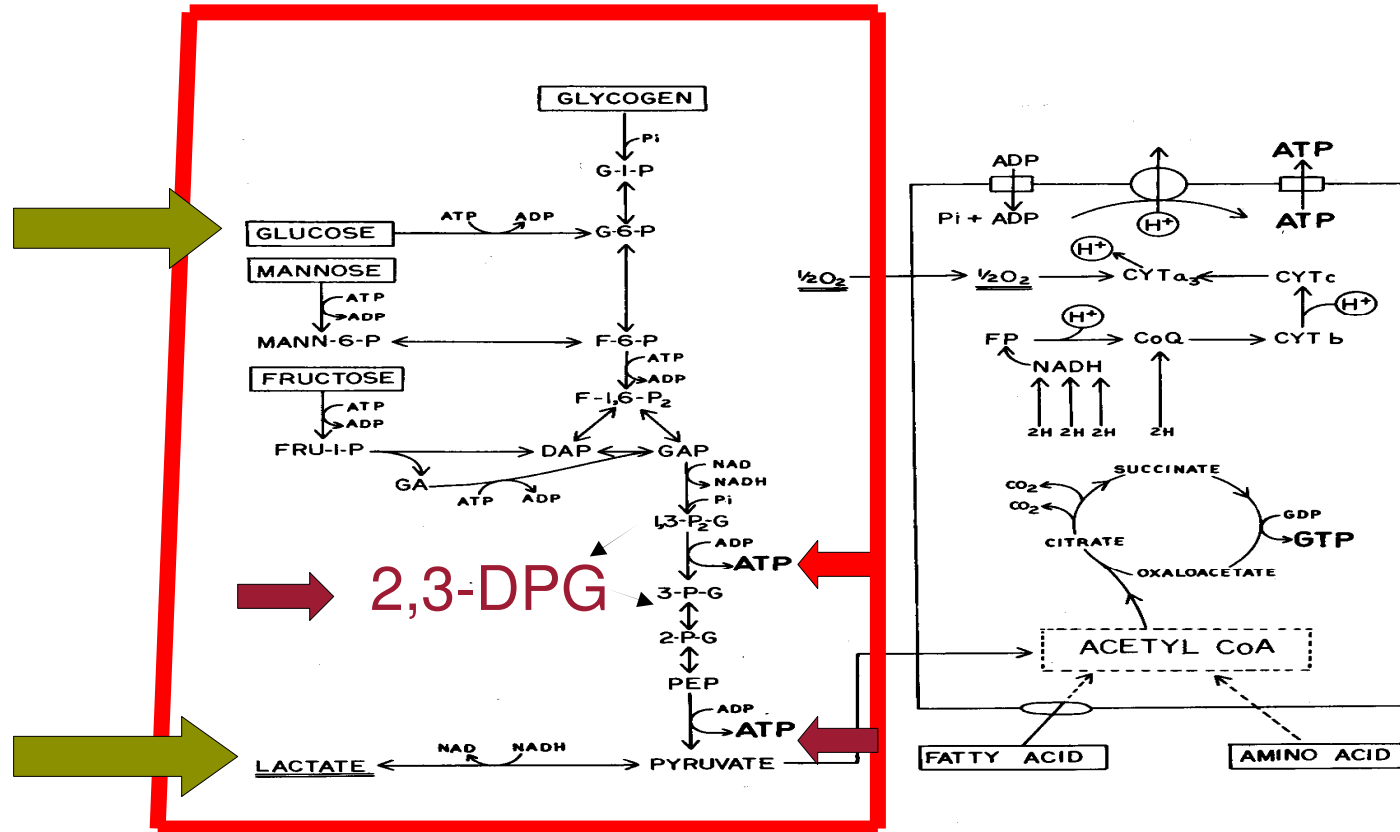
<u>Component:</u>	
Citrate	X
Adenine	X
Mannitol	X
Glucose	X
Phosphate	X



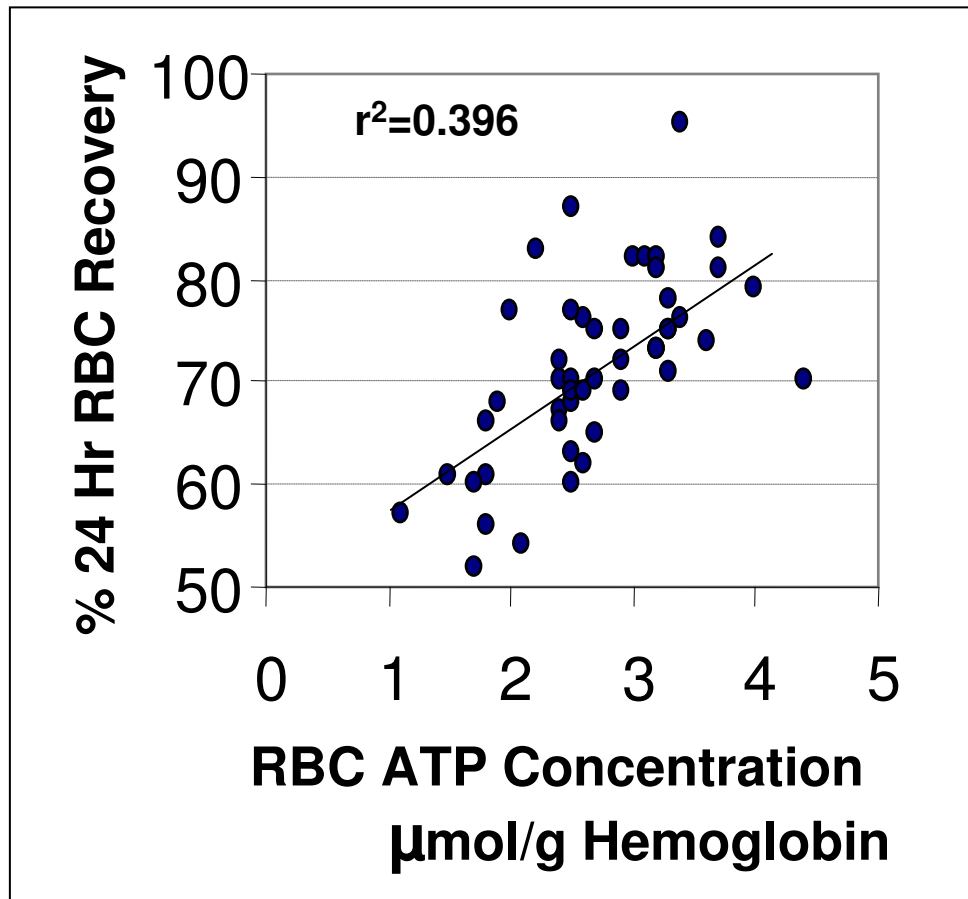
Blue line:
Non-PVC

Red line:
Standard
blood
container
(PVC/DEHP)

Red cell metabolism.



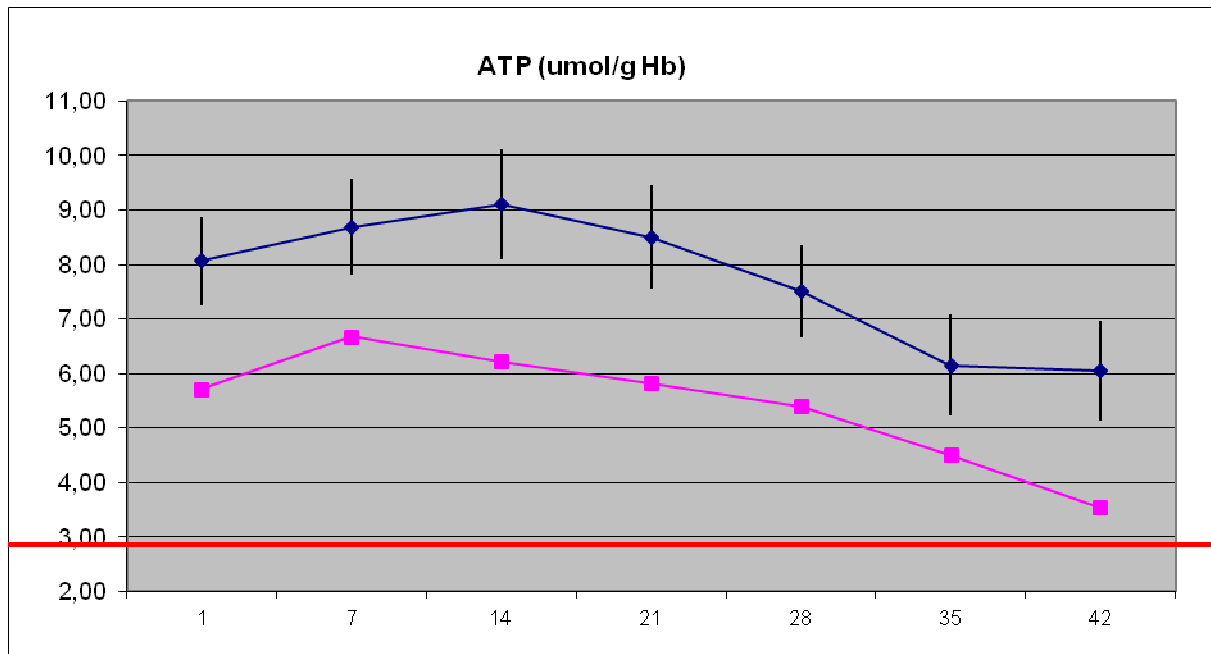
Correlation between ATP och viability of erythrocytes.



RBC ATP concentration correlates significantly with viability, but the predictive value of the correlation is not good. However, neither measure is precise. Repeat assays of ATP concentration differ by 5%. Repeat measures of RBC recovery also differ with a SD of 5%.

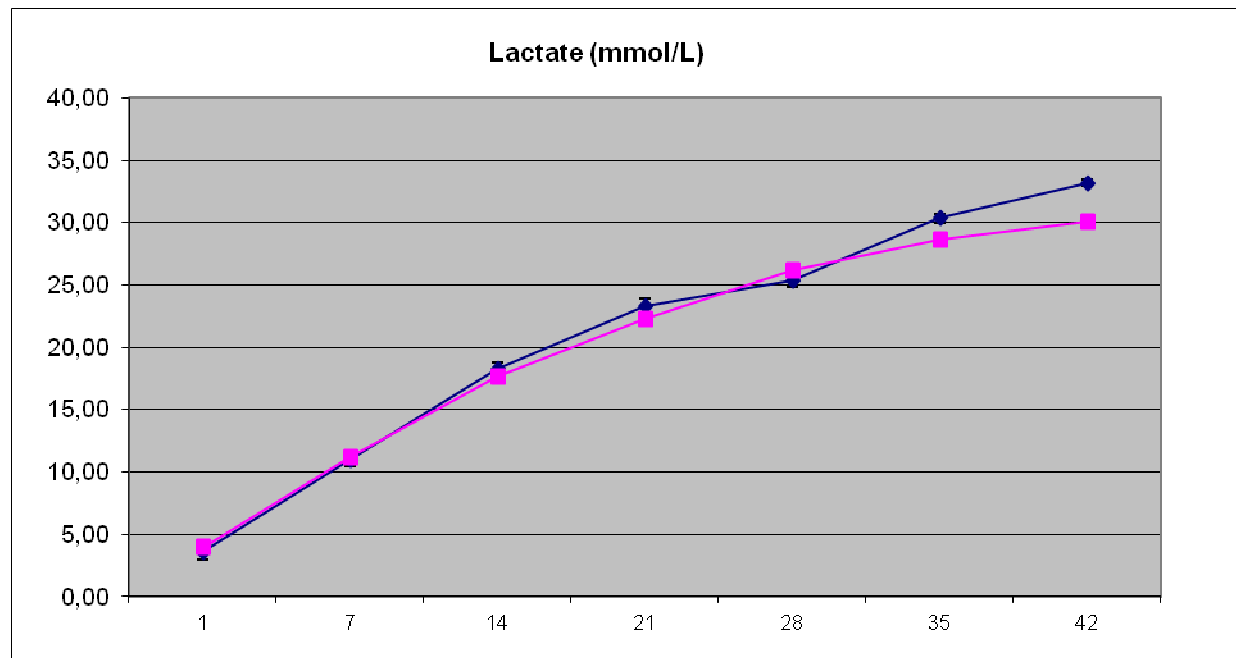
John R. Hess, MD, MPH; University of Maryland, Baltimore, USA:

“Understanding and Improving RBC Storage; BEST Working Party, May 2003 Frankfurt, Germany”.



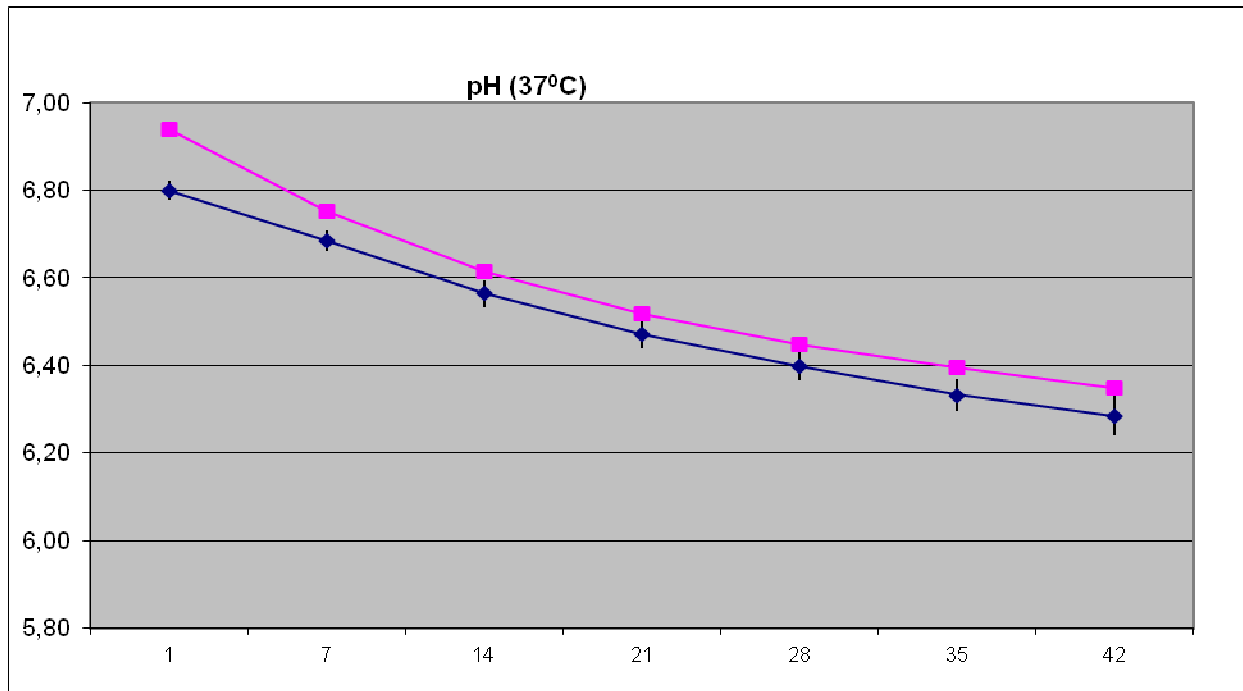
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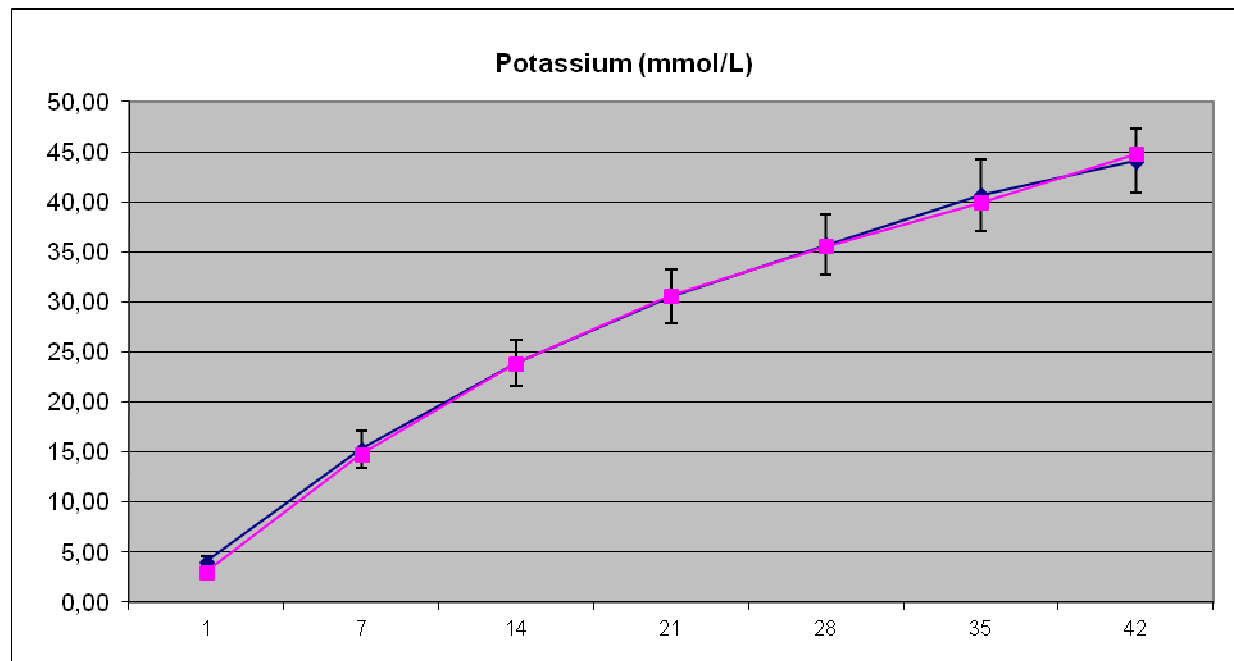
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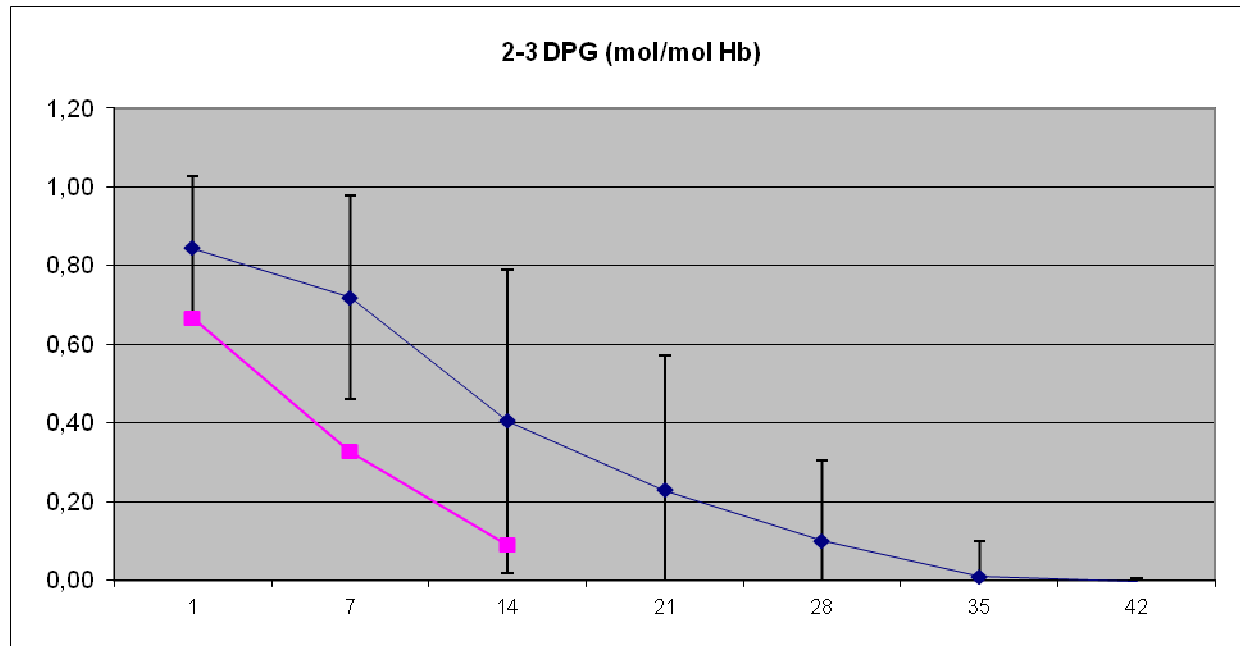
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Summary.

- ◆ From the time of introduction of plastic blood containers in the 1950s until the early 1980s, essentially all blood bags were produced from PVC plastics plasticized with di-2-ethylhexyl-phthalate (DEHP).
- ◆ PVC/DEHP meets all requirements regarding stability, transparency, durability, welding and blood cell storage, especially for storage of one of the blood components, the red cells.
- ◆ DEHP is classified as toxic to reproduction. For this reason, it should not be present in our blood containers since it is released into the blood components and in the next step, into the veins of the patients.
- ◆ From an environmental point of view, PVC is an undesirable substance that should be phased out according to the policies of Swedish County Councils.
- ◆ Efforts since decades to find plastic materials to replace PVC-DEHP.
- ◆ And now www.pvcfreebloodbag.eu.