DEHP Alternatives in NICU

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Integrated research activities ongoing at **BIOlab** are focused on the preparation, characterization, processing of polymeric materials for biomedical, pharmaceutical and environmental applications covering a spectrum of interests in Life and Materials Sciences.

**BIOlab Expertise:**
- Polymer Chemistry
- Materials Science & Technology
- Chemical and Biomedical Engineering
- Pharmaceutical Technology
- Cell and Molecular Biology
Outline of The Presentation

PVC and DEHP – Brief Introduction

1. DEHP in NICU
   Assessment of DEHP Release from Endotracheal Tubes
   as a Consequence of their Application in High Risk Newborns in NICU

2. Alternatives to DEHP in NICU
   Polymers as Alternative Plasticizers for PVC Based Medical Devices
Poly(vinyl chloride) (PVC) is one of the most common thermoplastic materials employed today, with applications ranging from packaging to healthcare devices, electrical wire insulation, clothes, furniture, packaging, interior decoration, building materials and the car industry.

PVC possesses the largest share of the medical market, constituting 40% of all dedicated polymeric materials.

Main advantages:
- Inertness
- High transparency
- Facility of Sterilization
- Strength
- Cost

Main disadvantage:
- Environmental Impact (production and disposal)
- High Glass Transition Temperature ($T_g = 80^\circ C$)

Addition of Plasticizers (decrease $T_g$, improve flexibility and processability)
PVC plasticized with (di(2-ethylhexyl) phthalate)

In general, medical procedures that requires hours/days (e.g. blood transfusion, total parenteral nutrition, enteral feeding, hemodialysis etc.) result in high DEHP exposure.

<table>
<thead>
<tr>
<th>PVC-type</th>
<th>Plasticiser content (w/w)</th>
<th>Medical applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rigid</td>
<td>&lt; 10%</td>
<td>Containers, Connectors, Syringes</td>
</tr>
<tr>
<td>SemiRigid</td>
<td>10-30%</td>
<td>Trays, Blister packaging, Hospital flooring</td>
</tr>
<tr>
<td>Flexible</td>
<td>30-50%</td>
<td>Bags for IV, Blood bags, Urology</td>
</tr>
</tbody>
</table>

DEHP is one member of a family of chemicals called phthalates used as plasticizer of Polyvinyl chloride (PVC) medical devices.

- Neonates in NICU are the most highly DEHP exposed patients because of their low weight and the regular use of many different DEHP-containing PVC products in this setting.

- DEHP levels to which high risk newborns are exposed in NICU are in excess of the No Observed Adverse Effect Level (NOAEL) in animal tests.

- In case of particular medical therapies, DEHP exposure may also exceed the FDA-derived “tolerable intake” (TI).
Studies concerning the quantification of plasticizer to which human are exposed are carried out mainly by two approaches:

- Quantification of DEHP and its metabolite (mono(2-ethylhexyl)phthalate MEHP) in blood, urine or tissues of patients treated with PVC medical devices

- Measurement of the amount of DEHP released from medical devices into different extraction media (ISO 1993-12)

- **No literature data** available to correlate the release of DEHP from medical devices as a consequence of their *in vivo* application.
Study performed in collaboration with **Dr. Giuseppe Latini** (Division of Neonatology, Perrino Hospital – Brindisi, Italy)

Infants were admitted to the Neonatal Intensive Care Unit (NICU) at the “Perrino” Hospital for respiratory distress syndrome (RDS) (N=10; males:7, females:3; intubation duration: median 56 hours; range: 18-168 hours).

A Physical-Chemical Approach to:
1. Determine occurrence of DEHP release from endotracheal tube as a consequence of their applications in high risk newborns
2. Evaluate the correlation between the intubation time and the leaching of the plasticizer.
DEHP Leaching from Endotracheal Tubes Employed in NICU: Physical-Chemical Investigations

- **Thermogravimetric Analysis (TGA)**
  - Determination of the percentage composition by weight of PVC and DEHP in endotracheal tubes before and after application in High Risk Newborns

- **Differential Scanning Calorimetry (DSC)**
  - Determination of Glass Transition Temperature ($T_g$) of PVC of endotracheal tubes before and after application in High Risk Newborns

- **High Performance Liquid Chromatography (HPLC)**
  - Assess the content of DEHP in used and virgin tubes according to the protocol reported by the International Pharmacopoeia Guidelines.
The obtained curves showed four steps of decomposition: the first and the second peak indicate DEHP evaporation and the other two steps correspond to PVC decomposition.

The peaks of DEHP in case of virgin tube is more intensive and shows a different trend to that of the used tubes.

Used tubes contained a quantity of DEHP corresponding to an average of 11%.

Virgins tubes had an average of 22% of DEHP with a statistically significant difference \((p<0.001)\) between the two means.

The release of DEHP occurs within the first 24 hours of application of the endotracheal tubes.
Differential Scanning Calorimetry (DSC)

The glass transition temperature ($T_g$) of an amorphous polymer is the critical temperature at which the material changes its behaviour from being 'glassy' (hard and brittle) to being 'rubbery' (elastic and flexible).

Tipically, the $T_g$ is characteristic for each virgin polymer and decreases by addition of a plasticizer into the polymer matrix.

A loss of DEHP from endotracheal tubes should be correlated to an increase in the $T_g$ value

The measured $T_g$ values of used PVC are higher in respect to the values obtained for the virgin ones, thus indicating a loss of plasticizer after their employment.

<table>
<thead>
<tr>
<th>Sample</th>
<th>$T_g \pm S.D.$ ($^\circ C$)</th>
<th>Diameter (mm)</th>
<th>Intubation Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$-6.5 \pm 1.1$</td>
<td>3.0</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>$-13.4 \pm 1.2$</td>
<td>3.0</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>$-13.0 \pm 1.8$</td>
<td>3.0</td>
<td>52</td>
</tr>
<tr>
<td>Control 1</td>
<td>$-18.0 \pm 1.4$</td>
<td>3.0</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>$-12.9 \pm 1.1$</td>
<td>3.5</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>$-9.5 \pm 1.6$</td>
<td>3.5</td>
<td>29</td>
</tr>
<tr>
<td>6</td>
<td>$-10.1 \pm 1.3$</td>
<td>3.5</td>
<td>29</td>
</tr>
<tr>
<td>7</td>
<td>$-9.4 \pm 1.5$</td>
<td>3.5</td>
<td>96</td>
</tr>
<tr>
<td>8</td>
<td>$-5.6 \pm 1.9$</td>
<td>3.5</td>
<td>127</td>
</tr>
<tr>
<td>9</td>
<td>$-11.2 \pm 1.2$</td>
<td>3.5</td>
<td>168</td>
</tr>
<tr>
<td>Control 2</td>
<td>$-15.5 \pm 1.2$</td>
<td>3.5</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>$-4.9 \pm 1.8$</td>
<td>4.0</td>
<td>100</td>
</tr>
<tr>
<td>Control 3</td>
<td>$-16.8 \pm 1.1$</td>
<td>4.0</td>
<td>-</td>
</tr>
</tbody>
</table>

The experimental $T_g$ values are in general $35^\circ C$ lower than theoretical values calculated by Fox equation.

DEHP does not form a miscible intimate blend with PVC but an heterogenous mixture.

Extraction of **DEHP** from tubes was performed with hexan as indicated by the protocol of the International Pharmacopoeia

<table>
<thead>
<tr>
<th>Sample</th>
<th>DEHP Concentration (ppm)</th>
<th>Diameter (mm)</th>
<th>Intubation Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1082,67</td>
<td>3,0</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>1117,51</td>
<td>3,0</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>1038,07</td>
<td>3,0</td>
<td>52</td>
</tr>
<tr>
<td>Control 1</td>
<td>1140,27</td>
<td>3,0</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>1013,74</td>
<td>3,5</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>1107,19</td>
<td>3,5</td>
<td>29</td>
</tr>
<tr>
<td>6</td>
<td>973,02</td>
<td>3,5</td>
<td>29</td>
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<tr>
<td>7</td>
<td>1033,63</td>
<td>3,5</td>
<td>96</td>
</tr>
<tr>
<td>8</td>
<td>1085,55</td>
<td>3,5</td>
<td>127</td>
</tr>
<tr>
<td>9</td>
<td>899,97</td>
<td>3,5</td>
<td>168</td>
</tr>
<tr>
<td>Control 2</td>
<td>1138,40</td>
<td>3,5</td>
<td>-</td>
</tr>
<tr>
<td>Control 3</td>
<td>1135,33</td>
<td>4,0</td>
<td>-</td>
</tr>
</tbody>
</table>

Used tubes showed a lower content of **DEHP** (average 1039,0 ppm) in respect to the amount found in virgin tubes taken as control (average 1138,0 ppm) indicating a loss of plasticizer from the used tubes.

The results of this study confirm the occurrence of DEHP release from endotracheal tubes after their application in high risk newborns and at the meantime reveal that the time of intubation is an important factor that can be harmful to the high risk newborn since the tubes start to release the DEHP immediately after their employment (within the first 24hrs).
The research for alternative plasticizers to DEHP is one of the most currently investigated approaches to overcoming the P-PVC concerns, but the main challenge is identifying plasticizers having competitive all-around performance comparable to that of DEHP.
### Alternatives to DEHP Plasticized PVC

<table>
<thead>
<tr>
<th>Approach</th>
<th>Advantages</th>
<th>Drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymeric Plasticizers alternative to DEHP</td>
<td>Reduced migratory and leaching aptitude upon contact with body fluids</td>
<td>Expensive</td>
</tr>
<tr>
<td></td>
<td>Potentially available from renewable resources</td>
<td>Overall reduced efficacy in plasticization and processing of PVC with respect to DEHP</td>
</tr>
</tbody>
</table>

**Perspectives:**

- The availability of plasticizers having a competitive all-round performance comparable to that of DEHP still represents a major challenge.

- Plasticizers of natural origins and preferably derived from renewable resources could represent valid alternatives to solve DEHP concerns.
A promising way to obtain safe plasticized PVC grades is to substitute phthalates and low molecular weight plasticizers, with analogous compatible and non-toxic polymeric plasticizers (e.g. elastomers or polyesters), thus generating a kind of “polymeric alloy”.

**Polycaprolactone based polymeric plasticizers**

**Branched PCL**

**PCL/Polycarbonate**

**PCL/PEG**

BIOFLEX-Renew project (contract QLK5-1999-01355)

Ferruti P. et al Biomacromolecules 2003
Polymeric Plasticizers
BIOFLEX: Advantages and Disadvantages

Advantages:

• The physical properties of the new PVC/PCL-PTMC blends very similar to those of commercial flexible DEHP-plasticized PVC formulations.

• Good processability and the transformation technology could be rapidly established.

• Prototypes such as endotracheal tubes, catheters and plastic bags were prepared and tested. Their colour and transparency was very close to that of the reference commercial commodities and their thermal stability was very good.

• Their mechanical performances were in all respect practically identical to those of the reference commercial products.

• The laboratory scale PVC/PCL-PTMC products purified by conventional solvent/non solvent precipitation exhibited complete lack of toxicity in vitro.

Disadvantages:

• The synthetic process was too expensive, since it included the synthesis of one oligomeric precursors, i.e. PTMC, and its co-polymerisation with commercial PCL.

• The scale up process needed to be optimised in the purification step, in order to rapidly extract even traces of phenol, the by-product of the polycondensation reaction.
Polymeric Plasticizers from Renewable and Sustainable Resources

**Poly(hydroxyalkanoate)s (PHA)s**

Over 150 different types of homopolymers and copolymers are isolated, offering a broad range of physical-chemical properties.

**Polyesters naturally produced by bacteria as storage of carbon and energy**

- Biodegradable
- Biocompatible
- Ideal substitutes of synthetic polymers of petrochemical origin
Polymeric Plasticizers from Renewable and Sustainable Resources

Optimization of PHAs Production

- Strain Development
- Improvement of fermentation process
- Cheap Substrates
- Industry Waste Materials

EC Funded Projects


2006-2008 EU/FP6 Craft COOP-CT-2006-032967 “Production of Poly(hydroxyalkanoates)s from Olive Oil Mills Waste Water” - POLYVER

2010 – 2012 EU/FP7-KBBE-2009-3-5-02 Collaborative Medium-scale focused research project on “Biotechnological Conversion of Carbon Containing Wastes for Eco-Efficient Production of High Added Value Products” - ANIMPOL
### Matching Requirements

<table>
<thead>
<tr>
<th>Flexibility</th>
<th>“Oligomeric” PHAs</th>
<th>Controlled thermal degradation of PHAs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>“Flexible” PHAs</td>
<td>PHAs with low Tg</td>
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</table>

<table>
<thead>
<tr>
<th>Chemical Compatibility</th>
<th>Hydrogen bonds between PHA and PVC chains</th>
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<table>
<thead>
<tr>
<th>Safety</th>
<th>Negligible migration and volatility</th>
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<tbody>
<tr>
<td></td>
<td>Biocompatible</td>
</tr>
<tr>
<td></td>
<td>Biodegradable</td>
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<table>
<thead>
<tr>
<th>Availability</th>
<th>Costs competitive with those of plasticizers of petrochemical origin</th>
<th>Cheap substrates obtained from Industrial waste materials</th>
</tr>
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</table>

**Promising Alternative to Conventional PVC Plasticizers**
Concluding Remarks

• The **substitution** or **modification** of commercial P-PVC formulations in medical applications is **increasingly demanded** due to the risks associated with exposure to DEHP.

• A **valid alternative** material should be **completely biocompatible** and **match** the overall performance of P-PVC in terms of **industrial processability** and **costs**.

• At present most of the strategies are devoted to **decreasing the leaching** of conventional plasticizers **rather than improving their safety profiles**.

• Research on **biocompatible plasticizers and/or materials**, possibly of natural origin, is a **safe approach** to overcome the P-PVC concerns. The exploitation of **waste and renewable resources** could be envisaged to overcome the economic drawbacks typically encountered in the production of materials from natural origin.

• A **synergistic multidisciplinary approach** is mandatory to determine the best alternative to P-PVC for the production of safe and often long-term effective medical devices.
Thank You for Your Attention