**DEHP Exposure**

**PVC and Plasticizers**
Polyvinyl chloride (PVC) plastic is used to manufacture a huge number of articles for daily life, e.g. toys, building material such as flooring, cables, as well as medical products.¹ Unplasticized PVC is hard and brittle at room temperature. As a result, plasticizers are necessary to impart flexibility to the polymer. Plasticizers are additives, most commonly phthalate ester, which work by embedding themselves between the chains of polymers, spacing them apart, and thus significantly making it softer (see Fig. 1). For plastics such as PVC, the more plasticizer added, the more flexible and durable it will be (see Fig. 4 for the average content of substances in PVC).²

**Common Plasticizers**
Besides di-(2-ethylhexyl) phthalate (DEHP), most commonly-used plasticizers today are phthalates, first and foremost, the following:
- DIDP (di-isodecyl-phthalate)
- DINP (di-isononyl-phthalate)
- DBP (di-butylphthalate)
- BBP (butylbenzylphthalate)

In addition to phthalates, there are also non-phthalates available on the market, although their current market share is only 8-10 %.
These include adipates, citrates, phosphates, trimellitates, etc. Common non-phthalates include TOTM and Hexamoll DINCH, as well as the newly developed DEHT/DOTP (DEHT = Di(2-ethylhexyl)terephthalate resp. DOTP = Dicaprylylterephthalate).

Various plasticizers have been used as plasticizers for PVC. The plasticizer of choice for PVC medical devices is DEHP (see Fig. 2).³ The content of DEHP in flexible polymer materials varies widely but is often around 30 % -35 % (w/w). Contrary to that, polyethylene and polypropylene normally do not contain any plasticizers.¹ ²

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**Fig. 1: Composition of PVC**
**Fig. 2: Calotte model of DEHP**
**Fig. 3: PVC World Consumption**
**Fig. 4: Average content of substances in PVC (Kermel report 4/97)**
Areas of use of DEHP

DEHP is not known to occur naturally.

The worldwide production of DEHP has been increasing during recent decades. PVC is the second largest commodity plastic after polyethylene with world production currently over 18 million tonnes a year (see Fig. 3 for world consumption). The chemical process for making PVC involves three steps: first, production of the monomer, vinyl chloride; then the linking of these monomer units in a polymerisation process; and finally the blending of the polymer with additives.9

The industrial use and end-use of DEHP can be divided into three main product groups:1:

1) PVC
2) non-PVC polymers
3) non-polymers

Around 97 % of DEHP is used as plasticizer in polymers, mainly PVC.

Polymers (PVC and non-PVC-polymers, see Fig. 5)

Some examples of flexible PVC end products containing DEHP are:
- Insulation of cables and wires
- Profiles, hoses
- Sheets, film, wall- and roof covering and flooring
- Coatings and leather imitations (car seats, home furniture), shoes and boots, out-door and rainwear
- Pastes for sealing and isolation and Plastisols e.g. car undercoating
- Toys and child-care articles (pacifiers, teething rings, squeeze toys, crib bumpers etc.)
- Medical products

Non-polymers

DEHP is used among other plasticizers as an additive to rubbers, latex, mastics and sealant, inks and pigments, lubricants (European Union Risk Assessment Report).1

Some examples of non-polymer end products containing DEHP:
- Lacquers and paints
- Adhesives and Fillers
- Printing inks
- Dielectric fluids in capacitors
- Ceramics

PVC and DEHP in medical products

The use of PVC in medical devices represents a very minor percentage of the total amounts of PVC manufactured each year. Nonetheless the use of plasticized PVC in a wide range of medical devices has been very important for a number of reasons10:
- Flexibility in a variety of physical forms from tubes to membranes
- Chemical stability and possibility to sterilise
- Low cost and wide availability
- Lack of evidence of significant adverse consequences in patients

Approximately 3×10^4 tons of plasticized PVC is used for medical applications annually in Europe12, such as IV and blood bags and infusion tubing, enteral and parenteral nutrition feeding bags, and tubing used in devices for cardiopulmonary bypass and extracorporeal membrane oxygenation (see Fig. 6, 7, 8).

Exposure to DEHP varies widely, and is depending on:
- The medical procedure,
- The lipophilicity of the fluid that comes into contact with the medical devices
- The PVC surface size
- The temperature
- The flow rate
- And the contact time13, 14, 15

Polyethylene linings of PVC articles (e.g. tubings) do not seem to substantially prevent the release of DEHP.14, 15

Fig. 6: PVC intravenous solutions bag
Fig. 7: PVC blood bag
Fig. 8: PVC infusion administration set
DEHP Exposure

Causes

Why are DEHP containing medical devices of concern?
Especially with IV fluid containers made of DEHP containing PVC, there are three main effects of concern:
- DEHP leaches out of the PVC into the solutions stored in the fluid container and is thus incorporated by patients with unclear but, with regards to substances affected (see Fig. 9, 13), very likely serious health consequences
- A significant number of drugs are not compatible with PVC and adhere to it (see Fig. 9)
- During the production and disposal process of PVC, dioxsins and furans, which are environmentally detrimental, are produced

These three points will be further discussed below:

Leaching of DEHP
Everyone is exposed to small levels of DEHP in day to day life. However, some individuals can be exposed to high levels of DEHP through certain medical procedures. DEHP can leach out of plastic medical devices into solutions that come in contact with the plastic (see Fig. 9).

The amount of DEHP that will leach out depends on the temperature, the lipid content of the liquid, and the duration of contact with the plastic. Seriously ill individuals often require more than one of these procedures, thus exposing them to even higher levels of DEHP. On a weight basis, DEHP may constitute 30–40 % of a typical blood bag. Jaeger and Rubin reported the leaching of DEHP from PVC blood bags into stored blood components; their data suggest a leaching rate of 0.25 mg DEHP/100 ml/day for whole blood stored at 4°C. For a blood transfusion in adults, a DEHP exposure of 600 mg has been reported.

For platelet concentrate stored in blood bags, a leaching of DEHP has been quantified in the stored platelets. It was estimated that each patient received a total of 26.4 to 82.4 mg DEHP for 5 bags. Because infusion of platelets requires typically 30 min, and assuming a linear leaching rate of DEHP with time, the tubing involved in administering platelets might contribute at most 1.0 mg, a minor contribution which may be ignored. Others have reported considerable amounts of DEHP leaching into infusion solutions stored in IV PVC bags, such as parental nutrition, cytostatics, or antibiotics.

Leaching: Substance from bag wall migrates into the solution
Sorption is a physical and chemical process by which one substance becomes attached to another. Specific cases of sorption are:
- Leaching: Substance from bag wall migrates into the solution
- Absorption: Drug from solution, e.g. isosorbide dinitrate, migrates into the bag wall

Interaction of drugs stored in PVC bags
Besides the amount of DEHP leaching from the container into its stored solution, the question whether the solutions are stable in their container has been investigated thoroughly. Storage in PVC usually is compared to storage in polyolefin materials, i.e. polyethylene (PE) and polypropylene (PP). There is a reasonable amount of drugs for which storage in PVC containers cannot be recommended since they are not completely stable, e.g. cytotoxic drugs, sedatives, and critical substances like nitroglycerine, isosorbide dinitrate, warfarin sodium and thyroxine.

Environmental exposure
Regarding the environment, two aspects have to be taken into consideration: One being the amount of DEHP which is released from plastics during or after the product lifetime, the other being side products during production and destruction of PVC.

Release of DEHP into the environment
Large amounts of DEHP in polymers are building up in:
- Landfills
- Waste remaining in the environment (pieces of polymer)
- Landfills
- Waste remaining in the environment (pieces of polymer)

DEHP is assumed to be persistent as long as the molecule remains in the technosphere (incl. the waste) is still increasing. The overall distribution of DEHP is 2 % to air, 21 % to water and 77 % to urban/industrial soil.

Side products of production and destruction of PVC
During production and especially incineration of PVC, a number of toxic by-products is released into the environment: Polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and dioxin-like polychlorinated biphenyls (PCBs) are a group of structurally related chemicals that persist in the environment and may bioaccumulate in animal sources of food and in human tissues. Their half-life time in the body is estimated to be seven to eleven years.
Consequences of leaching of DEHP

Negative effects of DEHP on human beings
Numerous studies have shown that the chemical group of the phthalates and especially DEHP impair testicular testosterone production in the rat. Very recent investigations have presented proof that DEHP can inhibit testosterone production in the adult human testis. Further more, adverse reproductive system outcomes, including reduced semen quality and altered male genital development, have been reported.

In support of that, many phthalates are identified as anti-androgenic endocrine disrupting chemicals in mammalian models. Endocrine disrupting compounds are chemicals that can alter hormonal signaling with potential effects on developing reproductive and nervous systems, metabolism, and cancer. Serious concerns have been raised on exposure of ill newborns and neonates to DEHP (see Fig. 12). Premature neonates in intensive care units, being dependent on multiple medical procedures, can receive even higher DEHP exposures than adults relative to their body weight. This exposure may be even higher than the doses observed to induce reproductive toxicity in animals.

Negative effects on developing fetuses
Animal studies have shown DEHP to be particularly harmful to developing fetuses leading to adverse effects in the reproductive system, including changes in the testes. Pregnant women exposed to high levels of phthalates may have increased risk of having sons with malformations of the genitals (hypospadias and cryptorchidism), low sperm count and increased risk of testis cancer (see Fig. 10, 11).

Carcinogenicity of DEHP
DEHP has been reported to be carcinogenic in liver in rats and mice with routes of induction being well investigated. Other adverse effects on lung, heart and kidney have been reported as well. The International Agency for Research on Cancer, part of the WHO, classified DEHP as possibly carcinogenic to humans (Group 2B), an opinion which has been adopted by many others, e.g. the US department of Health and Human Services. DEHP was downgraded by IARC in 2000, but massive criticism has been raised in the medical scientific community that IARC disregarded significant reports.

Lipophilic substances are of greatest concern
DEHP diffuses into lipophilic tissues and fluids and is thus distributed in the body, the route of ingestion, be it oral, parenteral, per inhalation or dermal, will not make a difference. Since this leaching effect is depending on time, temperature etc. especially long-term storage e.g. of drug solutions in PVC containers is of major concern. Short term contact with PVC devices, such as catheters or infusion sets, is regarded neglectable. Therefore, many authors advise the use of polyethylene or polypropylene containers rather than PVC, and an increasing number of manufacturers of pharmaceuticals exclude the use of PVC bags for their drug preparations, e.g. for paclitaxel or temsirolimus.

Thrombogenicity of DEHP
PVC materials are well known to be of thrombogenic nature and there is substantial evidence that the extent of platelet aggregation is due to the presence of DEHP in the material and not the PVC itself. In addition, complement activation, a process associated with adverse hematological effects, is greater following exposure of blood to DEHP-plasticized PVC than to other polymers. Each of these effects can have adverse clinical consequences in patients.

Peritoneal sclerosis associated with DEHP
Peritoneal sclerosis is a serious complication of peritoneal dialysis therapy. Beneath other factors, DEHP seems to have a role in the pathogenesis of this condition. Research results suggest that levels of DEHP in dialysate stored in DEHP bags are sufficient to initiate the process of peritoneal sclerosis and to produce sclerosis. The clinical significance of peritoneal sclerosis cannot be underestimated, because patients with reduced dialytic capacity of the peritoneal membrane must be switched to hemodialysis.
Consequences of sorption of PVC

Sorption of drugs to PVC and consequences for therapy

Whereas the discussion of leaching of plasticizers is focused on the toxicological properties of a drug packaging system, the sorption (superordinate of absorption and adsorption) of drug formulation compounds has an influence on the dosage of the active pharmaceutical ingredient resulting in a reduced drug delivery to the patient. Therefore, sorption has an influence on the effectiveness and success of the therapy. A list of drugs which are incompatible with PVC is given in Fig. 13. Considering these examples and their intended uses, the conceivable consequences result from significant underdosage of the substances:

- Underdosing of carmustine, an anti-cancer agent used for chemotherapy in glioblastoma (a brain tumor), might lead to non-effectiveness of the therapy and thus progression of cancer.
- Underdosing of heparin or warfarin, both anti-coagulating drugs, might result in blood clotting and/or lung embolism.
- Underdosing of thiopenthal, a rapid-onset short-acting barbiturate general anesthetic, might result in unintended awareness of the patient.
- Underdosing of isosorbide dinitrate and nitroglycerin, both dilating agents being used during angina pectoris, might be useless and angina pectoris might result in cardiac infarction.
- Chloridiazepoxide and diazepam are both sedatives and anxiolytics, might not be as effective as intended.

In case the effect of sorption is known to the user and thus the amount of drug given is increased, this results in considerable preventable additional cost to the provider and payer.

Chronic exposure of animals to dioxins has resulted in several types of cancer. TCDD was evaluated by the WHO’s International Agency for Research on Cancer (IARC) in 1997. Based on animal data and on human epidemiology data, TCDD was classified by IARC as a “known human carcinogen”.

The health effects from exposure to dioxins and furans have been documented intensively in epidemiologic and toxicological studies. As well, a number of significant consequences are known from serious accidents such as the disaster in Seveso, Italy, in 1976. A cloud of toxic chemicals, including 2,3,7,8-Tetrachlorodibenzo-p-dioxin, or TCDD, was released into the air and eventually contaminated an area of 15 square kilometres where 37,000 people lived.

The effects of dioxins and furans released into the environment during production and incineration of PVC have been shown to exert a number of toxic responses, including dermal toxicity, neuro-developmental deficits, immunotoxicity, reproductive effects and teratogenicity, endocrine disruption, metabolic syndrome and carcinogenicity.

In 1997, the International Agency For Research on Cancer classified TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin), most toxic compound of the group, as a group I carcinogen (sufficient evidence of carcinogenicity), and a recent review of both existing and new evidence supports this decision.

As described above (“Causes”), the amount of DEHP from building material, waste and landfills is continuing to increase in air, soil, and water. This environmental exposure adds to the exposure from food, medical devices and others and thus the described risks.

The dioxins and furans, toxic side products released by the production and destruction of PVC, (e.g. PCDDs, PCDFs and PCBs) are characterized by very long half-life times. Concentrations increase as they move up the food chain, mainly in fatty tissue. The median DEHP intake per age group is shown in Fig. 15.

DEHP Exposure

Table: Comparison of DEHP leaching into different IV container materials

<table>
<thead>
<tr>
<th>Drug</th>
<th>In PVC</th>
<th>In polyolefin (PE and PP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitriol</td>
<td>50 % loss / 24 h Stable</td>
<td></td>
</tr>
<tr>
<td>Carmustine</td>
<td>65 % loss / 2 h Insignificant loss / 2 h</td>
<td></td>
</tr>
<tr>
<td>Chloridiazepoxide</td>
<td>10-20 % loss / 2 h Stable</td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>80-90 % loss / 24 h Stable</td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td>15-25 % loss / 1-3 h Stable</td>
<td></td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>80-90 % loss / 24 h Insignificant loss / 24 h</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>70 % loss / 24 h Stable</td>
<td></td>
</tr>
<tr>
<td>Thioental</td>
<td>25 % loss / 8 h Stable</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>29 % loss / 8 h Stable</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 13: Overview of the sorption behavior and amount of selected drugs stored in different IV container materials (PE and PP)

Fig. 14: Conclusion of the “National Toxicology Program” regarding the possibilities that human development or reproduction might be adversely affected by exposure to DEHP.

Fig. 15: Median DEHP intake per age group

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Median DEHP intake (µg/kg bw/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult (20 – 70 years)</td>
<td>8.2</td>
</tr>
<tr>
<td>Teen (12 – 19 years)</td>
<td>10</td>
</tr>
<tr>
<td>Child (5 – 11 years)</td>
<td>18.9</td>
</tr>
<tr>
<td>Toddler (7 month – 4 years)</td>
<td>25.8</td>
</tr>
<tr>
<td>Infant (0 – 6 month)</td>
<td>5</td>
</tr>
<tr>
<td>Formula-fed Breast-fed</td>
<td>7.3</td>
</tr>
</tbody>
</table>

Fig. 15: Median DEHP intake per age group
DEHP Exposure

Consequences

Economic consequences

The exposure of human beings and especially developing children to DEHP can have significant health consequences, as shown above (see Fig. 14).

These disorders lead to significant economic consequences with more severe diseases leading to high economic burdens.

As an example, some of the health consequences to DEHP have been selected and their additional treatment costs according to reports from the current literature are displayed below (see Fig. 16).

These figures only take into account pure costs for treatment. Not included are any overall economic effects such as loss of labour, gross domestic product, joblessness, etc.

<table>
<thead>
<tr>
<th>Examples of complications resulting from DEHP exposure</th>
<th>Severity</th>
<th>Clinical Treatment</th>
<th>Additional Costs US$</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis</td>
<td>Moderate</td>
<td>Hospital treatment</td>
<td>3,911 – 9,590</td>
<td>Economic Analysis of Infant vs Postpubertal Orchidopexy to Prevent Testicular Cancer. Hoth M.H., Roth D.B., Meng M.V. Urology 2009 73:4 (776-781)</td>
</tr>
</tbody>
</table>


Cost of atherothrombotic diseases - Myocardial infarction, ischemic stroke and peripheral arterial occlusive disease - In Germany Brüggenjürgen B, Ruprecht H.-J., Spannagl M, Berger K, Ehlen B, Smula

Fig. 16: Estimation of possible additional costs as a consequence of complications caused by DEHP exposure. In order to facilitate the attribution of each complication to the cost calculation, severity levels (Dean & Barber Scale 1) were introduced.
DEHP Exposure

Preventive strategies

International and national laws and guidelines:

1. In the EU-regulation No. 143/2011, bis(2-ethylhexyl)phthalate (DEHP) is classified as toxic to the reproductive system. From January 21st 2015 onwards, the placing on the market and the use of DEHP without special permission will be prohibited.1, 2

2. The European Union recommends the use of other materials instead of DEHP-PVC for medical devices.3

3. The European Community’s regulation EC 1907/2006 “Registration, Evaluation, Authorisation and Restriction of Chemical substances” (REACH) came into force on June 1st, 2007. It classifies DEHP as substance of Very High Concern. Such substances are subject to authorization through the European Chemicals Agency (ECHA) in Helsinki.4

4. According to EC directive 2007/47, medical devices containing DEHP have to be labelled accordingly (see Fig. 17).5

5. Effective August 2008, the United States Congress signed the Consumer Product Safety Improvement Act (CPSIA) in which section 108 specified that as of February 10th, 2009, it is unlawful to manufacture for sale, offer for sale, distribute in commerce, or import any children’s toy or child care article that contains concentrations of more than 0.1 % of DEHP, DBP, or BBP.

6. In January 2010, the Australian Consumer Affairs Minister Craig Emerson announced a ban on items containing more than 1% DEHP because of reproductive difficulties.6

7. With regards to food packaging, the use of DEHP in food contact materials is already restricted under Commission Directive 2007/19/EC of 30 March 2007 relating to plastic materials and articles intended to come into contact with food and Council Directive 85/572/EEC laying down the list of simulants to be used for testing migration of constituents of plastic materials and articles intended to come into contact with foodstuffs.

8. For food, PVC packaging which may or may not contain DEHP, has been either banned or restricted in a number of countries, including Canada, Spain, South Korea and the Czech Republic.7

9. The German Federal Institute for Drugs and Medical Devices (BfArM) recommends using alternative products to DEHP-softened PVC medical devices for premature infants and newborns. BfArM also urges medical devices manufacturers to label products containing DEHP and put more effort into developing safer alternatives.8

10. Similarly, the US Food and Drug Administration has issued an FDA Safety Assessment and a Public Health Notification urging health care providers to use alternatives to DEHP-containing devices for certain, vulnerable patients.9

11. Health Canada’s scientific expert panel on DEHP recommended among others that storage bags used for the administration of lipophilic drugs, should not contain DEHP.10 As well, Health Canada has proposed to prohibit the sale, advertisement, and importation of toys for children under three years of age and products for children under three years of age that are likely to be mouthed and contain DEHP.11

12. Argentina, Austria, Cyprus, the Czech Republic, Denmark, Fiji, Finland, Germany, Greece, Italy, Japan, Mexico, Norway, and Sweden have restricted phthalates in children’s toys.12

13. The latest draft of the guideline 2002/95/EG RoHS on the restriction of the use of certain hazardous substances in electrical and electronic equipment, the European Union has included DEHP into the list of prohibited substances.


15. The requirements of the Stockholm Convention for releases of dioxins and other by-product Persistent Organic Pollutants (furans, hexachlorobenzene and PCBs) are that each party shall, at a minimum reduce the total releases derived from anthropogenic sources of each of the chemicals, ... with the goal of their continuing minimization and, where feasible, ultimate elimination.13

16. Concerns about dioxin from garbage incineration led the Japanese government to enact a new container and wrapping materials law requiring producers to recycle waste products by the year 2000. The law prompted several major Japanese makers of household goods and cosmetics to announce timetables by which they would switch to polypropylene and other materials for various types of cosmetic, food and pharmaceutical packaging.14

17. The Health Care Without Harm campaign is an international coalition of 420 organisations in 51 countries; organisations include hospitals and health care systems, medical professionals, community groups, health affected constituencies, labor unions, environmental and health organisations and religious groups. One of the goals of the campaign is to phase out the use of PVC and persistent toxic chemicals, and to build momentum for a broader PVC phase out campaign.15

As outlined in the previous chapters, there is common agreement that the use of DEHP as plasticizer is of concern and scientific panels throughout the world recommended to limit its use.1, 2, 3, 5, 6, 7, 8 Further more, there are nowadays a number of alternatives available, either using other plasticizers for PVC or completely different PVC-free materials.

A number of international, national and regional activities have resulted from that, partly with legislative action, in the health care sector as well as in a number of other industries, such as toys or food and beverages.

“...The available reproductive and developmental toxicity data and the limited but suggestive human exposure data indicate that human exposures in this situation approach toxic doses in rodents, which causes the panel serious concern that exposure may adversely affect male reproductive tract development.” 46

Fig. 17: According to EC-directive 2007/4714 medical devices containing DEHP have to be labelled accordingly.
Preventive strategies

Initiatives and campaigns

1. In November 2011, the Food and Drug Administration (FDA) has revealed a new maximum allowable level (0.006 mg/l) for diethylhexyl phthalate (DEHP) in bottled water and manufacturers are required to monitor the levels. 8
2. The managed health-care provider Kaiser Permanente said it will no longer purchase intravenous solution bags made from PVC or that contain the plasticizer as part of its continuing effort to better protect the health and safety of the 8.9 million people who get care at its hospitals, doctors’ offices and health-care facilities. 70
3. Kaiser Permanente, Miller Children’s Hospital in Long Beach, facilities who get care at its hospitals, doctors’ offices and health-care facilities. 70
4. The Confederation for Environmental and Nature Conservation Germany (Bund für Umwelt und Naturschutz Deutschland), Health Care Without Harm (HCWH) and the European Academy for Environmental Medicine (EUROPAEM) have started the initiative “pollution-free hospital”. The environmental organizations have called on the hospitals in Germany to forego PVC-containing medical devices. 71
5. In Spain, over 60 municipalities have approved PVC phase-out initiatives and campaigns have called on the hospitals in Germany to forego PVC-containing medical devices. 72 The Pediatric Clinic Glanzing of the Vienna Hospital Association is the first Neonatology Unit world wide to announce it will manage completely without PVC plastic. 71
6. The OSPAR List of Chemicals for Priority Action includes several substances which are by-products of the production of chlorine and PVC, or additives in PVC: dioxins & furans, chlorinated paraffins, mercury and organic mercury compounds, lead and organic lead compounds, organic tin compounds, certain phthalates (DBP & DEHP). 73

Research and Industry

1. B. Braun has bought and further developed Di(2-ethylhexyl) terephthalate resp. Diocyl terephthalate (DEHT or DOTP, resp.) a non-phthalate plasticizer with a different chemical structure. DEHT or DOTP is the only plasticizer known for flexible PVC which does not show any toxic side effects in tests (see Fig. 18). 7, 74
2. Alternative plasticizers have been developed and manufactured by a growing number of chemical manufacturers. Comprehensive and thorough research is necessary before these plasticizers will be approved, such as TOTM/TEHTM and Hexamoll® DINCH.
3. A number of medical device companies including B. Braun have invested into research on other materials than DEHP-PVC for medical devices (see Fig. 19).

Further details on these three approaches are given below (p. 17-19 and Fig. 22).

Characteristics of the alternative plasticizer DEHT
Di(2-ethylhexyl) terephthalate (DEHT) is a general purpose non-phthalate plasticizer which is in commercial use since 1975. For example, Coca-Cola and other companies have used DEHT ever since for their bottles. Terephthalate is the “T” in PET (see Fig. 20).
As well, the toy industry heavily uses this plasticizer.

DEHT has been invented and produced by the Eastman Company, thus, one of its trade names is Eastman 168.

Toxicity profile of DEHT
DEHT has been studied in a wide variety of in vitro and in vivo studies on its toxicity profile. Acute toxicity studies on oral, dermal, and ocular exposure as well as inhalation have been conducted, with focus on acute, sub-acute and sub-chronic toxicity. All studies have shown an excellent toxicological profile.

Developmental toxicity tests revealed neither an alteration of male rat sexual differentiation during development nor an effect on male organ development. There was no estrogenic effect either. Tests for genotoxicity and mutagenicity were all negative. There was no effect upon tumor incidence and tumorigenicty and there was no induction of liver peroxisomes, which are regarded as sign for potential tumorigenicty.

A GLP-conform toxicity study in male and female rats with continuous intravenous infusion of DEHT over 4 weeks showed that DEHT administered via IV infusion was tolerated systemically and locally without adverse effects up to and including 381.6mg/kg/day (NOAEL=381.6mg/kg/d). In particular, there were no effects on reproductive tissues/organs, kidneys, liver hepatocytes and peroxisomes, as known targets of DEHP-toxicity. A clinical study on 203 volunteers was conducted in order to test DEHT on its irritation skin potential. 75 DEHT was concluded to not be irritating, and did not induce contact sensitization.

These data indicate that DEHT (Eastman 168) plasticizer has a low order of acute toxicity, is essentially non-irritating, and is not likely to induce contact sensitization in humans. 76

- General purpose non-phthalate plasticizer
- In commercial use since 1975
- Chemical name: bis(2-ethylhexyl) – 1,4-benzenedicarboxylate synonyms: Di(2-ethylhexyl)terephthalate (DEHT)
- Terephthalate is the “T” in PET of soda bottles

Fig. 18: DEHT means Di(2-ethylhexyl)-terephthalate, also named DOTP (Diocylterephthalate). The chemical structure is not identical to the one of DEHP.

DEHP Exposure
DEHP Exposure

Regulatory profile of DEHT
DEHT Eastman 168 has been thoroughly evaluated by several government agencies around the world and placed on approved lists.
- USA: recognized by the Food Contact Notification (FCN) for a variety of Food Contact Applications
- European Union: European Food Safety Authority (EFSA) approval; SCENIHR review for use in medical applications. DEHT is not classified as CMR (carcinogenic, mutagenic or toxic to reproduction) by REACH.
- Products not containing DEHP can be marked as DEHP-free with appropriate symbols.
- Germany: approved for use in plasticized PVC including beverage tubing, cap liners, and food wrap by the Bundesinstitut für Risikobewertung (BfR), (German Institute for Risk Assessment)
- Switzerland: DEHT is not listed on Swiss toxic list, thus not considered as toxic
- Japan: Japan Hygienic PVC Association includes DEHT on its positive list

Environmental profile:
The solubility of DEHT in water is very low. In distilled water the solubility has been reported to be 0.4 µg/l. The aquatic toxicity data indicates that there were no acute or chronic effects for any species tested at concentrations at or near the water solubility limit of the material. One study also indicated no impact on survival at concentrations that were orders of magnitude above the solubility limit for the test conditions. Sub-lethal effects such as growth, reproduction, shell deposition, and egg hatchability were also not adversely impacted in any of the studies at the concentrations tested. Because DEHT would have a strong tendency to sorb to sediments in the aquatic environment, an OECD sediment-water chironomid toxicity test using spiked sediments was conducted to demonstrate that DEHT would not have cause adverse impacts to aquatic sediment dwelling organisms. The sediment test indicated that the EC50 was greater than the highest test concentration recommended by the method. With regards to biodegradation, studies have shown that 37-56% of the original DEHT was degraded in 28 days.

These studies indicate that DEHT is susceptible to both ultimate and primary degradation.

Further material for Medical Devices and Drug Containers
Bearing in mind the shortcomings of PVC, especially the sorption effects having an influence on the effectiveness and success of the therapy, other materials for medical devices and drug containers have been subject to research. More inert polymers like polyethylene terephthalate (PET) or polyamide (PA) result in a lower interaction. On the other hand, not every polymer is suitable for packaging of pharmaceuticals. Due to its rigid mechanical properties, PET for example can hardly be used for flexible tubes or bags.

Considerations like these have also led to compound materials such as multi-layer foils, where the inner layer is made of polypropylene and further outer layers consist of polyethylene and polyester.

Sorption behaviour of polyethylene / polypropylene
Polyethylene (PE) and polypropylene (PP), both belonging to the class of polyolefins, are two such materials which have been proven suitable for manufacturing of IV containers. Following the European Pharmacopoeia drug containers made from medical grade PE are free from plasticizers, additives and other compounds that may potentially migrate into the finished preparation. They are chemically inert and toxicologically safe.

As representative examples for the well known group of drugs exhibiting significant sorption to PVC, nitroglycerin and diazepam have been investigated for their sorption behaviour towards alternative plastics. For both drugs, PE and PP showed significantly lower sorption rates than standard PVC tubes (see Fig. 23).

A number of further studies have shown that PE/PP exert the lowest sorption potential on drugs, compared to other plastics (see Fig. 23). In general, modeling of the solution interaction properties of plastic materials used in pharmaceutical container systems has revealed that PP has the lowest binding propensity for drugs, followed closely by PE.

Environmental effects of polyethylene / polypropylene
Most of the medical waste is nowadays subject to incineration. For example, in the UK, the “Landfill Directive” sets the rule that clinical waste may not be disposed on landfills, but needs to be incinerated. As outlined before, disposal of PVC via incineration is associated with the generation and dispersal of polychlorinated dibenzo-p-dioxins (PCDDs) and polycarbonated dibenzo-p-furans (PCDFs) into the environment, both of which are present in flue gases and ash.

Polyethylene and polypropylene, like all hydrocarbons, are burning very well. The only residues from complete combustion are carbon dioxide and water as combustion products, which are not toxic and do not pose any environmental risk.

Dehydrogenation

$$(CH_2)_n \rightarrow CO_2 + H_2O$$

Fig. 21: DEHT has a positive regulatory profile

Fig. 22: Risk of common plasticizers

Fig. 23: PE and PP show lower sorption rates for drugs than PVC

Environmental profile:
The solubility of DEHT in water is very low. In distilled water the solubility has been reported to be 0.4 µg/l. The aquatic toxicity data indicates that there were no acute or chronic effects for any species tested at concentrations at or near the water solubility limit of the material. One study also indicated no impact on survival at concentrations that were orders of magnitude above the solubility limit for the test conditions. Sub-lethal effects such as growth, reproduction, shell deposition, and egg hatchability were also not adversely impacted in any of the studies at the concentrations tested. Because DEHT would have a strong tendency to sorb to sediments in the aquatic environment, an OECD sediment-water chironomid toxicity test using spiked sediments was conducted to demonstrate that DEHT would not have cause adverse impacts to aquatic sediment dwelling organisms. The sediment test indicated that the EC50 was greater than the highest test concentration recommended by the method. With regards to biodegradation, studies have shown that 37-56% of the original DEHT was degraded in 28 days.

These studies indicate that DEHT is susceptible to both ultimate and primary degradation.

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DEHP Exposure

Risk prevention

Ecoflac® plus
The state of the art IV solution container that offers safe and convenient application of all IV procedures from drug admixture to drug delivery. Container based incompatibilities are prevented by a special polyethylene container material which is:
- Chemically inert
- Toxicologically safe
- Free from plasticizers, additives and other compounds
- Free from substances that may potentially migrate into the finished preparation

ConComp®
Free database on drugs compatible with Ecoflac® plus.
- Offers information on interactions between certain drugs, carrier solutions and container materials
- Offers overview of scientific literature on drug compatibility with the container
www.concomp-partner.com

Mini-Plasco®
Mini-Plasco® is a family of small volume parenteral containers made of medical grade polyethylene or polypropylene. These polymers are chemically inert and toxicologically safe, free from plasticizers, additives and other compounds that may potentially migrate into the finished preparation.

NuTRIflex® System
The NuTRIflex® System is the “ready-to-infuse” multi-chamber bag system for Total Parenteral Nutrition (TPN).
It combines convenience with safety by ensuring the exact dosage of the drug to be administered to the patient. The NuTRIflex® System bag is Latex, DEHP and PVC-free.

Cyto-Set® System
The complete system solution for safe and easy toxic drug application, which prevents interactions between certain drugs and material:
- Consists of biocompatible tube material made of PUR (polyurethane) which is chemically inert (may be used with drugs which are not recommended to be applied with PVC material, e. g. Taxol®)
- Free from halogens (like chlorine): thus there are no problems regarding the disposal because no emissions of hydrochloric acid gas or Dioxin occur
- Free from plasticizers: harm to patients is excluded

Cyto-Set® System with transparent light protection
The complete system solution for safe and easy application of light sensitive toxic drugs.
Tubing does not contain DEHP plasticizer but the new type of safe plasticizer called DEHT (Eastman 168), which therefore prevents interactions between certain drugs and material:
- Is not genotoxic, and therefore not harmful for patients or environment
Intrafix® SafeSet Neutrapur® (PVC-free)
IV set for safe and convenient infusions, which prevents interactions between certain drugs and material:

- Consists of biocompatible tube material made of PUR (polyurethane) which is chemically inert (may be used with drugs which are not recommended to be applied with PVC material, e.g. Taxol®)
- Free from halogens (like chlorine): thus there are no problems regarding the disposal because no emissions of hydrochlorid acid gas or Dioxin occur
- Free from plasticizers: harm to patients is excluded

Needle free extension sets
Extension sets with integrated swabbable 2-way valves allow for safe manipulation away from the injection site. Extension sets are free of PVC, DEHP and Latex.

Discofix C extension sets
Extension sets with integrated 3-way stop cock allow for safe manipulation away from the injection site. Discofix C extension sets are free of DEHP and Latex.

Discofix C extension sets with integrated valve
Extension sets with integrated 3-way stop cock and swabbable valve allow for closed system manipulation away from the injection site. Discofix C extension sets are free of DEHP and Latex.

Venofix® Safety
Winged IV needle for short-term infusions, blood collection, injection and transfusion. Venofix® Safety is free of DEHP and Latex.
DEHP Exposure

Literature


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DEHP Exposure

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The summarized scientific information in this document has been prepared for healthcare professionals. It is based on an analysis of public literature and guidelines. The intention is to give an introduction to the risks commonly associated with infusion therapy and to increase the awareness of healthcare workers to these kinds of problems. Due to its summary nature, this text is limited to an overview and does not take into account all types of local conditions. B. Braun does not assume responsibility for any consequences that may result from therapeutical interventions based on this overview.