Non-toxic Healthcare:

Alternatives to Phthalates and Bisphenol A in Medical Devices

Health Care Without Harm

Table of contents

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Foreword

Prevention of disease is an essential part of healthcare. We vaccinate our children to stimulate immunity. We operate with sterile instruments to prevent infection. We educate pregnant mothers in order to promote foetal health. As physicians we took an oath to treat our patients in the best manner possible, and we swore to "first do no harm". Preventing disease is still better than treating it. And that is what this report is about: choosing better alternatives in daily healthcare, in order to prevent disease further down the line.

PVC (polyvinyl chloride) is a widely used plastic. It is often made more flexible by the use of the phthalate DEHP, long considered to have toxic characteristics. The European Union has banned the use of DEHP in toys for children under the age of 3 years (1999/815/EC). Young children tend to put toys in their mouths and DEHP leaches out of the plastics, exposing the developing child to the chemical. One of the first campaigns of HCWH Europe was to eliminate DEHP, the most commonly used phthalate, in intravenous drips. We've known for decades that phthalates leach out of medical devices such as tubing. Yet better alternatives were not available thirty years ago. That is no longer the case. It is then a matter of choice: do we choose better alternatives or do we choose to ignore the potential danger to the patients we are trying to treat? There is mounting evidence of endocrine disruption: unintentionally influencing hormone systems is unwise. We have seen an increase in breast and testicular cancers, in thyroid disorders, and infertility throughout Europe over the last decades. It is then alarming to note that these endocrine systems are influenced by phthalates.

Similarly, bisphenol A (BPA) has been linked to endocrine disruption. This report presents the evidence in a clear and concise manner. BPA was initially developed as a synthetic oestrogen in 1891. Due to the availability of more potent synthetic oestrogens, such as thalidomide, BPA was not widely used until the second half of the twentieth century. Now it is a major part of daily life: from the ink of cash register paper to the linings of beverage cans – and in medical devices. Until recently BPA was also found in baby bottles.

A number of years ago the American Medical Association issued a statement encouraging healthcare providers to reduce the use of products containing PVC and DEHP, and to choose better alternatives (Res. 502, A-06). Many European healthcare providers have also made a conscious choice to eliminate PVC, DEHP and BPA from daily healthcare. A number of examples are discussed in this report. But still not enough is being done. This is partly due to limited political will. Although a number of European countries, such as Denmark and France, have taken bold steps towards elimination, European legislation is still lacking. Currently, the EU Directives on medical devices are under revision and a new proposal for a regulation on medical devices is under discussion in the European institutions. It would be disappointing should economic issues prevail above doing what is right: protecting our patients and preventing disease.

This report presents evidence that policy makers should not ignore. The report is a plea to politicians and governing bodies to adopt stringent legislation to eliminate the use of PVC, DEHP and BPA in healthcare. Legislation would stimulate healthcare providers to choose better products.

What could be more important than the health of Europe's citizens?

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Executive Summary

Medical devices play a critical role in healthcare but may contain hazardous substances in their composition that can leach out into patients during their use, compromising patient safety. Concerns have been raised by different societal groups, including governmental bodies, healthcare professionals, scientific researchers and civil society organisations, regarding the potential health effects of chemical exposure through medical devices to vulnerable groups of the population.

"HCWH Europe's mission is to transform the healthcare sector so that it is ecologically sustainable and no longer a source of harm to public health and the environment."

At the end of 2012, the European Commission adopted a proposal for a Regulation to recast the existing Directives on medical devices. In its report, the European Parliament voted in favour of an amendment that would strengthen the current rules on hazardous substances in medical devices, enforcing the phase-out of these substances when safer alternatives are available.

Substances that are commonly present in medical devices and which are of particular concern are phthalates and bisphenol A (BPA). Phthalates are commonly used as softeners in PVC-based medical devices while BPA is used in a variety of plastics with applications in the medical device industry. One of the major reasons of concern with these substances is that they are endocrine disrupting chemicals that may interfere with the normal functioning of the endocrine system and present a hazard to different physiological and developmental processes.

Health Care Without Harm Europe's mission is to transform the healthcare sector so that it is ecologically sustainable and no longer a source of harm to public health and the environment. At the same time, this must happen without compromising patient safety or care. This report is part of HCWH Europe's work to raise awareness on the presence of hazardous substances in medical devices and the risks to patients, and most importantly to promote the substitution of these substances by showing that many alternatives with better toxicological profiles are available on the market. Change is not only possible but it is already on the way. This change is being led by certain manufacturers, governments, health systems, hospitals and health practitioners and needs to be further encouraged and supported by political and regulatory action.

HCWH Europe proposes a number of specific recommendations to promote a move towards non-toxic healthcare, minimising the hazards to patients without compromising medical care:

- European legislation should protect the most vulnerable groups and create the conditions to rapidly reduce or eliminate human exposure to hazardous chemicals such as phthalates and bisphenol A contained in medical devices;
- Standards for pre-market evaluation of medical devices should include more data on chemicals used in medical devices and allow a performance comparison of individual substances;
- The market authorisation process for medical devices needs increased transparency;
- Sustainable procurement guidelines should provide incentives for the substitution of hazardous chemicals in medical devices;
- Labelling requirements for hazardous chemicals in medical devices should be expanded;
- Funding for research and development of alternative substances and products and for clinical and epidemiological projects that compare the performance of these alternatives should be prioritised.

Introduction

Medical devices (see Box 1) are essential in healthcare, playing an important role in prevention, diagnosis, monitoring and treatment of diseases and disabilities. Hazardous chemicals are present in medical devices as additives to improve plastic performance. These additives can represent a high percentage of the final product and include, among others, plasticisers, flame retardants, fillers, colourings, impact modifiers and stabilisers. Many of these substances can leach out of the product and have adverse effects on human health and the environment.

Concerns regarding hazardous chemical exposure through medical devices are particularly relevant to groups of vulnerable patients that undergo multiple medical interventions or are exposed chronically over extended periods, including infants in neonatal care or dialysis patients.

Substances that are commonly found in medical devices and are of particular concern are phthalates and bisphenol A (BPA) (see Boxes 2 and 3). These substances have been the subject of an intense political debate in recent years due to their widespread use in consumer products and the risks they pose to human health and the environment.

In September 2012, the European Commission adopted a new proposal for the regulation of medical devices to recast the existing Directives on medical devices (Proposal for a Regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009). The Council of the European Union and the European Parliament are currently debating this new proposal. Despite the many claims that exposure to hazardous chemicals through medical devices represents a small proportion of an individual's overall exposure, the European Parliament has recognised that this exposure can be harmful for patients and should be avoided whenever possible. Therefore, the European Parliament approved an amendment to the medical devices proposal that calls for the phase-out of hazardous chemicals in medical devices where safer alternatives are available (1).

BOX 1

Definition of medical device under the European Union legislation (Directive 2007/47/EC)

"...any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, together with any accessories, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for medical purposes for human beings for the purpose of:

- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means."

Hazards of chemicals contained in medical devices

Human biomonitoring studies have detected hazardous chemicals like phthalates and BPA in almost every individual analysed and in a variety of human tissues and fluids such as placental tissue, breast milk, amniotic fluid, urine, blood and saliva (2-5). One of the major reasons for concern is that phthalates and BPA are endocrine disrupting chemicals (EDCs) that can mimic or otherwise interfere with hormone production or function—and as such can interfere with organ formation and growth, sexual maturation, stress response, behaviour, appetite and thirst (6). An increase in the incidence of diseases and illnesses in humans at the different stages of life, from neonatal and infancy through to adulthood, has been associated with exposure to these substances (5, 6).

As traditional risk assessment procedures lack integration of endocrinology concepts, the effects of EDCs in human health and the environment are mostly dismissed. In particular, effects from early life exposures, chronic low-dose exposures and the fact that humans are exposed to a large number of chemicals simultaneously are not taken into consideration.

Researchers and healthcare practitioners are particularly concerned that exposure to these substances through medical devices adds to exposure from other sources since these compounds are ubiquitous and the entire population is already exposed. Moreover, vulnerable population groups, such as babies, children, pregnant and breast-feeding women and the elderly are not adequately protected from the risk of exposure to these chemicals.

A precautionary approach, eliminating exposure to hazardous chemicals wherever possible is appropriate in the case of medical devices as the users will be primarily from these vulnerable populations or maybe rendered more susceptible to toxic insult through illness.

BOX 2

What are phthalates?

Phthalates are a group of chemical substances, primarily used as plasticisers (softeners) in plastics to make them more flexible. Depending on the number of carbon atoms in their alkyl side-chains they are divided into high-chain length (e.g., DINP, DIDP, DPHP and DIUP) with more than six carbons, transitional-chain length (e.g., DEHP, DBP, DIBP and BBP) with three to six carbons and low-chain length (e.g., DEP and DMP) with less than three carbons. They are abundant in polyvinyl chloride (PVC) medical devices such as blood bags, intravenous bags, nutrition pockets, tubing, catheters, respiratory masks or disposable gloves. More than 40% of all plastic-based disposable medical devices are made from PVC.

Di-2-ethylhexyl phthalate (DEHP) has been for many years the most commonly used phthalate ester plasticiser in medical devices. A recent survey among the Danish Medical Device Industry found that 95% of the products contained DEHP (7). DEHP can contribute up to 40% of weight of intravenous bags and up to 80% of weight in medical tubing (8). DEHP, like other phthalates, can leach out of the plastic matrix and accumulate in tissues. DEHP has received great attention due to its production volumes and wide usage, particularly in PVC plastic. Leaching of DEHP from PVC medical devices has been documented since the late 1960s (9, 10).

BOX 3

What is bisphenol A?

Bisphenol A (4,4-dihydroxy-2,2-diphenylpropane or BPA) is a chemical substance used as a monomer in the production of polymers such as polycarbonate (PC), epoxy resins, polysulfone, polyacrylate, as an antioxidant and inhibitor in the polymerisation of PVC and as a precursor for the synthesis of the flame retardant tetrabromobisphenol A (TBBPA). An estimated 1.5 million tonnes are used in Europe, the majority (80%) in the production of polycarbonates (11).

In healthcare settings, BPA applications include devices made of polycarbonate, polysulfone and PVC that have both direct and indirect contact with patients such as medical tubing, catheters, haemodialysers, newborn incubators, syringes, surgical trays, blood oxygenators, eye lenses, nebulisers and dental sealants and coatings (12). BPA derivatives are used also in dentistry applications. BPA has been shown to leach from various materials into liquids as a result of diffusion of residual BPA left during the manufacture and hydrolysis of PC polymers (13).

Hazards for human health

There is growing evidence that many phthalates and BPA can present a hazard to human health. Evidence comes from clinical and epidemiological studies, animal and *in vitro* studies encompassing both prenatal and postnatal exposures (see Box 4 for an overview of types of scientific evidence).

Some phthalates are documented or suspected endocrine disrupting substances, which can inhibit the production of testosterone in the testes (14). In human studies, *in utero* and post-natal exposure to phthalates has been linked with reduced ano-genital indices, reproductive alterations (low sperm concentration, endometriosis, hypospadias, shorter pregnancy duration, etc.), changes in neurobehaviour in neonates, infants and children, cholestasis, dermatitis, heart disease and perturbations in inflammatory responses (15-17). A recent study reinforced that even low level exposures to DEHP during pregnancy can affect male genital development (18). Exposure to phthalates has also been linked to obesity, diabetes and asthma (3, 10, 19).

In animal studies exposure to phthalates has been tied to toxicity in different organs, carcinogenicity and a series of reproductive problems in both males and females. The effects of DEHP in animals has been thoroughly revised in the latest Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) draft opinion on the safety of DEHP in medical devices (20). In the case of DEHP there are different sensitivities in reproductive endpoints in different age groups and in various animal species (20). Among other effects, exposure to phthalates has been tied to testicular dysgenesis, hypofertility, polycystic ovaries, birth defects, cancer, altered brain development, haematological, metabolic and pulmonary troubles (21).

BPA is an endocrine disrupting chemical able to interfere with the action of estrogenic hormones that are essential for the development and function of the reproductive system. It is also able to interfere with the action of other endocrine receptors, such as the thyroid hormones, which are important in the regulation of metabolism and the development of the nervous system (22). A recent review identified more than 75 studies where exposures to BPA were associated with health effects in humans, including reproductive effects (erectile dysfunction, miscarriage), thyroid, immune and metabolic diseases (diabetes) (22). Despite the different study designs, times of exposure and studies with subsets of populations and the difficulty of deducing causal links in epidemiology, the increasing numbers of studies associating exposure to BPA with effects on human health raises serious concerns. Exposure *in utero* has been linked with spontaneous abortion, childhood obesity, neurodevelopment impairments, respiratory conditions and behaviour alterations (anxiousness, hyperactivity, depression) (23-26). An expert appraisal by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) concluded that *"exposure of pregnant women to BPA posed a risk to the mammary gland of the unborn children"* (11). In animal studies, foetal exposure to BPA has been linked with earlier onset of puberty and increased rates of breast and prostate cancer (27).

BOX 4

Research needs

Clinical research
There is only a limited amount of research that has evaluated chemicals used in medical devices in healthcare settings. But such work could in theory provide relevant data to help establish the potential benefits of using one type of alternative over another. Clinical research can provide the strongest evidence of the potential toxic effects of a substance on human health, but there are obvious ethical limitations regarding human experimentation.

Epidemiological research
Epidemiological research is the most relevant for human health, but relies on finding strong correlations between exposure and disease, which may take many years to establish. However, it is very difficult to establish specific biological effects, as effects may occur at different periods after exposure and/or the effects can be very subtle.

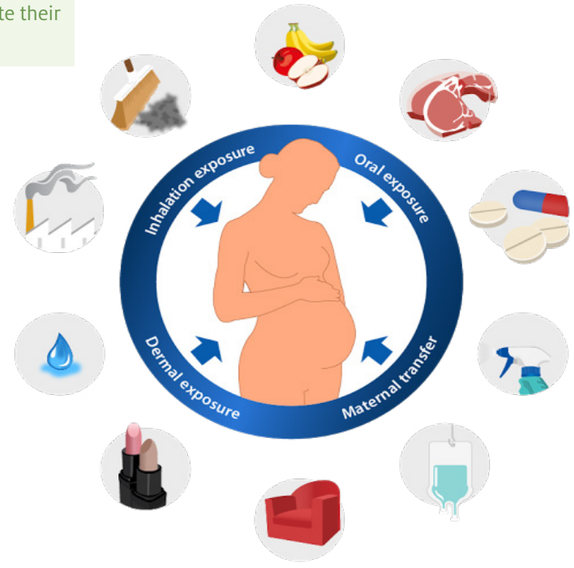
Animal studies
Fully controlled studies of the specific biological effects of particular substances using an animal model could be undertaken. In most cases such studies offer the best evidence available for a particular substance, although the results may not be extrapolated easily to humans.

In vitro studies
In vitro studies may allow the study in isolation of the mechanism by which a substance has an effect, but because they study the cells or biological molecules outside their normal biological context it can be challenging to extrapolate their results to human health.

Exposure through medical devices

Exposure to hazardous chemicals through medical devices can be enteral (digestive tract), parenteral (intravenous), transcutaneous or through inhalation. Dietary exposure to phthalates and BPA is expected to account for the majority of human exposure. However, non-dietary exposure has not always been well documented. In the case of phthalates, and particularly for DEHP, several studies have described leaching from medical devices and have recorded levels in urine and blood (28). According to the latest report on DEHP exposure through medical devices by SCENIHR, premature neonates in neonatal intensive care units, infants subjected to repeated medical treatment using medical devices and patients undergoing haemodialysis are at risk of DEHP-induced effects (20). Recent studies show exposure to phthalates in both premature and healthy full term infants (29). DEHP exposures in neonates in intensive care are much higher than estimated safe limits and might contribute to common early and chronic complications of prematurity (30).

FIG 1. Medical devices are one of a number of sources of exposure to phthalates and other endocrine disrupting chemicals.



For BPA, data on leaching and exposure in patients undergoing medical treatment is lacking. Nevertheless, leaching of BPA and increased levels in urine have been reported (31). Length of contact time, temperature and pH, among other parameters, have been shown to increase the release of BPA from polycarbonate (12). Several authors have also described leaching of BPA from haemodialysers (32).

A number of observations from the scientific literature follow, confirming the link between use of plastics in medical devices and exposure of patients to phthalates and/or BPA.

- Ventilated newborns with high levels of DEHP experienced respiratory degradation associated with progressive radiological infiltrates (33).
- Patients undergoing regular continuous ambulatory peritoneal dialysis using plasticiser-free devices had reduced levels of phthalates in urine and blood (34).
- Serum DEHP levels in blood from healthy donors that were subjected to apheresis increased by 232% (35).
- A strong monotonic association was found between the use of DEHP-containing medical devices and urinary concentrations of three DEHP metabolites in infants receiving care in two neonatal intensive care units (36).
- BPA was found to leach into the blood of patients during dialysis with a dialyser housing made of polycarbonate (37, 38).
- Infants in neonatal intensive care units using a large number of PVC-containing medical devices had urinary BPA concentrations one order of magnitude higher than the median concentration and almost twice that of the 95th percentile of the general population in the US (39).
- The use of infusion systems containing DEHP for total parenteral nutrition was linked with a 5-6 times increase in the risk of cholestasis in infants in neonatal intensive care units. Moreover, the level of cholestasis in neonates was reduced from 50% to 13% in neonates fed through a DEHP-free catheter (40).
- Premature infants in neonatal intensive care units undergoing treatment were found to have BPA levels 10 times higher than the general population, presumably from BPA leaching from medical devices (41).
- Women who had been recently subjected to a caesarean procedure had elevated levels of BPA and DEHP metabolites when compared with females who had had a natural delivery (2). The authors hypothesised that this was due to the use of urinary bags for those undergoing caesareans.
- DEHP leached from endotracheal tubes immediately after being used in high-risk newborns (42). Premature neonates receiving treatment through feeding tubes and endotracheal tubes had increased levels of DEHP in their urine (43).
- Levels of DEHP metabolites in urine were related to the number of DEHP-containing medical devices. Within six hours, neonates receiving lipid-based infusates through a PVC infusion line received a DEHP dose exceeding the lower limit of the tolerable total daily intake (14, 44).

BOX 5

Medical procedures with potential for high exposure to DEHP (12)

- Exchange transfusion of blood in neonates
- Extracorporeal membrane oxygenation (ECMO) treatment of neonates and of adults
- Total Parenteral Nutrition (TPN) in neonates
- Multiple procedures in sick neonates
- Haemodialysis in peripubertal males
- Haemodialysis in pregnant or lactating women
- Enteral nutrition in neonates and adults
- Heart transplantation or coronary artery bypass graft surgery
- Massive blood transfusion of red blood cells and plasma

BOX 6

Are neonates and children more vulnerable?

The levels of exposure to hazardous chemicals are of particular concern for unborn children, neonates and children. These groups are being exposed to hazardous chemicals at a highly vulnerable moment when various aspects of their development can be altered, perhaps with lifelong consequences. Furthermore, their low body weight means the exposure can be higher per kilogram than for adults. Premature babies are subject to an even higher risk due to their lower birth weight combined with the fact they require many medical interventions. In addition, the unborn and young are not able to metabolise chemical substances in the same way as adults, due to the on-going development of their organs and maturation of the different systems. For example, the glucuronidation mechanisms that are responsible for the excretion of some phthalate metabolites are not fully developed before the age of 3 months (3). Finally, expected longer life spans could mean that this group will be exposed for a longer time to these substances. All these factors may put this group at an increased risk of suffering deleterious effects.

Hazards for the environment

Phthalates and BPA have been detected in aquatic and marine environments, terrestrial ecosystems and in the atmosphere in concentrations that are likely to adversely affect a number of species (45, 46). These substances have also been shown to bioaccumulate in some species of molluscs and crustaceans (47).

Phthalates and BPA can reach the environment from industrial discharges, sewage, landfill leachates and natural breakdown of plastics in the environment. BPA is classified as “moderately toxic” and “toxic” to aquatic organisms by the European Commission and the US Environmental Protection Agency respectively based on data reported from aquatic invertebrates and vertebrates (46). Data collected from wildlife studies, laboratory experiments and *in vitro* studies show that exposure to environmentally relevant concentrations of BPA have shown detrimental effects in invertebrates and all vertebrate classes (46). Similarly, exposure to different phthalates and/or their metabolites has caused adverse effects at various endpoints in aquatic organisms at environmentally relevant exposures (48).

Besides the chemical contamination of a wide range of natural habitats, these compounds also create a waste management problem. The disposal of PVC medical waste can release dioxins and other persistent environmental pollutants, which can have a detrimental impact on human health and the environment.

The European legal framework on hazardous chemicals in medical devices

In the EU, manufacturers of medical devices have to comply not only with the Directives on medical devices but also with the regulations on chemicals in products – the EU Regulation 1907/2006 on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) and the EU Directive 2011/65/EU on the Restriction of Hazardous Substances in Electrical and Electronic Equipment (RoHS II).

The REACH Regulation

The REACH Regulation (Article 3.3) differentiates between medical devices that are chemical substances on their own or as mixtures (e.g., dental filling materials, bone cements, etc.) and articles where the function is not determined by the chemical composition (e.g., catheters, medical implants, diagnostic instruments, etc.). The first type of medical device is subject to most of the requirements of REACH, including registration, while articles are usually exempted (Articles 60(2) and 62(6)).

Article 60(2) states: *"The Commission shall not consider the risks to human health arising from the use of a substance in a medical device regulated by Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices, Council Directive 93/42/EEC of 14 June 1993 concerning medical devices or Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices."* Nonetheless, suppliers, distributors or retailers of medical devices have the duty to communicate information (within 45 days) about the presence of Substances of Very High Concern (SVHCs) if requested by a consumer (Article 33) (49).

Several phthalates are classified as toxic for reproduction under the EU Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures (the CLP Regulation) and are listed on the Candidate List of SVHCs under REACH (see Box 7). In the case of BPA, in March 2014, the Risk Assessment Committee of the European Chemicals Agency adopted an opinion that BPA should be classified as toxic to reproduction based on animal experiments – Category 1B (50). If BPA becomes officially recognised in this category, it will become eligible to be classified as an SVHC.

RoHS II Directive

The RoHS II Directive (2011/65/EU) was adopted to limit the concentration of six hazardous substances (including lead, mercury and toxic flame retardants) in electric and electronic products. From July 2014, the RoHS II Directive also applies to electric and electronic medical devices. *In vitro* medical devices will be covered from July 2016 and active implantable medical devices are exempted. Additional seven-year exemptions have been added (Annex IV) for products for which a reliable alternative is not available. Currently, RoHS II covers neither phthalates nor BPA, but a revision of the substances limited under RoHS is expected in the near future.

Medical Devices Directives

According to the current EU medical devices Directives (90/385/EEC, 93/42/EEC, 98/79/EC and 2007/47/EC), medical devices have to be manufactured so that the risks posed by leaking substances are reduced to a minimum, with special attention given to substances that are carcinogenic, mutagenic or toxic to reproduction (CMRs). However, the regulatory framework does not include concrete mechanisms to phase out these substances within specific deadlines or enforce the development of safer alternatives.

Instead there are only two specifications, the first on labelling (2007/47/EC): *"If parts of a device (or a device itself) intended to administer and/or remove medicines, body liquids or other substances to or from the body, or devices intended for transport and storage of such body fluids or substances, contain phthalates which are classified as carcinogenic, mutagenic or toxic to reproduction, of category 1 or 2, in accordance with Annex I to Directive 67/548/EEC, these devices must be labelled on the device itself and/or on the packaging for each unit or, where appropriate, on the sales packaging as a device containing phthalates"* (Figure 2). The Directive also specifies that if such devices are intended to treat children or pregnant or nursing women, the manufacturer should provide justification for the use of these substances, information on residual risks for these patient groups and if applicable, advise on appropriate precautionary measures.

The European Commission has adopted a new proposal - COM(2012) 542 final - to recast the existing Directives (Proposal for a Regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009). The proposal has been under intense debate. The European Parliament has voted favourably on several amendments to the Commission's text, while the Member States, through the Council of the European Union, have not yet adopted a position.

BOX 7

Phthalates in the Candidate List of Substances of Very High Concern (REACH)

- DHP: Dihexyl phthalate (CAS 84-75-3)
- DPP: Dipentyl phthalate (CAS 131-18-0)
- DIPP: Diisopentyl phthalate (CAS 605-50-5)
- DIBP: Diisobutyl phthalate (CAS 84-69-5)
- BBP: Benzylbutyl phthalate (CAS 85-68-7)
- DEHP: Bis(2-ethylhexyl) phthalate (CAS 117-81-7)
- DBP: Dibutyl phthalate (CAS 84-74-2)
- 1,2-benzenedicarboxylic acid, dipentylester, branched and linear (CAS 84777-06-0)
- PIPP: n-pentyl-isopentylphthalate (CAS 776297-69-9)
- DMEP: Bis(2-methoxyethyl) phthalate (CAS 117-82-8)

FIG 2. Example of DEHP labelling

Why publish this report now?

Alternative substances and materials have become available in recent years for many of the most hazardous chemicals used in medical devices, such as phthalates and BPA. Alternatives tend to appear when legislators, procurers and patients demand them. However, the surge of new alternatives has not been accompanied by a surge of data on their safety, and regrettable substitutions must be avoided. In this report, we discuss why society is demanding a phase-out of phthalates and BPA in medical devices, provide information on how these substitutions can be promoted and achieved, and give an overview of which alternatives are available for phthalates and BPA.

HCWH Europe is not alone in supporting a precautionary approach and the phase-out of hazardous chemicals in medical devices whenever possible. A number of non-governmental organisations, consumer organisations, unions, researchers, healthcare professionals and, more recently, the members of the European Parliament have noted that the substitution of hazardous chemicals by safer alternatives is needed. As Kambia and co-authors stated more than ten years ago in the International Journal of Pharmaceutics, when exposure to hazardous chemicals in medical devices can be avoided through careful selection of materials, not carrying out such substitution is both unprofessional and undesirable (51).

Chapter 1
Substituting hazardous chemicals in medical devices

Exposure to phthalates or BPA can be minimised by adopting a precautionary approach and replacing medical devices with phthalate-free and BPA-free devices which can provide the same efficiency. The precautionary principle is enshrined in Article 191 of the Treaty on the Functioning of the European Union (EU) and aims to ensure a high level of environmental, consumer and human health protection through preventive decision-making in the case of risk. Nevertheless, the principle is rarely applied in practice and decision makers prefer to wait until overwhelming scientific evidence is gathered – often taking a long time to achieve, and potentially delaying action to a point where risks and effects cannot be undone.

On the European market, several manufacturers offer products where phthalates/PVC or BPA have been replaced by alternative materials or substances. In the case of the phthalates, phthalate-free or PVC-free medical devices are available for nearly all product categories except blood bags. This is nonetheless expected to change in the near future thanks to an EU pilot project (see Box 8).

Many hospitals have already made considerable progress, having adopted phase-out policies and committing to using products that are less harmful for patients (see Chapter 4). However, most of these initiatives are happening in such hospitals only due to the commitment of individuals because of the lack of the necessary political or regulatory support.

In a project for the European Commission's Directorate General Environment, the Swedish Environmental Management Council developed a set of EU Green Public Procurement (GPP) criteria with regards to electrical and electronic medical devices. In July 2014, the Commission published these voluntary GPP criteria. The draft criterion on BPA entailed the phase-out of BPA in certain parts of specific medical devices that come into contact with the body of patients. Regrettably, the initially agreed and envisaged criterion on BPA was excluded and does not appear in the final published version.

BOX 8

The PVC-free Blood Bag Project

The PVC-free Blood Bag Project is a Life+ collaborative project between industry and the healthcare sector that aims to demonstrate that it is possible to produce a blood bag without using PVC and to increase market demand. Four European companies are working together to produce this blood bag. The project, which should be completed in 2016, is now in a testing phase. PVC-free blood bag prototypes are being tested in the Karolinska University Hospital in Sweden.

Readers working in the healthcare sector who would like to support the project are able to sign an online petition available at the project's website (www.pvcfreebloodbag.eu). This will help show demand for PVC-free blood bags.

PVCfreeBloodBag.eu

Governmental initiatives

Three European countries, Denmark, France and Germany, have taken legislative steps to reduce the use of phthalates and/or BPA. All three countries have addressed – to varying degrees – the issue of DEHP-containing medical devices. These actions provide welcome political support to efforts to improve healthcare in this regard. The Nordic Council of Ministers, the official inter-governmental body for cooperation in the Nordic Region also promotes the Swan Ecolabel, which among other product categories also includes certain healthcare products.

The Danish example

Denmark introduced a national ban on DEHP, DBP, DIBP and BBP under its national phthalate strategy, initially set for December 2013, later postponed to 2015, and challenged in July 2014 by the European Commission (52). The ban was only applicable to consumer products and did not cover medical devices. Nonetheless, the Danish Health Minister had also supported the phasing out of phthalates in medical devices, pushing for the creation of partnerships between industry, national authorities and experts to call for a European phase-out within a reasonable time frame (53).

THE MAIN GOAL IS TO:
"take initiatives to ensure a continued reduction of the use of classified phthalates in medical devices whenever possible without compromising patient safety and to constantly work to minimise the use of classified phthalates in general".

Within the phthalate strategy, in 2013 the Danish Health and Medicines Authority (DHMA) published a set of guidelines to help Danish regions and municipalities reduce the use of particular types of phthalates in medical devices by means of their general purchasing policy (54). The main goal is to: *"take initiatives to ensure a continued reduction of the use of classified phthalates in medical devices whenever possible without compromising patient safety and to constantly work to minimise the use of classified phthalates in general".*

The DHMA suggests including a *"free of classified phthalates"* requirement as a competition requirement in the tender process that would be preferably, but not necessarily, fulfilled. Thus suppliers would gain an advantage if they fulfilled this requirement, providing an incentive and contributing to phasing out phthalates in medical devices. The guidelines provide examples of requirements and suggest that requirements should also be established for invasive medical devices not covered by the labelling rules. The guidelines focus on a progressive phase-out of the use of phthalates in medical devices.

The Danish Ministry of Environment also collated a list of medical devices that do not contain any of the phthalates that are subject to compulsory labelling. The goal of the list was to inspire procurement officers and others involved in purchasing medical devices (55).

The French example

In December 2012, the French Senate approved a law that bans, for the first time, the use of tubes containing DEHP in paediatric, neonatology and maternity wards (Law No. 2012-1442 – Article L. 5214-1). The ban, which will enter into force in July 2015, foresees the possibility to also prohibit the use of DEHP and other phthalates like DBP and BBP in all medical devices if alternative materials are available and the safety of the device is guaranteed. The same legislative act also introduces a ban on food packaging containing BPA intended to come into direct contact with food.

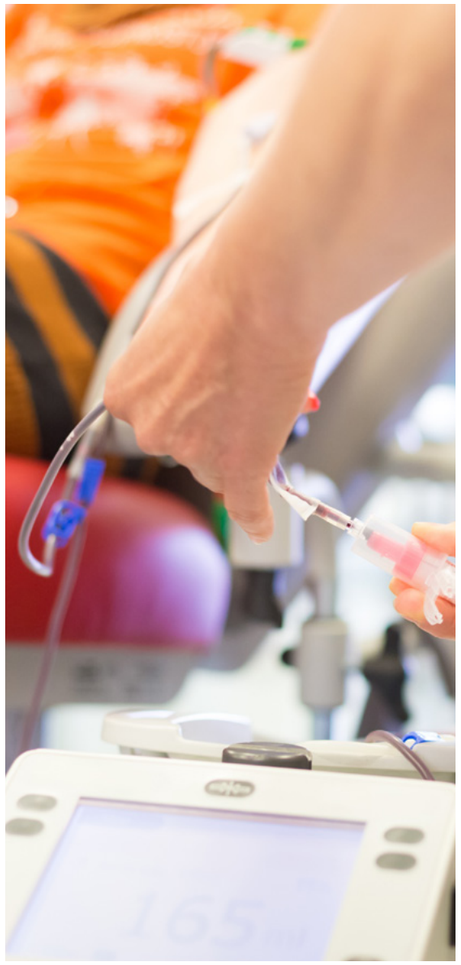
The German example

In May 2006, the German Federal Institute for Drugs and Medical Devices issued a recommendation (Reference Nr.: 9211/0506) to push hospitals to minimise or avoid the use of DEHP-containing medical devices in specific population groups, including premature babies and newborns, infants and toddlers, children and adolescents, pregnant women and nursing mothers (56). The recommendation also includes a call for manufacturers to step up their production of alternative products. However, as this recommendation is only voluntary it is difficult to assess how it has been applied across the different German hospitals.

The Nordic or Swan Ecolabel

The Nordic or Swan Ecolabel (www.nordic-ecolabel.org) is a known and trusted ecolabel. Introduced by the Nordic Council of Ministers, the label is an official, but voluntary, ecolabel for the Nordic countries. The label covers more than sixty product categories and now includes disposable healthcare products that do not contain PVC or harmful plasticisers. In the case of healthcare products it covers disposable products intended and marketed for intravenous (IV) infusion treatment, peritoneal dialysis treatment, treatment of urinary retention and incontinence and also ostomy pouches and accessories for treatment following ileostomy, colostomy or ureterostomy surgery. In the future, the label might be extended to more product categories, depending on request from manufacturers.

Manufacturers interested in carrying the ecolabel on their products agree to follow a number of requirements that include environmental, quality and health criteria (see Box 9) (57). Compliance with the requirements for a specific product is assessed via independent laboratories, certification procedures and on-site inspections.



BOX 9

Summary of environmental and health requirements for the Swan label on disposable healthcare products

- Halogenated plastics, such as PVC, are not allowed in the product.
- No plasticisers or other additives added to the plastic nor adhesives used in or on the various parts of the product may:
  - Be classified as, or meet different criteria, of hazard classes or categories of the EU Dangerous Substances Directive and Dangerous Preparations Directive 67/548/EC and 99/45/EC as amended and the CLP Regulation (EC) No 1272/2008.
  - Have properties categorised in REACH as substances of very high concern and similar substances including: CMR substances (carcinogenic, mutagenic or reprotoxic) categories 1, 2 and 3; PBT substances (persistent, bioaccumulative and toxic) and/or vPvB substances (very persistent and very bioaccumulative); substances considered to be or have potential to be endocrine disruptors (EDCs) in accordance with EU reports and lists concerning EDCs; other substances recorded on the EU's Candidate List of SVHC chemicals.
  - Contain the phthalates DEHP, BBP, DBP, DINP, DNOP and DIDP.
- The relevant national regulations, laws and/or industry-wide agreements on recycling systems for the packaging must comply with those of the Nordic countries in which the product will be marketed.

Non-governmental initiatives

The Safer Medical Devices Database by HCWH Europe

One of the issues that hospitals face when starting a phase-out programme for phthalates or BPA is knowing what alternatives are available and the impact of the new substance. Engagement and communication with manufacturers is therefore essential. However, this can be a very time-consuming activity for an individual hospital. To facilitate this task, HCWH has maintained lists with examples of phthalate-free or PVC-free medical devices available on the European and North American markets.

In July 2014, HCWH Europe took a step forward and launched an online listing of phthalate-free or PVC-free medical products available in the European market – the Safer Medical Devices Database (safermedicaldevices.org, see Box 10). The goals of the new open-access web-service are to enable healthcare procurers to identify medical devices that do not contain PVC and/or phthalates and that are already available on the European market, and to provide market evidence that the phase-out of phthalates and/or PVC in medical devices is feasible. For each product category, registered manufacturers can add their products directly into the database (which is maintained and administered by HCWH Europe). Registered healthcare professionals that procure or use these medical devices can leave comments on the feasibility of specific products. In the near future BPA-free products will also be listed on the database.

BOX 10

How to use the HCWH Europe Safer Medical Devices database

Users of the website (safermedicaldevices.org) can search the database by inputting a search term of interest. The search returns information on medical devices that contain the introduced word or combination of words - their Global Medical Device Nomenclature (GMDN) name, product category, manufacturer and country where the product is available. An optional tick box allows users to select only PVC-free products. The results of the search are downloadable in an excel file.

Manufacturers of medical devices can register free of charge on the database to add their products provided they follow the standard questionnaire and submit requested information.

Procurers and users of medical devices working in healthcare institutions can also register free of charge to provide comments about the performance and feasibility of particular products should they have specific knowledge of their use.

The Swedish Substitution List by the Substitution Group on chemicals

HCWH has not been alone in producing tools to help healthcare procurers. The Swedish regions and counties and the Swedish Environmental Management Council, through the national Substitution Group on chemicals, maintain and regularly update a Substitution List for hazardous substances in the healthcare sector, available online (www.kkv.se/upphandling/hallbar-upphandling/stall-hallbarhetskrav/kemikalier/nationella-substitutionsgruppen/).

The Substitution Group is a voluntary initiative of engaged personnel at Swedish hospitals and universities who exchange information on safer alternatives for both products and chemicals. The Substitution List compiles information on products available in the Swedish market to help healthcare procurers make healthier and more informed choices (58). Products are organised by product category (use), and possible alternatives of the hazardous substances are listed for each product, including at least one supplier.

The Substitution Portal by Kooperationsstelle Hamburg IFE GmbH and partners

The Substitution Support Portal – SUBSPORT (www.subsport.eu) - is a multi-lingual collaborative project coordinated by Kooperationsstelle Hamburg IFE GmbH (a consultancy based in Germany), the International Chemical Secretariat – ChemSec (a non-profit organisation based in Sweden), Grontmij (a consultancy

based in Denmark) and the Instituto Sindical de Trabajo, Ambiente y Salud - ISTAS (a technical body of one of the Spanish workers unions). The project aims to provide useful information on substitution and provide resources to those interested in substituting hazardous chemicals in products. The portal contains legal information on substitution throughout Europe, a database of restricted and priority substances, a compilation of criteria for the identification of hazardous substances, organisation of training programmes and provision of materials, discussion forums and a database comprising case stories.

The Case Story database in the portal can be searched by substance and/or by sector, including "human health, social work and veterinary activities". Under this sector, 61 results are available (in English) including the assessment of alternative substances for ten substances or groups of substances of high concern – including BPA – plus several case studies from hospitals (60).

The GreenScreen® Chemicals Alternative Assessment and the Plastics Scorecard by Clean Production Action

The GreenScreen® for Safer Chemicals (www.greenscreenchemicals.org), developed by the non-profit organisation Clean Production Action, employs an open, transparent methodology to perform chemical hazard assessment. It is used by a wide range of professionals, governmental and non-governmental bodies and manufacturers to assess the hazard of chemicals and their potential effect on human health and the environment. The goal is to push for the substitution of hazardous chemicals by safer alternatives.

Clean Production Action has used the GreenScreen® to assess and determine the hazard level of chemicals for its Plastics Scorecard report (61). The report details a method for evaluating the chemical footprint of plastics that can help guide business, hospitals and individuals to select safer alternatives. One of the case studies of the report is the comparison between two types of plastic IV bags - Polyolefin IV bags and PVC/DEHP IV bags.

Chapter 2
Alternatives to phthalates

DEHP has long been the principle phthalate used to soften PVC for the purpose of manufacturing medical devices. There are reports that the use of DEHP has diminished. However, these reports seem to be anecdotal. In a recent survey of the Denmark medical industry, 95% of the manufacturers still used DEHP (7). However, 60% of the companies have products which do not contain phthalates and 80% of those using phthalates believe that substitution should not be problematic over a period of 3-5 years (7). Alternative substances for replacing phthalates exist for a number of products, including the majority of applications in medical devices (8). The alternatives are sometimes other plasticisers and sometimes the substitution of PVC with other materials that do not need a plasticiser
(61, 62).

No clinical studies have systematically compared the health outcomes of different substances used in medical devices, particularly comparing DEHP and other phthalates with alternatives. Nonetheless, a few studies from manufacturers, regulatory agencies, researchers and NGOs have looked into alternatives for phthalates or PVC in medical devices (20, 60, 63-67). For example, the Dow Corning Corporation compared three common materials used in catheters: silicones, polyvinyl chloride (PVC) and latex rubber. The goal of the study was to provide a strong case for the use of catheters with silicone traded by Dow Corning Corporation, by focusing on the reduced risk of allergic responses to silicone as judged by the incidence of phlebitis, frequency of sepsis, encrustations, infections and deflation (63).

In 2014, the Danish Environmental Protection Agency published a report looking at alternative plasticisers in medical devices to DEHP, BBP, DBP and DIBP. The overall purpose of the report was to come up with a list of alternatives to help guide manufacturers of medical devices to substitute these plasticisers (65). The report screened available information existing in the REACH registration dossiers for a list of substances and found that the values of the "no effect level" (DNEL) for the general population were all higher in comparison with DEHP, meaning these substances would in principle be safer than DEHP (65). In the Plastics Scorecard report, the plastic footprint of polyolefin and PVC in IV bags was compared (60). The results of the comparison showed that the substitution of PVC bags by polyolefin-based polymers greatly reduced the chemical footprint of the products.

Two research studies also reviewed the existing alternatives to DEHP and PVC in medical devices and identified several research gaps (66, 67). These studies supplement a variety of other studies that have assessed the safety and performance of specific substances in specific categories of medical equipment (28).

In the following tables we summarise the applications, advantages, disadvantages, toxicity and main knowledge gaps of known alternative plasticisers to phthalates (Table 1) or known alternative polymers to PVC (Table 2) based on information available in existing reviews, assessments and studies.

TABLE 1. Applications, advantages, disadvantages, toxicity, lowest "no observed adverse effect level" (NOAEL) and main knowledge gaps of known alternative plasticisers to phthaates in medical devices (Adapted from references 57 and 58)

Alternative Plasticiser (CAS)	Advantages	Disadvantages	Toxicity Data	Lowest NOAEL (no observed adverse effect level) (critical endpoint) (65)	Application	Further Research needed
Acetyl-n-butyl citrate – ATBC (77-90-7)	NOAEL 20x higher than DEHP (20)	Leaching rate 10x higher than DEHP in feeding solutions (65, 66) High volatility (65) Can bioaccumulate in the environment (68)	No genotoxicity (65) Low acute toxicity (20) Low subchronic toxicity (20) Reproductive toxicity effects in body weight Inhibits the proliferation of lymph node T cells (68)	300 mg/kg bw/day (liver weight)	Blood bags and medical tubing (extra-corporeal tubing)	Effects from prolonged exposure unknown (65, 67) Data on reproductive toxicity lacking (65)
n-Butyryl-tri-n-hexyl-citrate – BTHC (82469-79-2)	Leachability into plasma lower than DEHP (66) Metabolised into physiologic compounds (66)	Cost (69) Incidents of occupational dermatitis reported (70)	Low acute toxicity (20) Low irritation and sensitisation (20) No mutagenic or genotoxic effects (20)	250 mg/kg bw/day (liver weight, enzyme activity)	Blood and storage bags	Data on reproductive and developmental toxicity and on endocrine activity are needed (65)
Acetyl-tri-n-hexyl citrate – ATHC (24817-92-3)	Reduced leaching into various medium (66)		Low acute toxicity (66) No genotoxicity (66)	No data		Data on human toxicity lacking (66)
Trioctyl trimellitate - TOTM/ TEHTM/TETM (3319-31-1)	Lower leaching (10x lower than DEHP)(28) UV resistance (71)	Chemical resemblance to DEHP (66) Bioaccumulates in the environment (68) Low biodegradability (68)	Weaker hepatoxicity than DEHP (20) Low potential for sensitization (20) Toxic via inhalation (68) Not mutagenic or carcinogenic (20) Moderate concern for reproductive toxicity(65)	100 mg/kg bw/day (reproduction)	Haemodialysis tubing, blood bags, infusion sets	Research needed on the toxicity, metabolism and long-term effects in humans (67) Limited data on environmental effects (68)
Di-iso-nonyl-cyclohexane -1,2-dicarboxylate – Hexamoll® DINCH (166412-78-8)	Reduced leaching (3x to 10x lower than DEHP) (72) Low environmental persistence (66) Low migration rate (65)	Controversy on toxicity results presented by the manufacturer and independent research (20, 68)	Low acute toxicity (73) No reproductive toxicity (20) Repeated exposure caused increased liver, kidney, thyroid and testicular weight (20) Moderate endocrine activity(65)	40 mg/kg bw/day (liver/kidney weight)	Enteral and haemodialysis tubing, bags, respiratory tubes, packaging for nutrient solutions, catheters, gloves and breathing masks	No data on effects of environmental exposures (64) Independent studies needed (66)
Di(2-ethylhexyl) adipate – DEHA (103-23-1)	Not bioaccumulative (68) Biodegradable (68) No endocrine potential (68)	More lipophilic and 3x greater potential to leach than DEHP (67) Might trigger peroxisome proliferation like DEHP (20)	No testicular effects (67) Low sensitisation (65) Mild acute toxicity (68) Mild to moderate developmental toxicity (68) Not genotoxic (67)	200 mg/kg bw/day (development and foetotoxicity)	Medical products and packaging	Research needed on reproductive toxicology (67)
Polyadipates (several CAS)	Leaching 10x to 100x times lower than DEHP (74) Low-cost (74) Durability (74) Biodegradable (68)	Migration can be a problem (65) Higher volatility (65)	Mild sensitisation (68)	No data	Gastric tubes	Developmental and reproductive toxicity data non existent (67) No data on bioaccumulation (68)
Sulfonic acids, C10-21-alkane, Ph esters – ASE (91082-17-6)	Low migration potential (65)			68 mg/kg bw/day (foetoxicity)	Medical devices circuits	No comprehensive study on toxic effects or environmental exposures (64)
Glycerides, castor-oil-mono-hydrogenated, acetates – COMGHA (736150-63-3)	Low migration potential (65) Low volatility (65)		No carcinogenicity No hazards or human health risks to workers(75)	> 1000 mg/kg bw/day	Tubing, connectors, dialysis catheters, fluid bags	Data on reproductive toxicity missing (65) No data on environmental exposures (68)
Epoxidized soybean oil – ESBO (8013-07-8)	Low volatility (65) Biodegradable in aerobic environments (68)	Asthma in workers (68) Bioaccumulative (68)	Skin and eye irritation (76) Repeated exposure suspected to have effects on kidney, liver, testis and uterus (76)	100 mg/kg bw/day (liver weight)		

TABLE 2. Applications, advantages, disadvantages, toxicity and main knowledge gaps of known alternative materials to PVC in medical devices (Adapted from reference (64)

Alternative Material (CAS)	Advantages	Disadvantages	Toxicity Data	Use	Further Research needed
Ethylene vinyl acetate – EVA (24937-78-8)	Biocompatibility (66, 67) Good flexibility (66, 67) Durability (66, 67) Resistance to UV (66, 67)	EVA-based devices are usually assembled with DEHP-made connectors (68)	No data available (67)	Parenteral and enteral administration devices Blood storage containers	No carcinogenicity or health data available (67)
Polyethylene – PE (9002-88-4)	Biocompatibility (66) Inertness (66) Lower leaching (66) Not biodegradable (68)	Need of additives (stabilisers) (66)	Low toxicity (64)	Tubing, packaging films, sutures, blood collection and infusion lines	No data on long-term effects on humans (66, 67)
Polypropylene – PP (9003-07-0)	Biocompatibility (66) Flexibility (66) Durability (66)	Need of additives (stabilisers) (66)	Propylene is a respiratory toxicant in high exposures in animals (77) Leachate not acutely toxic to aquatic organisms (78)	Tubing, bags and parenteral nutrition	No data on long-term effects on humans (66, 67)
Silicone (90337-93-2)	Durability (63) Higher patient compliance (67)	High price (66)	No reproductive or teratogenic effects (67) Low toxicity (79)	Catheters, tubing (endotracheal, etc), dialysis machines, blood oxygenators, chemotherapy ports, shunts, joint replacement, heart valves, wound care, and contact lenses	Data on developmental and reproductive toxicity missing (66, 67)
Polyurethane – PU (9009-54-5)	Durability (66) Sterilisation capacity (80) Biodegradability (80)	Use of hazardous intermediates (8) High cost (66)	Can cause irritation in dust form (64)	Endotracheal tubes	No toxicity data available (67)
Latex (98-82-8)	Durability (81) Excellent barrier to infection Cheap price	Allergic responses (82) Hazardous products used in the production	Allergic responses noted in healthcare workers, patients and the general population (82)	Catheters, surgical and examination gloves	No data on long term effects on humans
Acrylonitrile-butadiene-styrene – ABS (9003-56-9)		Acrylonitrile and styrene are classified as possible human carcinogens (83) Butadiene is a known human carcinogen (83) Volatility of styrene (83)	Leachate not acutely toxic to aquatic organisms (78)	Components of monitoring devices, urinary bags, intravenous bags	No data on long term effects on humans

A concern that has been raised by a study from Genay and coworkers is that not all DEHP-free devices are in practice DEHP-free, as DEHP continues to be used in smaller quantities below the thresholds of contamination defined by REACH (0.1% by weight) (84). According to this study only two out of nine tested medical devices (infusion and extension sets) manufactured with alternative plasticisers were truly DEHP free. These results point to the necessity for manufacturers to verify the purity of raw materials for all plastics used in the composition of the various parts of a medical device and not just PVC (84).

Chapter 3
Alternatives to bisphenol A

The hazardous properties of BPA and those of some of its alternatives have been reviewed recently in several studies (12, 59, 85, 86). None of these reviews looked specifically at BPA alternatives in the medical device industry. The SCENIHR report on BPA in medical devices made only a brief overall note of existing studies on both bisphenol S and bisphenol F toxicity (12). The most thorough review was the ANSES report, which identified 73 alternatives to BPA, including 21 for polycarbonate plastic, 18 for epoxy resins and 34 for thermic paper (85). One common conclusion from all the reviews is that because BPA is used ubiquitously, there is no single replacement for all industrial solutions. As for phthalates, the substitution of BPA can be done by replacing BPA with chemical alternatives or by substituting the plastic polymer with another plastic polymer or material.

Other bisphenols have been indicated as potential substitutes for BPA. This is the case for bisphenol S, bisphenol F and bisphenol AP (although there is no indication at the European level that bisphenol AP is being used in medical devices) (see Table 3). However, existing data shows that due to their similar structure they can have similar or even worse health effects than BPA (11, 87). Other bisphenols like bisphenol M and BADGE are used in medical devices but cannot be used as alternatives to BPA (11). Known alternatives to BPA or to the plastic polymer containing BPA that are used in medical devices include many of the alternatives for phthalates such as polyethylene, polypropylene, polyurethane, silicone and acetylonitrile-butadiene-styrene (see Table 2). Other common replacements that will not be detailed in this report include ceramic, stainless steel, glass and acrylic. The information available for the alternatives to BPA in medical devices is considerably less than that existing for phthalate alternatives. More specific BPA alternatives have only appeared more recently and information about them is much more sparse and the data gaps much bigger.

Manufacturers already replacing BPA in their medical devices include, for example, Didactic (www.didactic.fr) (88), Technoflex (www.technoflex.net) (89), Mamivac (www.mamivac.com), Fresenius Medical Care (www.fmc-ag.com) and Nipro Europe (www.nipro-europe.com).

Two recent studies, one of them including medical devices containing alternative substances to polycarbonate plastic, have found that many of the alternative products also leached chemicals with estrogenic activity (90, 91). However, one of the studies identified products made with glycol modified polyethylene terephthalate (PETG), and cyclic olefin polymer and co-polymer resins (COP and COC) as potential alternatives that did not release chemicals with detectable estrogenic activity under the conditions tested (91). The applications, advantages, disadvantages, toxicity data and main knowledge gaps for known replacements of BPA are presented in Table 4. A substance that has been indicated as a potential substitute for BPA in some reviews is a polyamide registered as Grilamid TR-90TM (CAS 163800-66-6). However, as little information was found about this polyamide and concrete use in medical devices we have not detailed its characteristics in the Table.

TABLE 3. Applications, advantages, disadvantages, toxicity and main knowledge gaps of possible bisphenol alternatives to BPA in medical devices.

Alternative Bisphenols (CAS)	Advantages	Disadvantages	Toxicity Data	Lowest NOAEL (no observed adverse effect level) (critical endpoint) (65)	Use	Further Research needed
Bisphenol S – BPS (80-09-1)	Stability Resistance to sunlight	Estrogenicity (92) Leaches from polymers Less degradable than BPA (93) Widespread exposure in human populations (94)	No genotoxicity (11) Uterotrophic activity (11)	10 mg/kg/d (hyperplasia and intestinal distension)	Medical and dentistry material	Very limited number of *in vivo* studies, no data on chronic and human toxicity (11)
Bisphenol F – BPF (620-92-8)		Estrogenicity (87) Anti-androgenic activity (11)	Genotoxic effects (11) Uterotrophic activity (11)	50 mg/kg/d (reproduction)	Medical and dentistry material	Very few *in vivo* and human studies (11)

BOX 11

Concerns about BPA in dental materials

BPA has been detected in the saliva of patients after dentistry treatments (103). In dental materials, BPA is used during the synthesis of the monomers of dental composites, sealants, cements and orthodontic appliances. The handling and polymerisation of these substances is partly done inside the oral cavity of patients.

The majority of dental composites are based on bisphenol A glycidyl methacrylate (bis-GMA), but can also contain bisphenol-A dimethacrylate (bis-DMA) or ethoxylated bisphenol A dimethacrylate (bis-EMA). BPA is never present in its pure state, but can appear either as an impurity from the synthesis process or can leach into the saliva as result of the hydrolysis of bis-DMA (104-106). A recent study found increased concentrations of BPA in both saliva and urine after composite placement (107). Different studies have also demonstrated that BPA is released from dentistry material into the oral cavity in a time-dependent manner (108). Most studies have found that levels of BPA in both saliva and urine return to pre-restoration levels in the space of hours or days, but additional studies are needed to address the effects of those peaks in human health and in patients with multiple large restorations. The SCHENIHR report on BPA in medical devices has reviewed thoroughly existing exposure and toxicity studies of BPA in dental materials (12).

Healthcare practitioners should be particularly cautious about placing composites containing BPA in pregnant women. Manufacturers should correctly label their products and develop materials with less estrogenic properties (105, 109). Practitioners of dental restoration work should prefer alternative materials that do not contain mercury, do not release BPA and that do not put at risk the health of patients.

TABLE 4. Applications, advantages, disadvantages, toxicity and main knowledge gaps of potential BPA replacements in medical devices.

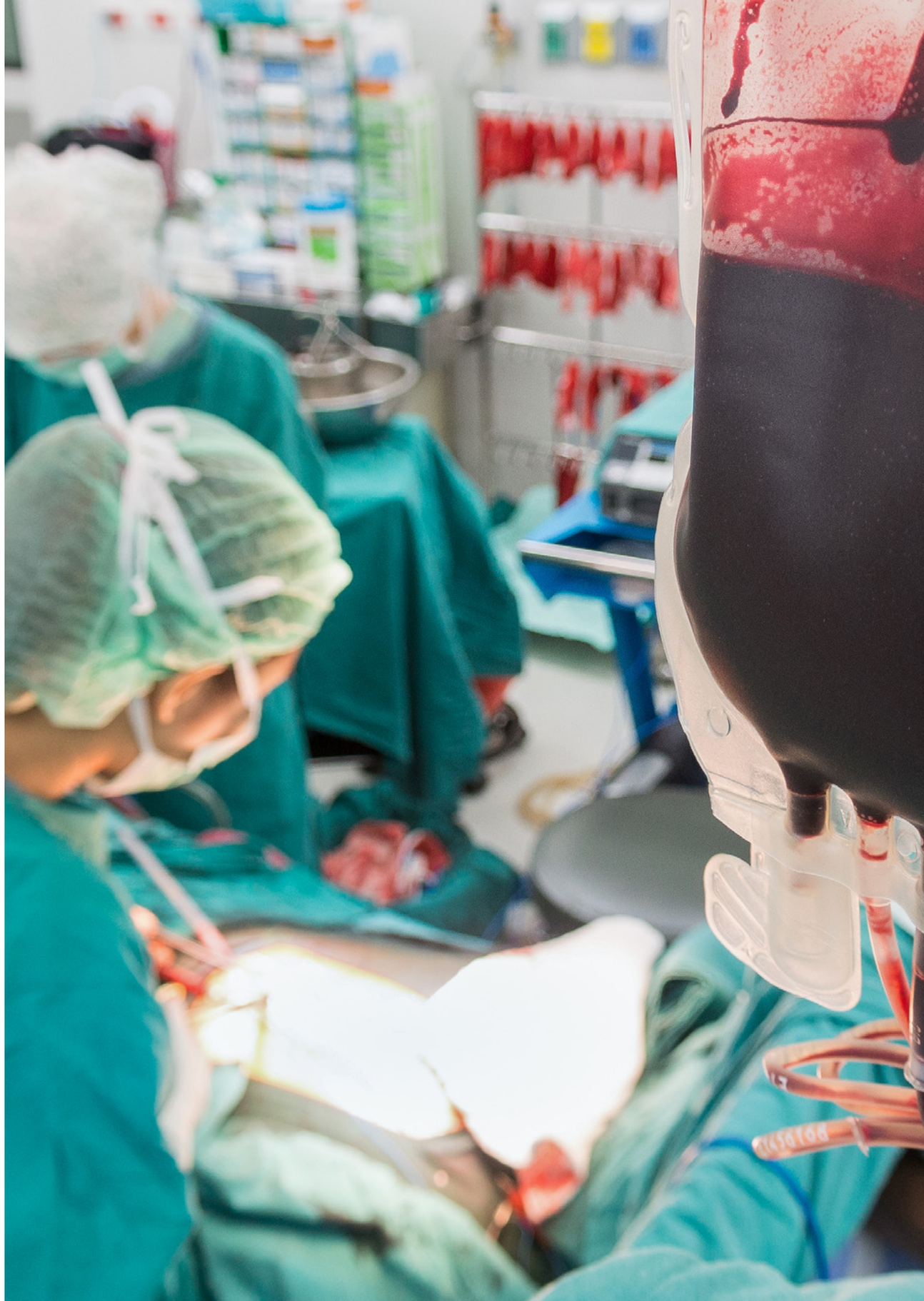
Alternative Material (CAS)	Advantages	Disadvantages	Toxicity Data	Use	Further Research needed
Cyclic olefin polymers - COC/COP (2600-43-2)	Clarity (85) Extended shelf-life (95) High purity (95) Sterilisation resistance (95) Biocompatibility (95)	Price (85) Styrene is classified as a possible human carcinogen (83)	Lack of estrogenic activity (91)	Medical syringes, catheters, medical diagnostic components	No information on toxicity or ecotoxicity
Poly-lactic acid – PLA (26199-51-6)	Biocompatibility (96) Produced from a renewable resource (86) No chemicals of concern (86) High cost (97) Slow degradation rate (97)	Might require plasticisers (86) Production can be problematic (86) Durability (86) Heat sensitive (98)	No known health effects (86)	Medical implants, bone fixation devices	No data on chronic and human toxicity
Polyetherimide (61128-46-9)	Good technical, mechanical and electrical properties (85) Heat resistance (85)		No known human health effects (4) Low acute toxicity	Resins for healthcare applications, sterilisation trays, dentist devices, pipettes	No data on chronic and human toxicity
Polyethersulfone – PESU (25667-42-9)	Durability (85) Sterilization resistance (85)	Releases chemicals with estrogenic activity (91) Very persistent in the environment Contains BPS (85)	PESU does not show estrogenic activity but its metabolites do (99)	Medical tubing, dialysers, orthopaedic, dental and surgical instruments	No data on chronic and human toxicity
Polyphenylsulfone – PPSU (25608-64-4)	Resistance to UV and temperature (85)	Not biodegradable (100) Might contain carbon black (potential carcinogenic substance) (100)	Not harmful to human health (100)	Medical tubing, orthopaedic, dental and surgical instruments	General lack of toxicity data
Terephthalate polymers – PET / PETG (several CAS)	Safe for use in medical devices (101) Stability (4) Cost (59)	Lack of performance at high temperatures (4) Some products might leach endocrine disrupting chemicals (4)	No genotoxicity (4) No toxicity (4) No suspected risks to human health (59) No suspected risks to the environment (59) Lack of estrogenic activity (91)	Heart valves, endovascular devices, sutures and vascular grafts	No data on chronic and human toxicity
Tritan copolyester™	Heat resistance (86) Clarity (86) Durability (86) Flexibility (86) Sterilisation (86)	Releases chemicals with estrogenic activity (90, 91) Higher cost (86)	Contradictory data regarding estrogenicity (86, 90, 102) No skin irritation or sensitisation (86)	IInfusion devices, syringes, medical devices housing, renal and blood apparatus components	Independent studies needed

Chapter 4
Best practices in European healthcare

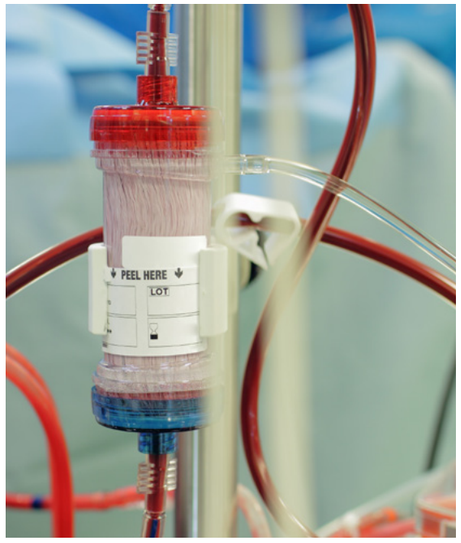
Healthcare facilities and professionals play an important role in the substitution of hazardous chemicals. They have both an ethical responsibility to use products that are less hazardous for patients and an enormous purchasing power that can push manufacturers in the right direction. In Europe, public procurement of goods accounts for 16% of the European market. In fact, public authorities purchase large amounts of products and services for the healthcare sector alone. Healthcare facilities are major consumers of standard products and materials — everything from electronic equipment to paper, hospital gowns, packaging materials, paper towels, surgical instruments, to name but a few — and eighty per cent of these products are thrown away after a single use.

Hospitals throughout Europe are working to minimise the exposure of their patients to hazardous chemicals. The first step of many hospitals has been to identify which products contain substances of concern and develop an internal substitution strategy/policy. Many have launched substitution projects, particularly targeting DEHP and PVC in medical devices. These strategies and policies help hospitals in their purchasing decisions.

In 2008, HCWH published a report with information, examples, and guidance for healthcare facilities to improve their purchasing decisions regarding chemicals – Guide to Choosing Safer Products and Chemicals: Implementing Chemicals Policy in Health Care (available online at noharm-uscanada.org/sites/default/files/documents-files/57/Guide_to_Safer_Chems.pdf). For the present report, HCWH Europe has collated information on best practices in European hospitals and approaches towards non-toxic healthcare.



Hospital of Southern Jutland substitution project (Denmark)



The Hospital of Southern Jutland started a substitution project in 2005 to replace medical devices containing PVC. The project focused on medical devices coming into contact with patients, primarily neonates and children. At the beginning of the project the alternatives were 2.5 to 3 times more expensive, but nowadays there is no difference in price at this hospital. The alternative products supplied by different manufacturers had the same quality and applicability as the products containing hazardous substances (110).

Stockholm County Council's phase-out list (Sweden)

Stockholm County Council has a strategy in place to phase out or reduce the use of certain groups of chemicals in all their realms of activity, including healthcare (111). The Swedish local and national governments were behind the implementation of the phase-out strategy, expected to be concluded by 2016. The strategy covers several chemical classes including phthalates, PVC, BPA, brominated flame-retardants, mercury and glutaraldehyde. Products that contain substances to be phased out cannot be purchased and products that contain substances to be reduced can only be purchased in exceptional cases. The phthalates BBP, DBP and DEHP are on the phase-out list whilst BPA and the phthalates di(2-methoexyethyl) phthalate, diisoheptyl phthalate, disobutyl phthalate, DIDP, DINP, DNOP are on the reduction list.

The County Council also started a project in 2004 to progressively phase out PVC examination gloves in its hospitals. These gloves are among the most extensively used products in healthcare settings and can contain as much as 50% of PVC. The adopted procurement guidelines required that gloves be free of phthalates, PVC, latex and powder and have only low levels of rubber additives. The guidelines address not only the hazard of phthalates but also the problem that both latex and powders in gloves can trigger allergenic reactions.

Nitrile, neoprene and polyurethane have been recommended as substitutes for PVC and latex in examination gloves. The procurement guidelines adopted by the Stockholm County Council not only allowed the replacement of PVC gloves but also resulted in a progressive lowering of the price of the nitrile gloves. Over a 5-year period, the price of nitrile gloves decreased by one half.

Karolinska University Hospital substitution programme (Sweden)

Karolinska University Hospital is conducting an active substitution programme in agreement with the Stockholm County Council chemicals strategy. Since 2006 the procurement of substances in the list has declined by 88%, with some substances having been completely phased out. All the divisions and departments of the hospital follow the substitution programme. Table 5 shows an overview of some of the products and the correspondent substitution levels for PVC and phthalates at the hospital.

TABLE 5. Karolinska University Hospital – substitution levels of PVC and phthalates in medical devices

Medical Device	Substitution Level
Anaesthesia products	60-80%
Blood collection products	80-100%
Blood monitoring systems	60-80%
Drainage systems	60-80%
Enteral and parenteral feeding products	0-20%
Gloves: Examination	80-100%
Gloves: Surgical	80-100%
Infusion products	60-80%
Laboratory products	80-100%
Parenteral infusion devices and sets	40-60%
Urology and incontinence products	80-100%

PVC-free Paediatrics and Neonatology Department in the Westfriesgasthuis (The Netherlands)

Doctors and nurses in the Westfriesgasthuis Hospital pushed for a procurement policy to phase out PVC medical devices in the Neonatology and Paediatrics Department. The policy covers all product categories used in the department and allows for substitution of a majority of the products (80-100%). The hospital has not carried out a thorough assessment of the costs, but estimated a slight increase in the costs in the short-term. Contrary to common belief, they found that some of the alternatives were cheaper than the PVC-containing ones.

PVC-free Neonatal Intensive Care Units of the Vienna Hospitals Association (Austria)

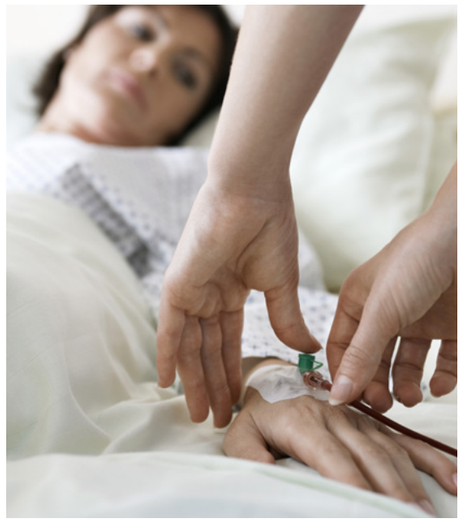
To avoid unnecessary health burdens for premature babies, the Vienna Hospitals Association adopted a PVC-free policy in their Neonatal Intensive Care Units. The criteria cover invasive consumables and products that come into contact with the skin of babies. In the Neonatology Unit of the Glanzing Children's Hospital, the phase-out of PVC started in 2001 and the PVC content of invasive medical products was halved by 2010, with an estimated increase in prices of less than 15% (112).

Chapter 5
Recommendations and Conclusions of Health Care Without Harm Europe

"Health Care Without Harm Europe will continue to raise awareness on the potential exposure of patients to hazardous chemicals via medical devices and to disseminate and promote safer alternatives."

A number of governments, regulatory authorities, healthcare systems, hospitals, healthcare professionals and medical devices manufacturers have endorsed a move towards medical devices that are free from hazardous chemicals, so that patients do not have to be exposed to unnecessary risks when safer alternatives are available. This is even more important when patients' exposure can be minimised without compromising medical care. It should be simple enough to prefer a device that does not increase health risks for patients. In June 2013, HCWH Europe launched a declaration asking for the phase-out of hazardous chemicals in medical devices. The declaration was supported by international and European organisations representing more than 500 hospitals, medical institutions and healthcare systems and 16 million healthcare professionals (noharm-europe.org/documents/declaration-safer-medical-devices).

This HCWH Europe report shows that the medical device industry is already phasing out hazardous chemicals like phthalates and BPA from their products. The availability of alternatives confirms that this change can be done and the existing research, even if limited, shows that the choice of a device can make a difference in exposure terms. Although concerns have been raised in the past regarding the higher cost of safer alternatives, this is not the experience of the healthcare providers that have undertaken substitution. Indeed, the health costs associated with the use of medical devices containing hazardous chemicals are either not accounted for or highly undervalued. For example, the United Nations Environment Programme, using existing numbers for 2004, reported that globally almost 10% of the deaths are related to environmental exposures (113). Furthermore, the case studies presented in this report show that there is not always a difference in price, and, if there is, it is likely to be negligible in the long term. Health Care Without Harm Europe will continue to raise awareness on the potential exposure of patients to hazardous chemicals via medical devices and to disseminate and promote safer alternatives.



HCWH Europe's Recommendations

Labelling requirements for hazardous chemicals in medical devices should be expanded

- Introduce obligatory labelling of hazardous substances in medical devices.
- Develop harmonised environmental criteria for hazardous chemicals in medical devices.

The labelling of DEHP introduced in Directive 2007/47/EC has been a driver for substitution by raising awareness in the healthcare community about the chemical composition of everyday products. Labelling increases information for healthcare staff. Therefore, labelling requirements should be expanded to other substances, besides DEHP, such as other phthalates and BPA. Improved disclosure of product ingredients would allow healthcare professionals to better understand where these substances are present and to prioritise their replacement. The EU Ecolabel and the Nordic Swan label, among others, can help establish harmonised environmental criteria for medical devices and different groups of hazardous chemicals to avoid any gaps or inconsistencies. Moreover, the adoption of obligatory labelling for hazardous chemicals in medical devices will increase general awareness on the issue pushing patients and healthcare professionals and facilities to demand safer products.

European legislation must protect European citizens and, in particular, the most vulnerable groups, by creating the conditions to rapidly reduce or eliminate human exposure to hazardous chemicals such as phthalates and bisphenol A contained in medical devices.

- Apply the precautionary principle in EU legislation by creating a regulatory framework that requires the phase-out of hazardous chemicals, such as phthalates and BPA contained in medical devices, and protects the safety of patients and healthcare workers.

Legislation has a crucial double role in both protecting patients and consumers from exposure to hazardous chemicals and in sparking innovation. The adoption of strict progressive pieces of legislation can be a huge driver of innovation and push for the invention and development of safer alternatives (112). The inclusion of certain phthalates in the Authorisation List under REACH, for example, has led to an increase in the number of patented alternatives (114). Therefore, an expected phase-out of hazardous chemicals in medical devices, under the new Medical Devices Regulation, would also ultimately lead to an increase in innovation in the health technology sector.

Standards for pre-market evaluation of medical devices should include more data on chemicals used in medical devices and allow a performance comparison of individual substances

- Avoid regrettable substitutions.
- Improve data requirements for medical devices approval.
- Subject medical devices (articles) to the requirements of the REACH Regulation.

Innovation cannot be the only driver for regulation. The safety evaluation of medical devices also needs to be improved. The substitution of a hazardous chemical with a structurally similar substance to minimise impact on the manufacturing of the product or with a substance for which toxicity data is not available must be avoided (114).

A key element for generating data on chemicals used in medical devices is reforming the existing data requirements, which hamper the development of adequate data and safer alternatives. Currently a medical device has to pass a minimum benchmark as defined by a series of standards (ISO 10993) in order to be approved for use. The benchmark itself produces little toxicological data. No comprehensive toxicological testing, of the sort that would allow relative performance of individual compounds, or post-marketing evaluation, which would

follow clinical outcomes caused by varying composition of devices, is apparently in place. Even worse, if a compound has a history of use, then its on-going use is assured. For example, continued use of DEHP is justified on the grounds that it has been used for many years and that it helps in treating patients, regardless of its negative health impacts. Better evidence and technical performance of alternatives is needed to guarantee that safer alternatives are used.

Increase transparency of the market authorisation process for medical devices

- Improve the access to the authorisation data on medical devices.

The market authorisation for medical devices needs to be improved to ensure that approved medical devices are both efficient and safe for patients. The European Commission's database on devices approved in the European market (Eudamed) should be publicly available, so that procurers, researchers and other stakeholders have easy access to data on the devices. Clinical data used to approve devices should also be made publicly available so that healthcare professionals can better evaluate the risks and benefits of the medical products and make informed decisions.

Sustainable procurement guidelines should provide incentives for the substitution of hazardous chemicals in medical devices

- Adopt EC Green Public Procurement (GPP) criteria for chemicals contained in medical devices.
- Adopt regional and national strategies and tools to phase out hazardous chemicals in medical devices, such as the substitution group of chemicals created by the Swedish Environmental Management Council and the Swedish County Councils (see p. 16).

Procurement practices can contribute to a quicker phase-out of certain hazardous chemicals in medical devices by driving manufacturers to develop alternatives to those chemicals/products and by assessing if the available alternatives are feasible. The healthcare sector is a growing industry with a high demand for equipment that can, through responsible purchasing policies, drive the market. Hospitals are increasingly demanding products that are free of certain groups of chemicals, thereby driving research, innovation and lowering the market price of the products. The introduction of green procurement criteria at the regional, national and European levels can lead to the phase-out of hazardous chemicals in medical devices. An attempt was made in 2014 while setting EU GPP criteria for electric and electronic medical devices (see p. 13).

Funding for research and development of alternative substances and products and for clinical and epidemiological projects that compare the performance of these alternatives should be prioritised

- Make available research funds for clinical and epidemiological studies on chemical exposure, particularly for comparing exposure and outcomes in patients being treated with similar devices but containing different chemicals.
- Prioritise research and innovation funding for the development of safer products that reduce chemical exposure of all types in the health technology sector.
- Provide more incentives for healthcare facilities to consider substitution.

Governmental authorities should support the development of safer alternatives to medical devices containing hazardous chemicals and prioritise funding for the development of those substitutes. The diversion of funding for these alternatives can be complementary to the adoption of stricter regulations.

Conclusions

European manufacturers of medical devices, under some regulatory pressure, have increased the development of alternatives to both phthalates and BPA in medical devices. In the case of phthalates, the Danish medical device industry has taken a lead and supported the view of many healthcare professionals and NGOs that a phase-out of phthalates is possible and should be promoted (7).

As new alternatives appear on the market, it is of utter importance to weigh their benefits. Unfortunately, for many of the new alternative substances and materials chronic and sub-chronic toxicity studies are still missing. However, different studies have pointed out that many of these alternatives show better toxicological profiles than certain phthalates and/or BPA (65-67). Our analysis of the existing alternatives reveals knowledge gaps for many of the alternatives, particularly the ones for BPA that in some cases have appeared more recently on the market.

However, inert polymers that leach fewer chemicals are less likely to cause harm than continued use of those that leach large quantities of phthalates or BPA. The benefits of substitution might take many years to be apparent, and the extent of the benefit may never be totally clear, but that does not mean it is not favourable to carry out substitution, reducing exposure to a potentially harmful substance. In the absence of sufficient data for a full risk-benefit analysis of a medical device, substitution is the best course of action.

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Notes

Notes

Health Care Without Harm (HCWH) Europe is a non-profit European coalition of over 70 hospitals, healthcare systems, healthcare professionals, local authorities, research/academic institutions and environmental and health organisations.

HCWH Europe works to transform the health sector so that it becomes ecologically sustainable and a leading advocate for environmental health and justice across the globe.

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