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OPINION
ON

Medical Devices Containing DEHP Plasticised PVC; Neonates and Other Groups Possibly at Risk from DEHP Toxicity

Adopted by
The Scientific Committee on Medicinal Products and Medical Devices
On 26 September 2002

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1 Introduction

Polyvinylchloride (PVC) is an inexpensive commodity plastic material that is used in a wide variety of industrial and domestic applications. In common with virtually all plastics, PVC is composed of a polymerised organic substance, in this case polymerised vinyl chloride, together with one or more additives that modify the characteristics of the polymer in order to optimise its suitability for a given application or process. PVC is used in some situations with minimal additives, in which case it is a hard rigid material and suitable for some construction purposes. Most usually, however, the best performance can be achieved when the material is made softer and more flexible. For this purpose, an additive described as a plasticiser is used, and the resulting plasticised, or soft, PVC finds extensive applications.

A plasticiser used in a plastic to confer softness to a polymer has to be a low molecular weight substance that effectively acts as a molecular lubricant. It is, therefore, mobile at a molecular level within the polymeric structure. In this case this implies there are no strong linkages to the polyvinylchloride molecules themselves. As a result, it is possible for the molecules of the plasticiser to diffuse throughout the solid polymer and leach out into its environment. This can lead to a change in the properties of the PVC material, particularly becoming more brittle, but also can lead to elevated levels of the plasticiser in that environment.

Because of its excellent and varied properties, PVC is used in a number of medical devices, often coming into direct or indirect contact with critically ill patients. Virtually all medical devices made from PVC utilise one plasticizer, di (2-ethylhexyl) phthalate, also known as di-octyl phthalate, universally referred to as DEHP. It has been known for a long time that DEHP can leach out of PVC, resulting in exposure to body tissues and fluids. It has also been suspected that this DEHP has certain toxicity characteristics that could be relevant to patient well-being and health under some circumstances. In particular, the release of DEHP into the circulation of a critically ill neonate has been a cause for concern amongst some authorities in view of the relatively high exposure levels that could result in such small individuals.

This matter has been addressed by various bodies and organisations over a number of years, with an increased level of concern being expressed during the last few years. A vast amount of data has been published on the subject, but as yet there is no common agreement concerning the actual level of risk or the relationship between benefit and risk with medical devices that contain PVC. At the request of DG Enterprise of the European Commission, this Opinion addresses the situation with respect to the concerns over the use of PVC in neonates and other groups possibly at risk. It does so by first identifying the nature of PVC and DEHP and the medical applications for which they are used, then reviewing the data on toxicity and exposure and finally discussing the clinical and epidemiological evidence of risk.

1.1 The Materials Science and Chemistry of PVC and its Plasticisers

The vinyl chloride monomer consists of a carbon - carbon double bond with one pendant chlorine and three hydrogen atoms. It polymerises through a free radical mechanism, the resulting polymer having the repeat unit – CH_2CHCl-.

This polymer is used as the basis for a number of plastic materials. Because of the disparity in the size of the pendant hydrogen and chlorine atoms of the molecular chain, polyvinylchloride is an intrinsically amorphous polymer and as such it will normally be transparent and brittle. The additive-free PVC, and especially the unplasticised PVC does have commercial and domestic uses, for example as window frames, pipes, floor tiles and bottles, but the brittleness and difficulty of processing limits the overall use.

For many years, some inherently brittle polymers have been made more practical and useful by the incorporation of a plasticiser into the structure. PVC has been the most obvious example of this but it is by no means the only polymer to be improved in this way. In the amorphous PVC structure, the individual molecules of the polymer lack mobility because of their mutual interference. At its simplest, the use of a plasticiser involves the introduction of a lower molecular weight substance into the structure that acts as a molecular lubricant, physically separating the chains and allowing them some mobility, thus giving flexibility. Obviously, the larger the volume of plasticiser, the greater the flexibility and softness. In reality, the mechanism of plasticisation is a little more complex. The incorporation of a plasticiser into PVC involves the penetration of the plasticiser into PVC resin particles, which causes them to swell. During this process, the polar groups in the PVC are separated and the plasticiser polar groups are able to interact with those of the resin. The structure of the resin is then re-established with full incorporation of the plasticiser in the polymer structure. This effectively provides ‘free volume’ in the polymer that allows for the molecular flexibility. Unplasticised PVC has negligible free volume.

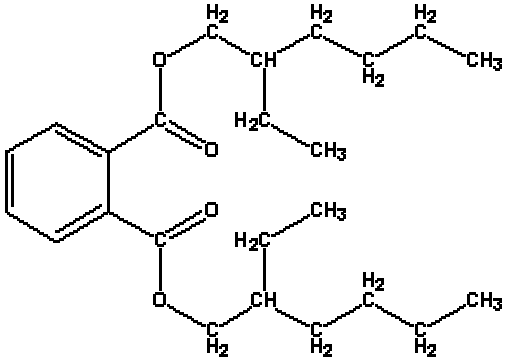
It is important to note that the nature of the plasticiser molecule, in relation to its molecular size, polarity, solid-gel transition temperature and so on, and the precise characteristics of the plasticiser – polymer interaction, quantified by a variety of interaction and activity parameters, controls the effectiveness of the plasticiser, both with respect to the flexibility introduced and to the retention of the plasticiser in the material. Very few substances can act as efficient plasticisers in PVC. Many putative plasticisers fail to interact with the PVC resin and produce little or no flexibility,

whilst some give flexibility but the final structure is such that the plasticiser cannot be retained under operational conditions and is lost over time, causing a reversion to the brittle state.

There are several different types of plasticiser that can be used in PVC. These include adipate esters, phosphate esters, citrates, trimellitate esters, sebacate and azelate esters and phthalate esters. These vary in their characteristics and performance, each having relative advantages and disadvantages under different circumstances. By far the greatest volume of plasticiser used in PVC is accounted for by the phthalate esters, these being produced from either orthophthalic acid or terephthalic acid, with the esters ranging from C1 to C17, although unusually in the range C4 to C13. Some 5 – 10 million tons of phthalates are manufactured and used for this purpose annually on a worldwide basis.

The three main examples of phthalates used as plasticiser in PVC are DINP, Di-isononyl phthalate, DIDP, Di-isodecyl phthalate and DEHP, Di-ethylhexyl phthalate, also known as DOP, Di-octyl phthalate. There are a few other highly specialized phthalates also in use. It is clear from a variety of sources that it is DEHP which is most commonly used, constituting approximately 50% of the market for PVC plasticisers in Western Europe. This widespread use is based upon the combination of properties, ease of manufacture and cost. Tensile strengths between 10 and 25 MPa and ultimate elongations between 200 and 450% can be achieved and this plasticised PVC may be processed and joined by a variety of techniques. This combination renders the plasticiser most suitable for the production of cost effective flexible tubes, sheet and other products required in many medical devices.

The structure of DEHP is as follows



The CAS identification number for DEHP is 117-81-7 and the EINECS number is 204-211-0. DEHP is a colorless oily liquid that is essentially insoluble in water (0.3 mg / l), but it does dissolve in most organic solvents and is miscible with many mineral oils and lipids such that it is reasonably soluble in some body fluids. Although there is a degree of incorporation of the plasticiser into the polymeric structure as noted above, without any covalent linkages to the polymers chains, the plasticiser must be considered mobile and capable of migration. In most cases the migration process is complex and difficult to describe precisely, there being several controlling factors. The important issue is the migration of the plasticiser to the

surface and its subsequent leaching (in fluid surroundings) or volatilization (in air) into the environment. The overall loss of plasticiser will depend on both the diffusion constants with respect to the polyvinyl chloride and the solubility or volatility at the surface. The vapour pressure is in fact quite low at 0.000034 Pa at 20^{o}C.

Exposure of the general population is mentioned later in this Opinion, although this is not the main focus of the discussion. It is important to bear in mind, however, when considering the possibility of the exposure of highly susceptible patients to measurable levels of DEHP directly as a result of their treatment, that the air, water and soil can all contain detectable levels of this substance, such that there will always be multiple origins of exposure.

1.2 Chronology of DEHP Concerns

The concerns about DEHP and plasticised PVC are not new and can be traced back over 30 years. The widespread use of the plasticised PVC in a variety of industrial and domestic applications, with a resulting significant increase in environmental exposure, has raised the awareness of risks of DEHP toxicity during this period, but the earliest concerns were focussed on the medical applications.

The use of PVC in medical devices first took prominence with the introduction of PVC blood bags. Blood transfusions became common during the Second World War but utilised glass as the container, the plastic blood bag being first introduced in 1949. PVC soon became the more popular material, with widespread use by the 1960's. In 1970 Jaeger and Rubin first pointed to the possibility of contamination of the blood stored in these bags in a letter to The Lancet (Jaeger and Rubin, 1970) and they followed up with detailed observations on the migration, extraction, localisation and metabolism of the phthalate plasticiser in relation to blood bags and tubing (Jaeger and Rubin, 1972, 1973). Autian discussed the significant biological response to plasticised PVC, especially in relation to *in vitro* toxicology and histology following implantation in experimental animals (Lawrence *et al*, 1974, 1975; Singh *et al*, 1974, 1975). Several other studies were published in the later 1970's that drew attention to the possibilities of exposure and the potential for adverse effects, although it was obvious that these concerns were not being accompanied by clinical observations of such effects. Such studies include those of Baker, Turner *et al*, Fayz *et al* and Gibson *et al* (Baker, 1978; Turner *et al*, 1974;Gibson *et al*, 1976; Fayz *et al*, 1977).

It is interesting to note that these concerns about DEHP followed concerns about another additive in PVC, an organo-tin stabiliser, which was incorporated into earlier versions of the plastic. It was again Autian and his colleagues who drew attention to potential problems (Guess and Autian, 1964; Guess and Stetson, 1968; Lawrence *et al*, 1963, 1969) and these concerns did focus attention on the need to be careful with the composition of plastic, as discussed in a 1968 Lancet editorial (Lancet, 1968). One clinical condition that was discussed in some detail at that time in relation to PVC and DEHP was neonatal necrotising enterocolitis, reviewed by Hastings (Hastings, 1982). Rogers and Dunn (1969) suggested that this condition could be related to the exchange transfusions received by these infants and there was much discussion in the literature in the ensuing years, but it could never be shown that the DEHP ever played a role.

Thus there have been general concerns about PVC and DEHP for many years, and many studies have attempted to identify the existence of any causality between DEHP and disease in man. The Opinion provided in this report is based on the data that are available on this specific issue.

1.3 Questions to SCMPMD on PVC and the Scope of the Opinion

In January 2002, the Scientific Committee on Medicinal Products and Medical Devices (SCMPMD) was invited to consider certain aspects of the use of PVC in medical devices, with the following remit:

> *Di- (2-ethylhexyl) phthalate (DEHP) is widely used in the production of flexible PVC. During the use of medical devices incorporating PVC, DEHP may leach out from the material, resulting in patient exposure. Exposure to DEHP, in particular for premature infants and new born receiving intensive care, may present health problems. Alternative DEHP-free materials have not generally substituted PVC products. Currently there is no consensus regarding risk/benefit assessment and the need for risk management measures for PVC.*
>
> *Therefore,*
>
> - *Taking into account recently available studies, are there particular medical devices containing DEHP plasticised PVC (e.g. naso-gastric feeding tubes) used for neonates which give cause for concern?*
> - *Are there any other patient groups which also would give cause for concern?*
> - *What Tolerable Intake Values of DEHP leaching from soft PVC should be used as a basis for risk assessment for neonates, taking into account gender and route of exposure?*

2 PVC in Medical Devices and Related Environments

As noted above, PVC is ubiquitous in the health care environment. Because of its properties, processibility and relatively low cost, PVC is used in a wide range of products in the hospital and at home. Some of these impact directly on patient care whilst others contribute to the overall environment of the patient, including floor and wall coverings and ancillary hospital and clinical equipment. DEHP is by far the most common plasticiser used in the PVC and it should be assumed in the following discussion that, unless stated otherwise, exposure to PVC in a medical device or product results in exposure to DEHP.

2.1 Specific Medical and Dental Applications of PVC

The flexibility and barrier properties of plasticised PVC have resulted in extensive uses as tubes, sheets, containers and coverings. The following sections provide a brief overview of the specific examples where these and some other characteristics are utilised in the clinical setting.

2.1.1 Blood and Blood Products

One of the oldest medical uses of plasticised PVC, as noted earlier, is the blood bag. PVC remains the material of choice for the storage of blood and blood products, including red cell preparations and platelet rich plasma. PVC is also used in intravenous tubing for blood collection and infusion.

2.1.2 Feeding Equipment

The most important product here in relation to the question asked of SCMPMD is the nasogastric tube, used in large numbers for short term feeding of neonates. Many other components are also included in this category, involving bags and tubes for the delivery of liquid food products.

2.1.3 Respiratory Support Equipment

A wide variety of components are used to assist patients in respiration, including oxygen masks and tubes, endotracheal and tracheostomy tubes, nasal cannulas, humidifier equipment, and resuscitator and ventilator components.

2.1.4 Organ Assistance

Some major medical procedures aimed at short, medium or long-term functional assistance to organs involve PVC tubes and components. This includes extracorporeal membrane oxygenation and haemodialysis.

2.1.5 Catheters

Many short-term catheters and drains are used in the clinic, including umbilical vessel catheters, wound drainage tubes and osteotomy shunts.

2.1.6 Products with Skin Contact

Examination gloves are obviously used very extensively in clinical and laboratory procedures and they employ a wide variety of materials, including plasticised PVC. A wide selection of other products, including identification bracelets are made of PVC and come into direct contact with the skin of patients.

2.1.7 Products with Oral Mucosal Contact

Orthodontic retainers are used in young children, typically between 7 and 14 years of age, in order to prevent misalignment. An ‘active’ retainer may be used over several months for several hours during the day and at night. Retainers may also be used to

stabilise the teeth in a predetermined position as the final part of orthodontic treatment, in which case they may be used for longer periods of time per day, possibly over several years. The use of these retainers is widespread. It has been estimated that in Finland, with a population of around 4 million, approximately 20 000 children use a retainer. Orthodontic retainers may be prefabricated and made for phthalate plasticised PVC. In many cases, functional appliances for guiding tooth positions in mixed dentition are custom made using autocuring or light curing methylmethacrylate that contains 6-8% of phthalates.

2.1.8 General Hospital Equipment

A number of fixtures of the hospital and clinic environment are constructed from PVC, including wall and floor coverings and screens, although some of these will involve un-plasticised PVC or non-phthalate plasticised material. Some mattresses also involve PVC.

2.2 Functional Performance of PVC and the Availability of Alternative Materials

The medical uses of plasticised PVC are based upon a combination of characteristics. With one possible exception, none of the functional characteristics of DEHP-PVC are unique. All can be individually replicated by other materials, particularly with respect to the mechanical characteristics that give the flexibility and softness coupled with reasonable strength and toughness. Thus there are other materials, including some non-DEHP plasticised PVC formulations, and some other polymers including polyethylenes, silicones and polyurethanes, which would be suitable for most medical applications. The value of DEHP-PVC lies within the combination of mechanical and barrier functional properties, coupled with the ease of fabrication, including the bonding of several components in medical devices, and the relatively low cost. It is, for example, possible to bond PVC components by solvent and welding techniques and the flexibility is ideally suited for catheter or tube insertion into the human body. In general, the cost of alternative polymers that could replicate the majority of the important properties of DEHP-PVC would be 5 to 10 times that of the PVC.

The one exception mentioned above is that of the performance of DEHP-PVC in blood bags. This is particularly relevant in the case of platelet concentrates, in which the plasticiser appears to provide a greater level of oxygen permeability thus giving extended platelet stability. This is difficult to replicate in other polymers.

The main alternative materials include ethylene vinyl acetate (EVA), polyesters, various polyolefins, silicone elastomers and certain polyurethanes. Neither EVA nor the polyesters have gained much acceptance because of limitations to properties and processibility in certain areas. Similarly, a variety of polyolefin blends and laminates have found some uses but with limitations. Both silicone elastomers and polyurethane thermoplastic elastomers have more acceptable properties and can be used for nasogastric tubes, venous and arterial cannulas and other tubing. A number of PVC products that come into contact with blood within the vascular system are coated with an anti-coagulant such as heparin in order to improve blood compatibility. Any surface coating should reduce the amount of DEHP that leaches from the surface,

although it is of course necessary to determine the stability of the coating and to carry out a risk analysis related to its own biocompatibility characteristics.

No effective PVC-free material is yet available for widespread blood product usage and for the vast majority of circumstances, non-DEHP-PVC materials are far from price competitive with DEHP-PVC.

3 DEHP Toxicity

In view of concerns from both environmental and medical device exposure perspectives, many studies of the possible toxic effects of DEHP have been undertaken. Recent overviews of DEHP toxicity and risk assessments include governmental reports, such as those from Health Canada (Health Canada, 2002), the Food and Drugs Administration of the USA (FDA, 2002a, 2002b), the Austrian Federal Ministry for Social Security and Generations (Schulte-Hermann *et al* 2001) and the European Commission (ECB, 2001; CSTEE, 1998, 1999, 2002), reports from independent or non-governmental bodies such as the International Association for Research in Cancer (IARC 2000), the World Health Organisation (WHO, 1992) and Health Care Without Harm (Health Care Without Harm, 2000; Rossi and Muehlberger, 2000), and individual researchers (e.g. Tickner *et al* 2001; Latini, 2000). These reviews generally conclude that there should be no concerns for the vast majority of adults in relation to toxicity following DEHP exposure. For children, the situation is different. On the basis of *in vitro* and *in vivo* toxicity studies, there are concerns for testicular toxicity, depressed fertility and reproductive developmental toxicity following oral exposure to PVC containing DEHP in children. In view of these concerns, the use of DEHP in soft toys has recently been forbidden in some areas (European Commission, 1999). However, there are no general concerns for either adults or children in relation to acute toxicity, irritation, sensitisation, mutagenicity or carcinogenicity

As noted earlier, PVC is used in a wide variety of medical products that are employed in the treatment of seriously or chronically ill individuals, either adult or children and consideration must be given to the fate of DEHP in this small minority of patients. Thus, it has been argued that other specific risks groups could be patients in contact with medical equipment resulting in very high short-term exposures or high exposures over sustained periods of time. These include adults undergoing long-term haemodialysis that involves PVC tubing and other components, patients requiring extensive blood or blood product transfusions that are stored in PVC bags, and patients undergoing extensive parenteral nutrition or extracorporeal membrane oxygenation. The basis for concern here is that in such cases the exposure could approach the doses that induce certain types of toxicity in rodents, especially those involving reproductive or developmental toxicity.

In the following sections, the data that are relevant to the conclusions about potential toxicity in these risk groups are discussed.

3.1 Reproductive Toxicology and Endocrine Disruption

There are very few data that characterise reproduction and developmental toxicity of DEHP in humans. Conclusions on human reproductive and developmental risks

therefore have to be drawn from studies in experimental animals. It has to be recognised here that species differences, especially in relation to the role of the peroxisome proliferator-activated receptor alpha (PPAR-a), an important factor in DEHP toxicity as discussed later, are critical.

In a recent two generation oral reproductive study of DEHP in rats (Schilling *et al*, 2001), the No Observed Adverse Effects Level (NOAEL) for reproductive performance and fertility was 340 mg / kg / d, and for developmental toxicity 113 mg / kg / d. A NOAEL in the same range following oral administration of DEHP was observed for reproductive and testicular toxicity in the rat (Wolfe *et al*, 2002). In a continuous breeding study in mice, DEHP decreased fertility in both males and females, with a NOAEL of 20 mg / kg / d (Lamb, 1987). The question of reversibility also arises. For testicular toxicity in mice, partial recovery was observed after chronic exposure of 78 weeks (at which time the incidence of testicular toxicity was significantly greater than controls), that was followed by a recovery period of 26 weeks, while in rats no recovery was seen (David, 2001). Also for liver and kidney toxicity, partial recovery was observed both in rats and mice.

The important observations of Sjoberg in relation to the evaluation and interpretation of DEHP toxicity studies (Sjoberg *et al*, 1985a, 1986) showed that developing males are more sensitive to DEHP-induced testicular toxicity after oral administration than sexually mature animals. Also, low levels of pre and post natal exposure to DEHP in drinking water in rats resulted in testicular effects that were reversible (Arcadia *et al*, 1998), these results being of potential relevance to the clinical situation, notwithstanding some limitations in experimental design.

Testicular toxicity has been noted in a number of repeated dose experiments in rats and mice. In a 90 day study in rats, dose dependent Sertoli cell vacuolation was demonstrated, with a NOAEL of 3.7 mg / kg /d (Poon, 1997). The Scientific Committee On Toxicology, Ecotoxicity and the Environment (CSTEE) of the European Commission has previously used this NOAEL value in its Opinion on DEHP, dated November 1998 (CSTEE, 1998). The results of the Poon study, however, may not be a suitable basis for the risk assessment of reproductive toxicity in humans, since the study was not designed to measure reproductive performance and since some minimal testicular tubular atrophy was observed in control animals.

According to Gray (Gray, 2000) and Moore *et al*, (Moore *et al*, 2001), combined *in utero* and lactational exposure to DEHP resulted in abnormal sexual development in male rats, with severe male reproductive system toxicity. A NOAEL of 375 mg / kg / d was observed by Moore *et al*.

3.2 Sensitisation / Immune System Effects

There are no clear indications that DEHP is a skin sensitiser in animals or humans. One recent case report suggested that the induction of contact urticaria syndrome could be due to DEHP (Sugiura *et al*, 2002) but this has not been observed elsewhere. There is no evidence that DEHP causes any respiratory symptoms related to sensitisation. A study of human infants indirectly linked bronchial obstruction to the presence of DEHP from PVC in floor material (Jaakkloa *et al*, 1999), although further analysis revealed an exposure-response relationship between the assessed amount of

PVC and other plasticiser-containing surface materials, so that a direct link between DEHP and bronchial adverse effects could not be confirmed.

When mixed with an antigen, DEHP was found to exert adjuvant activity by enhancing antibody responses to the model antigen ovalbumin (Larsen *et al*, 2001a). The major metabolite of DEHP, MEHP (monoethylhexylphthalate) induced immunosuppression, i.e. reduced antibody titres, when the same protocol was used (Larsen *et al* 2001b), indicating that DEHP and its metabolites have the potential to interact with the immune system in various ways, although it is unknown whether such effects are observed in humans after oral or parenteral exposition to DEHP.

3.3 Mutagenicity and Carcinogenicity

The genotoxicity of DEHP has been studied extensively in a wide range of in vitro and in vivo test systems, including in vivo carcinogenicity. DEHP induces liver tumours in rats and mice by the activation of the PPARa receptor, a mechanism considered not to be relevant in humans (IARC, 2000). Risk assessment data do not support a classification of DEHP, or indeed MEHP, as either genotoxic or carcinogenic (ECB 2001; CSTEE, 2002)

3.4 Acute Toxicity

DEHP has a very low toxic potential by oral (LD50 > 25 g / kg in rats and mice) and inhalation routes. Acute toxicity studies by the dermal route are lacking, although the toxic potential following dermal exposure must be considered minimal when taking into account the low dermal bioavailability (ECB, 2001; CSTEE 2002). The intravenous acute toxicity of DEHP is higher, with an LD50 in the region of 200 – 250 mg / kg in rats. The acute toxicity of MEHP is about five times higher than that of DEHP.

3.5 Toxicokinetics and Bioavailability

The determination of the toxicokinetics and bioavailability of a compound relies on data from experimental animals, and it is well known that there are variations between species, including man. For DEHP, there appear to be both similarities and differences when comparing, for example, rats, mice and monkeys (ECB 2001), although it is important to note that there is a similar degree of oral absorption in these species.

The first stage in the metabolism of DEHP is hydrolysis to MEHP and 2-ethylhexanol. Very little parent compound is detected in rat urine since the hydrolysis to MEHP takes place rapidly in the intestine, and further hydrolysis takes place after absorption. MEHP is the major metabolite found in mouse and monkey urine, but is not detectable in rat urine, whilst in both rats and, to a lesser extent, monkeys, MEHP is further metabolised via an oxidation pathway. In addition, in monkeys a substantial part of the excreted metabolites consists of glucuronic acid conjugates, but these are absent or negligible in rats.

Most studies indicate approximately 50% urinary excretion, indicating 50% oral bioavailability. Experiments with cannulated rats show biliary excretion at 5 – 10%

of an oral dose. It is therefore conceivable that up to 70% of an oral dose of DEHP could be absorbed from the intestine in rats (CSTEE, 2002). In rats, almost all of the remaining dose of orally administered DEHP is recovered in the faeces. In lactating rats, both DEHP and MEHP may be demonstrated in the milk after high oral doses (Dostal *et al*, 1987).

Little data exists on bioavailability in humans. One experiment with 2 adult male volunteers showed a urinary elimination of 15 – 25% of DEHP given orally at 10 mg / kg over 4 days (Schmid and Schlatter, 1985) whilst in another experiment one adult volunteer eliminated 31% of a single oral dose of 66 mg DEHP in the urine.

There are no oral absorption data from human infants. In the risk characterisation for infants and children, a 100% systemic bioavailability was assumed for young children in comparison to 50% for adults. This adjustment factor of 2 was used for bioavailability of DEHP in children aged between 6 months and 3 years on the basis of information from a rat study (Sjoberg *et al*, 1985a). As this experiment was performed at a very high single dose of DEHP, 1000 mg / kg, a dose at which DEHP hydrolysis appears to become saturated in rats, the CSTEE found it difficult to support the use of the bioavailability adjustment factor of 2 (CSTEE, 2000).

Nevertheless, the best approximations for bioavailability of DEHP in humans are 50% after oral ingestion in adults, 100% in children aged between 6 months and 3 years after oral ingestion, 75 % in both adults and children after inhalation and 5 % in adults and children after dermal exposure.

3.6 Target organs for DEHP Toxicity

Critical target organs in laboratory animals with respect to DEHP toxicity are the liver, kidney and testis. In particular, effects on the liver, (hepatomegaly), are linked to the effect of DEHP and its metabolite MEHP, mediated via PPARa. There are, however, marked species differences in the PPARa – mediated effects of DEHP, such that the hepatotoxic effects of DEHP in rodents are not judged to be relevant for humans (IARC, 2000).

The involvement of the PPARa receptor in the toxic effects of DEHP in kidney and testis was demonstrated by the use of knock-out mice lacking PPARa (Ward *et al*, 1998). In these mice, kidney and testicular toxicity was less pronounced after feeding with a diet containing DEHP for 4, 8 and 24 weeks, compared to wild-type mice. However, prolonged treatment for 24 weeks resulted in mild cystic lesions in the kidney and severe tubular lesions in the testis of the knock-out mice, indicating a degree of PPARa-independent toxicity. The cystic tubular kidney lesions induced in both wild type and knock out mice by high doses of DEHP resemble those seen in renal dialysis patients, although there is no evidence of any causal relationship in these patients (Ward, 1998; Woodward, 1988).

The risk assessment of ECB (ECB 2001) assigns a NOAEL for kidney toxicity of 28.9 mg / kg /d in males and 36.1 mg / kg / d in females on the basis of increased absolute and relative kidney weights in 2 year old rats (Moore, 1996). The CSTEE is in agreement with these values (CSTEE, 2002).

Endpoints for the evaluation of DEHP toxicity in rats are the effects on kidney and testis, of which the most critical effect for risk characterisation is testicular toxicity. A number of critical points have to be taken into account. Sjoberg (1985a) found that immature young animals were susceptible to testicular toxicity after oral administration of DEHP, whilst older, more mature animals were not. In contrast, intravenous administration did not show a difference in testicular toxicity between old and young animals (Sjoberg, 1985b). However, in studies in 12 to 15 month marmoset monkeys exposed to DEHP at levels of 100, 500 and 2500 mg / kg / d for 13 weeks, no testicular or other effects were observed (Kurata *et al*, 1998). In contrast, abnormal liver histology was observed in rhesus monkeys undergoing long-term transfusion with platelet rich plasma stored in DEHP-PVC (Kevy and Jacobsen 1982). These studies were performed in older animals and it is also possible that younger animals may be more sensitive towards testicular toxicity

3.7 Comment

The above discussion suggests that on the basis of animal experiments and observations, there are demonstrable effects of DEHP with respect to kidney toxicity and to testicular toxicity and reproductive behaviour. Major questions arise, however, with respect to the levels of exposure in animals that can result in such effects, the reversibility of toxic effects and the relevance of mechanisms of toxicity in rodents that are primarily PPARa dependent to toxicity in humans. One study has suggested that the NOAEL could be as low as 3.7 mg / kg / d, although the criteria for toxicity was Sertoli cell vacuolation believed to be a precursor for tubular atrophy in the context of testicular toxicity. Most other studies with different end-points produce NOAEL values ranging from 30 to 300 mg / kg /d. It is unclear what duration of exposure is necessary to induce effects or whether these effects are reversible on cessation of exposure. The vast majority of evidence concerning the existence of DEHP related toxic effects has been derived from rodent studies and it is clear that there are significant differences even within these species concerning the effects. Even more noticeable are the differences between rodents and other species, and no toxicity has been observed in marmosets. Extrapolation of the rodent results to humans has not been demonstrated. It should be pointed out, however, that there is evidence of greater sensitivity to DEHP in young immature animals compared to mature animals, and this has to be taken into account in the consideration of risks to human neonates.

4. EXPOSURE TO DEHP

4.1 Environmental Exposure

As noted earlier, several million tons of di(2-ethylhexyl) phthalate (DEHP) are produced per year and used in many consumer goods and construction materials, especially those made of flexible PVC. Consequently, it can be detected as an ubiquitous contaminant in the home, workplace and the environment in general (Huber *et al* 1996; Moore *et al*, 2001). A comprehensive review of the DEHP fate in the environment has been published by Staples *et al* (Staples *et al* 1997).

The main source of exposure to DEHP for the general population is dietary, including drinking water, followed by inhalation of air. Food contains DEHP, especially in fat (fish, milk, oils), derived from environmental contamination by this agent and bioaccumulation along the food chain, and from leaching during the process of manufacturing, packaging and storing (Huber, 1996; Moore *et al*, 2001, Hinberg, 2002).

The average level of exposure to DEHP from all sources in the general population has been estimated to be in the range of 3 to 30 µg / kg body weight / day (Huber 1996, Doull *et al* 1999, Moore *et al* 2001, Health Canada 2002). Nonetheless, there exist important differences among populations and individuals associated with various dietary habits and lifestyles such that in certain cases daily intakes in the order of a few mg / kg can arise (Staples *et al*, 1997; Schultze-Hermann *et al* 2001). It has also been reported that the daily intake is higher in 0.5–4-year-old children than in adults (Health Canada, 2002).

The EU Scientific Committee on Food has recommended a tolerable daily intake (TDI) for DEHP of 50 µg / kg (SCF, 1996). Likewise, for the exposure of children to DEHP from PVC toys a TDI of 50 µg / kg / d was estimated by the EU Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE, 1998, 2002).

Maximum occupational exposures to DEHP, mainly by inhalation, are generally set at 0.7 mg / kg /d when the workplace air concentrations meet the TWA (Time Weighted Average) standard for 8 h, usually 5 mg / m^3 (Doull *et al*, 1999; Schultze-Hermann *et al*, 2001).

4.2 Experimental and clinical data on exposure following medical and dental treatments

It has been known for many years that patients treated with DEHP-containing PVC medical devices can show high levels of blood and tissue DEHP and its main metabolite mono(2-ethylhexyl) phthalate (MEHP). The exposure to DEHP leaching from PVC varies widely according to the medical procedure, the type of device and the substances with which it is in contact. The following paragraphs summarise the most relevant data relating to children exposure collected from the literature.

4.2.1 DEHP in blood components

Infusion of blood and its components is one of the major routes of exposure to DEHP in infants and adults. DEHP leaches from the PVC blood bag during storage and from the tubing used during infusion, and MEHP is formed by the metabolism of DEHP by blood during storage. Whole blood has been reported to contain from 20 to 115 mg / l of DEHP and up to 5 mg/l of MEHP depending on the conditions of storage (Latini 2000; Loff et al 2000; Schulte-Hermann *et al* 2001). DEHP content in platelet-rich plasma may be up to 181 mg / l and MEHP up to 31 mg / l while in platelet concentrates the levels are 180-650 mg / l and up to 76 mg / l, respectively. High concentrations of DEHP are also found in fresh frozen plasma, up to 405 mg/l, and even higher levels in stored plasma (Loff *et al*, 2000; Schulte-Hermann *et al*, 2001).

In neonatal tissues, after infusion of blood products, DEHP has been detected in amounts of 0.66-1.27 µg / g in the heart and of 0.02-0.13 µg / g in the intestine (Hillman *et al* 1975, Latini 2000). In replacement blood transfusions it has been calculated that infants receive a DEHP dose of 1.2-22.6 mg / kg / d (Plonait *et al* 1993).

4.2.2 Parenteral nutrition

Parenteral and enteral feeding represent important sources of exposure in neonates for which there are only scarce and indirect reports in the literature. Estimates of exposure based on the data of Mazur *et al*, (1989) and Loff *et al*, (2000) indicate that total parenteral nutrition (TPN) for a neonate involves the infusion of 10-20 mg / day of DEHP. This implies an average dose of 5.1 mg / kg /d. Loff *et al* (2000) relate this DEHP exposure from TPN to a hepatobiliary dysfunction observed in children, as discussed later.

4.2.3 Extracorporeal membrane oxygenation (ECMO)

Exposures from this procedure in neonates have been estimated as important, ranging up to 35 µg DEHP / ml plasma. Karle *et a*l (1997) have reported, in a group of 18 infants requiring ECMO, that the average highest concentration of DEHP in plasma at any time on bypass is 8.3 ± 5.7 µg / ml. They associate chronic exposure to DEHP with the possibility of toxic side effects observed in infants, including, in this category, cardiac (Barry *et al* 1989) and liver dysfunction (Jacobson *et al* 1977), testicular atrophy (Woodward 1988), shock lung and hepatomas (Schultz *et al* 1975).

4.2.4 Artificial ventilation.

In neonates and pre-term infants with artificial ventilation, exposure to DEHP may reach amounts up to 4.2 mg / hour. Extraction of DEHP from endotracheal tubes ranges from 60 to 120 µg / mg of sample (Latini, 2000).

4.2.5 Other exposures in neonates

The two following tables, data taken from the Report prepared for Health Canada, summarize provisionally other exposures to DEHP and MEHP in neonates not yet described here.

Note that MEHP always accompanies DEHP, which is almost always present in much larger concentrations. Total MEHP exposure is therefore the sum of exposure from MEHP formed *in vitro* and exposure from MEHP formed by *in vivo* hydrolysis of DEHP. There are no reliable data on the rate of *in vivo* conversion of circulating DEHP to MEHP and estimates of the total MEHP exposure from different medical procedures are unavailable.

Table 1

Reported DEHP Exposures in Neonates (*data from Health Canada, 2002*)

Medical Procedure	[DEHP], µg/mL Mean (Range)	Exposure Time	Dose Mean (range)	Comments	Reference
Congenital Heart Repair	1.8 (0.73–4.66)	1 - 4 hr	1.8 (0.3 – 4.7) µg/mL/hr	Dose in whole blood; difference before and after procedure	Barry (1989)
Exchange Transfusion	47.0 (4.3–123.1)	1.3–3 hr	Not available	Pre- and post-treatment [DEHP] measured	Plonait (1993)
Exchange Transfusion	58.5 (36.82 - 84.9)	Not Stated	2,950 1,710 - 4,220 µg/kg bw	Calculated from [DEHP] in whole blood stored in bags	Sjoberg (1985a)
Double Volume Exchange Transfusion	38 (13.8 - 71.9)	Not Stated	1,770 (840-3,300) µg/kg bw	Area under curve calculation	Sjoberg (1985b)
ECMO	26.9 33.5	3 - 10 days 24 days	Up to 140,000 µg/kg bw/	Estimate of maximum exposure based on blood levels and certain assumptions. (See text).	Shneider (1989)
ECMO	0 - 34.9[1]	10 days	0 - 35,000 µg/kg bw	Estimates based on blood levels and *in vitro* leaching rates measured on the three circuits.	Karle (1997)

[1]Depending on the circuit.

Table 2

MEHP Exposure from Medical Procedures (*data from Health Canada, 2002*)

Procedure	[MEHP] µg/mL	Procedure Time	Dose/Time	Comments/Source
ADULTS				
CABG	0.15–1.7	83.9 ± 15.9 minutes	2,200–80,000 µg/operation	Calculated from post-measurements (Barry, 1989)
Heart Transplant	not given	1.3–5.6 hours	450–2,500 µg/operation	Calculated from post-measurements (Barry, 1989)
Artificial Heart Transplant: Jarvik Bridging	not given	several days	250–18,800 µg/day	Barry, 1989
CAPD	0.001–0.022 controls 0.0145 (0.005–0.023)	Not stated	Not stated	(Mettang, 1996)
CAPD	0	Not Stated	None absorbed	(Nassberger, 1987)
Hemodialysis	1.33±0.58	4 hours	not given	AUC, circulating MEHP (Pollack, 1985)
NEONATES				
Congenital Heart Repair	0.66–2.66		0.6 (0.03–2.7) µg/mL/hr	Retained dose in whole blood, difference before and after procedure (Barry, 1989)
Exchange Transfusion	5 (Maximum)		100 (5–200) µg/kg	AUC calculation (Sjoberg, 1985a)
Exchange Transfusion	7.06 (3.03–15.6)		360 (160–680) µg/kg	Assumes linear extraction (Sjoberg, 1985b)

4.2.6 Exposure to DEHP Following orthodontic treatment

In relation to the orthodontic treatment involving the use of PVC based retainers, very little data is available. One report has evaluated the potential daily intake of DEHP based on the mass loss sustained by retainers in organic solvents (Liilanen *et al*, 2000). The migration was calculated to be of the order of 1 mg / hour, which could lead to a daily oral intake of 10 mg.

5 Clinical and Epidemiological Evidence of DEHP Toxicity

Humans are exposed to DEHP as the consequence of medical treatment with devices containing PVC. As noted in the above sections, patients receiving haemodialysis or peritoneal dialysis, blood transfusions, artificial ventilation and exchange transfusions are at risk. A particular risk group as far as exposure is concerned is that of premature infants who may be exposed to relatively high amounts of DEHP when they receive blood transfusions, extracorporeal membrane oxygenation and respiratory therapy (Sjoberg *et al* 1985a, 1985b; Roth *et al*, 1988; Plonait *et al*, 1993). The following sections summarise the evidence for toxicity caused by the clinical use of PVC containing medical devices.

5.1 Clinical Case Studies

The ample evidence for DEHP toxicity in experimental animals was discussed in Section 3. The clinical evidence for toxicity is, however, much more sparse. An accumulation of DEHP in various tissues after blood transfusions has been described (Jaeger and Rubin, 1972) while other studies show no appreciable tissue accumulation (KEMI, 2000). The evidence for toxicity in clinical settings is best discussed in relation to the different target organs.

5.1.2 Testicular Toxicity

The well-documented toxicity in rodents has not been found in primates (Kurata et al, 1998) and there are no reports of testicular toxicity in humans, even in cases where the dose received corresponds to doses that cause reduced fertility in rodents. The reason may be that primate cells are probably less sensitive to DEHP and MEHP because of lower levels of the PPARa receptor (Gonzales *et al*, 1998).

5.1.3 Developmental Toxicity

In spite of numerous reports of toxicity in rodents, no cases of developmental toxicity (teratogenesis) in humans or sub-human primates have been described.

5.1.4 Nephrotoxicity

There are suspicions of the possible development of polycystic kidney disease in patients undergoing chronic haemodialysis on the basis of experiments in rats (Crocker *et al*, 1988) but no clinical evidence has been reported.

5.1.5 Pulmonary toxicity

A respiratory distress syndrome is caused in rats after intravenous administration of high doses (200 mg / kg) of DEHP (Huber *et al*, 1996). One report has been published on pathological changes in the lungs in mechanically ventilated pre-term infants where PVC tubes had been used. The five infants had been exposed to up to 4.2 mg / hour of DEHP from the tubing, although no causation can be determined from these observations.

5.1.6 Cardiotoxicity

There are no clinical reports of cardiotoxicity associated with DEHP.

5.1.7 Hepatotoxicity

Liver abnormalities have been observed in rodents, rhesus monkeys and humans after DEHP exposure, these abnormalities including the development of peroxisomes, effects on metabolic enzyme activity and reduction in liver function. Rhesus monkeys receiving plasma transfusions from DEHP-containing PVC blood bags for periods up to one year, with an accumulated yearly dose of 1500 mg DEHP, developed abnormalities in liver histology, including hepatocyte degeneration and necrosis and binucleate cells, and in liver function, as measured by sulphobromophthalein transport, that persisted for up to 26 months after treatment (Jacobsen *et al* 1977, Kevy and Jacobsen, 1982). Liver biopsies from patients undergoing haemodialysis two to three times per week showed histological abnormalities, including the induction of peroxisomes, after one year of dialysis but not after one month (Ganning *et al*, 1984, 1987). These patients had not received any drugs known to have peroxisome-proliferating effects. In a study of 29 infants with serum levels of 18-98 µg DEHP / ml following an extracorporeal membrane oxygenation therapy session, Schneider *et al* found that the degree of cholestasis was significantly correlated with DEHP exposure (Shneider *et al*, 1991). Plonait *et al* did not detect evidence of cholestasis in infants exposed to smaller amounts of DEHP (Plonait *et al*, 1993).

5.1.8 Carcinogenicity

In rats and mice, DEHP causes malignant hepatocellular tumours (Kluwe *et al*, 1982; KEMI, 2000). The increase in hepatocellular adenomas in male mice is dose-dependent at doses ranging from 98.5 to 1226 mg / kg /d, and in rats at doses ranging from 146 to 789 mg / kg / d compared to controls (Moore, 1996, 1997). However, there is debate as to whether this is relevant to humans (Melnick and Kohn, 1996). Recent research has shown that PPAR plays a central role in mediating the carcinogenic effect of peroxisome proliferators, and as noted above, PPARa knockout mice do not exhibit the same carcinogenic responses in the liver (Gonzales *et al* 1998, Ward *et al*, 1998). Because humans have less than one-tenth the level of PPARa expression in the liver compared to the mice, and because many PPAR-binding sites in humans may be occupied by competing proteins, they may be less likely to develop liver cancer after exposure to peroxisome proliferators (Doull *et al*, 1999). Despite evidence that the mechanism of DEHP induced carcinogenesis in animals may not be applicable to humans, some researchers conclude that the possibility of DEHP-related carcinogenic responses in humans cannot be ruled out (Melnick and Kohn, 1996).

5.2 The Importance of PPARa Receptor for Pathogenic Effects of DEHP

For non-carcinogenic effects of DEHP, recent studies in mice lacking the PPARa receptor show that fetotoxicity, teratogenicity, testicular lesions and kidney effects of DEHP occur at least partly independent of peroxisome proliferation (Peters *et al*, 1997; Ward *et al*, 1998). Thus studies of these effects in various animal models are likely to be directly relevant to humans. For example, the testicular toxicity of DEHP appears to be at least partially explained by interference with the binding of follicle-

stimulating hormone to its receptor on Sertoli cells (Lloyd and Foster, 1988). In an *in vivo* study, Maloney and Waxmen (1999) found that MEHP activated both mouse and human PPAR?. PPAR? is highly expressed in various human tissues including adipose tissue and immune cells (Roberts, 1999). However, the mechanisms of DEHP toxicity are likely to be multiple and variable, depending on the organ, age and species studied.

5.3 Clinical Reviews

A number of recent reviews have evaluated the evidence for clinical toxicity of DEHP. Huber *et al* (1996) comment on the hepatocarcinogenic potential of DEHP in rodents and possible extrapolations to carcinogenicity in humans. They conclude that carcinogenicity caused by DEHP is highly unlikely in humans. The same authors (Schulte-Hermann *et al,* 2001) have made a comprehensive review for the Austrian government on possible effects of DEHP and its metabolites on reproduction. A number of documented effects in rodents are reported, but two studies in subhuman primates (Kurata *et al,* 1998; Pugh *et al,* 2000) show no evidence of toxicity. They conclude, however, that a risk for testicular damage by DEHP exposure in humans cannot be denied. Latini (2000) makes the general comment that more in-depth studies should be made on the effect of long-term exposure, especially in pregnant women and children. Hill *et al* (2001) have evaluated the possible health risks that are associated with DEHP plasticised PVC in medical devices and comment on the so-called Blue Ribbon or Koop report (American Council on Science and Health, 1999) that concluded that DEHP in medical devices was not harmful regardless of the medical treatment of the individual. Hill *et al* (2001) did not agree with this conclusion and suggested that more research is needed to clarify the situation. Gourlay (2001) has discussed the problems associated with the materials used for cardiopulmonary bypass and has suggested that an inappropriate inflammatory response develops, which they consider to be probably due to DEHP. They suggest that this could be avoided by removing the plasticiser or coating the tubes with heparin. As noted elsewhere in this opinion, there are other potential sources of inflammation associated with the use of extracorporeal circulation equipment and the coating of PVC is not necessarily without its own problems. Finally, Tickner *et al* (2001) have reviewed the toxicity data from studies in animals and humans with respect to different organs. They have concluded that the observed toxicity of DEHP and the availability of alternatives present a compelling argument for moving assertively, but carefully, to the substitution of other materials for PVC in medical devices.

5.4 Epidemiology

There is no doubt that many different patient treatment technologies result in relatively high DEHP exposure. These technologies are varied with respect to the manner in which they expose the patients to DEHP. For example, DEHP exposure levels related to blood transfusions are strongly affected by the temperature of pre-treatment storage of blood bags, and those that are the subject of thrombocyte infusion may have relatively high exposure. Parenteral lipid nutrition is a particularly abundant source of DEHP whereas haemodialysis patients may experience an exposure up to 12 grams per year.

Many paediatric patient groups are exposed to fairly high DEHP levels, for example those who undergo open-heart surgery and pre-term infants who receive DEHP through multiple sources. Premature infants provide a special case with respect to length, level and timing of exposure. A recent study by Loff *et al* has established very high DEHP exposure levels for pre term neonates (Loff *et al* 2000). According to this study, pre-term neonates are exposed to 10 mg / kg / d DEHP over several weeks, a level that is over 1100 times greater than that of the average adult (in Canada where the study was carried out). This study has raised particular concerns about the hazards associated with current neonatal care as these levels come close to rodent toxicity levels or even exceed the exposure levels at which Sertoli cell vacuolation effects have been observed in rat testes. It must also be remembered that premature babies are exposed to high DEHP levels from multiple sources, starting from the late second trimester when organogenesis has been completed but when practically all tissues are still immature.

In view of the conclusion that pre-term and newborn infants may be the highest risk group with respect to DEHP exposure, it is important to explore the data concerning their development and morbidity over time. In the context of this Opinion, it is particularly important to address the natural history of those who are born alive and survive the early hours with very or extremely low birth weights.

5.4.1 Pre-term Infants

Very Low Birth Weight (VLBW) infants are those that weigh more than 1000 grams but less than 1500 grams. Extremely Low Birth Weight (ELBW) infants weigh less than 1000 grams. In general, Low Birth Weight (LBW) infants are those babies that are born less than 2500 grams irrespective of gestational age.

The history of VLBW patients goes back to the late 1960's and early 1970's, before which date the infants with such birth weights were unlikely to survive. During the 1980's and 1990's there was a rapid development of ELBW patient survival. Initial mortality of VLBW and ELBW patients has been described in detail (e.g. Tommiska *et al* 2001). The incidence of VLBW and ELBW infants accounts for approximately 0.6 % per annum of all births, less than half belonging to the ELBW category (Ikeda *et al*, 1997). In the European Union, slightly less than 20 000 VLBW and ELBW children are born annually. Taking into account this history, the rarity of this obstetric phenomenon and clinical mortality data, it may be assumed that there are a few hundred thousand children and young adults in the European Union now alive that would have been classed as VLBW or ELBW at birth, and who have probably been exposed to high levels of DEHP.

5.4.2 Health Status and Development of ELBW and VLBW Cohorts

Recent reports from Scandinavia and the USA have demonstrated again the high initial mortality, in the very early hours or days, of these groups of infants. Subsequent mortality and morbidity of ELBW individuals remains high compared to

children of normal birth weight, although the morbidity of VLBW children comes close to the controls. In the most recent Finnish study, initial mortality is very high and 51% of total deaths occur before the 12th hour and 86% before seven days. Neither the temporal nature of death, nor the causes of death themselves give any indication of early acute effects by phthalates, or any other unknown exposure, and the underlying causes are plausibly explained by the generally grave problems of these premature infants (Tommiska *et al*, 2001). Survival rates with ELBW infants is positively dependent on gestational age, those ELBW infants who reach 30 weeks having an almost 100% survival, whilst very few of those born before 24 weeks survive.

A typical study investigating subsequent morbidity and well-being of VLBWs and ELBWs focused on neurodevelopmental patterns, other developmental parameters and respiratory health (Hack and Fanaroff, 1999). Studies usually consist of one or two hundred individuals born pre-term (Hack *et al* 2002). An exceptionally large cohort from a multi-centred study in the USA included 1151 ELBW children and developmental parameters were reported up to the age of 22 months (Vohr *et al*, 2000). A long 20 year follow-up study on 242 VLBW (n=184) and ELBW (n=58) individuals was recently reported (Hack *et al*, 2002), in which it was evident that ELBW individuals lag in neurodevelopment parameters, but show no apparent difference concerning male fertility. There was a slightly decreased risk of pregnancy (29% vs 41%) in women among the VLBW category. An older Australian study found similar age of onset of puberty among ELBW individuals compared to controls (Kitchen *et al*, 1987).

5.4.3 Hepatoblastoma and Pre-term Infants

Publications from the Japanese National Cancer surveillance programme are of potential significance to the question of whether early life exposure to phthalates might have hepatotoxic effects (Ikeda *et al*, 1997,1998). This Japanese programme covers 50-60% of all childhood malignancies. Through this passive surveillance, a relatively high risk of hepatoblastoma was established. The Japanese investigators reported hepatoblastoma in 9 pre-term infants. The follow-up period was 1985 to 1993 and 8 out of the 9 individuals developed the tumours in the latter period, the highest risk being among the ELBW infants. The investigators calculated the incidence to be 1 in 10 000 in 1992. The baseline incidence of hepatoblastoma is 1 in 1 million, which indicates that the 1992 ELBW individuals had a 100 fold relative risk compared to the baseline.

An independent corroboration of the Japanese study was published by radiologists from the Children's Hospital in Michigan (Ribons and Slovis, 1998). They described a series of hepatoblastomas in which ELBW patients were grossly over-represented, 6 out of 15 affected patients in a 10-year period belonging to this group. Assuming that 0.2% of individuals belong to the category of ELBW, an estimate of the risk gives an Odds Ratio of 323. This clearly overestimates the relative risk as the proportion represented by affected cases is much greater than 10%.

The patients in the Japanese study were usually diagnosed before their second birthday, with a median of 21 months, whereas the range in the USA study was 3 to 9

months. A further USA study has shown a small number of cases of hepatoblastoma in children (Ross and Gurney, 1998).

It is important to note that none of the authors of the above epidemiological studies have discussed their findings in relation to DEHP and no causal relationship has been reported.

5.4.4 Comment

There has been no hint of any acute toxicity related to DEHP among ELBW and VLBW infants and there has been no suggestion of any estrogen – like effects in maturing young adults, although it is admitted that the literature concerning this subject is very sparse. In general, the investigations of VLBW and ELBW children have not addressed DEHP since there are far more profound factors that affect their survival and development. DEHP is not a matter of concern for the majority of neonatologists in this context.

It is tempting to draw attention to the possible causality between hepatoblastoma and DEHP, as DEHP has multiple potential physiological effects, including an effect on hepatic enzyme activity. The fact that a 26 month old infant who weighed 900 grams at birth and who experienced prolonged periods of total parenteral nutrition could have developed hepatocellular cancer should be noted. To date, however, no association between this condition and any of the possible causes , such as viral infections, liver intoxication as a result of treatment related agents, alcohol abuse during pregnancy and contraceptive intake has been established. In this context, there are several factors that suggest that DEHP is not the causative agent. In particular, clinical and epidemiology data would suggest that hepatoblastoma is an embryonal tumour that results from developmental disturbances during organogenesis, occurring in the first trimester of pregnancy. The very short incubation period, apparently a couple of months in the major USA study, further suggests that genetic predisposition is the major factor, as externally induced malignancies usually require longer incubation times. Clearly there are many other agents to which mother and child are exposed and DEHP is a very minor concern.

6 Recommendations of Other Bodies

As noted earlier, several other organisations have reviewed the subject of DEHP toxicity in recent year and some have drawn specific conclusions and recommendations. These are summarised as follows.

6.1 The US Food and Drugs Administration

Most significantly, the Centre for Devices and Radiological Health of the FDA has released a draft document for comment which gives guidance for the medical device industry on this subject (FDA, 2002b). This document, which follows the publication of a substantial safety assessment of DEHP related to PVC medical devices (FDA, 2002a) specifically states that although the toxic and carcinogenic effects of DEHP

have been demonstrated in laboratory animals, there are no human studies that have shown such effects. It is known, however, that there are certain invasive medical procedures during which exposure to DEHP could exceed the lowest levels that cause adverse effects in animals, which suggests the possibility of adverse effects in patients. The FDA recognise that many devices with DEHP-PVC are not used in ways that result in significant human exposure to DEHP, and propose to focus only on small sub-sets of PVC medical devices. These sub-sets include certain intravascular tubing and catheters, products that store and deliver enteral and total parenteral nutrition formulae, and tubing used in enteral nutrition, including nasogastric tubes, with an emphasis on the use of such devices in neonates. The FDA are recommending that manufacturers consider eliminating the use of DEHP in such devices that can result in high exposure in sensitive patients and that certain products be labelled with their DEHP content. Advice will be given on how manufacturers should deal with PVC in relation to regulatory procedures.

6.2 Health Canada

An expert advisory panel was formed to advise Health Canada on the scientific evidence for any risk in relation to DEHP in medical devices, and possible actions that would reduce or eliminate exposure, and therefore any possible risks. The panel reported in January 2002 (Health Canada, 2002). Their recommendations included the following:

- Alternative products such as heparin coated tubes should be used for all extracorporeal membrane oxygenation (ECMO) procedures in neonates and infants,

- Tubing and storage bags used for the administration of lipophilic drugs that contain surfactants, should not contain DEHP,

- Total parenteral nutrition (TPN) solutions should be administered to newborns and infants only via products that do not contain DEHP.

- Research into further methods for reducing the release of DEHP from medical products should be urgently encouraged.

- The greatest risk groups are newborns including premature newborns, infants and young children, ECMO patients, cardiopulmonary bypass patients, exchange transfusion infant and children patients, patients receiving certain IV therapies, particularly those on TPN and those receiving lipophilic drug formulations.

- Additional groups possibly at risk include trauma patients receiving multiple blood transfusions, haemodialysis patients, oxygen therapy patients, children of breast feeding females, pregnant women and pre-pubescent males.

- Alternative measures are immediately justifiable to protect those patients most at risk.

- DEHP should continue to be used in blood bags.

- Labelling of products should reflect DEHP content.

- Health Canada should support and facilitate research that defines the real level of risk to humans from DEHP exposure.

6.3 The European Union

Various opinions of the Scientific Committees of the European Commission have dealt with DEHP and PVC in recent years, most notably concerning the Scientific Committee on Toxicity, Ecotoxicity and Environment (CSTEE). As already noted, this committee produced a report on soft toys and child care articles in 1998 (CSTEE, 1998), in which they concluded that the estimated margin of safety with respect to DINP and DEHP were rather low, at 8.8 and 67 respectively, whilst for other plasticisers the margins of safety were much higher. The committee recommended that guidelines for extractable amounts of individual phthalates in toys be produced, incorporating a margin of safety of at least 100 between exposure and NOAEL values.

The same committee has reviewed the risk assessment of the European Chemical Bureau (ECB 2001) and agrees with the majority of the conclusions of that assessment (CSTEE, 2002), both with respect to the environment and to human health.

7 Conclusions and Opinion

DEHP plasticised PVC has been used for several decades in medical devices. The functional characteristics and processibility of the material makes it very suitable for the construction of a wide variety of these devices, some of which are crucial to the delivery of care to critically or chronically ill patients. The contribution of DEHP-PVC to the delivery of health care should be taken into account in the consideration of the potential risks of adverse effects of DEHP in these patients.

It is recognised that the DEHP is able to diffuse through PVC and may leach out into its environment, including the environment of the human body should a DEHP-PVC article be in contact with that body. This is inherent in the structure and performance of plasticisers. The rate of leaching will vary with the nature of the plasticizer and of the environment.

As a result of this leaching process, patients may be exposed to DEHP. The extent of this exposure will vary, depending on device, treatment and individual variables. It is recognised that there may be multiple sources of exposure, including not only the specific medical device in question but also on the presence of PVC containing products in the general hospital, clinic or home environment, and on general environmental factors, including the presence of DEHP in water, food and the air.

Both *in vitro* and animal studies indicate several mechanisms of DEHP toxicity. The main target organs for DEHP toxicity are the liver, kidney and testes, with most

attention being paid to testicular toxicity. This is of concern since, in animal models, exposure has been shown to be more significant in neonates or very young animals compared to any other age, with the testes as the most susceptible organs. DEHP may possibly act as an anti-androgen. It is widely believed that the toxicity seen in rodents is largely mediated via peroxisome proliferation and the PPARa receptor, which are far less relevant in human toxicity, but there is some evidence that peroxisome receptor-independent toxicity my also occur. The majority of observations have been made in rats and mice. In limited studies, no testicular effects have been seen in non-human primates, even at high doses. Animal studies also have shown some effects in relation to developmental toxicity, with special relevance to exposure *in utero* and to the post natal period. There are no concerns over carcinogenicity in humans on the basis of animal studies. The general view of DEHP toxicity is therefore that mechanisms for adverse effects do exist in rodents, but that these do not appear to be of great significance in non-human primates and that the evidence that such mechanisms could be operative in humans is lacking.

Nevertheless, the levels of DEHP that induce toxic effects in rodents are of the same order as the exposure experienced by some neonates in clinical practice. This is the basis of concerns that have been expressed by a number of organisations concerning the potential of DEHP toxicity in humans.

However there are no reports concerning any adverse effects in humans following exposure to DEHP-PVC, even in neonates or other groups of relatively high exposure.

So far, for example, there are no indications that neonates of high DEHP exposure have any altered long-term fertility patterns.

Since this clinical view is based on limited studies and since there is still uncertainty over mechanisms of DEHP toxicity in animals and their extrapolation to humans, some concerns must still exist in spite of the lack of any reports of adverse events in any human patient group. It is recognised that a lack of data does not lead to a conclusion that DEHP is without adverse effects. Specifically it is agreed that in critically ill neonates, who constitute an inherently high-risk group of patients, the lack of evidence of causation between DEHP-PVC and any disease or adverse effect does not mean that there are no risks.

There are also other groups of patients or individuals who experience prolonged periods of elevated DEHP exposure, including patients on haemodialysis or in receipt of repeated blood product transfusions, where risks and benefits should be considered carefully. At the present there is no evidence that any of these groups do experience DEHP related adverse effects. Attention is drawn to those situations where the benefits of PVC are less clear, and specifically to the use of PVC orthodontic retainers.

In any consideration of restrictions on the use of PVC materials in medical devices, and especially DEHP-PVC materials, full account must be taken of the actual benefits of these materials and the balance between these benefits and risks. There are some alternative materials that can replace DEHP-PVC under some conditions, and indeed some coatings that could limit DEHP leaching, but it is always necessary to evaluate the risks and benefits of these alternatives.

In view of the lack of a full analysis of all risks associated with potential alternative materials, at this moment no specific recommendations can be made to limit the use of DEHP in any particular patient group. Nevertheless it is strongly proposed that detailed studies are performed and further data collected in order to monitor this situation.

On the basis of the evidence presented in this report, no Tolerable Intake Value for DEHP in medical devices can be recommended.

8 References

American Council on Science and Health, (1999) A Blue Ribbon Panel Report: A Scientific evaluation of Health Effects of Two Plasticisers Used in Medical Devices and Toys, (Chair, C. Everett Koop)

Arcadi RA, Costa CE, Imperatore C, Marchese A, Rapisarda A, Salemi M, Trimarchi G. and Costa G, (1998) Oral toxicity of DEHP during pregnancy and suckling in the Long-Evans rat, *Food Chem. Toxicol.*, **36**, 963-970.

Baker RWR, (1978) Diethyl phthalate as a factor in blood transfusion and haemodialysis, *Toxicology*, **9**, 319-329.

Barry YA, Labow RS, Keon WJ, Tocchi M and Rock G, (1989) Perioperative exposure to plasticisers in patients undergoing cardiopulmonary by-pass, *J.Thoracic Cardiovasc.Surg*., **97**, 900-905.

Crocker J, Safe S and Acott P, (1988) Effects of chronic phthalate exposure on the kidney, *J.Toxicol. Environ.Health*, **23**, 433-444.

CSTEE, (1998) Opinion on 'Phthalate migration from soft toys and child care articles' Scientific Committee on Toxicity, Ecotoxicity and the Environment, European Commission, Adopted on 24th April, 1998, Brussels, Belgium.

CSTEE, (1999) Opinion on 'The toxicological characteristics and risks of certain citrates and adipates used as a substitute for phthalates as plasticisers in certain soft PVC products, Scientific Committee on Toxicity, Ecotoxicity and the Environment, European Commission, Adopted on 28th Sept, 1999, Brussels, Belgium.

CSTEE, (2002) Opinion on The results of the Risk Assessment of bis (2-ethylhexyl) phthalate (DEHP). Report version Human Health, September 2001. Scientific Committee on Toxicity, Ecotoxicity and the Environment, European Commission, Adopted on 9th Jan 2002, Brussels, Belgium.

David RM, Moore MR, Finney DC and Guest D, (2001) Reversibility of the chronic effects of di(2-ethylhexyl) phthalate, *Toxicol. Pathol.*, **29**, 430-439.

Dostal LA, Weaver RP and Schwetz BA, (1987) Transfer of di(2-ethylhexyl) phthalate through rat milk and effects on milk composition and the mammary gland. *Toxicol. Appl. Pharmacol.,* **87**, 81-90.

Doull J, Cattley R, Elcombe C, Lake BG, Swenberg J, Wilkinson C, Williams G, and van Gemert M, (1999) A cancer risk assessment of di(2-ethylhexyl)phthalate: application of the new US EPA Risk Assessment Guidelines, *Reg. Toxicol. Pharmacol.,* **29**, 327-357.

ECB (European Chemicals Bureau), (2001) Risk assessment bis(2-ethylhexyl) phthalate. Consolidated Final Report Institute for Health and Consumer Protection, Joint Research Centre, Ispra, Italy: September 2001, (Doc R042 0109 env hh 0-3, and Doc R042 0109 env hh 4-6)

European Commission, (1999) The marketing of soft PVC toys and childcare articles, EC Decision 198/815/EC, 7th December 1999, Official Journal OJCE L315. 9th December 1999, Brussels, Belgium.

Fayz S, Herbert R and Martin AM, (1977) The release of plasticizer from polyvinyl chloride haemodialysis tubing, *J. Pharm. Pharmacol.,*, **29**, 407-412.

FDA, (2002a) Safety assessment of di(2-ethylhexyl) phthalate (DEHP) released from medical devices, FDA Centre for Devices and Radiological Health, 2002.

FDA, (2002b) Medical devices made with polyvinylchloride (PVC) using the plasticiser di-(2-ethylhexyl) phthalate (DEHP); Draft guidance for industry and FDA. Draft released for comment, FDA Centre for Devices and Radiological Health, Sept 6th 2002.

Ganning AE, Brunk U and Dallner G, (1984) Phthalate esters and their effect on the liver, *Hepatology*, **4,** 541-547.

Ganning AE, Brunk U, Edlund C, Elhammer A and Dallner G, (1987) Effects of prolonged administration of phthalate esters on the liver, *Environ. Health Perspect*., **73,** 251-258.

Gibson TP, Briggs WA and Boone BJ, (1976) Delivery of di-2-ethylhexyl phthalate to patients during haemodialysis, *J.Lab.Clin.Med*., **87**, 519-524.

Gonzales FJ, Peters JM and Cattley RC, (1998) Mechanism of action of the nongenotoxic peroxisome proliferators; role of the peroxisome proliferator-activator receptor alpha, *J.Natl.Cancer Inst*., **90**, 1702-1709.

Gourlay T, (2001) Biomaterial development for cardiopulmonary by-pass, *Perfusion UK*, **16,** 381-390.

Gray LE, Ostby J, Furr J, Price M, Veeramachaneni DNR and Parks L, (2000), Perinatal exposure to the phthalates DEHP, BBP and DINP, but not DEP, DMP or DOTP alters sexual differentiation of the male rat, *Toxicol.Sci.,* **58**, 350 –365.

Guess WL and Autian J, (1964) Biological testing of plastics to be used in medical practise, *Am.J.Hosp.Pharm*., **21**, 260-268.

Guess WL and Stetson JB, (1968) Tissue reaction to organo-tin stabilized PVC catheters, *JAMA*, **204**, 580-584.

Hack M and Fanaroff AA, (1999) Outcomes of children of extremely low birth weight and gestational age in the 1990's, *Early Human Development*, **53**, 193-218.

Hack M, Flannery DJ, Schluchter M Cartar L, Borawski E and Klein N, (2002) Outcomes in young adulthood for very-low-birth-weight infants, *N Engl J Med*, **346**, 149-57.

Hastings GW, (1982) Catheters in neonatology, In Williams, DF, (ed.), *Biocompatibility in Clinical Practice*, Vol.1, CRC Press, Boca Raton, 35-46.

Health Canada, (2002) DEHP in Medical Devices: an exposure and toxicity assessment. Medical Devices Bureau, Therapeutic Products Directorate, Health Products and Food Branch, Health Canada. Ottawa, Canada.

Health Care Without Harm, (2002) Neonatal exposure to DEHP and opportunities for prevention.

Hill SS, Shaw BR and Wu AHB, (2001) The clinical effects of plasticizers, antioxidants and other contaminants in medical polyvinylchloride tubing during respiratory and non-respiratory exposure, *Clinica Chimica Acta*, **304**, 1-8.

Hillman LS, Goodwin SL and Sherman WR, (1975) Identification and measurement of plasticiser in neonatal tissues after umbilical catheters and blood products, *New England J.Med*., **292**, 381-386.

Huber W.W, Grasl-Kraupp B and Schulte-Hermann R.(1996) Hepatocarcinogenic potential of di(2-ethylhexyl)phthalate in rodents and its implications on human risk. *Crit. Rev Toxicol.*, **26**, 365-481.

IARC, (2000) IARC Monograph on the evaluation of carcinogenic risks to humans. Some industrial chemicals. Di (2-ethylhexyl) phatalate, **77**, 41-148.

Ikeda H, Matsuyama S and Masako T, (1997) Association bewteen hepatoblastoma and very low birth weight: a trend or chance, *J.Paedriatrics*, **130,** 557-560.

Ikeda H, Hachitanda Y, Tanimura M, Mauyama K, Koizumi T and Tsuchida Y, (1998) Development of unfavorable hepatoblastoma in children of very low birth weight: results of a surgical and pathologic review, *Cancer*, **82**,1789-96.

Jaakkola JJ, Oie L, Nafstad P, Botten G, Samuelsen So and Magnus P. (1999) Interior surface materials in the home and the development of bronchial obstruction in young children in Oslo, Norway. *Am. J. Public Health*, **89**, 188-192.

Jacobsen MS, Kevy SV and Grand RJ, (1977) Effects of a plasticiser leached from polyvinylchloride on the subhuman primate; a consequence of chronic transfusion therapy, *J.Lab.Clin.Med.*, **89**, 1066-1079.

Jaeger RJ and Rubin RJ, (1970) Contamination of blood stored in plastic packs. *The Lancet*, 2, 151.

Jaeger RJ and Rubin RJ, (1972) Migration of a phthalate ester plasticiser from polyvinyl chloride blood bags into stored human blood and its localization in human tissues. *New England J.Med.*, **287**, 1114-1118.

Jaeger RJ and Rubin RJ, (1973) Extraction, localization and metabolism of di-2-ethylhexyl phthalate from PVC plastic medical devices, DHEW Publication IVIH 73-318, *Environ. Health. Perspect*., 3, 95-102.

Karle VA, Short BL, Martin GR, Bulas DI, Getson PR, Luban NL, O'Brien AM and Rubin RJ, (1997) Extracorporeal membrane oxygenation exposes infants to the plasticizer, di(2-ethylhexyl) phthalate, *Critical Care Medicine*, **25**, 696-703.

KEMI (2000) Risk assessment of bis(2-ethylhexyl) phthalate- CAS No 117-81-7, EINECS No 204-211, December 2000.

Kevy SV and Jacobson MS, (1982) Hepatic effects of a phthalate ester plasticizer leached from poly(vinyl chloride) blood bags following transfusion. *Environ. Health Perspect*., **45**, 57-64.

Kitchen WH, Ryan MM and Rickards AL, (1987) Longitudinal study of very low birth weight infants: impairments, health and growth distance to 14 years of age, *Australian Paediatric Journal* **23**:333-8.

Kluwe WM, Haseman JK, Douglas JF and Huff JE, (1982) The carcinogenicity of dietary di-(2-ethylhexyl) phthalate (DEHP) in Fischer 344 rats and B6C3F1 mice, *J. Toxicol. Environ. Health*, **10**, 797-815.

Kurata Y, Kidachi F, Yokoyama M, Toyota N, Tsuchitani M and Katoh M, (1998) Subchronic toxicity of Di(2-ethylhexyl)phthalate in common marmosets: lack of hepatic peroxisome proliferation, testicular atrophy, or pancreatic acinar cell hyperplasia. *Toxicol. Sci.*, **42**, 49-56.

Lamb JC, Chapin RE, Teague J, Lawton AD and Reel JR, (1987) Reproductive effects of four phthalic acid esters in the mouse. *Toxicol. Appl. Pharmacol.*, **88**, 255-269.

Lancet Editorial, (1968) What's in PVC, *The Lancet*, 2, 34.

Larsen ST, Hansen JS, Thygesen P, Begtrup M, Poulsen OM and Nielsen GD (2001b) Adjuvant and immunosuppressive effect of six monophthalates in a subcutaneous injection model with BALB/c mice. *Toxicology* **169**, 37-51,

Larsen ST, Lund RM, Nielsen GD, Thygesen P and Poulsen OM, (2001a) Di-(2-ethylhexyl) phthalate possesses an adjuvant effect in a subcutaneous injection model with BALB/c mice, *Toxicology Letters* **125**, 11-18.

Latini G, (2000) Potential hazards of exposure to di-(2-ethylhexyl)-phthalate in babies, *Biol. Neonate* **78**, 269-276.

Lawrence WH, Malik M and Autian J, (1974) Development of a toxicity evaluation program for dental materials and products II Screening for systemic toxicity, *J.Biomed.Mater.Res.*, **8**, 11-34.

Lawrence WH, Malik M, Turner JE, Singh AR and Autian J, (1975) A toxicological evaluation of some acute, short-term and chronic effects of administering di(2-ethylhexyl phthalate (DEHP) and other phthalate esters, *Environ. Res.*, **9**, 1-11.

Lawrence WH, Mitchell JL, Guess WL and Autian J. (1963) Toxicity of plastics used in medical practice, *J.Pharm.Sci.*, **52**, 958-964.

Lawrence WH, Turner JE and Autian J, (1969) Re-examination of plastic tubing currently used. *J.Biomed.Mater.Res.*, **3**, 291-298.

Liilanen K, Keranen J, Kuokkala V-T and Lepisto T, (2000) Phthalate migration and retainers in the Finnish market. National Agency for Medicines, Medical Device Centre, Finland, Unpublished report, 23rd August 2000.

Lloyd SC and Foster PM, (1988) Effect of mono-(2-ethylhexyl) phthalate on follicle-stimulating hormone responsiveness of cultured rat Sertoli cells. *Toxicol Appl Pharmacol*, **95**, 484-489.

Loff S, Kabs F, Witt K, Sartoris J, Mandl B, Niessen KH, and Waag KL, (2000) Polyvinylchloride infusion lines expose infants to large amounts of toxic plasticizers. *J. Pediatr. Surg.*, **35**, 1775-1781.

Maloney EK and Waxman GD, (1999) Trans-activation of PPAR alpha and PPAR gamma by structurally diverse environmental chemicals, *Toxicol. Appl. Pharmacol*,, **161**, 209-218.

Mazur HI, Stennett DJ, Egging PK, (1989) Extraction of diethylhexylphthalate from total nutrient solution containing polyvinyl chloride bags. *J. Parenter, Enteral Nutr.*, **13**, 59-62.

Melnick RL, (2001) Is peroxisome proliferation an obligatory precursor step in the carcinogenicity of di(2-ethylhexyl)phthalate (DEHP)? *Environ. Health Perspect*., **109**, 437-442.

Melnick RL, Kohn MC and Porter CJ, (1996) Implications for risk assessment of suggested nongentoxic mechanisms of chemical carcinogenesis, *Environ. Health Perspect*., **104**, Suppl 1, 123-134.

Mettang T, Thoas S, Kiefer T, Fischer FP, Kuhlmann U, Wodarz R and Rettenmeier AW, (1996) Uraemic patients and exposure to DEHP in haemodialysis patients, *Nephrol.Dial.Transplant*, **11**, 2439-2443.

Moore MR, (1996) Oncogenicity study in rats with di (2-ethylhexyl) phthalate including ancillary hepatocellular proliferation and biochemical analyses, Corning Hazelton Inc Study CHV 663-134, (Cited in KEMI, 2000).

Moore MR, (1997) Oncogenicity study in rats with di (2-ethylhexyl) phthalate including ancillary hepatocellular proliferation and biochemical analyses, Corning Hazelton Inc Study CHV 663-135, (Cited in KEMI, 2000).

Moore RW, Rudy TA, Lin T-M, Ko K and Peterson RE, (2001) Abnormalities of sexual development in male rats with *in utero* and lactational exposure to the androgenic plasticizer di(2-ethylhexyl) phthalate. *Environ. Health Perspect.*, **109**, 229-237.

Nassenberger L, Arbin A and Ostelius J, (1987) Exposure of patients to phthalates from polyvinyl chloride tubes and bags during dialysis, *Nephron,*, **45**, 286-290.

Peters JM, Taubeneck MW and Keen CL, (1997) DEHP induces a functional zinc deficiency during pregnancy and teratogenesis that is independent of peroxisome proliferator-activated receptor-alpha, *Teratology,* **56**, 311-316.

Plonait SL, Nau H, Maier RF and Wittfoht W M O. (1993) Exposure of newborn infants to di-(ethylhexyl)-phthalate and 2-ethylhexanoic acid following exchange transfusion with polyvinylchloride catheters. *Transfusion* **33**, 598-605.

Pollack GM, Buchanan JF, Slaughter RL, Kohl RK and Shen DD, (1985) Circulating concentrations of di(2-ethylhexyl) phthalate and its de-esterified phthalic acid products following plasticizer exposure in patients receiving haemodialysis, *Toxicol.Appl.Pharmacol.,* **79**, 257-267.

Poon R, Lecavalier P, Mueller R, Valli VE, Procter BG and Chu I, (1997) Subchronic oral toxicity of di-n-octylphthalate and di (2-ethylhexyl) phthalate in the rat. *Food Chem. Toxicol.*, **35**, 225-239.

Pugh G, Isenberg JS, Kamendulis LM, Ackley DC, Clare LJ, Brown R, Lington AW, Smith JH and Klaunig JE, (2000) effects of di-isononyl phthalate, di-2-ethylhexylphthalate and clofibrate in cynomolgus monkeys, *Toxicol.Sci.* **56**, 181-188.

Ribons L and Slovis TL, (1998) Hepatoblastoma and birth weight. *J Pediatrics*; **132**:750.

Roberts RA, (1999) Peroxisome proliferators: mechanisms of adverse effects in rodents and molecular basis for species differences, *Arch.Toxicol.*, **73**, 413-418.

Rogers AF and Dunn PM, (1968) Intestinal perforation, exchange transfusion and PVC, *The Lancet*, 2, 1246.

Ross JA and Gurney JG, (1998). Hepatoblastoma incidence in the United States from 1973 to 1992, *Medical and Pediatric Oncology* **30**, 141-142.

Rossi M and Muehlberger M, (2000) Neonatal exposure to DEHP (di-2-ethylhexyl phthalate) and opportunities for prevention in Europe. Health Care Without Harm, Centre national d'information indépendante sur les dechets, CNIID, Paris,

Roth B, Herkenrath P, Lehmann HJ, Ohles HD, Homig HJ, Benz-Bohm G, Kreuder J and Younossi-Hartenstein A, (1989) Di(2-ethylhexyl) phthalate as plasticizer in PVC respiratory tubing systems: indications of hazardous effects on pulmonary function in mechanically ventilated pre-term infants, *Eur.J.Paedriatrics*, **147**, 41-46.

SCF (1996) Opinion on phthalates in infant formulae, Scientific Committee on Food, European Commission, Adopted on 7th June 1996, Brussels, Belgium

Schilling K, Gembardt C and Hellwig J. (2001) Di-2-ethylhexyl phthalate -two generation reproduction toxicity study in Wistar rats by continuous dietary administration. Laboratory Project Identification 70R049/97139. Department of Experimental Toxicology and Ecology, BASF Aktiengesellschaft, 67056 Ludwigshafen, Report to the European Council for Plasticizers and Intermediates, CEFIC, Brussels, Belgium.

Schmid P and Schlatter C, (1985). Excretion and metabolism of di-(2-ethylhexyl) phthalate in man. *Xenobiotica,* 15, 251-256.

Schulte-Hermann R, Parzefall W and Huber W, (2001), A comprehensive literature review and toxicological risk assessment of possible effects on reproduction of di-(2-ethylhexyl) phthalate (DEHP) and its metabolites from PVC-containing medical devices. Report to Austrian Ministry for social Security and Generations (BMSG), July 13th 2001.

Shneider B, Cronin J, Van Marter L, Maller E, Truog R, Jacobsen M and Kevy S, (1991) A prospective analysis of cholestasis in infants supported with extracorporeal membrane oxygenation. *J.Paediatr.Gastroenterol.Nutr.*, **13**, 285-289,

Shneider B, Schena J, Truog R, Jacobsen M and Kevy S, (1989) Exposure to di(2-ethylhexyl) phthalate in infants receiving extracorporeal membrane oxygenation, *New Engl.J.Med.*, **320**, 1563.

Singh AR, Lawrence WH and Autian J, (1974) Mutagenic and antifertility sensitivities of mice to di(2-ethylhexyl) phthalate (DEHP) and dimethoxyethylphthalate (DMEP). *Toxicol.Appl.Pharmacol.*, **29**, 35-46

Singh AR, Lawrence WH and Autian J, (1975) Maternal-foetal transfer of ^{14}C-(di-ethylhexyl) phthalate in rats, *J.Pharm.Sci.*, **64**, 1347-1350.

Sjoberg P, Bondesson U, Kjellen L, Lindquist N.G, Montin G. and Ploen,L, (1985a) Kinetics of di-(2-ethylhexyl) phthalate in immature and mature rats and effect on testis. *Acta Pharmacol.Toxicol.(Copenh*)., **56**, 30-37.

Sjoberg P, Lindqvist NG, Monti G, and Ploen L, (1985b) Effects of repeated intravenous infusions of the plasticizer di-(2-ethylhexyl) phthalate in young male rats. *Arch. Toxicol.,* **58**, 78-83,

Sjoberg P, Lindqvist NG and Ploen L, (1986) Age dependent response of the rat testis to di(2-ethylhexyl) phthalate. *Environ. Health Perspect.* 65, 237-242.

Staples CA, Peterson DR, Parkerton TF and Adams WJ, (1997) The environmental fate of phthalate esters: a literature review. *Chemosphere,* **35**, 667-749.

Sugiura K, Sugiura M, Hayakawa R, Shamoto M and Sasaki K, (2002) A case of contact urticaria syndrome due to di(2-ethylhexyl) phthalate (DOP) in work clothes. *Contact Dermatitis,* **46**, 13-16.

Tickner JA, Schettler T, Guidotti T, McCally M, and Rossi M, (2001) Health risks posed by the use of di-2-ethylhexyl phthalate (DEHP) in PVC medical devices: a critical review. *Am. J. Ind. Med.,* **39**, 100-111.

Tommiska V, Heinonen K, Ikonen S, Kero P, Pokela M-L, Renlund M, Virtanen M, Fellman V, (2001) A national short-term follow-up study of extremely low birth weight infants born in Finland in 1996-1997. *Pediatrics*, **107**:e2.

Turner JH, Petricciani JC, Crouch ML and Wenger S, (1974) An evaluation of the effects of di-(2-ethylhexyl phthalate (DEHP) on mitotically capable cells in blood packs, *Transfusion*, **14**, 560-566.

Vohr BR, Wright LL, Dusick AM, Mele L, Verter J, Steichen JJ, Simon NP, Wilson DC, Broyles S, Bauer CR, Delaney-Black V, Yolton KA, Fleischer BE, Papile Lu-Ann, Kaplan MD, (2000) Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994. *Pediatrics* ,**105**, 1216-26.

Ward JM, Peters JM, Perella CM and Gonzalez FJ, (1998) Receptor and nonreceptor-mediated organ-specific toxicity of di(2-ethylhexyl)phthalate (DEHP) in peroxisome proliferator-activated receptor alpha-null mice. *Toxicol. Pathol*., **26**, 240-245.

Wolfe GW, Layton K, Nehrebeckyj L, Wang Y, Chapin R, Rouselle SD and Bishop J, (2002) reproductive effects of diethylhexylphthalate (DEHP) in Sprague-Dawley rats when assessed by the continuo's breeding protocol, *The Toxicologist* Supplement 66 S-1, p234 Abstract 1147.

Woodward KN, (1988) Phthalate Esters: Toxicity and Metabolism, Vol 1 CRC Press, Boca Raton, Florida.

World Health Organisation, WHO, (1992) Diethylhexyl phathalate. *Environmental Health Criteria 131*. International Programme on Chemical Safety (IPCS)–World Health Organisation, Geneva.

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