DET ØKOLOGISKE RÅD
FREMTIDENS MILJØ SKABES I DAG

Health Care Without Harm

Proposal for the recast of the Medical Devices Directives 93/42/EEC, 90/385/EEC and 98/79/EC

Presented by the Danish Ecological Council and Health Care Without Harm (HCWH) Europe

The Danish Ecological Council and Health Care Without Harm Europe call upon EU to:

1. Identify, and phase out endocrine disrupting chemicals (EDCs) in all medical devices unless there are no substitutes available, in this case EDCs should be clearly labelled and sufficient information should be given to healthcare staff and patients. Medical devices, which contain EDCs should be subject to restrictions or authorisation and phased out if safer alternatives are available. Priority should be assigned based on their hazardous properties and the likelihood of coming into contact with the patient, particularly with vulnerable patient groups, such as infants, children, women of childbearing age and pregnant women.

2. Give special attention to phasing out the PVC softening group of chemicals called phthalates. Phthalates are abundant in PVC based medical devices such as blood bags, tubes, catheters and disposable gloves, primarily in the form of the phthalate di-(2-ethylhexyl)phthalate (DEHP). PVC free alternatives products should be mandatory, unless they are no substitutes available for specific uses.

3. Demand clinical trials performed on all medical devices to be implanted or used in direct connection with the patient, or to be used as a storage device for substances – such as blood, fluid, electrolytes or nutrition mixtures.

4. Prohibit the application of all harmful chemicals in all medical devices – including chemicals known to have either carcinogenic, mutagenic, reprotoxic (CMR) or endocrine disrupting effects (as covered in point 1).

The review of the Medical Device Directives, 93/42/EØF, 90/385/EØF and 98/79/EF, and the transition from directives to regulation, is a good opportunity to expand the protective role of the directives. The recent high profile cases – the silicone breast implant containing industrial silicone

The Danish Ecological Council, Blegdamsvej 4 B, DK 2200 København N. ph: +4533150977.
http://www.ecocouncil.dk/ e-mail: info@ecocouncil.dk
HCWH Europe, 1 Rue de la Pepiniere, B1000 Brussels, Belgium, ph: +49 15253978103,
http://noharm.org/ e-mail: anja.leetz@hcwh.org

(PIP) and the metal-on-metal (MoM) hip implants shedding microscopic toxic metals into the body – have brought focus on the need for a stricter regulation on medical devices.

A critical and somewhat overlooked hazardous group of chemicals allowed in medical devices are phthalates. There are strong indications that phthalates are endocrine disruptors, and EDCs in general interfere with the hormone systems of living creatures, which is potentially very damaging, as it is our hormones which control many biological functions, including reproduction and metabolism. EDCs have been increasingly linked to a range of health problems including altered brain development giving rise to behavioural, cognitive or attention deficit disorders[1,2], cancers (particularly including breast, prostate and testicular cancer)[3,4], diabetes[5], reproductive disorders[6], and impaired fertility[7] in wildlife and/or humans[8].

The phthalate DEHP is currently on several warning lists, including the EU candidate list, the EU endocrine disruptor priority list and the SIN 2.0 list produced by Swedish ChemSec. Studies have found phthalate metabolites in the urine of neonates in intensive units, and phthalates and their metabolites in general are found in urine, blood, naval cord blood, semen, breast milk, placental tissue and amniotic fluid. Medical products containing DEHP have to be labelled, and the use of DEHP is already prohibited in toys and childcare products in the EU (1999/815/EC). There are many alternative products available to substitute the phthalate containing devices on the market, and various listings have been made by e.g. the Danish EPA[9] and HCWH[10]. An example of an alternative plasticizer is SOFT N' SAFE manufactured by the Danish company Danisco. This plasticizer is produced from American castor oil and has no negative toxicological and ecotoxicological impact. Another example of an alternative product is phthalate free plastic granulate from Melitek.

<u>Background information for proposals</u>

Re.1 The criteria for EDCs are still being established, and we advocate that if a substance has endocrine properties, the absence of precise scientific knowledge of how it exerts its effects (mechanisms of action) should not hinder or impede the regulation of such a chemical. Thus, it is important that the criteria are not restricted to chemicals for which

[1] Ishido et al., 2007, Mesencephalic neurodegeneration in the orally administered bisphenol A-caused hyperactive rats. Toxicol Lett., 173:66–72
[2] Jurewicz and Hanke, 2011, Exposure to phthalates: Reproductive outcome and children health. A review of epidemiological studies. International Journal of Occupational Medicine and Environmental Health, 24:115-141
[3]] Soto and Sonnenschein, 2010, Environmental causes of cancer: endocrine disruptors as carcinogens. Endocrinology, 6:363-370
[4] Jenkins et al., 2007, Prenatal TCDD exposure predisposes for mammary cancer in rats. Reprod. Toxicol., 23:391-396
[5] Lim et al., 2008, Association of Brominated Flame Retardants with Diabetes and Metabolic Syndrome in the U.S. Population, 2003–2004. Diabetes Care, 31:1802–1807
[6] Markey et al., 2005, Long-term effects of fetal exposure to low doses of the xenoestrogen bisphenol-A in the female mouse genital tract. Biol Reprod. 72:1344-1351
[7] Cohn et al., 2003, DDT and DDE exposure in mothers and time to pregnancy in daughters. Lancet, 361:2205-2206
[8] Damstra et al., 2002, Global Assessment of the State-of-the Science of Endocrine Disrupters. WHO/I PCS/EDC/02.2. World Health Organization/International Programme on Chemical Safety, Geneva
[9] http://www.eco-forum.dk/medicoartikler/Produktliste.pdf

there is absolute proof that they exert adverse effects as a consequence of an endocrine disruption mechanism of action. Moreover, the criteria should not be restricted to endpoints covered by existing test methods; such that it should be considered how new knowledge can be easily included when available. Furthermore, it is important to adopt hazard-based criteria, which do not include any potency thresholds for the identification of EDCs. This is because it is the time of exposure rather than the dose that seems to be the most important with regard to the effects of EDCs. The criteria should apply across all relevant EU legislation.

Re.2 At a medical facility there are many modes of exposure to phthalates, such as through intravenous (IV) administration, enteral nutrition, direct contact, inhalation and dermal. Most at risk is the foetus, the prematurely born and the seriously ill children. They are in the developing growth phase where hormones play a critical role in the normal development of the child, including the brain. They also have a less effective blood-brain and blood-testis barriers and have less total body fat, resulting in a higher concentration of toxins. Studies show that enteral nutrition at the neonate intensive care unit (NICU) results in an exposure to DEHP of 40-140 µg/kg body weight per day, compared to a "normal" daily exposure of 3-30 µg/kg BW/day. Parenteral nutrition at the NICU was shown to give an exposure of up to 2500 µg/kg BW/day. These numbers clearly show an unacceptably high exposure, and this is only from one exposure route out of many each day. Another example is exchange transfusion or extracorporeal membrane oxygenation, which has also shown to dramatically increase the serum levels of DEHP in infants[11]. Chronically ill patients undergoing continual treatment, such as dialysis, are also highly exposed. It has been known for 30 years that DEHP leaks out of medical devices, and it is suspected of teratogenicity (causing birth defects) and endocrine disruption. Furthermore, animal studies show that exposure to DEHP can damage the liver, kidneys, lungs, and reproductive system, particularly the developing testes of prenatal and neonatal males. Therefore we propose that steps are taken immediately to phase out the application of phthalates in medical devices. Numerous alternative products exist, and experiences from many hospitals, e.g. Westfriesgasthuis in the Netherlands, where the Pediatric ward has substituted nearly all PVC/phthalate products, shows that it can be done in a cost effective manner. In addition, HCWH has made a report of hospitals phasing out PVC and phthalates[12].

Re.3 Within the scope of CE labeling, a special risk analysis and clinical assessment is carried out for every single medical device. It is only for products which have a so-called

[10] http://www.noharm.org/lib/downloads/pvc/PVC_Alternatives_Europe.pdf
[11] Plonait S.L. et al., 1993. Exposure of newborn infants to di-(2-ethylhexyl)-phthalate and 2-ethylhexanoic acid following exchange transfusion with polyvinylchloride catheters. Transfusion 33(7):598-605
[12] http://www.noharm.org/lib/downloads/pvc/PVC_DEHP_Phase-Out_Europe.pdf

'increased risk', such as medical implants, that a clinical trial must be conducted as well. The pre-market authorisation process of medical devices needs to be more stringent, as does the post-market surveillance. In order to avoid cases such as the widespread use of the breast implants containing industrial-grade silicone (PIP), and metal-on-metal hip implants, leaching metal micro particles such as cadmium, cobalt and chromium into the body, all medical devices need to undergo vigorous clinical trials.
We call for legislators to go in the direction of the pharmaceutical industry, where more clinical evidence requirements are needed for approval.
90/385/EØF article 1(k) states that clinical data can be sourced from clinical investigation(s) or other studies reported in the scientific literature, of a similar device for which equivalence to the device in question can be demonstrated.." This shows a severe lack of regulation and is the basis for the hip implant case, where the new hip implants were not required to undergo clinical trials, as they were deemed sufficiently similar to the previous plastic/ceramic/metal implants. This loophole in the directive needs to be addressed in order to assure that all new products undergo clinical trials before released onto the market.

Re.4 Like EDCs, no carcinogenic, mutagenic or reprotoxic chemicals may be used in, or found to leach from, medical devices. In the previously mentioned case with the metal-on-metal hip implants, cadmium, cobalt and chrome were found to leach from the implants, and cause severe damage to nearby tissue and the whole body.