DEHP in Medical Devices:

Risks Still Unclear After Decades of EU Scientific Scrutiny

Are medical devices containing DEHP-plasticized PVC or other plasticizers safe for neonates and other groups possibly at risk? That is the key question which authorities have sought to answer for the last several decades. This article compares the three opinions – the latest in 2015 – by the EU scientific committees. The bottom line: medical devices containing DEHP save lives and should therefore not be avoided. However, phthalate exposure should be reduced as much as possible.

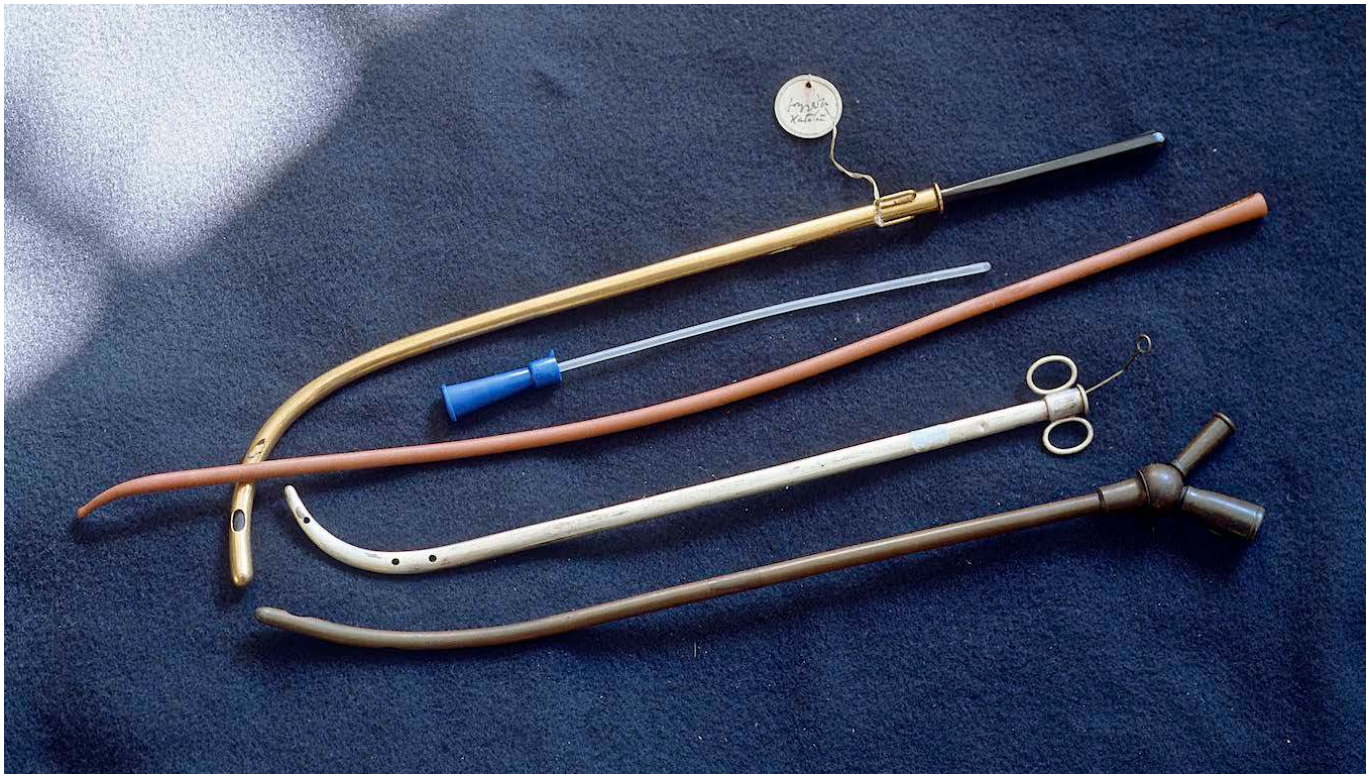
By Tobias Johnsen, MA

"Phthalate" is hard to pronounce, but the word has nevertheless become commonplace. We often hear it in its plural form when a media outlet breaks yet another story about phthalates' adversary effects on human health. In the US, a gloomy picture is painted. Take a recent headline from *NBC News*, "Chemical Phthalates in Food Packaging Linked With Lower IQ in Kids." The article—published online December 12, 2014—builds on a string of studies that supposedly links phthalates with "health effects ranging from behavioral disorders to deformations of the sex organs."[1] Across the pond the situation is just as dire, if we are to believe the *Irish Times*. According to an online article dated August 12, 2014, phthalates are "hormone-disrupting chemicals" which "can cause detrimental health effects if a person is exposed to significant levels over a period of time."[2] These are just two examples of an alarmist agenda that portrays phthalates as something to get rid of, rather today than tomorrow. But is it really that simple?

1 Fox 2014
2 McGuire 2014

DEHP: a curse or a blessing?

The reason why phthalates have joined everyday language is because of the ubiquity of plastics, especially in medical devices, and the chemistry behind. PVC (polyvinyl chloride) is the most widely used polymer in medical devices and provides for critical equipment such as blood bags and tubing. In its virgin state PVC is hard and rigid, which limits its use to containers, piping and like products. Of the total PVC used in medical devices, this type accounts for 10-20%. In order to make the polymer soft and flexible, a so-called "plasticizer" is added in the production process. Phthalates are the most common form of plasticizer, with di(2-ethylhexyl) (DEHP) being the most common phthalate when it comes to PVC medical devices, due to its properties, cost-effectiveness and ease of manufacture.



PVC revolutionized healthcare when the material was introduced in the middle of the 20th century. Suddenly it was possible to produce safe single-use medical devices at a low cost. Today, PVC is the most used plastic material for disposable medical applications with a market share of about 40 %.

Much media attention centers on DEHP because of concerns among scientists that the chemical might have adverse effects on human health. It is well-established in academia that the plasticizer leaches into the body from tubes, blood bags and other medical devices, and a number of animal studies show that DEHP can potentially cause cancers and harm reproduction, liver and kidneys. At the heart of the matter is whether DEHP puts the most vulnerable patients at risk: new-born babies, or neonates. Because of their low body weight, scientists worry that the same adverse effects seen in animals might be present for neonates, and those born premature in particular. In other words, there are worries that the same medical devices that save lives might be harmful in the long run.

The EU Scientific Committees

For the same reason, the European Commission, by way of its Scientific Committees, has turned its attention to DEHP in medical devices and published so-called opinions on the matter in 2002, 2008 and 2014—the latter a preliminary update to the 2008 opinion that is currently under review. The first opinion was published by the Scientific Committee on Medicinal Products and Medical Devices, a now defunct body that operated from 1997 to 2004. The second and third opinions were the work of the Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR), which was one of three Scientific Committees set up following Commission Decision 2008/721/EC1 (the other centering on Consumer Safety and Health and Environmental Risks respectively).

According to the Decision, the Committees must give "sound and timely scientific advice" to the Commission on matters relevant to "proposals, decisions and policy," based on "the principles of excellence, independence, impartiality [and] transparency."[3] The impact of the Scientific Committees is therefore significant, since their opinions form the knowledge base of the legislative process regarding public health, consumer safety and the environment in the European Union.

SCENIHR's mandate and composition

SCENIHR's field of competence is broad, and covers, as the name hints at, emerging or newly-identified health and environmental risks as well as assessment of risks to consumer safety or public health and related issues not covered by the other EU risk assessment bodies. Examples of activities are antimicrobial resistance, fertility reduction, blood products and medical devices. Usually a request for a so-called opinion is filed with the Committee, which can call in help from a shared Pool of Scientific Advisors on Risk Assessment or external experts if need be. The body can also publish opinions and statements at its own initiative.

The members, fixed at 15, are appointed for a period of three years by the Commission on the basis of expertise and geographic and gender distribution. In March 2013, 11 men and 4 women were appointed. Except one Canadian, all members are Europeans and come from Bul-

3 European Commission 2008, 21

garia, Netherlands, Belgium, Italy (2x), Spain, Austria, France, Germany, Greece and Slovenia.

The members share a background in European public research institutions, with 10 being employed at universities. As one would expect, all are doctors or professors, but the exact educational background is more diverse. The spectrum covers mechanics, clinical microbiology, allergic and immunologic diseases, public health, nanoscience, health care engineering, environmental engineering, occupational epidemiology, medical physics and toxicology—the latter being the most common field of competence with 5 members engaged here.

The 2002 opinion

After reviewing the existing literature and data, the Scientific Committee on Medicinal Products and Medical Devices reached a pretty clear conclusion: "... 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."[4] Further, the Committee stressed that the benefits must be balanced with the risks and that DEHP-PVC had contributed tremendously to health care by making possible the production of life-saving medical devices. However, the Committee did not sanctify the phthalate—just because there was a lack of data did not mean that the adverse effects seen in animals could be ruled out. Therefore, the authors called for further research.

The 2008 opinion

Six years later, a new opinion saw the light day. In "Opinion on the Safety of Medical Devices Containing DEHP – Plasticized PVC or other Plasticizers on Neonates and Other Groups Possibly at Risk," SCENIHR assessed new data on toxicity in animal and human studies. Another task was to evaluate alternative plasticizers for their availability, suitability and safety. The main conclusion here mainly followed the 2002 opinion: "So far, there is no conclusive evidence that DEHP exposure via medical treatments has harmful effects in humans."[5] Again, the importance of PVC-DEHP medical devices was stressed. Yet compared to the previous opinion, SCENIHR was more cautious in 2008: "... the new information indicates that there is still a reason for some concern for prematurely born male neonates,"[6] because of the high human exposure during medical procedures where the dose could be well above what caused reproductive toxicity in animal studies. Further studies were recommended to confirm or reject adverse effects of DEHP in humans.

In regards to alternative plasticizers, the authors advised a case-to-case approach. Some plasticizers could be suitable to replace DEHP, while others would not have the same functionality. Because of lack of data, a risk assessment of the alternatives could not be performed.

The controversy

Following the 2008 opinion, the issue of DEHP in medical devices did not disappear from the agenda of policy makers and other stakeholders. In May 2012, the EU funded Life+ project PVCfreeBloodBag issued a press release, which asserted that a new study showed that PVC-DEHP bags "pose a significant risk to human health, due to both PVC and DEHP."[7] This controversial conclusion was reached by the Swedish consultant agency eco2win, which had undertaken a so-called life-cycle assessment of PVC-DEHP blood bags. For the PVC industry, this was breaking news to say the least, since no study yet had proved such a risk. In fact, eco2win's findings contradicted the two opinions by the EU Scientific Committees. Shortly after the press release, the European Council of Vinyl Manufacturers commissioned a review of the life-cycle assessment to be conducted by the University of Manchester. In July 2012, a scathing critique was published. Professor Adisa Azapagic, who had carried out the review, did not mince any words—she found the life-cycle assessment misleading, biased, and scientifically and methodologically invalid.

The review reached the European Commission, which prompted a request for an update to the 2008 opinion based on recent scientific developments and with a deadline set for March 2013. In particular, SCENIHR was requested to evaluate whether there was cause for concern to neonates and children in pediatric care, in regards to male fertility and tissue development. Also, the Committee should identify other risk groups. And lastly, the Committee should either identify possible alternatives to DEHP, or formulate research recommendations if that task proved impossible.

The 2014 update

Despite being a year and a half late and significantly longer than the previous opinion, no clear answers are given in the report, put together by a working group consisting of three SCENIHR members, two Scientific Committee on Consumer Safety members as well as six external experts. In answering the first question regarding developmental and reproductive toxicity, the authors conclude that male neonates are still at high risk of DEHP exposure during medical procedures due to their low body weight. Especially neonates in intensive care units receive doses in the range that caused developmental and reproductive toxicity in animals. Accordingly, this poses "a cause of concern in pediatric care."[8] Further, blood transfusion for infants using plasticized PVC

4 Scientific Committee on Medicinal Products and Medical Devices 2002, 26

5 Scientific Committee on Emerging and Newly Identified Health Risks 2008, 49

6 Scientific Committee on Emerging and Newly Identified Health Risks 2008, 49

7 PVCfreeBloodBag 2012

8 Scientific Committee on Emerging and Newly Identified Health Risks 2014, 82

medical devices "might represent a health concern."[9] However, since these conclusions are alone based on animal studies and one follow-up study of highly exposed neonates, and no large-scale or long-term human studies have been conducted, the authors consider the matter an "unresolved issue."

In identifying other groups at risks, the authors put emphasis on patients undergoing haemodialysis, because this treatment is often long-term. Logically, the cumulative exposure is highest for this group. Of the short-term procedures, blood transfusions to trauma adult patients or cardiac and respiratory support to patients in intensive care units result in the highest acute exposure.

In terms of alternative plasticizers, the update largely follows the 2008 opinion. First, the authors find limited additional information on alternatives. Second, while some alternative plasticizers are evaluated for their toxicity and carcinogenic potential—a few of which are potentially more harmful than DEHP—there is scant human exposure data and information on leaching. For other plasticizers, data on the toxicological profile is insufficient. Therefore a risk assessment of the alternatives is not possible, which hinders a clear answer to whether DEHP can be substituted. The report ends with a call for further research.

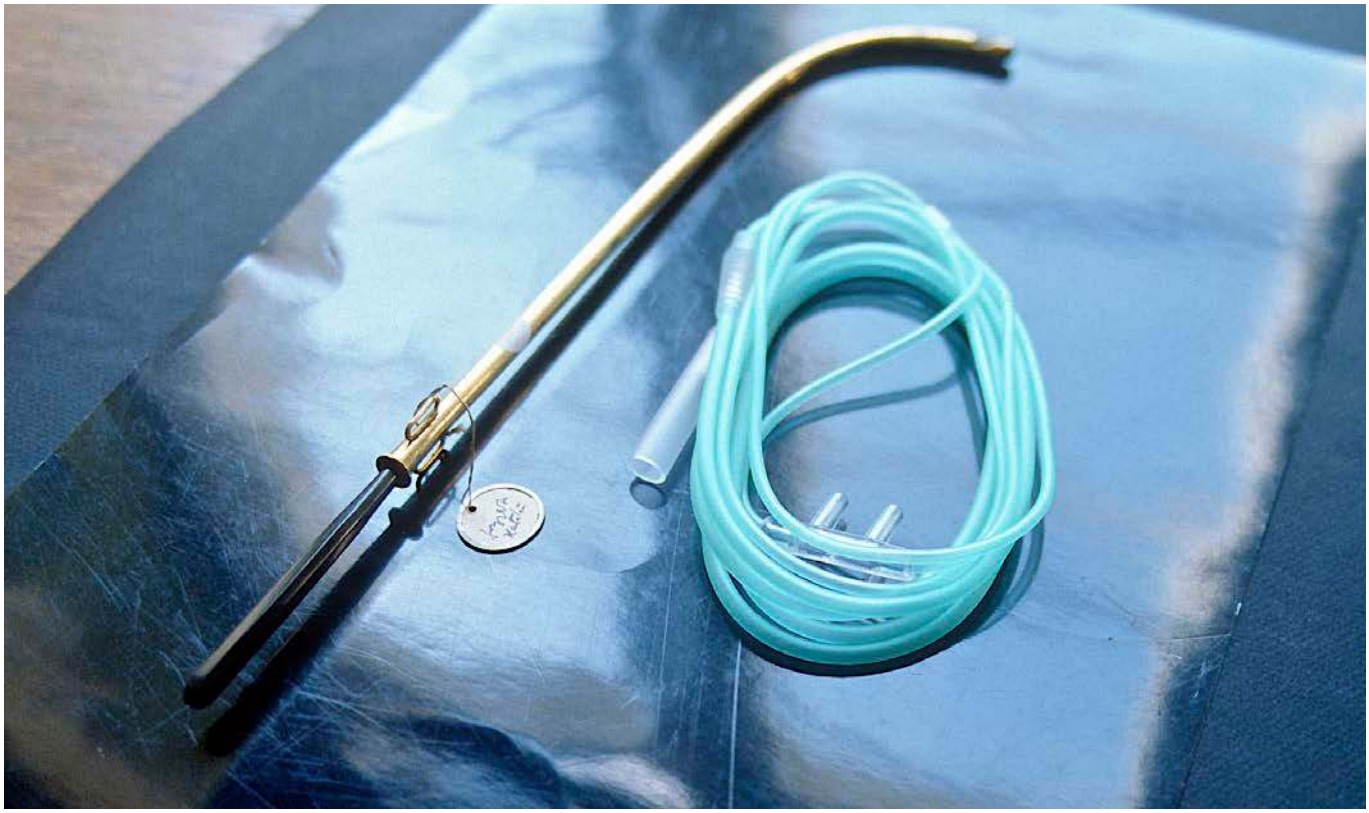
An inconclusive conclusion

Thus, the 2014 update in its current form is rather inconclusive and poses more questions than answers. Simply put, those who hoped for clarity regarding PVC-DEHP in medical devices will be disappointed after reading the opinion. On the other hand, there is some basis for calming the waters when it comes to the concerns over the link between DEHP and adverse effects on human health, such as testosterone production, breast tumors, childhood growth, obesity, insulin resistance and type 2-diabetes. In the author's review of the epidemiological and clinical studies of the asserted links, there are either "considerable variation," "inconsistency in the results," "weak association," "no association," "inconclusive evidence" or "no evidence."[10] Lastly, SCENIHR again emphasizes the importance of taking a cautious approach when dealing with medical devices that on a daily basis are critical for survival of newborns, children and adults. In other words, risk and benefit should be considered with great care when assessing alternatives to DEHP.

As such, the body was not asked to confirm or reject the claim that led to the controversy in 2012: does PVC and DEHP pose a risk to human health? Therefore, one does not find a direct answer to that question in the update. But based on the preliminary version of the opinion, eco2win's statement is not underpinned by SCENIHR's findings.

9 SCENIHR 2014, 82

10 SCENIHR 2014, 79-80



The soft PVC tubing to the right ensures comfort and safety for patients and good working conditions for healthcare professionals. Fortunately, the metal catheter to the left, which most of all resembles a torture instrument, belongs in a museum.

The road ahead

When it comes to finding alternatives, the world is not standing still. The industry is actively working with relevant governmental bodies to find alternatives to DEHP in medical devices. For instance, the Danish Environmental Protection Agency released a report in March 2014, *Alternatives to classified phthalates in medical devices,* which identified 10 alternatives to DEHP and other phthalates in medical devices already in use. Most of these showed a better toxicological profile than DEHP, but more research is needed to confirm their potential. The report was the joint effort of the independent consulting firm DHI, the Danish Environmental Protection Agency, the Danish Health and Medicines Authority and the PVCMed Alliance, a European trade association of PVC medical device, plasticizer and resin manufacturers. The results were presented at an international conference in Copenhagen in March 2014, "Alternatives to Classified Phthalates in PVC Medical Devices," held by the Danish EPA, the Danish Health and Medicines Authority and the PVCMed Alliance. Taken together, the report and conference show that it is an arduous task to substitute DEHP, but that it might be doable if industry and governmental bodies cooperate.

Note

After a public consultation, the preliminary opinion was finalised in July 2015. No alterations were made to the conclusions. Thus, the content of this article remains valid.

Final opinion: http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_047.pdf

European Commission fact sheet: http://ec.europa.eu/health/scientific_committees/docs/citizens_dehp_en.pdf

Results of public consultation: http://ec.europa.eu/health/scientific_committees/emerging/docs/followup_cons_dehp_en.pdf

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