Results of the public consultation on SCENIHR's preliminary Opinion on the safety of medical devices containing DEHP- plasticized PVC or other plasticizers on neonates and other groups possibly at risk (2015 update)

A public consultation on this Opinion was opened on the website of the non-food scientific committees from 22 October 2014 to 30 November 2014. Information about the public consultation was broadly communicated to national authorities, international organisations and other stakeholders.

15 organisations and individuals participated in the public consultation providing 69 comments to different chapters and sections of the Opinion. Each submission was carefully considered by the SCENIHR and the scientific Opinion has been revised to take account of relevant comments. The literature has been accordingly updated with relevant publications.

The SCENIHR thanks all contributors for their comments and for references sent during the public consultation.

The table below shows all the comments made about each of the questions posed in the Opinion and the SCENIHR's response to them. It is also indicated if the comment resulted in a change of the Opinion.

Comments received during the public consultation on the SCENIHR preliminary Opinion on the safety of medical devices containing DEHP- plasticized PVC or other plasticizers on neonates and other groups possibly at risk (2015 update)

No.	Name of individual/ organisation	Table of content to which comment refers	Comment	Scientific Committees Response
1.	Berzanskis Laurel, Health Care Without Harm Europe, laurel.berzanskis@hcwh.org, Belgium	ABSTRACT	Abstract; page 5; ln 29: Describes using the TDI as a "conservative approach". But a statement on page 14; ln 23-27 explains why using the TDI is not appropriate for this evaluation when considering high exposures in a special group of patients. "The TDI for DEHP is 48 µg per kg bw per day, which was based on a No Observed Adverse Effect Level (NOAEL) for reproductive effects in rats. In view of the potential high exposure to DEHP during certain medical procedures and a very special group of patients involved, the use of TDI is not considered appropriate in these procedures". "Not appropriate" is not the same as "conservative".	The text in the abstract has been changed in order to explain why the use of TDI is considered 'a conservative approach'. This is the reason why in some cases the use of TDI could be seen as 'not appropriate' (relative high exposures in certain patient groups for very short time). The text in the Background is provided by the Commission and cannot be changed. It refers to the previous SCENIHR Opinion and the lack of appropriateness was exactly related to the reason now explained in the abstract. However, the SCENIHR does not feel that this represents a contradiction.
2.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	ABSTRACT	page 5, 4th para: using the TDI oral may not be justified for the evaluation of intravenous exposure by medical devices page 6: DINCH is missing. Especially for this plasticizer data reduced migration (e.g. concentration at the end of a 42 days storage period in blood bags) leading to significantly reduced exposure of patients are available in the published literature.	The SCENIHR agrees that considering the oral absorption being around 50% (with respect to a 100% bioavailability related to parenteral administration) could affect the final outcome, asking for a refinement of the risk assessment process. It should be considered however, that for the scenarios at risk, the MoS is very low or non-existent, thus a refinement was not considered necessary. For other scenarios, on the contrary, the MoS was high enough without requiring any additional refinement as well. The acute toxicity of DEHP was, on the other hand, quite low, therefore high

				acute exposure levels were not considered to be of concern. In addition it is worthwhile to note that ECHA (2013) mentioned an almost complete oral absorption for DEHP in its recent evaluation of DINP. DINCH has been added in the abstract, indicating a lower reproductive toxicity when compared to DEHP. Detailes about alternatives (including migration data, when available) are then given in the main text.
3.	Sterk Thecla, Eucomed, thecla.sterk@eucomed.org, Belgium	ABSTRACT	General remarks: This Abstract summarises multiple pieces of different information but does not explicitly link the information to the Terms of Reference listed on Page 15. To help the reader understand which information refers to 'new' findings, and which is a repeat of information from the 2008 Opinion, we suggest that the paragraphs of the Abstract be organised under different headings – ideally, these headings should mirror the Terms of Reference. Alternatively, the Abstract should conclude with a paragraph summarising the SCENIHR's findings vis-à-vis the Terms of Reference. • PVC in the medical device field and especially for dialysis application has no valid alternative so far offering the same advantages in terms of costs, quality and performances. For production of soft PVC, e.g. for tubing systems, plasticisers are mandatory. So DEHP is largely used, even if other alternatives like TOTM, DINCH, DEHA and DEHT gain in importance. • The availability of more information and data, e.g. generated by REACH and other sources, will keep the toxicological evaluation of such plasticisers consistently in discussion. Unfortunately, most evaluations focus on few specific substances. This leads to inconsistencies	This is the usual format in which data are reported in the Abstract. The specific request is addressed in paragraph 4.2, Responses to the questions in the Terms of Reference (see page 81), again following the usual format of the SCENIHR Opinion. No action needed. No need to change the text of the Opinion. The SCENIHR agrees that availability of more information obtained by REACH would be beneficial to fill the gaps. The SCENIHR also agrees that for this group of chemicals in any case, a combined evaluation of exposure as well as of human health effects would be more appropriate than for single chemicals. However,

			and remaining data gaps (especially related to potential DEHP alternatives) which impede appropriate risk assessments and question any decision on substitution in the medical devices industry. • Thus an integral approach and evaluation of plasticisers for medical devices would be needed to create a more reliable basis for future risk assessments, and finally, the required decisions on materials (and plasticisers) to be used in design and development of future medical devices. • In any case, it must be taken into account that substitution of DEHP or P-PVC in medical devices by other plasticisers and materials, respectively is technically very challenging and might not be possible in all cases. An example is slight differences in material properties that seriously affect the machine disposable interface and by this patient's safety. • It would be good to have a list of tables and figures as graphic summary. It should be taken into consideration to have human data per each material , which has no human data, in accordance, not only for scientific considerations, but also for regulatory compliance with relevant requirements.	data on the REACH database on alternatives are often available only as 'robust summaries' prepared by Industries and not checked by ECHA. The decisions on materials (and plasticizers) to be used in the design and development of medical devices as they pertain to risk management measures is outside of the mandate of the SC. The substitution of DEHP or P-PVC in medical devices as they pertain to risk management measures is outside of the mandate of the SC.
4.	Sterk Thecla, Eucomed, thecla.sterk@eucomed.org, Belgium	ABSTRACT	Page 4: The following sentence in the 3rd paragraph - "Several procedures…may lead to high exposure to DEHP" - should say "Several procedures…may lead to high exposure to DEHP and any other chemicals that potentially leach from the device used." Rationale: To underline that leaching of chemicals is a key risk management consideration for all of the medical procedures given as examples. The reader should therefore be reminded that any substitute chemicals that might potentially replace DEHP (or other plasticizers) may also present 'high exposure' to the patient, by virtue of the potential for leaching and the	Since exposure level depends on the leaching rate, the comment is only partially right. The text has been partially modified, but reference to other compounds is considered unnecessary. Reference to alternatives is given at the end of the abstract, where release is mentioned.

			purpose of the devices. Page 5: The abstract contains the following statement: "However, the lack of data on their release from medical devices and consequent human exposure does not allow an appropriate risk assessment to be carried out, for which aggregate exposure should be taken into account, because dust and air samples may contain these plasticizers." This statement is potentially misleading based on the data presented in the document. The vapour pressure of DEHP (presented in Table 1 of the document) is extremely low, which does not support DEHP volatilization as a source of exposure from medical devices. The data presented for airborne levels does not differentiate the contribution from dust due to mechanically induced sources in the environment. Risk assessment is possible and appropriate for DEHP in medical device applications where the only realistic risk of exposure is volatilization, such as internal components within medical equipment (e.g. wire insulation). Page 5, 3rd from last paragraph: We propose the following modification to the last sentence: Therefore patients subject to haemodialysis procedures are may be at risk of DEHP induced effects. (This is based on deductions as there is no real proof today that there is an explicit effect on humans). Page 5: It is important to note that harmonized classification of DEHP according to the EU CLP Regulation is category 1B for reproductive toxicity. The first paragraph should finish by saying "Thus, DEHP has been classified since the 2008 Opinion as possible carcinogenic to humans (Group 2B)," to underline that this is new information. Page 6: It is not clear from the Abstract alone whether	The text has been modified to avoid any mis-intepretation. The text has been changed as requested. The SCENIHR agrees with this comment. The text has been changed as requested. The Opinion reports both 'old' (i.e. already cited in the

			the 6th paragraph – the one that starts with "Exposure to DEHP may exceed the TDI in some specific groups" – is reporting any new information compared to 2008. The 4th paragraph states that the SCENIHR supports the prior TDI but this 6th paragraph does not specify whether the 'various studies' that report median exposure levels for patients undergoing haemodialysis are studies since 2008 or prior. If the studies were not available for the 2008 Opinion, this paragraph should specify that they are new. If the studies were used in the 2008 Opinion, the purpose of this paragraph is questionable. We propose to move to the beginning the paragraph "abbreviations" together with "definitions" to help the reader to get familiar with such terminology. We propose to use consistent units throughout the report for example Paragraph 2 mentions ug/kg bw/d whereas para 4 mentions mg/kg bw/d.	previous Opinion) and 'new' data that were considered together and evaluated based on the WoE approach, as described in the methodology paragraph. To make a clear-cut distinction between old and new information is therefore not possible. This applies to the entire document. The SCENIHR agrees. The text has been changed as requested.
5.	Sterk Thecla, Eucomed, thecla.sterk@eucomed.org, Belgium	1. ATBC (Acetyl tri-n-butyl citrate)	Only 2 studies on small animal are not enough to justify the usage and the size of the rats is not comparable with the human being. Moreover are not available clinical study on humans, this lack can concern stakeholders.	This issue is addressed in section 4.1.7, where it is stated: "Concluding, for some alternatives (DINP, TOTM and DEHA), available toxicological data indicate a lower intrinsic reproductive toxicity when compared to DEHP, although toxicity data on other end-points are lacking. In addition, a risk assessment of these alternative plasticizers could not be performed because of a lack of information on leaching properties and consequent human exposure. For others, information on the toxicological profile was inadequate even to identify the hazard. This limits evaluation of potential alternatives for DEHP." No need to change the text of the Opinion.

6.	Sterk Thecla, Eucomed, thecla.sterk@eucomed.org, Belgium	2. BTHC (n-Butyryl-tri-n-hexyl citrate)	No data on human beings can be considered not appropriate the material.	The issue is addressed in section 4.1.7. See also the previous answer.
7.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	3. COMGHA (Glycerides, Castor-oil-mono-, hydrogenated, acetates)	This file should be updated, at least with the information publicly available from REACH Registration. At the moment, the conclusion seems not to be backed by the mentioned lack of data, see e.g. page 13: COMGHA ... could not be evaluated ...due to lack of toxicological data. Further, data on the intravenous route, a Major route for medical devices, are not reported in the SCENIHR Report, which again questions the conclusions presented	With respect to the information publicly available from REACH registration, it is noted that this information includes study summaries and not original study reports. Study summaries are given on ECHA's dissemination website, and the following information is given: (http://echa.europa.eu/qa-display/-/qadisplay/5s1R/view/reach/echapublicdatabasewithinformationonregisteredsubstances). "The information in this database originates from registration dossiers submitted by companies. Companies have the obligation to provide accurate and up-to-date information in their registration dossiers. ECHA's IT systems verify that the information is complete, meaning that all the information fields required for a registration in a particular tonnage band are filled in in the dossier. However, the European Chemicals Agency (ECHA) does not verify the information before its publication on the internet. ECHA can not therefore guarantee the correctness or adequacy of the information or that the dossiers are compliant with REACH." Thus, information on ECHA's dissemination website is considered as second-hand information since original studies are not available for evaluation. Further, ECHA's website mentions: "Reproduction or further distribution of this information may be subject to copyright protection. Use of the information without obtaining the permission from the owner(s) of the respective information might violate the rights of the owner. The Agency does not take any responsibility whatsoever for any copyright or other infringements that

				may be caused by using the information." Therefore, relevant study data which should be included in the SCENIHR Opinion should be provided directly to the SCENIHR.
8.	Berzanskis Laurel, Health Care Without Harm Europe, laurel.berzanskis@hcwh.org, Belgium	3.1. Introduction	Pg 18, ln 8: The committee was asked on P15, ln 15: "If it is possible to propose possible alternative approaches that could reduce potential risks either by identifying alternative practices or by identifying alternatives to the use of DEHP in PVC plasticized in medical devices. If no clear answer can be provided on this point, the SCENIHR is asked to formulate recommendations for research that could help provide scientific evidence to that end." But on Pg 18; ln 8: the committee failed to consider non-PVC products at all. Clearly, non-PVC alternatives are one way to reduce DEHP exposures from PVC-plasticized medical devices. Pg 18; next to last paragraph section 3.1; beginning ln. 22: The committee uses a weight of evidence approach (as defined in 2012 SCENIHR document); requires "consistency" for establishing causality. The 2012 document outlines steps for evaluating quality and consistency of studies. SCENIHR 2012 also includes considerable discussion of "utility" and uncertainties." The draft document largely fails to include any evaluation of either utility or uncertainties in the summaries of various studies. Also see overall comment on weighing evidence above.	Non-PVC products were not considered by the SCENIHR because of data gaps for their evaluation. The steps and concepts as reported in the SCENIHR 2012 Document were followed by the SC, although not explicitly written for each single study when the uncertainty of some results were evidently due to the limited quality of the study design or of stated interpretations. However, the SCENIHR agrees that a specific uncertainty analysis was not conducted.

9.	FOLLEA Gilles, European blood Alliance, g.follea@europeanbloodalliance.eu, Netherlands	3.1. Introduction	P 17, when reference is given to the LCA report at least it should be mentioned that a critical review has been published (A AZAPAGIC, "Life Cycle Assessment, LCA, study of PVC blood bags." 2012, see attachment). The scientific validity of the LCA report is questionable as the methodology used did not follow the international standards on principles and frameworks for life cycle assessment, ISO 14040:2006. In addition there is a lack of transparency with respect to the assumptions, data, calculation methods and results. The report as a whole does not meet the criteria of sound science and cannot be used as a basis for a scientific review. Another important critique point is that the LCA study is comparing PVC-DEHP blood bags with a fictional HDPE blood bag, because this fictional bag would not be able to withstand the physical stresses and strains needed for blood bags. This is due to the fact that Polyethylene does not have the required characteristics needed to withstand autoclave sterilization (necessary in blood bag production steps) and centrifugal forces (which would require strong welds). P 18 In Introduction (just before last paragraph) reference is given to SCENIHR (2012), this is not in the reference list	It has been clarified that conclusions are related to the study authors' interpretation. In addition, a sentence has been added to make the limitations of the study explicit. *The study authors considered a PVC blood bag to have a higher potential to harm human health in view of its release of DEHP and dioxin emissions at waste incineration. However, the SCENIHR considers that the study has some serious limitations in the study design and methodology, also related to the use of a 'fictional' blood bag as reference.* The SCENIHR 2012 has been added to the list of references.

10.	Sterk Thecla, Eucomed, thecla.sterk@eucomed.org, Belgium	3.1. Introduction	Page 17: We propose to remove the last sentence referencing the LCA report as this is very biased and poorly done. Regarding the LCA study, Eucomed would like to remind the SCENIHR of our analysis of the LCA report we submitted in 2012: "we still don't believe that the study provides enough evidence from a patient and blood safety point of view to support moving away from PVC blood bags for the following reasons: questionable methodology, scientific validity and unrealistic choice of the quantitative reference (i.e. an HDPE blood bag). Questionable methodology and scientific validity The scientific validity of the report is questionable as the methodology used did not follow the international standards on principles and frameworks for life cycle assessment, ISO 14040:2006. In addition there is a lack of transparency with respect to the assumptions, data, calculation methods and results. The report as a whole does not meet the criteria of sound science and cannot be used as a basis for a scientific review. Another example of the questionable methodology is the impractical recommendation with regards to recycling of blood bags with no consideration for transmission of pathogens, a contributor to healthcare-acquired infections.n HDPE blood bags: a "fictional" (and unrealistic) example The LCA study is based on fiction. The HDPE blood bag remains fictional because it would not be able to withstand the physical stresses and strains needed for blood bags due to the fact that Polyethylene does not have the required characteristics needed to withstand autoclave sterilization (necessary in blood bag production steps) and centrifugal forces (which would require strong welds). When replacing one material by another for blood bags assessing the technical/physical material properties and the physiological features of both the known and the new material are of the utmost importance. Pros and cons	Please, see the answer to Comment n°9. The paragraph has not been deleted, since the LCA report was also mentioned in the background prepared by the Commission. However, the SCENIHR have not used the results from the study in its evaluation due to its limitations. This is the only citation in the document. The limitations were made explicit in the new amended text.

			have to be weighed very carefully before making the decision to replace the known and trusted material. One of SCENIHR's conclusions (2002, 2008) [2][3] was that there still is a lack of human exposure data with regards to alternative materials for plasticized PVC such as currently used in blood bags. According to new review articles [4] this gap has yet to be closed, especially with regards to toxicological behavior and environmental impact. The SCENIHR report of 2008 further acknowledged that "medical devices made from plasticized PVC provide many effective treatments and that DEHP is a particularly effective plasticizer. In addition to its beneficial effect on mechanical properties, DEHP also stabilizes the membranes of red blood cells enabling blood product storage in PVC blood bags for several weeks". Having reviewed the above studies, we are convinced that there is still not enough evidence from a patient and blood safety point of view to move to a PVC free blood bag."	This issue is addressed in the conclusions in a different part of the Opinion (see abstract, executive summary, main text). No need to change the text of the Opinion.
11.	Sterk Thecla, Eucomed, thecla.sterk@eucomed.org, Belgium	3.2. Present use of plasticized PVC in medical devices	The last sentence of section 3.2 "However, this probably cannot be achieved for all medical procedures." – We should seriously offer the flexibility of allowing currently unreplaceable PVC device exempted from any will-be banned list to assure a balance between cons and pros. For those devises for which there are potential alternative materials, the implications of conversion need to be considered; functionality of the product and COGS. This section appears to be generally aligned with prior 2008 summary… does emphasize the significance of consideration of medical benefit versus potential risk (to identified populations and procedures). Still notes no direct, demonstrable effects in human populations. Conclusions still primarily based on potential risk	The issue of risk/benefit due to the use of alternative materials has been addressed in the Opinion, although very briefly, since banning some products and conducting a cost-benefit analysis are issues outside of the SC mandate. No need to change the text of the Opinion.

			("may" exist even in the absence of definitive cause-effect data in humans).	
12.	Berzanskis Laurel, Health Care Without Harm Europe, laurel.berzanskis@hcwh.org, Belgium	3.3. Physicochemical properties of plasticizers	Pg 20: in the chart, log Kow for DEHP should be 7.5; not 7,5	The text has been modified.
13.	Sterk Thecla, Eucomed, thecla.sterk@eucomed.org, Belgium	3.3. Physicochemical properties of plasticizers	In Table 1, kerosene extractability data is not an appropriate parameter to assess extractable plasticizers from PVC due to the fact that kerosene can dissolve PVC. An oil extractable test, if available, would be more appropriate. Potentially instead using 40% ethanol, as is used by some manufacturers. The kerosene appears to be included only as a measure of DEHP/plasticizers lipophilicity. As long as the same solvent is used for all in the comparison, end results probably OK. Not meant to be clinically relevant or even relevant for extractability per se. We would certainly agree that other solvents would be more appropriate for extractables definition, or that this should be stated more as a "total"/"exhaustive" extraction based on potential dissolution of polymer matrix. This presumably reflects some accepted industry standard measurement for chemical lipophilicity.	Available data on extraction (leaching) by kerosene was included in the table (considering that the matrix was not dissolved in the kerosene). This is explained in the column heading and in footnote b. No need to change the text of the Opinion.
14.	Vecchi Luigi, Sorin Group Italia Srl, luigi.vecchi@sorin.com, Italy	3.4. DEHP (di(2-ethylhexyl) phthalate)	3.4.3.6. Adult exposure during medical procedures In the overall report the term ECMO (extracorporeal membrane oxygenation) is used as a synonym to describe procedures of Cardiopulmonary bypass during artificial heart transplant and it is indicated as a short-term exposures: however in the above mentioned section (table 4) there is a clear distinction among "ECMO" and "Cardiopulmonary bypass during artificial	The text in table 4 implies a normal ECMO treatment including use of 21-46 blood components. The word 'process' has been added for clarity. This process may be repeated (as can many others) and only in this case does it become a long-term exposure. ECMO and cardiopulmonary bypass procedures are indicated as separate exposure possibilities in the report

			heart transplant" in terms of Daily DEHP dose (µg/kg/d) (the former procedure having a dose of 3000-10000 while the latter is ranging upon 2400 and 81 ± 40). Typically Cardiopulmonary bypass procedures (coronary artery bypass graft surgeries, valvular replacements, heart congenital defect corrections, etc) are short term exposures as the time of contact of blood with the extra corporeal tubing sets is usually not exceeding six hours while the ECMO procedures imply a longer contact time which might justify the higher amount of DEHP dose found in such procedures). We believe that this distinction as reported in the above mentioned paragraph better reflect the difference among ECMO procedures and generic Cardiopulmonary bypass procedures and therefore should be addressed in the whole report	and not used as synonyms of each other (see for example the listing on page 33 and 76). Also in other locations of the document, both procedures are mentioned separately as part of a listing of possible exposures.
15.	Berzanskis Laurel, Health Care Without Harm Europe, laurel.berzanskis@hcwh.org, Belgium	3.4. DEHP (di(2-ethylhexyl) phthalate)	Pg 24: Next to last paragraph (beginning line 38) [or somewhere in this section of the draft] should include discussion about age-related differences in glucuronidation in humans. Infants have higher levels of glucuronidases and lower levels of glucuronyl transferases than adults. Moreover, the distribution of metabolites differs with age. (Frederiksen, 2014) Thus, results of toxicokinetic studies in adults (e.g. Kurata, 2012) should not be extrapolated to fetuses, infants, and young children. Miyagi S, Collier A. Pediatric development of glucuronidation: the ontogeny of hepatic UGT1A4. Drug Metab Dispos. 2007 Sep;35(9):1587-92. Frederiksen H, Kuiri-Hänninen T, Main KM, Dunkel L, Sankilampi U.A longitudinal study of urinary phthalate excretion in 58 full-term and 67 preterm infants from birth through 14 months. Environ Health Perspect 2014 Sep;122(9):998-1005. (The distribution of metabolites of DEHP varies in preterm vs. full term infants)	Information related to the age-related differences in glucuronidation coming from Frederiksen, 2014 is reported in the paragraph. There is no need to cite the paper by MiYagi *et al*, since it refers specifically to an UDPGT isoform, which is known to be involved in DEHP or other phthalates metabolism. The new information coming from the Hopf paper is now included in the revised version.

			Pg 25: beginning line 17; paragraph discussing dermal absorption: More recent studies find much more vehicle-dependent dermal absorption. Neat DEHP is poorly absorbed whereas DEHP in aqueous suspension is much more rapidly and completely absorbed. Hopf NB, Berthet A, Vernez D, Langard E, Spring P, Gaudin R. Skin permeation and metabolism of di(2-ethylhexyl) phthalate (DEHP). Toxicol Lett. 2014 Jan 3;224(1):47-53. Pg 26: first paragraph: If dust contributes about 20% of total DEHP exposure, as previously noted, it cannot be considered "trivial" (line 6), even though it accounts for less than dietary sources. Moreover, others have reached varying conclusions. Guo et al. recently calculated that house dust could contribute 10-58% of total DEHP exposure to residents in a sample from Albany, New York. Using biomonitoring data and modeling, Shin et al. estimated that 39% of DEHP levels were attributable to indoor dust ingestion and 14% to inhalation. Guo, Y and Kannan, K, (2011). 'Comparative assessment of human exposure to phthalate esters from house dust in China and the United States'. Environmental Science & Technology, 45: pp 3788-3794. Shin, H, McKone, T, and Bennett, D, (2014). Attributing population-scale human exposure to various source categories: merging exposure models and biomonitoring data. Environment International, 70: pp 183-191.	The SCENIHR agrees that the term trivial was not appropriate and has been replaced by 'less relevant'. The paper Guo and Kannan, although already cited in the Opinion, was described in some more detail. The paper by Shin *et al* was also cited.

16.	Berzanskis Laurel, Health Care Without Harm Europe, laurel.berzanskis@hcwh.org, Belgium	3.4. DEHP (di(2-ethylhexyl) phthalate)	Pg 36: Section 3.4.3.7: first paragraph: add differences in toxicokinetics as an additional reason for vulnerability of the developing foetus and neonate. (see comment on page 24) Pg 40: Section 3.4.3.9 (this is a summary of the previous sections on exposures) The discussion of fetal and infant exposures to DEHP should also specifically mention higher exposure to unconjugated, biologically active metabolites compared to older children and adults. Pg 42: 2nd paragraph, beginning ln 10: This sentence needs to be edited. "Hepatic dysfunctions and cholestasis have been reported, not observed, in the group for polyethylene containers and tubes were used." Pg 42. Ln 25: This statement needs a reference. "In a repeated exposure study, 16 rats were pretreated with 100 mg/m3 for 2 weeks (aerosol) 6h per day, 5 days per week. The study indicates that following repeated inhalation exposure long-term retention does not occur." It is also unclear why that paragraph is included in the section addressing "Toxicity". Subsequent discussion of impacts on immune function and inflammatory cells in BAL fluid is relevant to respiratory effects. See, for example, Hansen J, Larsen S, Poulsen L, Nielsen G. Adjuvant effects of inhaled mono-2-ethylhexyl phthalate in BALB/cJ mice. Toxicology. 2007; 22;232(1-2):79-88. Pg 42: last sentence in discussion of DEHP mutagenicity; 5 lines from bottom of page: "Thus, in a WoE approach, it can be considered that DEHP and its major metabolites are non-mutagenic substances." The draft and IARC 2012 make clear that DNA damage has been reported in some assays although it is unclear whether that might be the result of oxidative stress "or other events." IARC 2012 also says, "Studies of in-vivo mutagenicity in two different transgenic mouse models have been conducted,	Reference to Frederiksen *et al*., 2014 has been included in the paragraph as well as in the summary. The wording was changed. The SCENIHR thanks the contributor for pointing out the missing words. The SCENIHR agrees, the study was not relevant here and the text was deleted. The SCENIHR disagrees. Results on *in vivo* are reported in the Opinion exactly as by IARC. The overall results indicate that a direct interaction with DNA is highly unlikely. Therefore, the conclusion remains stated as it is.

			but the results are conflicting, which confounds the interpretation of these findings." Thus, the conclusion should be "Uncertain overall weight of evidence: due to conflicting information from different lines of evidence that cannot be explained adequately in scientific terms." [SCENIHR, 2012] (with respect to mutagenicity) Same comment about same statement in summary on pg. 49; ln 7-8. Pg 46: paragraph discussing human fetal xenographs; ln 25 forward: Mitchell et al (2012) reported no change in testosterone production after DBP and MBP exposure, but did note "in the same samples there were certain changes to germ cells (e.g. aggregation; our unpublished data). The scale and significance of these germ cell effects is under further investigation." Comment from Richard Sharpe in Habert et al (2014) "Richard Sharpe (Edinburgh, UK): There are differences depending on the endpoint assessed. Effects are variable for some endpoints (e.g. steroidogenesis), but there is more consistency when looking at the effects on germ cells. It is difficult to extrapolate from in vitro results to the in vivo situation, however." (these differences are further discussed in the next section of the draft) Habert R, Muczynski V, Grisin T, et al. Concerns about the widespread use of rodent models for human risk assessments of endocrine disruptors. Reproduction. 2014 Mar 6;147(4):R119-29. Pg 49: next to last paragraph contains this sentence; ln. 9-10 from bottom. "There is some indication about the possibility of alteration of the timing of differentiation of foetal germ cells." This deserves more explanation and detail. It's not only timing of differentiation that can be altered but also other changes have been described in germ cells. (apoptosis, aggregation—see Habert, 2014) In addition considerable inter-individual variation in studies of human tissue cultures has been described.	Some additional description on germ cell effects has been included. Some changes in the text have been introduced, however it should be noted that, as reported in the Opinion, the meaning of these alterations is not clear and it is difficult to extrapolate from *in vitro* results to the *in vivo* situation.

			(See Habert, et al, 2014, cited above)	
17.	Berzanskis Laurel, Health Care Without Harm Europe, laurel.berzanskis@hcwh.org, Belgium	3.4. DEHP (di(2-ethylhexyl) phthalate)	Pg 50: This begins the discussion of epidemiologic studies and would benefit from some mention of differences in methods for estimating exposures to phthalates. (See reference above: Christensen, et al 2014, and the implications for drawing conclusions from disparate studies) Christensen K, Sobus J, Phillips M, et al. Changes in epidemiologic associations with different exposure metrics: A case study of phthalate exposure associations with body mass index and waist circumference. Environ Int. 2014; 73:66-76. Pg 52: ln 7: discussion of birth weight includes the statement that a 1.2 week difference in gestational age is "unlikely to be of any clinical significance." That statement is unlikely to be true and should be qualified. See for example: Wade M, Browne DT, Madigan S, et al. Normal Birth Weight Variation and Children's Neuropsychological Functioning: Links between Language, Executive Functioning, and Theory of Mind. J Int Neuropsychol Soc. 2014; 29:1-11. The length of normal human pregnancies shows variability that may be influenced by early events. We should not presume to know the long term consequences of a one-week difference in gestational age, even in normal birth weight infants. See Jukic A, Baird D, Weinberg C, et al. Length of human pregnancy and contributors to its natural variation. Hum Reprod. 2013; 28(10):2848-55. Pg 52-53: Consider adding summary of Ferguson et al (2014) describing higher biomarkers of oxidative stress in pregnant women exposed to higher levels of DEHP during pregnancy. Ferguson K, Cantonwine D, Rivera-Gonzalez L, Loch-Caruso R, et al. Urinary phthalate metabolite associations with biomarkers of inflammation	A short paragraph to address the issue has been included at the beginning of the epidemiological section. Since the text refers to '1.1 days' and not weeks, the SCENIHR is of the Opinion that the statement should not be changed.

			and oxidative stress across pregnancy in Puerto Rico. Environ Sci Technol. 2014; 48(12):7018-7025. Pg. 57, 2nd paragraph. Summary of Araki et al (2014) and Meeker et al (2014) should be added to the second paragraph. Araki A, Mitsui T, Miyashita C, Nakajima T, et al. Association between Maternal Exposure to di(2-ethylhexyl) Phthalate and Reproductive Hormone Levels in Fetal Blood: The Hokkaido Study on Environment and Children's Health. PLoS One. 2014 Oct 8;9(10):e109039. doi: 10.1371/journal.pone.0109039. eCollection 2014. Meeker J, Ferguson K. Urinary phthalate metabolites are associated with decreased serum testosterone in men, women, and children from NHANES 2011-2012. J Clin Endocrinol Metab. 2014; 99(11): 4346-4352. Pg 57-59: Add summary and discussion of Specht et al (2014) in section on gonadal hormone and semen quality. Note the discussion of methods in the paper; estimates of exposure through serum biomarkers; differs from other studies examining similar endpoints. Specht I, Toft G, Hougaard K, Lindh C, et al. Associations between phthalates and biomarkers of reproductive function in 589 adult men. Environ Int. 2014; 66:146-156. Pg 62. Summary of Whyatt et al. (2014) should be added to the asthma discussion. Whyatt RM, Perzanowski MS, Just AC, Rundle AG, et al. Asthma in Inner-City Children at 5-11 Years of Age and Prenatal Exposure to Phthalates: The Columbia Center for Children's Environmental Health Cohort. Environ Health Perspect. 2014; 122(10):1141-6.	The summary of the Ferguson study has been included in the revised version. The summaries of the two studies have been included in the revised version. The summary of the study has been included in the revised version. The summary of the study has been included in the revised version.

18.	Berzanskis Laurel, Health Care Without Harm, laurel.berzanskis@hcwh.org, Belgium	3.4. DEHP (di(2-ethylhexyl) phthalate)	Pg 64: 2nd paragraph: A brief discussion of animal studies addressing the effects of DEHP exposure on insulin sensitivity and diet-induced obesity shows up in the middle of a discussion of epidemiologic studies. Animal studies are the topic of section 3.4.4.1. The choice of animal studies is odd and limited. It would also help to separate the epidemiologic studies from the lab animal studies. Another option would be to include a more complete discussion of the animal data addressing obesity and insulin resistance in the animal toxicity section of the draft report. Fiege, et al. are interested in exploring the role of PPARα in the protective effect of DEHP on diet-induced obesity. They use the "PPARα-humanized mice" to show that PPARα does play a role. But, this paragraph includes no mention of a more extensive literature on the role of PPARγ in adipogenesis and obesity. MEHP is a ligand for PPARγ as well (Hurst, 2003), and the role of PPARγ in adipogenesis is known. This section should include a more detailed discussion of the experimental literature reporting the PPAR-mediated activity of DEHP and potential role in adipogenesis and obesity in humans. (not just the role of PPARα) We do need to be aware of species differences, but we also need to keep species similarities in mind. Mechanistic understanding of phthalates as PPARγ agonists lends support to the hypothesis that phthalates may be related to obesity and metabolic disorders. The last sentence in this paragraph (ln 4, pg 65)"Few studies used cross-sectional analyses and thus could not be used to test causal hypotheses" should be changed to indicate that most of these studies are cross-sectional and therefore cannot be used to test causal hypotheses. See for example: Ellero-Simatos S1, Claus SP, Benelli C, Forest C, et al. Combined transcriptomic-(1)H NMR metabonomic study reveals that monoethylhexyl phthalate stimulates adipogenesis and glyceroneogenesis in human adipocytes. J Proteome Res. 2011;	That paragraph was presented to show the possible species differences in these effects. In addition, whenever the PPARα is involved in some AOP, it is not considered very relvant to human beings, since the differences compared with the rat receptor are significant. See also what has been discussed for the carcinogenity mediated by peroxisome proliferation in rodents vs man. The comments also refer to PPARγ: the SCENIHR is aware that papers on animal models or *in vitro* have been published on the issue, but the meaning of these findings for human health have not been clearly defined yet. Because epidemiological studies are available, we prefered to directly include them. The last sentence has been changed.

			2;10(12):5493-502. Desvergne B, Feige JN, Casals-Casas C. PPAR-mediated activity of phthalates: A link to the obesity epidemic? Mol Cell Endocrinol. 2009 May 25;304(1-2):43-8. Hurst C, Waxman D. Activation of PPAR alpha and PPAR gamma by environmental phthalate monoesters. Toxicol. Sci.2003, 74(2), 297–308.	
19.	Berzanskis Laurel, Health Care Without Harm Europe, laurel.berzanskis@hcwh.org, Belgium	3.4. DEHP (di(2-ethylhexyl) phthalate)	Pg 65: S3.4.6: The first paragraph of the conclusions begins with the subtitle (Effects on Testosterone Production). But the paragraph also draws conclusions about sperm counts and sperm quality. This is more generally about testicular effects and the title should be modified to reflect that. In the summary of studies of DEHP exposures and associations with hormone levels, the draft as well as the studies cited, describe a fairly consistent inverse relationship between various measures of DEHP exposure and gonadal hormone levels (Meeker, Mendiola, Pan). The draft summary says: "Overall, the association between DEHP (or other phthalate) exposure and a decrease in testosterone/free testosterone levels and/or with small adverse changes in aspects of sperm function (e.g. motility) or DNA damage is weak. The described effects are small and unlikely to be of biological significance." These two sentences combine and inappropriately simplify conclusions from the cited studies. The evidence of an association with altered hormone levels is quite consistent and should not be described as "weak". Moreover, the draft should not draw conclusions about clinical significance without more detailed explanation and justification. These changes may be highly significant for individuals whose hormone status or fertility status are marginal. And population-wide consequences may be substantial when exposures to a chemical like DEHP are virtually ubiquitous. The draft should also make clear that data addressing	The subtitle has been changed. The two concepts (testosterone decrease and sperm quality) have been separated to further clarify the text, but the final conclusions were not changed, because although some studies provide information about a negative correlation between DEHP exposure and decreased testosterone levels, the entuity of this change is limited and the SCENIHR conclusions are based on this. Because this is a summary, it cannot repeat all the detailed information about the studies that are described in the previous paragraphs.

			the consequences of hormone changes associated with higher DEHP exposure in human fetuses and infants are unknown. Consistent impacts of DEHP/MEHP exposures on testosterone levels in infants across species (including non-human primates) as well as changes in germ cells in various species were previously described. Pg 65: 9 lines from bottom of page. "Decreased anogenital distance - Published studies so far show inconsistent evidence for a possible association between maternal phthalate including DEHP exposure in pregnancy and decreased anogenital distance in male offspring." Omit "possible". Some studies do show an association while some do not. Pg 65; 6 lines from bottom: See comment on pg 79, ln 24 and following, (in next comment).	The word 'possible' has been deleted.
20.	FOLLEA Gilles, European Blood Alliance, g.follea@europeanbloodalliance.eu, Netherlands	3.4. DEHP (di(2-ethylhexyl) phthalate)	In the 2008 version \$3, 4, last paragraph the text was: "It should be noted that medical devices made from plasticized PVC provide many effective treatments and that DEHP is a particularly effective plasticizer. In addition to its beneficial effect on mechanical properties, DEHP also stabilises the membranes of red blood cells enabling blood product storage in PVC blood bags for several weeks." In the new version this has been weakened and only the stabilizing effect has remained in the text. No arguments has been given to establish that the first part of the original sentence was no longer true, still DEHP is the plasticizer of choice for many products and PVC is the material of choice.	The structure of the present report is different from that of 2008. The text indicated by Dr. Follea can be found on page 76-77, suggesting "High exposure levels during certain medical procedures need to be assessed based on the treatment needed and the availability of suitable alternatives for each medical treatment and in some cases, DEHP-containing plasticized PVC devices are important for many treatments and they are justified because of the benefits of these procedures. An additional benefit of DEHP is that it stabilises the membranes of red blood cells enabling blood product storage in PVC blood bags for several weeks". The present text is basically the same as the previous text of 2008 and admits the need of PVC/DEHP until acceptable alternatives are available.

21.	Sterk Thecla, Eucomed, thecla.sterk@eucomed.org, Belgium	3.4. DEHP (di(2-ethylhexyl) phthalate)	The opinion showed clear analysis of the studies carried out on various subjects involved as well as evidence on short /long term effects on epidemiological clinical studies. Recent studies explained each aspect of any pathology and the results as well as the observations concerning particular patients, es. haemodialysis, which the patient undergo to serious problem. Other studies should be taken into account. In the last paragraph of section 3.4 it states that there "are now several studies that demonstrate that >90% of exposure to DEHP occurs via food for the general population." We think this is an important point to note in balancing out the risk of exposure to DEHP in medical devices compared to the critical value those devices deliver. 3.4.2.: p.21, 4th line from bottom: change "concentration" into "curve".3.4.3.: p.26, 2nd line from top: typo DHEP should be DEHP. 3.4.3.3.: Exposures in general population relatively consistent with prior 2008 summary assessment. Work does reflect additional focus on maternal/fetal exposures, etc. Not significantly new information. 3.4.3.5.: This section provides some new literature on leaching versus solution lipophilicity, exposure times and temperature; as well as device types. We believe that the data would need to be compared to prior data to see if any significant impact on conclusions; although it does not appear so. The focus appears to still be the same in terms of exposure scenarios (clinical procedures, device types, "at risk" patient populations). 3.4.3.6.: p.36, 2nd alinea, first line: "…was was…" delete one "was". 3.4.3.7 and 3.4.3.8: Some updated studies with some apparently higher exposures measured. Nonetheless, largely aligned in terms of focus of commentary.	New studies published in 2014 have been summarised and included in the revised version. The typos are now corrected. No need to change the text of the Opinion.

22.	Sterk Thecla, Eucomed, thecla.sterk@eucomed.org, Belgium	3.4. DEHP (di(2-ethylhexyl) phthalate)	3.4.4.1: The studies referenced appear mostly to be the same literature as in the 2008 assessment. There appear to be some newer studies, but still essentially the same conclusions (compare to see if IARC changed category in 2012). More studies on reproductive and developmental toxicity, and specifically male testicular toxicity; with significant focus on mechanism and species differences. Evidence mixed and very arcane with respect to drawing overall conclusions. 3.4.4.1.: p.42, 2nd alinea, 4th line: replace "for" by "where". 3.4.5: Epidemiology – This section contains a large number of studies on all types of reproductive and developmental endpoints. However, the results are largely mixed or confounded. 3.4.5. page 51: The Swan study (and others) were at the time criticized for the lack of relationship between the statistical data and the conclusions. We believe that this draft Opinion should be more critical and should mention this in the text body. We do acknowledge their conclusions (Chapter 4), that there does not seem to be a conclusive connection between plasticizer levels and certain physiological data such as anogenital distance, waist circumference, etc. 3.4.5. p.62, 2nd paragraph: asthma patients often get rooms with hard floor covers to minimize the dust particles. Therefore, one should carefully consider what is cause and what is effect before drawing conclusions. SCENIHR might have overlooked the reciprocal relationship (no wording) that asthma patients have chosen PVC floor covers, instead of that hard PVC floor covers provoking asthma. 3.4.6 Conclusions: Same as above – weak associations, confounding variables, inconsistent results between studies…. Conclude "no cause-effect relationship for	No need to change the text of the Opinion. The text has been changed. The issue has been already addressed. Indeed it is clearly stated: *However, the study had several limitations, namely it was retrospective, AGI was measured across a wide age range in boys and the number of subjects was small.* This is only one of the possible confounding factors, related to exposure assessment. All of these issues were already addressed in the

			harmful effects in humans." Still assert potential risk in male neonates and male fetuses of pregnant/nursing women as before, based on weight of evidence of animal data and mechanistic studies. Major confounder is other sources, specifically diet (>90% of exposure), with more emphasis on this aspect in this updated summary.	conclusions. No action needed.
23.	Mantovani Alberto Mantovani, LIFE - EDESIA project Consortium (http://www.iss.it/life), alberto.mantovani@iss.it, Italy	3.4. DEHP (di(2-ethylhexyl) phthalate)	3.4.3. DEHP exposure of the general population This whole interesting chapter, and in particular the conclusions on mean body burden (Table 3) will benefit from a brief discussion of the several papers (some of them quoted in other parts of the draft opinion) that report levels of MEHP in plasma/serum of humans as a result of the continuos, low-level exposure to DEHP present in foods and living environment. The more recent findings on healthy subjects report median levels in the magnitude order of 5-10 ngml in samples over the LOD (generally in a proportion above 50%, see, e.g., La Rocca et al., 2014), which might indeed support the overall conclusions on body burden of the draft Opinion Here some references: Cobellis et al., 2003 quoted in the Draft Opinion; Colon et al., 2000 quoted in the Draft Opinion; La Rocca C, Tait S, Guerranti C, Busani L, Ciardo F, Bergamasco B, Stecca L, Perra G, Mancini FR, Marci R, Bordi G, Caserta D, Focardi S, Moscarini M, Mantovani A. Exposure to endocrine disrupters and nuclear receptors gene expression in infertile and fertile women from different Italian areas. International Journal of Environmental Research and Public Health 2014 11, 10146-10164; Lind et al. (2012) quoted in the Draft	The paper by La Rocca *et al* has been included. All the other papers are already cited in the Opinion, although in other paragraphs. The SCENIHR considers it inappropriate to repeat the exposure data from studies in which they have been correlated to health parameters, also taking into account that the main scope of this mandate was related to medical device mediated exposure. The exposure of the general population from other sources has been included to put the specific source into contest.

			Opinion; Specht, I.O.; Toft, G.; Hougaard, K.S.; Lindh, C.H.; Lenters, V.; Jönsson, B.A.; Heederik, D.; Giwercman, A.; Bonde, J.P.E. Associations between serum phthalates and biomarkers of reproductive function in 589 adult men. Environ. Int. 2014, 66, 146–156)	
24.	Mantovani Alberto, LIFE EDESIA project consortium (http://www.iss.it/life), alberto.mantovani@iss.it, Italy	3.4. DEHP (di(2-ethylhexyl) phthalate)	3.4.4. Toxicity The opinion should quote the assessment performed by the EFSA (2005), that defined the TDI on the basis of the NOAEL of 4.8 mg/kg bw/day for testicular toxicity and developmental toxicity (see http://www.efsa.europa.eu/en/efsajournal/pub/243.htm) 3.4.4.1 Animal studies Please see also comment to 3.4.5. This section appears not fully integrated with the ensuing chapter on clinical and epidemiological studies (3.4.5). The human studies investigated the possible association of DEHP exposure with a number of health effects, such as preterm birth/lower birth weight, precocious female puberty, endometriosis, neurobehavioural development, increased risk of obesity. It is recommended to summarize the experimental or mechanistic studies that are relevant to the main effects investigated in the human studies, and to assess whether these studies may support or not the biological plausibility of the epidemiological findings. In the current draft opinion this appears to be done for male fertility/male reproductive development and diabetes: however, experimental evidence (or lack of such evidence) for other putative human effects should be discussed as well.	The EFSA Opinion (2005) has been repeatedly cited in the document, starting from the abstract. The mechanism of action is already discussed in relation to carcinogenesis as well as for reproductive toxicity. In addition, a summary and conclusion paragraph reports information considered relevant for effects on human health. No need to change the text of the Opinion.
25.	Mantovani Alberto, LIFE EDESIA project consortrium (http://www.iss.it/life), alberto.mantovani@iss.it,	3.4. DEHP (di(2-ethylhexyl) phthalate)	3.4.4.1 Animal studies - Mechanisms of action of carcinogenicity An additional point may be quoted. Intrauterine oral DEHP exposure in mice alters liver programming and delays the hepatocyte maturation (proliferation/differentiation balance) in post-natal	The paper has been cited.

	Italy		offspring by eliciting a cell phenotype characterized by glycogen accumulation, intracytoplasmic localization of beta-catenin and increased AFP gene expression. Thus, a potential developmental effect increasing the predisposition of liver tissue tu tumours later in life should not be ruled out (Maranghi F, Lorenzetti S, Tassinari R, Moracci G, Tassinari V, Marcoccia D, Di Virgilio A, Eusepi A, Romeo A, Magrelli A, Salvatore M, Tosto F, Viganotti M, Antoccia A, Di Masi A, Azzalin G, Tanzarella C, Macino G, Taruscio D, Mantovani A. In utero exposure to di-(2-ethylhexyl) phthalate affects liver morphology and metabolism in post-natal CD-1 mice. Reprod Toxicol. 2010 Jul;29(4):427-32) - Reproductive toxicity Attention should be given also to female reproductive effects observed in rodents (see above). In particular, ovarian effects have been described by (Lovekamp-Swan, T.; Davis, B.J. Mechanisms of phthalate ester toxicity in the female reproductive system. Environ. Health Perspect. 2003, 111, 139; Liu T, Li N, Zhu J, Yu G, Guo K, Zhou L, Zheng D, Qu X, Huang J, Chen X, Wang S, Ye L. Effects of di-(2-ethylhexyl) phthalate on the hypothalamus-pituitary-ovarian axis in adult female rats. Reprod Toxicol. 2014;46:141-7; Inada H, Chihara K, Yamashita A, Miyawaki I, Fukuda C, Tateishi Y, Kunimatsu T, Kimura J, Funabashi H, Miyano T. Evaluation of ovarian toxicity of mono-(2-ethylhexyl) phthalate (MEHP) using cultured rat ovarian follicles. J Toxicol Sci. 2012;37(3):483-90). - Mechanisms of reproductive toxicity are reported essentialy to be due to DEHP-PPAR interaction. However, the opinion should mention also the interactions of DEHP with other nuclear receptors which may be also highly relevant to altered steroid biosynthesis and/or metabolism: human Pregnane X receptor (Hurst, C.H.; Waxman, D.J. Environmental phthalate monoesters activate pregnane X	A short paragraph about the effects on the female reproductive system is now included. A reference to the possible role of other receptors has been included.

			receptor-mediated transcription. Toxicol. Appl. Pharmacol. 2004, 199, 266–274; Mnif, W.; Pascussi, J.M.; Pillon, A.; Escande, A.; Bartegi, A.; Nicolas, J.C.; Cavailles, V.; Duchesne, M.J.; Balaguer, P. Estrogens and antiestrogens activate hPXR. Toxicol. Lett. 2007, 170, 19–29) human Constitutive Androstane Receptor (DeKeyser JG, Laurenzana EM, Peterson EC, Chen T, Omiecinski CJ. Selective phthalate activation of naturally occurring human constitutive androstane receptor splice variants and the pregnane X receptor. Toxicol Sci. 2011 Apr;120(2):381-91)	
26.	Mantovani Alberto, LIFE EDESIA project consortium (http://www.iss.it/life) , alberto.mantovani@iss.it, Italy	3.4. DEHP (di(2-ethylhexyl) phthalate)	3.4.5. Evidence from epidemiological and clinical studies. Please see also comment to 3.4.4.1 The chapter appears not fully integrated with the preceding section on animal studies (3.4.4.1). The human studies investigated the possible association of DEHP exposure with a number of health effects, such as preterm birth/lower birth weight, precocious female puberty, endometriosis, neurobehavioural development, increased risk of obesity. However, it is not clear whether the experimental or mechanistic studies suggest or not that an association of DEHP exposure with such effects is biologically plausible. In the current draft opinion this appears to be done for male fertility/male reproductive development and diabetes: however,the link (or the absence of such link) between other putative human effects and experimental evidence should be discussed as well. This chapter might mention also the recent paper (La Rocca C, Tait S, Guerranti C, Busani L, Ciardo F, Bergamasco B, Stecca L, Perra G, Mancini FR, Marci R, Bordi G, Caserta D, Focardi S, Moscarini M, Mantovani A. Exposure to endocrine disrupters and nuclear receptors gene expression in infertile and fertile women from different Italian areas. International Journal of Environmental Research and Public Health 2014 11,	The paper of la Rocca *et al* has been cited in the exposure paragraph, making a comment about the differences noted between the fertile and the infertile women. However, due to the limited number of enrolled individuals and the detection of only one metabolite, the study was not considered to add relevant information to the epidemiological part of the Opinion.

			10146-10164) indicating that MEHP serum levels are significant higher in Italian infertile women from the Metropolitan area of Roma and that MEHP levels were singnificantly correlated with an enhanced expression of ERα, ERβ, AR, AhR and PXR, but not of PPARγ, in peripheral blood mononuclear cells. If considered appropriate, the paper could be mentioned in the current section on "Endometriosis", which could then become "Endometriosis and female fertility".	
27.	Mantovani Alberto, LIFE EDESIA project consortium (http://www.iss.it/life), alberto.mantovani@iss.it, Italy	3.4. DEHP (di(2-ethylhexyl) phthalate)	3.4.6. Conclusion on clinical and epidemiological evidence The section is rather a summary than a conclusion. Whereas it is correct to summarize the main evidence, the section should also indicate the most relevant adverse human health effects for which the current evidence prompts to further investigation. To my best understanding, these are: altered anogenital distance in both sexes, low birth weight, precocious female puberty, endometriosis, reduced neurobehavioural scores (particularly in males) obesity, allergic diseases. In addition, the conclusions sgould point out whether the current evidence support a biologically plausible link with DEHP exposure. As final note, the effects that have been investigated in humans, and for which a potential link with DEHP cannot be ruled alltogether, suggest that DEHP toxicity in exposed populations might go beyond the male reproductive effects that form the basis of the TDI. This consideration further support the requirement to investigate additional endpoints (e.g., neuronal development, adipogenesis, puberty regulation) by well-aimed experimental and mechanistic studies.	The data available do not allow any clear-cut conclusions to be drawn due to contrasting results and/or poor exposure assessment (single snap shot urine, confounding factors including diet not taken into account, study design not suitable for establishing causal link). These issues have been addressed in the Opinion. On this basis, the identification of the most relevant human health effects is a matter of interpretation, which could be biased by personal knowledge. However, research needs are addressed elsewhere.

28.	Vecchi Luigi, Sorin Group italia Srl, luigi.vecchi@sorin.com, Italy	3.5. Alternative plasticizers in PVC medical devices	3.5.3. Exposure to alternative plasticizers The summary of the Takahashi study as reported into the above mentioned section is not clear; the summary is reported as follow: Takahashi et al. (2008) measured overall extraction of DEHP during cardiopulmonary bypass when DEHP TOTM tubing was used. Sixteen patients undergoing coronary artery bypass grafting were randomly divided into 2 groups of 8 each. Group A had tubing containing DEHP in the circuit and the non-DEHP tubing for group B contained TOTM. Plasma diethylhexylphthalate levels at the end of cardiopulmonary bypass were significantly increased compared to before anaesthesia in both groups (group A: 103 ± 60 to 2,094 ± 1,046 ng/mL; group B: 135 ± 60 to 472 ± 141 ng/mL) and were significantly higher in group A compared to group B. This study demonstrated that using tubing free from DEHP significantly reduced the release during cardiopulmonary bypass. The release of TOTM from non-DEHP tubing was not measured in this study We assume that the non DEHP tubing is not releasing DEHP; being so if the release of TOTM from non DEHP tubing (group B) was not measured as mentioned in the study, we do not understand what is actually the substance for which the study demonstrate a significant reduced release during CPB.	The SCENIHR agrees that the text was not clear enough and it was changed accordingly.

29.	Berzanskis Laurel, Health Care Without Harm Europe, laurel.berzanskis@hcwh.org, Belgium	3.5. Alternative plasticizers in PVC medical devices	Pg. 67, lines 1-14; (Section 3.5). These two paragraphs are confusing and would benefit from editing: "In the search for alternatives for plasticised PVC, researchers followed 3 main strategies, which include the development of safe plasticizer alternatives to DEHP, reduction of the leaching aptitude of plasticizers and the substitution of P-PVC with alternative safe polymers.[Comment: It's unclear why the draft fails to consider "alternative safe polymers" as a possible solution inasmuch as it is one of the three main strategies] Finding alternative plastizers [sic](van Vliet et al., 2011) for DEHP is important, because it is necessary to have the appropriate mechanical and processing issues solved to significantly reduce potential health risks and the evaluation for untoward effects on blood and blood components must be carefully undertaken. An alternative to DEHP must be biocompatible and maintain mechanical properties during its entire working life. Several classes of chemicals proposed as potential alternatives to DEHP are of synthetic origin: their safety profiles have been often underestimated [Comment: the meaning of "their safety profiles have been often underestimated" is unclear], especially regarding long-term periods. Exploiting plasticizers of natural origin would overcome concerns related to biocompatibility, not necessarily the safety issue, [Comment: the intended meaning of this sentence is unclear] and in addition their use is hampered by economic reasons. Waste and renewable resources could supply cheap and safe plasticizers, as the best solution to P-PVC concerns." [Comment: The meaning of this sentence is unclear. Moreover, this seems to be a risk management statement without any explanatory justification. Polymers that do not require plasticizers are another solution.] Pg 70; beginning ln. 17: "Standard test methods for measuring the leaching rates of components from	In order to make the text clearer, the two paragraphs have been edited.

			medical devices (ISO 10993) are available and information may be obtained from studies in which leaching of alternative plasticizers is compared under identical conditions, but studies for DEHP alternatives were not available for this opinion." Please clarify why studies of DEHP alternatives were not available and utilized in this opinion. Pg 72; ln 7: "NOAEL is lowest in male or female rats." The meaning of this is unclear. Pg. 72; Section 3.5.5; line 8: "The information on leaching from alternative plasticizers is sparse, but is expected to be of the same order of magnitude as DEHP." This is confusing. Above, the draft describes differential leaching. In fact, it says that TOTM leaching is several orders of magnitude less than DEHP (pg 71). See also comment on pg. 70; ln 17. Pg 73, Table 11: Confusing and limited. Annex 1 discusses additional endpoints for alternative plasticizers. Why is table 11 limited to genotoxicity, carcinogenicity, and maternal toxicity?	The SCENIHR agrees: the sentence on natural origin and waste has been deleted. The text has been edited to make the meaning clear to the readers. The text has been edited to make the meaning clear to the readers.
30.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	3.5. Alternative plasticizers in PVC medical devices	Page 67, 2nd para: why would plasticizers of "natural origin" overcome concerns related to biocompatibility. There are plenty of "natural" products showing extreme cytotoxicity. This whole Statement needs to be supported by evidence or the whole paragraph should be deleted as also the Statement re "waste and renewable resources" seems to be very speculative page 69, follwing Dumont et al, further literature should be included: Lagerberg et al. (2014), accepted August 8, 2014, publication ahead; doi: 10.1111/trf.12870 Haishima et al. (2014), JOURNAL OF BIOMEDICAL MATERIALS RESEARCH B: APPLIED BIOMATERIALS | MAY 2014 VOL 102B, ISSUE 4, 721-728 Crespo et al. (2005), J.Appl. Polymer Sci 104, 1215-1220 also a market overview by analytical detection of	The sentences have been deleted. The information coming from the new references are now included in the revised version. Leaching has been replaced by Migration as

			plasticizers Needs to be added: Gimeno et al. (2014), J.Journal of Chromatography B, Volumes 949–950, 15 February 2014, Pages 99–108 page 71: check the table 9 re the wording leaching, we think it should read "Migration" Further, data for other plasticizers like e.g. DINCH should be included from the EFSA opinions (respective opinion for DINCH is uploaded): The EFSA Journal (2006) 395 to 401, 1-21, page 73, last paragraph: what is meant by the Statement that some plasticizers are leading to the same Metabolite i.e. 2-Ethylhexanol as DEHP. The testing data on DEHA, DOTP and TOTM do reflect the sum of effects of all metabolites formed. Therefore, this sentence re the same metabolite is unclear and Needs to be explained in more Detail or should be deleted.	suggested. The EFSA Opinion has been addressed in the annex. The text has been edited to make the meaning clear to the readers.
31.	Sterk Thecla, Eucomed, thecla.sterk@eucomed.org, Belgium	3.5. Alternative plasticizers in PVC medical devices	Special cautions should be considered and understood whether adequate long-term and comprehensive studies have been conducted on potential alternatives. The summary does recognize the less well understood toxicity profiles of alternatives, and acknowledges the importance of finding alternatives that provide required physical performance. Odd, unsupported comment regarding preference for naturally derived versus synthetic alternatives (overcome biocompatibility issues (?)). Includes discussion of leaching information as well as comparative toxicity potentials, and concludes that margins of safety are approximately 20-fold higher for alternative plasticizers (reproductive toxicity). Seems a more thorough review than prior. Still clearly acknowledges limitations to toxicity information as well as leaching potential in clinical medical device applications but expected to be of the same order of magnitude as DEHP.	The text has been edited to make the meaning clear to the readers. No further action needed.

32.	FOLLEA Gilles, European Blood Alliance, g.follea@europeanbloodalliance.eu, Netherlands	3.6. Combined exposure to plasticizers	P 73, 1st paragraph, This seems speculative and not in keeping with a facts based data review.	The text has been edited to make the meaning clear to the readers. This paragraph is a sort of general conclusion, since detailed information on alternatives is included in the Annex.
33.	Sterk Thecla, Eucomed, thecla.sterk@eucomed.org, Belgium	3.6. Combined exposure to plasticizers	Pretty straightforward intuitive development, specifics limited by available data, etc. However, Most of these compounds are experimental (Ferruti et al., 2003) and insufficient information is available to assess the use and safety of these compounds in medical devices. Page 73, 1st paragraph: This seems speculative and not in line with keeping with a facts based data review.	The text has been edited to make the meaning clear to the readers. This paragraph is a sort of general conclusion, since the detailed information on alternatives is included in the Annex.
34.	Sterk Thecla, Eucomed, thecla.sterk@eucomed.org, Belgium	3.7. Potential alternative polymer plasticizers in PVC medical devices	Has some potential but scope of impact could be very limited – Should not rely on these approaches. We agree that we need to be cautious here as well in regards to assuming safe alternatives are readily available. Also agree, and the document appears reasonably cautious about suggesting these as workable alternatives. Consider fairly well balanced considering the source and intent.	No need to change the text of the Opinion.
35.	Berzanskis Laurel, Health Care Without Harm Europe, laurel.berzanskis@hcwh.org, Belgium	4. DEHA (Di(2-ethylhexyl)adipate)	Pg 132: Annex 1; section 4: DEHA. Silva et al (2013) describe additional metabolites of DEHA which may be useful in biomonitoring studies. (paper submitted)	Apparently Silva 2015 is meant. Results of this paper have been taken up in the revised Opinion. Further information stems from biomonitoring projects in Germany: secondary metabolites from adipic acid(ethylhexyl)monoester might be useful in biomonitoring, whereas 2-ethylhexanol and 2-ethylhexanoic acid and adipic acid are considered as unspecific metabolites. In the meantime, DEHA has been taken up in biomonitoring activities in Germany: http://www.bmub.bund.de/en/press/press-

				releases/detailansicht-en/artikel/federal-environment-ministry-and-german-chemical-industry-association-set-new-targets-for-human-biomonitoring-1/
36.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	4. DEHA (Di(2-ethylhexyl)adipate)	Page 132: the substance is also used in Food contact applications. therefore, the purity of the Commercial product is in most cases greater than 99.5 % (Area %, GC) => REACH reg files! page 134: carcinogenicity/ key study missing in SCENIHR file: add NTP TR-212: positive in mice, negative in rats DEHA is REACH registered. In the context of the compliance check, ECHA requested a developmental toxicity test on a non-rodent species. The REACH Registrants have finalized the requested study according to OECD 414 on rabbbits: no teratogenic effects were seen. Study results should be added to the file and the summary	The NTP study has been already considered in the 2008 Opinion. However, it was cited as Kluwe, 1986. This publication is a summary of several pthalic acid esters and related compounds. But now more explicit language was used to make it clearly understood that this study had been considered. With respect to the requested developmental toxicity study, the study should be made available to the SCENIHR as ECHA only reports study summaries (see also reply to comment 7).
37.	FOLLEA Gilles, European Blood Alliance, g.follea@europeanbloodalliance.eu, France	4. OPINION	P 75, See Executive Summary, same comment, Opinion should clearly show the difference with the original Opinion from 2008	The Opinion reports both 'old' (i.e. already cited in the previous Opinion) and 'new' data that were considered together and evaluated based on the WoE approach, as described in the methodology paragraph. To make a clear-cut distinction between old and new information is therefore not possible. This applies to the entire document.

38.	Berzanskis Laurel, Health Care Without Harm Europe, laurel.berzanskis@hcwh.org, Belgium	4.1 Scientific Rationale	Pg 77; section 4.1.3: This section should again mention the different levels of glucuronidase and glucuronyl transferase in fetuses, infants, children, and adults. Pg 78; 1st line: "Thus, in a WoE approach, it can be considered that DEHP and its major metabolites are non-mutagenic substances" should be changed to indicate "Uncertain overall weight of evidence: due to conflicting information from different lines of evidence that cannot be explained adequately in scientific terms." [SCENIHR, 2012]. See comment on pg 42 above. Pg 78; section 4.1.4: This section should include a discussion of experimental data showing mechanisms by which DEHP/MEHP interacts with PPARs, influencing adipogenesis and insulin sensitivity. References provided. See comments on pg 64 above. This is important because the next section briefly mentions the inconsistencies in the epidemiologic studies, but the final "opinion" on animal data is silent on this topic. Pg 79; sect 4.1.5: Same comment as on page 65 (above), from which this summary is drawn. Pg 79, beginning ln 21: Decreased anogenital distance: Same comment as on pg 65 (above). Some studies do show an association and the word "possible" should be omitted. Pg 79, ln 24 and following; The title of this section, "mother/infant exposure levels," should be changed to reflect the endpoints "birth weight and gestational length", or something comparable, since this is a summary of endpoints—not exposures. And, what is written here does not adequately reflect the conclusion in the section on pg 53: "Taken together, the association of phthalate exposure and preterm birth/birth weight is suggestive of an association, although this relationship is inconsistent." The same comment applies to the same section on pg 65 beginning 6 lines from the bottom. Pre-term birth and low birth weights are highly consequential and complex public health concerns. Potential links to	Addressed. For detailed answers, please see the corresponding ones to similar comments previously made by the same commenter.

			phthalate exposures should be more systematically studied based on this suggestive association. This should be reflected in the conclusions and recommendations in the final document. Pg 81: Section 4.1.7: First sentence: the discussion in 3.5.3 includes useful information about leaching of DEHP alternatives, but none of that is reflected in this first sentence in 4.1.7. Section 4.1.7 also fails to mention DINCH at all.	
39.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	4.1 Scientific Rationale	4.1.7. DINCH is not mentioned. All relevant studies available for DINCH Show Absence of any toxicity to reproduction. Further the last sentence states the lack of data re COMGHA, BTHC and TOTM. Here, we would recommed to verify this Statement based on the publicly available REACH Registration data available form the ECHA dissimination Website page 83: we miss the conclusion on DINCH, especially taking into account the Information on the single and repeated dose studies (5d and 28 d) on the intravenous route. Study Information has been provided and should have been available to SCENIHR (=> will be checked with SCENIHR) As there are Hexamoll DINCH based medical devices with CE certification on the market, this Information should have been added to the responses	For detailed answers, please see the corresponding ones to similar comments previously made by the same commenter. With respect to information available from the REACH dissemination website, see the answer to Comment #7: information on the REACH dissemination website is considered as second-hand information. The information has not been assessed by ECHA, but is instead based on industry summaries. In order to use the information available, original study reports should be made available.
40.	Sterk Thecla, Eucomed, thecla.sterk@eucomed.org, Belgium	4.1 Scientific Rationale	The statement at the end of section 4.1.2. is very important to note: "High exposure levels during certain medical procedures need to be assessed based on the treatment needed and the availability of suitable alternatives for each medical treatment and in some cases, DEHP-containing plasticized PVC devices are important for many treatments and their justified because of the benefits of these procedures." Especially	No need to change the text of the Opinion.

			examples such as "An additional benefit of DEHP it that it stabilizes the membranes of red blood cells enabling blood product storage in PVC blood bags for several weeks." The risk of unintended consequences of DEHP or PVC alternatives in the functionality of the product, under all use conditions, needs to be taken into consideration for any material change. And, can be nearly impossible to fully assess. We agree that this is of critical importance. Again, this document seems fairly balanced in light of the source and intent. This entire opinion section appears largely unchanged from prior 2008 review and conclusions, and recapitulates the prior sections on toxicity and epidemiology. If anything, recent studies on core target toxicities appear to have introduced more potential doubt into reproductive and/or developmental effects in humans, with mixed results and general recommendation for more study (almost obligatory recommendation). Overall conclusions remain unchanged with respect to potentially susceptible populations and medical procedures of possible concern. The updated data review appears to not have provided any elevated levels of concern (or lower thresholds), again with potential additional ambiguities in human-relevant studies. Basic position retained – all risk cannot be precluded, therefore retain prior opinion. Page 75, 3rd paragraph, last sentence, and Page 76, 4th paragraph, last sentence: We suggest to replace the word significant with 'transient elevated' and add at the end of the sentence, 'however voluntary donations are not provided by groups deemed to be at risk for reproductive toxicity (pregnant and nursing mothers and neonates). Page 76: The FDA has reviewed the use of DEHP in medical devices and it is suggested to have different TIs (same as TDI) for enteral and parenteral route since the metabolism through enteral route would yield more toxic metabolites. The TI for parenteral is 600 micorg/kg/day	The sentence has been added. Data available seems to indicate -as stated in the

			and for enteral is 40 micorg/kg/day. Eucomed recommends to the SCENIHR to consider using different TDIs for parenteral and enteral routes. Page 81, 4th paragraph, 1st sentence: We suggest removing 'but may be expected to be not lower than DEHP on the basis of their physico-chemical features' as it is speculative.	Opinion- that the metabolite pattern is not qualitatively different depending on the exposure route. Therefore a distinction on that basis seems inappropriate. What is certainly different is the bioavailability: the oral absorption being around 50% (with respect to a 100% bioavailability related to parenteral administration). This could affect the significance of a TDI derived from an oral study for a parenteral exposure, asking for a refinement of the Risk assessment process. This was clearly explained in the TK paragraph. It should be considered however, that 1) considering the exposure duration the use of a TDI is a conservative approach and 2) for the scenarios at risk, the MoS is very low or non-existant, thus a refinement was not considered necessary. For other scenarios, on the contrary, the MoS was high enough without requiring any further refinement. The acute toxicity of DEHP was on the other hand quite low, therefore high acute exposure levels were not considered to be of concern. The paragraph has been changed to address other comments and that sentence has been deleted.
41.	Jorbenadze Liza, LTD H-Group , liza.j@list.ru, Other	4.2 Responses to the questions in the Terms of Reference		No need to change the text of the Opinion.

42.	FOLLEA Gilles, European Blood Alliance, g.follea@europeanbloodalliance.eu, Netherlands	4.2 Responses to the questions in the Terms of Reference	Again, it is not clear if these answers are really different from the original answers in the 2008 Opinion, it takes readers a very long time before the differences between 2008 Opinion and 2014 Opinion can be found and it would help very much if these differences were clearly stated.	The current Opinion is an update of the 2008 DEHP Opinion, and indeed also contains part of the 2008 Opinion as far as still relevant. However, with the publication of this new 2015 Opinion, the previous Opinion is no longer valid. The 2015 Opinion is the Opinion that should be used as it includes the latest scientific evidence. So, there is no need to compare the two Opinions. It is an overall state of the art description, and includes what remains valid from the 2008 Opinion. On that basis, the present Opinion reports both 'old' (i.e. already cited in the previous Opinion) and 'new' data that were considered together and evaluated based on the WoE approach, as described in the methodology paragraph. To make a clear-cut distinction between old and new information is therefore not possible. This applies to the entire document.
43.	Sterk Thecla, Eucomed, thecla.sterk@eucomed.org, Belgium	4.2 Responses to the questions in the Terms of Reference	This section suggests that the SCENIHR position remains essentially unchanged from the prior 2008 summary report. A note is made to a follow-up study in highly exposed male human neonates with no observable toxic effects. Still concludes that data is inconsistent overall (reflects quite intensive investigations by numerous parties), errs on side of "caution". Page 82, 3rd paragraph from bottom: We would welcome additional studies with a wider patient group in order to determine whether there is a cause for concern. Page 83: This page finishes by saying that the "risk and benefit (of alternative plasticisers to DEHP) should be carefully evaluated for each individual medical device and each medical procedure in which the alternative needs to be used." However, earlier in the same paragraph it is stated that a risk assessment could not be performed on the alternative plasticisers under	No need to change the text of the Opinion. This is implicit in the text of the paragraph, but was also clearly indicated in the paragraph on reseasch needs. The text has been modified for greater clarification.

			discussion. This inability to conduct a risk assessment suggests that it is not possible to make an adequate risk/benefit calculation in cases where it is decided to attempt substitution of DEHP with one of these alternative plasticisers. It also suggests that it is not possible to establish in the first place that substitution of DEHP with one of these alternative plasticisers "needs" to be done. The final sentence of this page should therefore be deleted. Page 83: It appears from the content of the Preliminary Opinion that the SCENIHR has not concluded any significant changes to the risk profile of DEHP, as compared to 2008 when the last Opinion on this matter was commissioned. Although the document mentions in various places that much of the 2008 Opinion remains valid, it would be appropriate to restate the point on Page 83, as it comprises the last page of substantive content.	The preliminary Opinion is repeatedly cited. Indeed, the current Opinion is an update of the 2008 DEHP Opinion, and contains part of the 2008 Opinion as far as still relevant. However, with the publication of this new 2015 Opinion, the previous Opinion is no longer valid. The 2015 Opinion is the Opinion that should be used as it includes the latest scientific evidence. So, there is no need to compare the two Opinions. It is an overall state of the art description, and including what remains valid from the 2008 Opinion.
44.	Swedish Chemicals Agency, anne-marie.vass@kemi.se, Sweden	4.2 Responses to the questions in the Terms of Reference	Page 83, row 18 or row 31. Essentially we find that "the possible alternative approaches that could reduce potential risks" presented by SCENIHR are consistent with our own experience from assessment of alternatives to phthalates. However, since many readers concentrate their reading on any of the summaries in a report, section 4.2 would benefit from a repetition of the clarification about the materials not included in the assessment in the preliminary opinion. Thus we propose that the text from section 3.1. page 18 or section 4.1 , page 75 is repeated either in the beginning or at the end of this section (row 18 or row 31), i.e. add "Whilst recognising that there are several non-PVC based materials that can be effective in medical devices production and use, this opinion does not address these materials.".	Addressed. The sentence has been added.

45.	Mantovani Alberto, LIFE EDESIA project consortium (http://www.iss.it/life), alberto.mantovani@iss.it, Italy	4.2 Responses to the questions in the Terms of Reference	Question: "• If it is possible to propose possible alternative approaches that could reduce potential risks either by identifying alternative practices or by identifying alternatives to the use of DEHP in PVC plasticized in medical devices. If no clear answer can be provided on this point the SCENIHR is asked to formulate recommendations for research that could help provide scientific evidence to that end." The response to this questions in the current draft opinion is only partly satisfactory: - The statement "Thus, the conclusions of the 2008 opinion are still mainly valid." should be integrated by the consideration (consistent with the core of the draft opinion) that the health concerns over the safety of medical devices containing DEHP plasticized PVC have grown since 2008; therefore, it is appropriate and urgent to develop safer alternatives. - The alternatives to DEHP could be placed at different levels of evidence as potential safer substitutes, giving a more clear and transparent indication to risk managers. For instance to my best understanding, TOTM could be currently the candidate in top position, based on lack of genotoxicity (although no data on carcinogenicity) and reproductive toxicity much lower (i.e., occurring at dose levels 20 fold higher than DEHP), with the remaining major issue of leaching (background human exposure would be unlikely to be greater than DEHP).	The need to develop safer alternatives is implicit throughout the whole document, since some risky scenarios have been identified. And the need to have good, reliable data related to the toxicological profile as well as to the leaching potential is also addressed in the research needs section. Regarding the prioritisation/recommendation for one alternative vs. the others, this could not be done on the basis of the available data: in addition, it strictly depends on the medical devices under consideration and the medical treatments as well. Therefore a generic statement suggesting a 'lead' candidate cannot be made here,

46.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	5. DINCH (1,2-Cyclohexanedicarboxylic acid, diisononylester)	please correct the text under the chemical structure, BASF has already requested to correct this false entry at the last Version. Based on the production process, DINCH can only contain strictly C9 alcohols, there are no C8 or C10 alcohols!!! The text should read: Cyclohexane-1,2-dicarboxylic acid, diisononylester (DINCH) contains only isomeric (branched and linear) C9 alcohols. The alcohol composition is identical with the one on the starting material, i.e. DINP2 which is core-hydrogenated in a catalytic process to the respective cylcoaliphatic structure. Based on the production process, DINCH consists of 90 % cis and 10 % trans Isomers. (see e.g. EFSA opinion or NICNAS public Evaluation Report) page 136: BASF production capacity was doubled in 2014 i.e. 200 kt page 137, Exposure data by human biomonitoring should be added. e.g. NHANES 4th update Report [http://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Jul2014.pdf] page 137: Schossler (2011) et. al., citing only the emission rate gives a completely wrong impression. Please consider that after 600 h the max. equilibrium concentration of DINCH at room temperature in this test chamber was 0,5 Mikrogramm of DINCH per cubic meter ! The authors stated higher concentrations can not be expected! Therefore, this should be selected as the Point of departure for any worst case risk assessments. page 138: single dose and repeated dose toxicity studies on the intravenous route Need to be added. There was no substance specific systemic toxicity at nominal concentrations of up to 300 mg/kg bw/day on the intravenous route. It should be kept in mind that These dose Levels were orders of magnitue higher than those that can be expected in most medical applciations. For stored red blood cells, the DINCH concentration at the end of a 42 days storage period was 4.5 Mikrogramm/Milliliter and in bags containing platelets for pediatric use only 2.7 Mikrogramm/Milliliter were	Information on structure has been updated and other indications were taken up. Exposure data from human biomonitoring studies have already been taken up (information from Schütze *et al*, 2012 and 2013). They point to increasing levels from 2006 to 2012. As this is European data, this has been preferred to NHANES data. Remark concerning Schlosser publication: noted. The text has been extensively revised (both in the general chapter as well as in the Annex) to take into account the various comments received. Chiellini paper is now cited.

			detected.Taking this into account, it can be concluded that DINCH did not Show any systemic toxic effects (no testicular toxicity, no kidney effects) and confirmed no peroxisome Proliferation after single or continous Infusion for up to 29 days. (studies can be made available to SCENIHR for Review). page 139: please add re the OECD 414 with rats, "by gavage", ie. it should read: "The NOAEL was equal to the highest dose administered by gavage beeing 1,200 mg/kg bw/d." page 140: please note in the "other Information" chapter that Lambright et al. (2011) has been followed up by the publication of Furr et al.(2014) (has been provided already with our comments). further, the following literature should be added also to the chapter on DINCH (: Chiellini F, Ferri M, Morelli A, Dipaola L, Latini G, PERSPECTIVES ON ALTERNATIVES TO PHTHALATE PLASTICIZED POLY(VINYL CHLORIDE) IN MEDICAL DEVICES APPLICATIONS, Progress in Polymer Science (2013), http://dx.doi.org/10.1016/j.progpolymsci.2013.03.001 A conclusion should be added by SCENIHR taking into account that DINCH based medical devices are on the market worldwide. In Europe there are CE certified devices for pediatric used in use since 2 years, Oxygen masks etc. This means, the conclusion should read: DINCH is a fully functional replacement for DEHP in medical applications.	
47.	Berzanskis Laurel, Health Care Without Harm Europe, laurel.berzanskis@hcwh.org, Belgium	5. Research needs	Page 84, comment on Research Needs: The committee should consider expanding these comments to make them most useful to anyone using this document to make decisions. For example, what would a well-designed epidemiologic study of neonates highly exposed to DEHP within intensive care units entail? What would be the measures of exposure and health outcomes? How large a study would be necessary in order to have adequate power to detect effects, if	The criteria to define a reliable, qualitatively valid epidemiological study are well known. There is no need to repeat them here.

			present? How long would such a study take? Is this practical? The suggested association between maternal phthalate exposure during pregnancy and pre-term birth and/or birth weight should also be mentioned as an urgent research need. The emphasis in the second paragraph is limited to "blood establishments". There is a need for research into alternative plasticizers or non-PVC alternatives for other purposes as well. Moreover, alternatives already exist and are in use for a number of applications.	Medical devices for all purposes have been added.
48.	FOLLEA Gilles, European Blood Alliance, g.follea@europeanbloodalliance.eu, Netherlands	5. Research needs	We just want to draw attention to two recent publications on DEHP alternatives for use in transfusion medicine (see attachments; Dumont et al. TRANSFUSION 2012, 52:1439-1445 and Lagerberg et al. TRANSFUSION 2014 online doi: 10.1111/trf.12870), to show that the blood establishments, in cooperation with blood bag manufacturers, are very active in research on alternatives. However it is important to emphasise that there are restrictions, first concerning patient safety. When replacing one material by another for blood bags, assessing the technical/physical properties and the physiological features for blood component properties and storage for both the known and the new tested material is of the utmost importance. These comparative validations are indispensable to ensure optimal quality and safety for patients. The only validations available so far have been limited to in vitro studies (see references above). The next step will be to validate new material(s) in clinical studies. After these validations, pros and cons will have to be weighed very carefully before considering licensing a new material and finally having the decision made to replace the current material. So, this research and these validations of new materials, although very active, will still take a long time.	The two papers are cited in the main text of the Opinion. No need to change the text of the Opinion.

49.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	5. Research needs	page 84, line 2: what is meant by "negative effects in humans?" did you mean "adverse?" or did the authors want to include studies reporting associations between symptoms and phthalate exposure? These studies Need further, detailed and critical Evaluations.	The word 'adverse' is now used in the sentence.
50.	Sterk Thecla, Eucomed, thecla.sterk@eucomed.org, Belgium	5. Research needs	It is important for blood establishments, suppliers and manufacturers to work together to ensure that research into alternative plasticizers, or non-PVC alternatives, for use in blood establishments continues to progress both in the area of defining the toxicological profile and the leaching potential in the intended conditions of use, to evaluate the human exposure. In general, we agree with the scientific content. However we would appreciate more specific recommendations, since this status is not very different from the previous SCENIHR report. For example: these specific toxicological endpoints for alternative plasticizers X, Y & Z should be reviewed/tested. This is the case if PVC based material will be used as an alternative. We would also like to see some indications on the non-PVC alternatives that may be suitable for further investigation. If one alternative substance looks promising, the leaching potential for substance X, Y & Z should be reviewed. At this moment the leaching potential of (DINP, TOTM and DEHA) is assumed to be similar to DEHP. See paragraph 4.1.7 toxicity of alternative plasticizers. We also would like to see an alternative plasticizer assessment process for the different treatments: short term neonates, adults versus chronic treatment long term adults neonates. Outcome of a suitable/acceptable alternative may vary depending on the treatment (acute versus Chronic) and the patient (adult / neonates) and risk assessment approach (risk benefit or NOAEL). In general, there needs to be more research in this area carried out by legitimate scientific organizations.	Regarding the possibility to give information on specific tests and data or prioritisation/ recommendation for one (more) alternatives vs. the others, it could not be done on the basis it strictly depends on the medical device and the medical treatment under consideration. Therefore a generic statement suggesting any 'lead' candidate cannot be made here, and the testing strategy could vary depending on the medical device.

51.	Mantovani Alberto, LIFE EDESIA project consortium (http://www.iss.it/life), alberto.mantovani@iss.it, Italy	5. Research needs	The recommendation for research needs on the possible DEHP alternatives is too generic and it does not provide effective indications for the selection of safer substitutes for such a concern compound as DEHP. Consistent with the core data of the draft opinion, such substitution is required and urgent. A clear list of requirements concerning technological suitability for use (e.g., a safe but easily breakable substance would be of no avail), toxicological characteristics and leakage properies should be given.	The text has been revised.
52.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	6. DINP(di-iso-nonyl phthalate)	page 142: Synonyms: should read: - 1,2-Benzenedicarboxylic acid, di C8-C10 branched Alkyl Esters, C9-rich (DINP-1). please add: - Diisononylphthalate for DINP-2 both are also referred to as DINP as technically they are interchangeable; see justification for Joint risk assessment in the EU RAR (2003) page 143: There are more recent exposure data available (should be added) page 144: please add the following reference Kimber et. al (2010, attached) and also the conclusions: "Taken together, these data suggest that, although some phthalates may have an intrinsic ability to modify adaptive immune responses (under strictly defined conditions, and via mechanisms that have yet to be elucidated), there is no evidence to suggest that these chemicals have a consistent and proven ability to enhance allergic sensitisation under conditions of exposure that are relevant for human health. It is premature therefore to implicate phthalates as having contributed to the increasing prevalence of atopic allergy and asthma." Purity. This Statement should be corrected. Neither	Synonym: added Information from ECHA, 2012 has been taken up for more recent exposure data. Kimber *et al* 2010 is a more general publication on the immunotoxicity of phthalates and has been considered in section 3.4.4. 1,2-Benzenedicarboxylic acid, di C8-C10 branched Alkyl Esters, C9-rich (DINP-1) and - Diisononylphthalate for DINP-2 are mixtures by definition. The comment that purity is greater than 99.5 % (Area %/GC) may be correct, but ECB 2003 describes it as >99.5%. The statement on mixture is a citation from ECB (2003) and has not been deleted, but information on purities and impurities has been made more precise. Furr *et al* 2014 is a more general publication on an *in vitro* methodology to assess foetal testosterone production, which is not specifically relevant here.

			DINP-1 (68515-48-0) nor DINP2 (28553-12-0) are "mixtures". The different DINPs are product streams produced in technical high production volume processes with constant composition (please refer to the respective Explanation of the polygas process (DINP1) or the butene-dimerization process (DINP2) in the EU RAR. also the Statement regarding impurities Needs to be corrected to: greater than 99.5 % (Area %/GC) 6.2 use: please specify that the use in toys is restricted according to Regulation (EU) No 1907/2006, Annex XVII, 52 i.e. not to be used for toys and childcare articles that can be mouthed . It should be mentioned that we consider DINP to be a product where the intended use is predominantly in technical applications. Application of such technical products in medical applications Need a proper case by case evaluation. DINP is listed in Regulation (EU) No 10/2011 (with the respective restriction) however, for such applications like Food contact, compliance with the basic requirement for food contact materials as specified in Regulation (EC) No 1935/2004 is mandatory. This may also Limit the use of DINP for medical applications Furr et al. (2014) should be added as a reference (already provided with other comments)	
53.	Content Stephane, CEFIC ECPI, sco@cefic.be, Belgium	6. DINP(di-iso-nonyl phthalate)	Note: In attachment, CEFIC ECPI comments on several chapters: 3.4 for DEHP 3.6 on combined exposure 4.1.7 on toxicity 6 on DINP Below are comments specifically referring to chapter 6 on DINP page 142: Synonyms: should read: - 1,2-Benzenedicarboxylic acid, di C8-C10 branched Alkyl Esters, C9-rich (DINP-1) please add: Diisononylphthalate for DINP-2both are also referred to as DINP as technically they are interchangeable; see justification for Joint risk assessment in the EU RAR (2003) page 143: There are more recent exposure data available (should be added)	The comment is essentially the same as comment # 53 provided by R. Otter. Please see the answer to that comment.

			page 144: please add the following reference Kimber et. al (2010, attached) and also the conclusions: "Taken together, these data suggest that, although some phthalates may have an intrinsic ability to modify adaptive immune responses (under strictly defined conditions, and via mechanisms that have yet to be elucidated), there is no evidence to suggest that these chemicals have a consistent and proven ability to enhance allergic sensitisation under conditions of exposure that are relevant for human health. It is premature therefore to implicate phthalates as having contributed to the increasing prevalence of atopic allergy and asthma." Purity. This Statement should be corrected. Neither DINP-1 (68515-48-0) nor DINP2 (28553-12-0) are "mixtures". The different DINPs are product streams produced in technical high production volume processes with constant composition (please refer to the respective Explanation of the polygas process (DINP1) or the butene-dimerization process (DINP2) in the EU RAR. also the Statement regarding impurities Needs to be corrected to: greater than 99.5 % (Area %/GC) 6.2 use: please specify that the use in toys is restricted according to Regulation (EU) No 1907/2006, Annex XVII, 52 i.e. not to be used for toys and childcare articles that can be mouthed DINP is not used in invasive medical applications and such use if proposed would need an appropriate evaluation of safety. Application of such technical products in medical applications Need a proper case by case evaluation. DINP is permitted in certain food contact applications under Regulation (EU) No 10/2011 Furr et al. (2014) should be added as a reference (already provided with other comments)	

54.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	7. DEHT (Di(2-ethylhexyl) terephtalate)	Chapter should be updated to include Information available on the dissiminiated REACH Registration @ ECHA	Some information is now included. The SCENIHR is aware that study summaries are given on ECHA's dissemination website. However, the following information is also given on ECHA's dissemination website: (http://echa.europa.eu/qa-display/-/qadisplay/5s1R/view/reach/echapublicdatabasewithinformationonregisteredsubstances). "The information in this database originates from registration dossiers submitted by companies. Companies have the obligation to provide accurate and up-to-date information in their registration dossiers. ECHA's IT systems verify that the information is complete, meaning that all the information fields required for a registration in a particular tonnage band are filled in in the dossier. However, the European Chemicals Agency (ECHA) does not verify the information before its publication on the internet. ECHA can therefore not guarantee the correctness or adequacy of the information or that the dossiers are compliant with REACH." Thus, information on ECHA's dissemination website is considered as second-hand information, since original studies are not available for evaluation. Further, ECHA's website mentions: "Reproduction or further distribution of this information may be subject to copyright protection. Use of the information without obtaining the permission from the owner(s) of the respective information might violate the rights of the owner. The Agency does not take any responsibility whatsoever for any copyright or other infringements that may be caused by using the information." Therefore, relevant study data which should be included in the SCENIHR Opinion should be provided

				directly to the SCENIHR.
55.	Sterk Thecla, Eucomed, thecla.sterk@eucomed.org, Belgium	7. DEHT (Di(2-ethylhexyl) terephtalate)	The mentioned study shows too little evidence, which could not be sufficient to demonstrate the usage of this material.	The issue is addressed in section 4.1.7
56.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	8. TOTM (Trioctyltrimellitate)	Data on purity and impurities should be added. Further, TOTM is currently in the CoRAP process (as mentioned), therefore results and conclusions of this process should be included in this updated SCENIHR opinion	Data on purity and impurities has been included. The information on CoRAP outcome has been taken up in the revised Opinion.
57.	Sterk Thecla, Eucomed, thecla.sterk@eucomed.org, Belgium	8. TOTM (Trioctyltrimellitate)	Good exposure of the data.	No need to change the text of the Opinion.
58.	Auzzi Anna, Polynt S.p.A., anna.auzzi@polynt.com, Italy	8. TOTM (Trioctyltrimellitate)	3.3 tab1 pag 20; cap 3.5.4 tab 10 pag 72; tab 11 pag 73; cap 4.1.7 pag 81; annex 1 Cap 8.5	The meaning of the comment is not clear enough to give an answer.
59.	Berzanskis Laurel, Health Care Without Harm Europe, laurel.berzanskis@hcwh.org, Belgium	EXECUTIVE SUMMARY	Overall comment - There is a lack of discussion of possible reasons for inconsistent findings in human studies of DEHP exposure and health outcomes: The draft document cites epidemiologic studies in which associations between various measures of phthalate exposure and health outcomes are reported. When more than one study reports an association of phthalate exposure with the same health outcome, the results are frequently described as "inconsistent" when the findings are not in agreement. The draft would benefit from some discussion of possible reasons for these	The problems in data interpretation, especially when epidemiological data are concerned, are often related to different ways (if any) to measure exposure of the enrolled populations, as well as on the meaning a snap-shot urine sample can have for the onset of disease with a long lag-phase. This was repeatedly addressed in the document, in the biomonitoring section as well as in the epidemiological section. Another issue is related to effects which are very limited (although differences can be statistically

			"inconsistencies" to enable a more informed interpretation of the literature. Phthalates, including DEHP, have relatively short half-lives. As noted in the draft, DEHP also has a number of metabolites with varying toxic potencies. In human studies, scientists must decide which metabolite(s) to measure, at what time, and how often in order to estimate actual exposure levels when looking for associations with adverse outcomes. These measures often differ in studies with "inconsistent" outcomes. Christensen et al (2014) discuss the challenge this way: "Depending on the study hypothesis and health outcome of interest, the 'ideal' exposure metric may be the peak internal dose during a critical life-stage, the long-term average dose, the dose at a target tissue, or some other value. These dose levels generally cannot be measured directly in epidemiological studies, so biomarker measurements are often used either as direct surrogates for dose, or a means to calculate exposure/dose levels. Further complicating the selection of an exposure metric is the fact that there are multiple possible units of measurement for any given biomarker. For example, urinary biomarkers can be presented in units of concentration and creatinine-adjusted concentration, and each of these values can be used to reconstruct an external exposure. Thus, it is important to carefully examine the selection of a biomarker, and its measurement units, on at least three different levels. First, what is the relevance of the biomarker to the desired exposure/dose metric? For example, how well does a spot measurement of a urinary metabolite reflect a target dose? Second, what is the representativeness of the measurement with respect to the desired exposure/dose metric? For example, does a urinary biomarker concentration mostly reflect recent exposure, urine output, or a combination of these and other factors? Third, how does the selection of an exposure	significant), for which a real biological meaning is not clear. These concepts will also be repeated in the Executive Summary to make the text more understandable to the readers. Christensen *et al* (2014) has been cited in the main text.

			metric impact study results and conclusions? In other words, is a lack of relevance and/or representativeness in the selected exposure surrogate likely to lead to biased or inaccurate conclusions about the exposure–outcome relationship?" Decision-makers using this document would benefit from some discussion of the implications of the selection of different biomarkers of DEHP exposure in the various studies. Inconsistencies in associations between estimates of DEHP exposures and adverse outcomes may be explained wholly or in part by different biomarker measures as well as the timing and methods of analysis. Christensen K, Sobus J, Phillips M, et al. Changes in epidemiologic associations with different exposure metrics: A case study of phthalate exposure associations with body mass index and waist circumference. Environ Int. 2014; 73:66-76. See also: Lorber M, Koch H, Angerer J. A critical evaluation of the creatinine correction approach: can it underestimate intakes of phthalates? A case study with di-2-ethylhexyl phthalate. J Expo Sci Environ Epidemiol. 2011; 21(6):576-86.	
60.	Berzanskis Laurel, Health Care Without Harm Europe, laurel.berzanskis@hcwh.org, Belgium	EXECUTIVE SUMMARY	Overall comment - Lack of discussion of study quality: With some exceptions, the draft document provides little interpretation of the quality of the summarized studies. What are their strengths and weaknesses? What should anyone reading this conclude about inconsistencies in study findings and what might be causing them? SCENIHR 2012 (document on weight of evidence) includes a good discussion of study design and quality. How do we weigh evidence? Woodruff and Sutton (2014) [paper provided] describe a systematic approach to weighing evidence in environmental health sciences that addresses these issues.	So far the WoE was based essentially on the expert judgment following the SCENIHR 2012. A systematic approach was not defined. The SCs are working with other Commission bodies to define it.
61.	FOLLEA Gilles, European Blood Alliance,	EXECUTIVE	The executive summary should clearly present what is the new information in the revised opinion on DEHP and	The Opinion reports both 'old' (i.e. already cited in the previous Opinion) and 'new' data that were

	g.follea@europeanbloodalliance.eu, Netherlands	SUMMARY	how this information did change, or not, the opinion from 2008. Now it is rather vague if there was new information leading to change the original opinion, and in other words, if the reason to revise the initial opinion was valid. Thus, the decision to ask for an update of the 2008 Opinion was based on the assumption that there was new evidence establishing that DEPH had negative health effects on humans. In the 2008 Opinion, it was concluded that there was only evidence for negative health effects in animals	considered together and evaluated based on the WoE approach, as described in the methodology paragraph. To make a clear-cut distinction between old and new information is therefore not possible. This applies to the entire document.
62.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	EXECUTIVE SUMMARY	Page 11, 4th para: the metabolic pathway may qualtitatively be Independent on the exposure pathway, but regarding toxikokinetics there is a big difference regarding oral and intravenous exposure. Therefore, we think it is mandatory to provide i.v. data to support safe use determinations. page 12: Medical devices may result in intravenous exposure. Therefore, using the TDI oral may not be justified for intravenous exposure. Cammack et al. (2003), NOEL of 60 mg/kg bw./day, i.v. should be used for the evaluation of intravenous exposure Scenarios. page 13: it is stated that COMGHA and TOTM could not be evaluated due to lack of toxicological data. Provided this is the case for COMGHA it is not clear how the conclusion on page 131 was reached i.e. " fully functional replacement" => this needs to be explained page 13: The conclusion on DINCH is missing i.e. it is a fully functional replacement for DEHP as medical devices including blood product bags that are CE certified are already in use in the EU since two years for e.g.pediatric applications. Literature and results should have been available to SCENIHR but will be provided again to be considered in a revised opinion. Especially it needs to be stated that DINCH is suitable to stabilize the red blood cell in a way that storage time and hemolysis rate are acceptable and	SCENIR agrees that when the differences in bioavailability are significant, specific studies should be carried out. However, regarding DEHP, this is not necessary. Recently ECHA-RAC (2013) considered that from DEHP data obtained in adults as described above (Koch *et al*., 2005; Anderson *et al.,* 2011; Kessler *et al.,* 2012) a 50% absorption can be estimated. However, these studies indicate a rather high absorption rate in adults, taking into account that the amount recovered in the urine depends on the number of urinary metabolites measured and the unknown amount of excretion via bile. Therefore an almost complete absorption can be used in risk characterisation. The RAC also considers there is no indication that adults absorb less phthalate esters than children (ECHA, 2013). This can be very relevant for COMGHA and TOTM, which are poorly absorbed in the gastrointestinal tract. This has been clarified in the revised version. During the revison process that sentence was deleted. The text related to DINCH was also extensively revised.

			equal to DEHP based blood bags	
63.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	EXECUTIVE SUMMARY	page 71, last para and 72/ first para: Why is the dust issue mentioned here? Especially regarding the Evaluation of the safety of medical devices this is ambigous. Further, dust is known not to be a suitable Matrix to determine human exposure see e.g. Becker et al (2004) and Fromme et al (2003) Further, e.g. DINCH exposure has been shown to be very low and at safe levels e.g. in Germany and the US. Schütze (2014), US NHANES, 4th update Report [http://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Jul2014.pdf] and a recent publication by the German Environmental Protection Agency (UMID2)	The reference to dust is one of the possible sources of aggreagate exposure: this is now clarified in the revised version.
64.	Sterk Thecla, Eucomed, thecla.sterk@eucomed.org, Belgium	EXECUTIVE SUMMARY	Page 10: The 1st paragraph finishes by saying that "Most of the 2008 SCENIHR Opinion remains valid," but the document appears to lack a concise break-down of those aspects of the 2008 Opinion that are no longer considered valid. This Executive Summary, and/or the above Abstract, would seem appropriate locations for this break-down. Page 10, last sentence: Replace the word significant with 'transient elevated' and add at the end of the sentence, 'however voluntary donations are not provided by groups deemed to be at risk for reproductive toxicity (pregnant and nursing mothers and neonates)'.	The Opinion reports both 'old' (i.e. already cited in the previous opinion) and 'new' data that were considered together and evaluated based on the WoE approach, as described in the methodology paragraph. To make a clear-cut distinction between old and new information is therefore not possible. This applies to the entire document. The comment was addressed in the revised version. The comment was addressed in the revised version.

			Page 11, 2nd paragraph: Consistency of units – (i.e. 8000 ug/kg/d for a neonate of 1.5kg bw) compared to p4, para 4 where it is give as 6000 ug/kg bw/d. Page 13: The 2nd paragraph appears to be saying that it is not yet possible, in the SCENIHR's (preliminary) opinion to support the replacement of DEHP with alternative materials from a risk assessment point of view. However, this opinion has not been explicitly stated, either in this paragraph or elsewhere in the document. Page 14: The first sentence should be amended to say; "According to (the MDD), Medical Devices may only be placed on the market if they meet the essential requirements laid down in Annex I of the Directive, and if the manufacturer has established a positive risk/benefit ratio." Page 14, 2nd to last paragraph: Referring to a "recently issued" press release seems out of place as the LCA report came out in 2012. We propose to integrate the executive summary with charts and tables to highlight the outcome of the report.	This is outside of the mandate of the SC. LCA is not mentioned in the ES. Charts and tables are present in the main text and it is not useful to burden a summary with the same information.
65.	Drew Sam, Summit Medical, sam.drew@summit-medical.com, United Kingdom	EXECUTIVE SUMMARY	Although the potential risks of DEHP (and other related plasticisers) with regards to neonates, pregnant/ nursing mothers and other risk groups is well publicised, this body of evidence does not, in our opinion, support the EU Parliament's proposal of a blanket ban of DEHP and other plasticisers. From a product risk perspective, the risk posed by plasticisers in many devices is minimal. Where there is short term contact between body fluids and the device in low risk indications, for instance, there is insufficient duration for a significant level of plasticiser to accumulate. In devices where there is no contact with any body fluid, the risk to the patient from plasticisers is infinitesimally small, and the benefits in performance granted by the plasticisers in question far outweigh the risk. This extremely low product risk, coupled with the current lack of adequate alternative plasticisers, means	This is a risk management issue, outside of the mandate of the SC.

			that many medical devices containing plasticisers have a high level of clinical benefit. The current body of knowledge supporting the use of alternative plasticisers is also too limited to support the adoption of these in place of currently used chemicals, especially regarding their performance and safety characteristics.	
66.	Drew Sam, Summit Medical, sam.drew@summit-medical.co.uk, United Kingdom	EXECUTIVE SUMMARY	Although the potential risks of DEHP (and other related plasticisers) with regards to neonates, pregnant/ nursing mothers and other risk groups is well publicised, this body of evidence does not, in our opinion, support the EU Parliament's proposal of a blanket ban of DEHP and other plasticisers. From a product risk perspective, the risk posed by plasticisers in many devices is minimal. Where there is short term contact between body fluids and the device in low risk indications, for instance, there is insufficient duration for a significant level of plasticiser to accumulate. In devices where there is no contact with any body fluid, the risk to the patient from plasticisers is infinitesimally small, and the benefits in performance granted by the plasticisers in question far outweigh the risk. This extremely low product risk, coupled with the current lack of adequate alternative plasticisers, means that many medical devices containing plasticisers have a high level of clinical benefit. The current body of knowledge supporting the use of alternative plasticisers is also too limited to support the adoption of these in place of currently used chemicals, especially regarding their performance and safety characteristics.	Same comment as n° 66. Please see the corresponding answer.
67.	Sterk Thecla, Eucomed, thecla.sterk@eucomed.org, Belgium	ANNEX I: EVALUATION OF INDIVIDUAL PLASTICIZERS	This section does not attempt to verify overall data for alternative plasticizers. All sections appear to be primarily a summary of literature information, with no risk assessment (e.g. no thresholds derived, etc.). Limited conclusions statements for each with some comparisons to DEHP. Again, there does not appear to	The Annex has been extensively revised to address a number of comments and new data provided.

			be anything recognized as 'new' since 2008 review(s).	

Contributions received by e-mail

No	Name of individual/ organisation	Comment	Scientific Committees Response
68.	French Governement	 Letter.PDF  Comments.PDF  Translation: SANCO-2014-07145-00-00-EN-TRA-00.do	Thanks for the comments; they have led to some modifications of the text, whenever necessary and possible.
69.	DG SANTE	Juste un petit courriel pour vous informer que les résultats d'une nouvelle étude américaine (université de Columbia, NY) viennent d'être publiés et repris très largement dans la presse. Ces résultats font notamment état d'impacts sur le développement intellectuel	The paper has been cited in the main text.

		des enfants exposés in utero à des niveaux élevés de certains phtalates. Je suppose que le SCENIHR aura connaissance de la conduite de cette étude mais, étant donné la publication récente de ses résultats i.e. 10/12/2014, j'ai préféré vous en faire part.  Factor-Litvak Persistent Associatior	

Contributions received after public consultation

The comments below and several additional references were received by the SCENIHR after the closure of the public consultation. The Committee exceptionally accepted to take them into account and, where relevant, the text of the report was revised accordingly. However, the main conclusions and the Opinion part itself (4. Opinion) remained unchanged. The modifications resulted in a new version of the final Opinion, called Revision February 2016.

No	Name of individual/ organisation	Comment	Scientific Committees Response
1.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 6, 2nd para, Either two or all alternatives should be mentioned in the abstract	SCENIHR agrees that other alternatives could be mentioned and has added : ATBC (acetyl tri-N-butyl citrate), BTHC (N-butyryl-tri-N-hexyl citrate), DINP (di-iso-nonyl phthalate), DEHT (di(2-ethylhexyl) terephthalate)
2.	Otter Rainer, BASF SE, rainer.otter@basf.com,	Page 12, 2nd para: FDA Should be U.S. FDA	Correction made

	Germany		
3.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page12, 3rd para: Not sure! At high dose levels plasticizer solubility may be exceeded and the plasticizer is released from an intravasal depot into circulation	A parental administration results in all of the injected dose being bioavailable: this is a default assumption (and text book knowledge). Even if there would be an intravasal depot, this depot is also bioavailable. In addition, for medical devices it cannot be expected that the dose would be so high that the solubility might be exceeded.
4.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 12, 4th para : These data are available: Koch, Filser, Otter, BfR-Workshop 2011	This is the executive summary in which references are generally not included. The toxicokinetics and metabolism are extensively discussed in section 3.4.2. No need to change the text here (except for some editorial content).
5.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 12, 5th para: However, quantitatively there is a difference when comparing the oral versus the intravenous route. Proof: The NOEL testicular toxicity is different on the oral (5mg/kg bw) and the intravenous route (60 mg/kg bw)	The comment is incorrect. 5th paragraph does not deal with excretion. The last sentence of the 4th paragraph read: The metabolic pathway as well as the excretion pattern of DEHP in humans is qualitatively independent from the exposure routes (oral or i.v.). The reported NOELs refer to animals and not to humans. In addition, since for medical devices the exposure is not only by parenteral route, for the risk assessment the lowest NOAEL is used. No need to change text.
6.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 13, 1st para: Two (ii). Second one should be (iii)	Correction made
7.	Otter Rainer, BASF SE, rainer.otter@basf.com,	Page 13, 2nd para: Sentence should be moved later or to the end. Doesn't fit where it is.	Text now gives first the statement and then follows with the explanation. This is a matter of taste. As other substances are also mentioned, it was put up front. No need to change text.

	Germany		
8.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 14, 2nd para: What about intravenous route? Cammack et al.(2003), NOEL testicular toxicity 60 mm/kg bw/day, MADL, adult, i.v. (US OEHHA): 4200 µg/day; MADL, infant, i.v. 600 µg/day	For risk assessment the lowest NOAEL is used. As indicated in the text on page 14, this is used as starting point for the RA.
9.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 14, 4th para: Need a comma after "… infants"	Correction made
10.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 14, 5th para: This statement seems odd. Where are all the data for DEHP? For specific alternative plasticizers dedicated exposure data are available. Risk assessment is possible and further supported by human biomonitoring data. Also, the reference to combined exposure should be critically challenged as for a patient in a hospital, the exposure scenario is different from a healthy person getting exposed by other sources.	Data for DEHP are included in the Opinion. And exposure scenarios could be established (section 3.4.3). For the alternatives, few data on leaching from medical devices were available. Some data for alternatives are presented as well (Section 3.5.3). With the exception of DEHP, data were insufficient for a risk assessment considering medical devices.
11.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 14, 3rd para: Disagree! The TDI oral should not be used as there are quantitative differences regarding the formation of the active monoester MEHP on the oral versus the intravenous route.	This has been addressed in the answers to the PC (#2) document as well.
12.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 16, 5th para: It should be mentioned here that this LCA is not real – it was a hypothetical bag that doesn't exist	This is part of the mandate and cannot be changed. SCENIHR addressed this on pages 19/20 of the Opinion and discards the whole idea of a fictional product. No need to change text
13.	Otter Rainer, BASF SE, rainer.otter@basf.com,	Page 18, 1st para: Should read "…plasticizers, and in particular phthalates."	Correction made

	Germany		
14.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 18, 3rd para: PVC-containing plasticizers are incorrect. Remove hyphen.	Correction made
15.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 18, 6th para: 2nd sentence may come from Health Canada recommendation, but isn't attributed.	It is quoted at the beginning of the paragraph and in the first line on page 19. No need to change text.
16.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 19, 1st para: French ban is on DEHP-containing tubing, not pipes.	Correction made
17.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 19, 1st para: Correct name is U.S. Food and Drug Adminstration – no hyphen.	Correction made
18.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 19, 1st para: Correct name is U.S. Food and Drug Adminstration – no hyphen.	Correction made
19.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 19, 1st para: Alternatives to classified phthalates in medical devices, DK EPA Environmental Project No. 1557, 2014, Sweden: KEMI report 4/15 and BfArM (Germany): DEHP als Weichmacher in Medizinprodukten aus PVC, Referenz-Nr.: 9211/0506,	KEMI report and probably DK EPA report published after publication of preliminary Opinion on DEHP. They are now included as references in the main text. BfR is a not dated reference to website fo BfR.

		http://www.bfarm.de/SharedDocs/Risikoinformationen/Medizinprodukte/DE/dehp.html Are missing and should be added	DK EPA report indicates also the availability of less data compared to DEHP. It mainly focusses on toxicological and environmental hazard
20.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 19, 1st para: Why does the report mention this – it is out of context. Should be deleted	It indicates general regulatory measures to limit use of DEHP, so it is appropriate to indicate this. No need to change text
21.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 21, 3rd para: Add PVC-DINCH is used routinely for pediatric platelet bags since 3 years in The Netherlands (Sanquin)	Examples are presented. SCENIHR agrees to add one more example.
22.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 21, 4th para: No, disagree: it should read: …. Alternatives to plasticized DEHP-PVC.	Correction made
23.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 21, 4th para: Remove hyphen from "…PVC-containing…" It is not correct	Correction made
24.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 21, 5/6th para: Should be changed to "migration". The statement "very little information is available on leaching" is ambiguous, for all the plasticizers with food contact approval, the publicly available EFSA opinions do show migration data either in real food or into simulants. Physic-chemical data like Pow, water solubility are part of the REACH registration data and available from the ECHA REACh dissemination database	Partially agree. Migration is indeed used for movement of DEHP into food in FCM. However, in the risk assessment of medical devices the terminology is "leaching" of chemical substances from a medical device as it is simulated in extraction methods used for toxicology studies of medical devices as described in the ISO 10993 series. The issue is to have data 'under conditions relevant to the usage in plasticized products', which for medical device is different from FCM. Phys-chem data are reported. The meaning of the comment on

			REACh data is unclear. No need to change text
25.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 22: Table 1 There is experimental data available for water solubility and vapor pressure for DEHT	The practically nil water solubility now added. The only experimental data available is obtained at a very high temperature (215°C). No need to change the estimated value.
26.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 22, 2nd para: Several studies were provided showing extraction and migration for DEHT. Where are they?	No specific references were provided for section 3.3. No need to change text
27.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 23, 3.4.2: Citation should be corrected to Kurata 2012b	Correction made
28.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 23, 3.4.2: Citation should be corrected to Kurata 2012b Further, at such high dose levels (2500 mg/kg bw) only a fraction of 10 % is absorbed and subsequently excreted via urine. The wording used in the opinion could be misinterpreted in that 90 % would not be excreted	Correction made Text changed accordingly, to make the meaning clearer.
29.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 23, 3.4.2: Citation should be corrected to Kurata 2012b	Correction made
30.	Otter Rainer, BASF SE, rainer.otter@basf.com,	Page 25, Figure 1: Not clear why the metabolism scheme by Koch and Angerer was changed to Silva	This was considered a more appropriate figure.

	Germany		
31.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 26, 4th para: Needs to be corrected to 2012b	Correction made
32.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 26, 5th para: Needs to be corrected to 2012a	Correction made
33.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 26, 6th para: Needs to be corrected to Schmid and Schlatter	Corrected in the text: it was correctly reported in reference list.
34.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 27, 4th para: Needs to be corrected to 2012b	Correction made
35.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 28, 2nd para: Needs to be corrected to "due to migration of plasticizer into food"; Rudel et al deals with packed foodstuff	This was already indicated in the text, and the reference is also correct and indicates food packaging. Text also indicates other possible sources than food packaging e.g. contamination during processing. No need to change text
36.	Otter Rainer, BASF SE, rainer.otter@basf.com,	Page 29, last para: This method leads to an overestimation of exposure. Human biomonitoring data should be given priority.	This is informative text. In the text, the two methods of estimating DEHP intake were compared and explained in detail. No need to change text.

	Germany		
37.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 35, 4th para: This is a misunderstanding. See Calafat (2004): Materials and Methods:β-glucuronidase enzyme was used: The sample was incubated at 37° C for 90 min to allow for the deglucuronidation of the phthalate metabolites. Kavlock (2006) stated: These data are still scant, but may be of particular concern if the toxic metabolites of DEHP are present in breast milk or amniotic fluid in free (unconjugated) form. DEHP Kavlock refers to Silva (2004) regarding amniotic fluid and again, Silva also analyzed deglucuronidated samples. This means, the statement in the SCENIHR opinion is wrong and needs to be corrected.	Agreed. We apologize. There was a mistake in the reference here, erroneously cited as Calafat (2004b). The text has been changed accordingly. Calafat AM, AR Slakman, MJ. Silva, AR Herbert, LL Needham. Automated solid phase extraction and quantitative analysis of human milk for 13 phthalate metabolites. J Chromatogr B 2004b; 805: 49-56.
38.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 35, 5th paragraph: Add DK EPA, Kemi (Sweden) and BfArM (Germany)	Not necessarily needed here. The same references added elsewhere.
39.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 36: This is an error and needs to be corrected: Not DOP but noDOP® = TEHTM was used See Greiner , Materials and Methods: – Flexible PVC tubing systems (Raumedic AG, Münchberg, Germany) (n=12) containing DEHP as a plasticizer – Carmeda® (Medtronic GmbH, 40670 Meerbusch, Germany) (n=12) containing DEHP as a plasticizer (but surfaces coated with heparin) – noDOP® (Raumedic AG, Münchberg, Germany) (n=12) containing TEHTM as a plasticizer	The text was cited as it was formulated in the abstract of the paper. Text has been corrected.
40.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 37, (3): Citation recommended: Inoue K et al., Clinica Chimica Acta 358 (2005) 159–166	Correction made
41.	Otter Rainer,	Page 38, 2nd para: Add Inoue K.	Correction made

	BASF SE, rainer.otter@basf.com, Germany		
42.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Statement unjustified: Inoue K. et al. show detailed data	This statement deals with the possibilityof establishing a conversion rate of DEHP into MEHP. Although the paper provided (and now included as additional reference report) detailed data, they cannot be used to build up a kinetic model to estimate on the basis of the DEHP detected how much MEHP is expected over time. No need to change the text.
43.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 52, para 3: Kavlock, 2006 (US NTP CERHR, DEHP Monograph) evaluated the study results to be ambiguous: "The lack of a dose response with the oxidative metabolites, combined with a lack of clear understanding of the mechanism by which these compounds reduced luciferase activity, reduces the usefulness of these data." Therefore, SCENIHR should delete the unjustified statement re antiandrogenic metabolites	The citation is pointing to a possible mechanism. Not a firm statement that this is a fact. The text says. ….one report suggests that at least in rats ….However, the criticisms have been added.
44.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 56, 2nd para: Meeker JD (2009b), Environmental Health Perspectives 117, 1587-1592 needs to be added to citation list: Meeker JD (2009a) is listed but deals with steroid homone levels in men	Correction made
45.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 58, 2nd para: The major limitation of the study is not mentioned. The authors did not analytically measure DEHP exposure by ECMO. They only refer to Snider et al. (1989) who reports DEHP exposure by 3-10 days of ECMO to result in exposure of the 4 kg infant of 42-140 mg/kg. Essential information regarding sampling time after ECMO, change of DEHP concentration in blood over time is missing. However, V. Karlé, [Crit. Care Med (1997), 25, 696-703] determined much lower exposure for ECMO patients (2 mg/kg bw.) but recognizes that DEHP exposure was greater in the early course of ECMO	They refer to Schneider et al., 1989 in their discussion. As the study subjects were 16-year-old children, it is unlikely that reliable ECMO exposure data were available. The following text has been added: In addition, data on the actual exposure during neonatal ECMO were lacking.
46.	Otter Rainer, BASF SE,	Page 58, 3rd para: Agree, the study has a lot of limitations, however, the authors did not presume a high DEHP exposure, they	This assumption was expressed by SCENIHR. Text has been changed accordingly.

	rainer.otter@basf.com, Germany	have identified other confounders	It can be assumed that the latter have had a high DEHP exposure as a consequence of their treatment/management in the NICU.
47.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 61, 2nd para: But for DEHP, the newborn/young marmoset failed to show any evidence of testicular toxicity: Rhodes et al, 1986; Kurata et al´. 1998, cited in the SCENIHR opinion on page 48 Further, see page 49, more recent studies Hallmark, 2007, Lambrot, 2009 and Mitchell, 2012 as well as Habert, 2014,do also not support such a statement	Agreed. But this is not a conclusion. It is the introduction to the following literature overview on male reproductive toxicity as indicated by the last sentence of this paragraph. "Several epidemiological studies have addressed this and/or have assessed in adult men if there is any association between phthalate exposure and semen quality or fertility. No need to change the text.
48.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 74, 3rd para: Please refer to materials section of the publication: The plastisols contained 1.7 parts per hundred resin (phr) of stabilizer and 70 phr of the respective plasticizers. This means that ca. 1 % stabilizer and ca. 41 % plasticizer was used."	Reference to lack of concentration has been deleted.
49.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 74, 5th para: However, it should be referred to the publication:" While SAG-M is hypertonic, the other solutions are isotonic or slightly hypotonic……While with SAG-M, DEHP seems to be an essential additive to maintain RBC stability, with the new ASs, with improved maintenance of osmotic stability, and reduced microvesiculation, the role of DEHP to maintain RBC stability may be less important." "	It is a conclusion made by SCENIHR. Use of other additives reducing hemolysis is mentioned. This level of detail indicated by the comment is not needed here.
50.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	This is a wrong interpretation of the results shown in Table 5: 1.4 mg/l DEHP is background from e.g. lab equipment, solvents used. The important information is: PLT storage for 7 days, results only in a doubling of the DINCH concentration (DEHP background was essentially the same). In the DEHP-PVC system, DEHP concentration increased by a factor of 20, i.e. from 1.4 mg/l to 27 mg/l and additionally in 13 mg/l of MEHP, which is the metabolite responsible for toxicity to reproduction in rodents.	Agreed. Text changed as follows. For paediatric PLT concentrates, DEHP leakage was similar at day 1 after storage and probably due to DEHP-PVC in the tubing system used. At day 7, DINCH leakage was 10 fold less in the non-DEHP system compared to the current DEHP containing system.

51.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 75, 2nd para: A completely incorrect name is given for DOTP. Should be DEHT which is di(ethylhexyl) terephthalate	Correction made
52.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 75, 5th para: Somebody within SCENIHR seems to prefer "leaching", however, it should read "to mimic migration" as this is the wording used in Council Regulation (EU) No 10/2011	Migration is indeed used in the food contact materials. However, for medical devices in general leaching is used as a risk assessment is performed on substances leaching from medical devices as described in the ISO 10993 series used in the safety evaluation of medical devices. SCENIHR therefore prefers to use the word leaching.
53.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 75, para 6: Are you sure? Where are the data? 10993 does not specifiy/list threshold limit values Further, for an alternative the data that need to be provided is the migration and the worst case dose level taken up by the relevant route of exposure for the intended use and the NOAEL on that route.	Exposure data on DEHP from medical devices is presented in section 3.4.3.4. This cross reference is now added for clarification.
54.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 76, para 1: This procedure may only be appropriate if a solid justification can be provided. Preferable are measured data re exposure in the intended use!	Agreed. That is why a reliable risk assessment was not possible. No need to change text.
55.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 76, para 2: DEHP is a production process related impurity of TOTM; this DEHP impurity migrates.	Text changed for clarity Leaching of DEHP from TOTM-containing products was associated with DEHP impurities related to the TOTM production process.
56.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 76, para 3: Should read: … production process related DEHP impurities in the commercial TOTM	Text changed. …related to the TOTM production process

57.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 76, last para: Unclear where the data re migration of DEHP; DEHA, ATBC and BTHC are coming from; not included in Subotic et al.! probably citation missing	The reference to the table data was missing. It is now included.
58.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 77, para 1: Is a Danish newpaper/magazine of the Chemical Engineering Association (IDA) and the Danish Chemical Association a reliable source? This seems to be a Danisco promotion article The EFSA migration data are the valid data. Please confirm the Danisco data as the statement re differing results may not be justified.	The problem is that no other data were available. So, Kristoffersen 2005 is included. Difficulty in comparing data (whatever the source) is already mentioned. No need to change text. Table number is corrected Table 12 in text should be Table 9
59.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 77, para 2: This statement is only valid for TOTM, as DEHP is a production process related impurity of TOTM. Based on the production process DEHP is not an impurity of DINCH!	Use of both plasticizers results in DEHP leakage. As it is not a production related impurity, the text on impurity is deleted.
60.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 77, 2nd para: Again, the extraction and migration studies on DEHT provided to the SCENIHR appear to have been ignored or misplaced during the review. Unacceptable!	Any missing study should be provided in order to be considered. SCENIHR, as extensively explained in the answer to the PC, did not rely on data on the REACH public domain in case the original reports were not made available. One paper was found in PubMed Bernard et al., 2015 Int J Pharm., however, it was published after publication of the Opinion.
61.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 77, para 3: This is not justified, as it is well known that dust concentration of high molecular weight plasticizers does not correlate with urinary metabolite levels.	Dust is indicated as other source of potential aggregated exposure. The text makes no link to any urinary measurements. No need to change text.
62.	Otter Rainer, BASF SE, rainer.otter@basf.com,	Page 77, para 3: dust is not a reliable matrix to conclude on human exposure, therefore this sentence should be corrected. Further, for DINCH, human biomonitoring data are available indicating the exposure of the general population is exposed to 0.14 µg/kg bw/day (50. percentile), 1,07 µg/kg bw/day (95. percentile)	The text is an introduction to the toxicity of alternative plasticizers, and not on exposure. It presents an introduction to possible sources of exposures. Dust might be a confounder in exposure estimates.

	Germany		
63.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 78, para 1: Some of the effects are not relevant to humans, therefore the whole paragraph may be challenged. Further, why do you assume 100 % bioavailability for the parenteral route. Plasticizers at high dose levels can be injected or infused intravenously, however, based on the dose the plasticizers may not be soluble resulting in intravasal precipitation or depot building. There are old i.v. studies with DEHP leading to increased lungs and mortality based on precipitation of the test substance in an inappropriate vehicle.	The parenteral route is assumed to be 100% by definition. Therefore whenever data on the oral route (for which a very limited bioavailability has been reported) are available, the relevance for the risk assessment associated to exposure via medical devices is limited. See also comment n°3 page 1
64.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 78, table 10: What are the criteria?	Toxicity for foetus as indicated under critical endpoint.
65.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	What is the justification for "NO" regarding toxicity to reproduction when essential data are missing?: For BTHC there is no multi-generation study, developmental toxicity testing, and endocrine activity is missing. Repeat dose toxicity data (90 day/chronic toxicity studies) are missing. 28d, intravenous, rat: not meeting current regulatory requirements, not only liver weight increased but also histopathological changes reported, therefore it is questionable whether 500 mg is a NOAEL or better a LOAEL. It is not appropriate to compare the DEHP NOAEL of 4,8 mg/kg bw/day from a multigeneration study with a the BTHC data. Further, is 250 mg/kg bw/day a solid NOAEL? The column 2 ratio with DEHP factor is wrong as the data cannot be compared based on differences in study duration and endpoint How can SCENIHR compare a NOAEL oral of DEHP with a NOAEL(?) i.v. for BTHC?	The commenter is asked to read the BHTC information in the Appendix. For the risk assessment, a NOAEL is used independently of the effect, be it liver, kidney or reproductive toxicity. By comparison it now gives an indication of relative risks in relation to possible exposure. So, the risk can be considered as equal (as there is a NOAEL) but you need higher exposure doses to reach the level of risk (of possibly causing harm).
66.	Otter Rainer, BASF SE,	Why "yes" for reproductive toxicity => this should be a clear "NO"!	It has been specified that there are developmental effects

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67.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 78, table 11: What are the criteria?	See Annex I with data on the various alternative plasticizers.
68.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 79, table 11: There is nothing uncertain about the carcinogenicity potential of DEHT. It is a clear no.	In view of results presented in Table 10, it can be considered uncertain. This is a matter of interpretation. No need to change
69.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 79, para 1: What is uncertain with DINCH? Why is SCENIHR not capable to conclude. The full study reports were available for SCENIHR and there a justification is given for biological non-relevance of the effects occurring in a range finder study. This has been accepted by several competent authorities around the world. SCENIHR needs to specify why they evaluate the data as uncertain.	The uncertainty for DINCH is explained regarding the biological relevance of the findings. The AGD is however considered a biomarker for adverse effects (see the enhanced OECD one generation study Test Guidelines). No need to change the text.
70.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Is not justified. This should read: DINP caused liver carcinoma in rodents. DEHA caused liver carcinoma in mice but not in rats. In both cases, the liver carcinoma are related to peroxisome proliferation, a mechanism that is evaluated not to be relevant to humans. The thyroid adenomas related to DINCH were evaluated by EFSA: "Considering the absence of genotoxic properties, the induction of follicular cell hyperplasia and adenomas in rat thyroid can be attributed to a non-genotoxic, indirect mechanism. As rodents are far more sensitive than humans to chemical disturbance of thyroid function (IARC, 1999), the effects on thyroid observed in 90 days and chronic toxicity/carcinogenicity studies are not appropriate to set a TDI.", i.e. in line with IARC, EFSA evaluates the thyroid adenomas not to be relevant to humans	An explanation about the relevance is already provided on page 79. Therefore there is no discrepancy in the data interpretation. No need to change the text.
71.	Otter Rainer,	Page 79, para 3: Should be corrected to (Borch et al. 2004)	Correction made

	BASF SE, rainer.otter@basf.com, Germany		
72.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 79, last para, page 80 para 1: Odd statement. The toxicological data on these plasticizers include the effects of any metabolite as physiologically formed.	The statement indicates that an accumulation of MEHP is possible from various sources of plasiticizers, especially in aggregated exposure. So, even when exposure to the single chemicals may be low, the aggregated exposure may result in toxicity due to MEHP formation.
73.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 80, para 2: Polymeric adipates are not solid! They are liquid.	To be more 'general' and to also include adipates, the word solid has been deleted.
74.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 80, 3rd para: This phrase is not real. Please edit to be relevant.	Correction made
75.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 81, para 1: Reference to BfR is missing Reference to EFSA 2005 (The EFSA Journal (2005) 243, 1-20) is missing	EFSA 2005 and BfR 2013 are cited in paragraph 1 at the end.
76.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 83, para 1: The result is misguiding, as the calculation assumed 3000 µg x 4 kg= 12000 µg and then divided by 1,5 kg. This method is not appropriate as the flow and the volumes are different for a smaller baby.	This is the calculation reported by FDA, which is cited as the source.
77.	Otter Rainer, BASF SE, rainer.otter@ba	Page 83, para 3: Only at low dose levels that are achieved by the intended use of medical devices	See above. This has been addressed already.

	sf.com, Germany		
78.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 83, para 4: These data are already available: These data are available: Koch, Filser, Otter, BfR-Workshop 2011 Published e.g. by Kessler (2012) and Kurata (2012a)	Data have been presented in main text. To make it clearer, 'may be' has been replaced by' is'. This is the overall concluding section in which not all data are repeated.
79.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 83, para 4: Yes, but qualitatively there are important differences related to the route of exposure. Based on the action of released pancreatic lipase following oral uptake, the initial MEHP increase is much higher on this route as compared to the intravenous route. Further, oral bioavailability shows saturation with increasing dose levels.	This is explained in the main text. The overall concluding section cannot report all the details.
80.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Agreed, but these little children seem to be able to preferably oxidize MEHP to the oxidized metabolites (Hydroxy- and oxo-MEHP) which are then found in urine Cf. Calafat et al. (2004a), as cited in the SCENIHR opinion	This is explained in the main text. The overall concluding section cannot report all the details.
81.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 84, para 2: Add: Jacobsen (1977) and Kevy (1982)	These references are quite old. Do not forget that this is an update of the previous Opinion.
82.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 84, para 3: Agreed, but ECB (2004) should be cited as parts of the text are already copied from there	This is explained in the main text. The overall concluding section cannot report all the details.
83.	Otter Rainer, BASF SE,	Page 84, para 6: Where is the justification for such a statement? Rhodes 1986:	The commenter should carefully read the whole paragraph (as well as the detailed main text).

	rainer.otter@basf.com, Germany	The oral and intraperitoneal administration of di(2-ethylhexyl) phthalate {DEHP) lo the marmoset monkey at doses up to 5 mmole DEHP/kg body weight/day for 14 days did not induce morpho1ogical or biochemical changes in the liver or testis comparable with those obtained in rats given the same amount of DEHP. Kurata (2012): There are obvious species differences in the sensitivity to adverse hepatic and testicular effects between two species; the levels of DEHP that produced hepatic and/or testicular effects in rodents had no effect on these organs in non-human primates (Rhodes (1986); Astill (1989); Short (1987); Kurata (1998); Pugh (2000))	In the previous sentences, the same concept reported in the comment is clearly explained. Some effects limited to post-natal exposure are also mentioned. No need to change the text.
84.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 85, para 2: Citation missing, most likely: Lambrot et al. (2009)	Details and references are reported in the main text. The commenter should have noted that citations are not fully reported here, as this is the concluding section and by definition not inclusive.
85.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 85, para 4: At least parts of it are published in: Klincoyne et al., Proceedings of the National Academy of Sciences of the USA vol 111 issue 18 (2014) E1924	Details and references are reported in the main text. The commenter should have noted that citations are not fully reported here, as this is the concluding section and by definition not inclusive.
86.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 85, para 5: Kimber et al, Larsen et al.	Details and references are reported in the main text. The commenter should have noted that citations are not fully reported here, as this is the concluding section and by definition not inclusive.
87.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 85-87: Citations should be added	Details and references are reported in the main text. The commenter should have noted that citations are not fully reported here, as this is the concluding section and by definition not inclusive.

88.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 87, para 4/5: this TDI is valid for the oral route!	Since for medical devices the exposure is not only by parenteral route, for the risk assessment the lowest NOAEL is used. No need to change text.
89.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 87: Citations to be added/completed	Details and references are reported in the main text. The commenter should have noted that citations are not fully reported here, as this is the concluding section and by definition not inclusive.
90.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 88, para 1: Plonait (1993), but maximum calculated DEHP exposure was 22600 µg/kg bw/d	It was used as an approximation; the actual value is now included, but this would not change the outcome.
91.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 88, all	Details and references are reported in the main text. The commenter should have noted that citations are not fully reported here, as this is the concluding section and by definition not inclusive.
92.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 88, para 2: Where does this come from? Citation missing. FDA 2002, Safety assessment of DEHP …. gives a combined exposure of 3000 µg/kg bw/day for a 4 kg baby	The value comes from the Calafat studies. See the main text for details
93.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 88, para 4: For TOTM this could be as DEHP is a production process related impurity in TOTM DINCH cannot have DEHP as an impurity. DEHP is either analytical background of the lab solvents in the analytical lab (i.e. does not come from DINCH) or the medical device is contaminated in the production process with DEHP from former production batches. Steam sterilization of medical devices in the autoclave where previously DEHP based devices were sterilized can also be a	The expression 'like due to impurities' referring exclusively to TOMT was deleted for greater clarity.

		possible source of DEHP contamination	
94.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 88, para 4: Change to DEHT	They are synonymous. No need to change it. See the abbreviations.
95.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 88, para 4: According to studies provided to SCENIHR, DEHT has lower migration than DEHP in every case	No specific references were provided for this section No need to change
96.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 88, para 5: Please edit for every instance of TOTM	Correction made
97.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 88, para 5: Should read BTHC	Correction made
98.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 88, para 5: Unjustified statement see comment page 79, para 1	Please see the relevant answer
99.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 88, para 5: For DEHP, exposure of the general public decreased during the last 10 years. Today, DEHP exposure is in the area of 5 to 10 µg/kg bw/day, and further decreasing. For some of the alternative plasticizers, most recent human biomonitoring data are available, e.g. for DINCH the median (95th percentile) DINCH intake in 2012 was calculated to be 0.14 (1.07)	Beside the background (environmental) exposure, the specific use of other products containing phthalates should be considered anyway. This is true also in cases where it might be concluded that the exposure due to some medical device use (not necessarily in all the possible scenarios) is much higher than the other possible sources. No need to change the text.

		g/kg body weight/day which is considerably below daily intakes currently deemed tolerable. Further, it should be taken into account that background exposure changes significantly when a person leaves home and has to go to a hospital, i.e. different food and environment. Also, most of the medical applications lead to exposure levels that are orders of magnitude higher as compared to background exposure.	
100.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 89, para 4: What is meant?	The term sensitivity has been replaced by individual susceptibility to improve clarity.
101.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 89, para 5: Citation missing (Plonait et al 1993); value is 22600 µg/kg bw/day. Further, please keep in mind the procedure (triple volume exchange transfusion) may be obsolete today.	Please, see the previous answer to the same comment.
102.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 89, para 7: They were assumed to be highly exposed; exposure has not been measured. Keep in mind that heparin may have reduced exposure (V. Karle, 1997)	This has been clarified here, although already explained in the main text.
103.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 90, para 3: The TDI derived from studies on the oral route! Based on toxicokinetic differences between the oral and the intravenous route, this approach is not appropriate.	Please see the answer to the same comment given above.
104.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 90, para 5: Not appropriate. It would have been better to refer to Cammack et al (2003) and use the MADL derived by the US OEHHA	This was the SCENIHR's opinion.

105.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 90, para 7: See comments to page 88, para 4.	Please see the relevant answer.
106.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 90, para 8: BTHC data re reproductive toxicity are inadequate! There are no uncertain results of DINCH! These plasticizers do not have a carcinogenic potential! This should read alpha-2-µ-microglobulin	Please see the answer given to previous comments on the same issues. No need to change the text. The irrelevance for human health is already addressed in the opinion. No need to change the text. Sorry for the typo. It has been corrected.
107.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 92, para 1: The major question is why SCENIHR failed to take into account the relevant studies on the intravenous route available for DEHP, DEHT and DINCH? Further, why does SCENIHR tolerate the use of DEHP in NICUs, while there are no data to support the use.	Please see the previous answer to the same comment. This comment cannot be understood. We have clearly indicated that neonates in NICU are a group at risk. The possible decision to be taken pertains to risk management measures, which are outside the mandate and the remit of the SC.
108.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 92, para 1: This should also include analytical exposure assessment	This was implicit (a well performed epi study should include an adequate exposure assessment). However it has now been made explicit.
109.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 92, para 1: Any idea how to deal with the confounders low birth weight, prematurity etc.?	This is outside the mandate of the Opinion.
110.	Otter Rainer, BASF SE, rainer.otter@basf.com,	Page 123: nclude on page 124 in alphabetical order	Correction made

	Germany		
111.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 132: CSTEE opinion 1999: http://ec.europa.eu/health/archive/ph_risk/committees/sct/documents/out45_en.pdf Further, migration data can be found at: The EFSA Journal (2005) 273, p. 19 of 26	The data reported in the cited references are related to FCM, therefore of limited relevance for medical devices. That is why they were not included. Some information has now been added for completeness, but this does not alter the final outcome .
112.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 133, para 5: OECD 414 missing, => data gap, why not addressed? OECD 414, second non-rodent species missing => data gap, why not addressed? i.v. study missing	SCENIHR reported the available studies, concluding whenever possible. The single data gaps were not identified.
113.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 134: REACH registered? Information missing	How could this information affect the Opinion? No need to change.
114.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 135, para 4: Delete this sentence as n-hexanol is a hazardous substance and respectively labelled!	1-hexanol is classified as H302 - Harmful if swallowed with a CLP Hazard Class and Category Code: Acute Tox. 4 * It has no structural alert for any specific toxicity. The sentence was not incorrect, but it was edited to avoid misinterpretation.
115.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 136, para 3: This looks at least like a hemolytic activity, compensated by the bone marrow. Why is this not mentioned? Guideline study? Limit dose for repeat dose toxicity is 1000 mg/kg bw., why only 500 mg/kg bw. tested, justification for reduced dosing missing. Effects following intravenous injection: need to be more detailed Study on repeated intravenous application: missing Regarding repeat dose toxicity only 28 d studies available; lack of 90 d study should be acknowledged with REACG default time extrapolation uncertainty factor (3 x)	Fulfilling this request would not fit with a brief description of the toxicological profiles of all the alternatives. The most relevant information has been reported. It is incorrect that the study on repeated intravenous application is missing as claimed by the commenter: indeed the same study commented some lines above is an. i.v. administration for 28 days. A study cannot be criticized simple because the limit dose was not used, also because at the highest dose tested (although not the limit dose) effects were already evident. An additional study with the same experimental design was also conducted in neonatal rats. No reference value has been suggested, therefore the request to use

			any assessment factor is not applicable.
116.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 141: ECHA 2011: is the restriction report proposal of the DK EPA? EFSA citation needs to be completed: The EFSA Journal (2004)109, 1-26	Completed.
117.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 141: DEHA does not warrant classification and labeling regarding toxicity to reproduction. The substance is under evaluation in CoRAP; further studies as requested by ECHA are available, e.g. OECD 414, rabbit.	It can be added, which we did, that the substance is under evaluation, but SCENIHR cannot use the rest of information without having access to the original reports (or the final decision adopted by ECHA and published)
118.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 142: Human biomonitoring method is under development within the German HBM (VCI/BMU) program	Good to know, but SCENIHR cannot use the information without having access to the data (which seem to be in progress). No need to change text.
119.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 142, para 4, Page 144, last paragraph: Should read." probably carcinogenic in male mice…"	Correction made
120.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 146, para 2: Tonnage band: > 10000 t per annum	Not relevant here. No need to change text.
121.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 146, para 5: published: Silva et al., Environmental Research 126 (2013) 159–163 citation should be added	Correction made, changed in the text. However, the reference was correctly cited in the reference list.
122.	Otter Rainer,	Page 147, para 2: Welle et al. (2005), change „leaching" to	SCENIHR has used "leaching" as this is commonly used terminology

	BASF SE, rainer.otter@basf.com, Germany	„migration", and para 2 and 3 should be one paragraph	for the release of chemicals from medical devices. Migration is the term used in the FVM area. See also the previous answer to similar comments.
123.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 147, para4: There is no release of DEHP from PVC-DINCH-based medical devices. There seems to be a misunderstanding/misinterpretation of the analytical data	The wording has been edited for clarity, but data in the paper are clear and not likely to be misinterpreted. The citation has been updated, since at the time of the Opinion's publication, the paper was only available on-line and not in print.
124.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 147, para 6: Emission is not linear but shows saturation. The authors concluded that gas phase concentrations higher than 0.5 µg/m3 not expected.	Since the reported data is 0.41 µg/m3 it is not at all in contradiction with the information reported in the Opinion. No need to change.
125.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 148, para 6: New information, citation: David, R.M., White, R.D., Larson, M.J., Herman, J.K., Otter, R.,Toxicity of Hexamollregd DINCHregd following intravenous administration, Toxicology Letters (2015), http://dx.doi.org/10.1016/j.toxlet.2015.07.013 No effects on thyroid hormone levels, also on the intravenous route no indication for peroxisome proliferation.	Unfortunately the paper, although very interesting, was published after the adoption of the Opinion in June 2015 (it was available online as of 26 July 2015). It is now not possible to include all the papers published after the adoption.
126.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 150, para 3: published: Furr et al. (2014), Toxicol. Sci. 140(2), 403–424 2014, doi: 10.1093/toxsci/kfu081	Correction made
127.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 150, para 4: Secondary to enzyme induction, therefore evaluated not to be relevant to humans => see EFSA, 2005, With reference to the US EPA guidance document for thyroid effects, Bhat et al. 2014, applied a benmark dose low concept using an interspecies extrapolation factor of 1:	The enzyme induction was not measured and this is for the time being still a hypothesis. This is why in the Opinion it is stated: it has to be determined whether or not the mode of action is relavant to humans. Once proven, SCENIHR agrees that this kind of mechanism in relation to thyroid effects is not relevant to humans. And this is reported with

		Virunya S. Bhat, Jennifer L. Durham, Gwendolyn L. Ball & J. Caroline English (2014) Derivation of an Oral Reference Dose (RfD) for the Nonphthalate Alternative Plasticizer 1,2-Cyclohexane Dicarboxylic Acid, Di-Isononyl Ester (DINCH), Journal of Toxicology and Environmental Health, Part B: Critical Reviews, 17:2, 63-94, DOI: 10.1080/10937404.2013.876288 No thyroid effects are identified following 29d of intravenous infusion, i.e. as with other plasticizers, there are difference regarding oral versus the intravenous route. The most important difference is that less of the monoester/time unit is formed on the intravenous route as compared to the oral route. Further, in blood, the monoester is predominantly in glucuronidated.	the exactly same conclusion in the cited reference (by Bath et al., now also cited) using the effects on Thyroid as Point of Departure to derive a health-based reference value. No need to change the text.
128.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 156, para 4: Furr et al. (2014), Toxicol. Sci. 140(2), 403–424 2014, doi: 10.1093/toxsci/kfu081	Correction made
129.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 157, para 2: Beyond the risk management measures in place (Regulation (EC) 1907/2006, Annex XVII,52)	This is why it is specified 'further action'. No need to change the text
130.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 158: Citation should be moved to the DEHP chapter	Correction made
131.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 158, DEHT: Totally incorrect data. Actual is <0.001 Pa – certainly not hPa.	Correction made
132.	Otter Rainer,	Newer QSAR models show significantly higher numbers between	Since experimental data are reported, why should SCENIHR make

	BASF SE, rainer.otter@basf.com, Germany	7.5 and 9.5	reference to QSAR data? In addition, if the commenter was aware of new data, they should have provided it.
133.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Not updated since 2008 report. DEHT is manufactured globally in very high volumes. Data can be shared from public sources.	How could this change the outcome of the Opinion? It is not relevant here.
134.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 159, 2nd para: Extremely outdated information. Third sentence should just be deleted.	SCENIHR agrees. The text has been changed accordingly.
135.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 159, 4th para: Sentence is ambiguous and should be clarified to say that DEHP forms stabilized monoesters but DEHT does not.	Ambiguity eliminated
136.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 161: SCENIHR wants to recheck or was it just not deleted for the final version?	Correction made
137.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Gray LE Jr, Ostby J, Furr J, Price M, Veeramachaneni DN, Parks L. Perinatal exposure to the phthalates DEHP, BBP and DINP, but not DEP, DMP, or DOTP, alters sexual differentiation of the male rat. Toxicol Sci. 2000; 58(2):350-65	Correction made
138.	Otter Rainer, BASF SE, rainer.otter@ba	Furr et al. (2014), Toxicol. Sci. 140(2), 403–424 2014, doi: 10.1093/toxsci/kfu081	Correction made

	sf.com, Germany		
139.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Wirnitzer U. et al. (2011), Toxicology Letters 205 (2011) 8–14	Correction made
140.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 165, para 3 Same in references page 166: Should read: Christensson A.	Correction made
141.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 165, para 3, Same in references page 166: Needs to be added. Welle et al showed that the process related impurity DEHP migrates into the enteral nutrition and results in exceedance of the TDI.	Is this relevant to TOTM?
142.	Otter Rainer, BASF SE, rainer.otter@basf.com, Germany	Page 165, para 3, Same in references page 166: Information is missing => data gap regarding its use in medical devices	See the answer to similar comments.