Results of the public consultation on SCENIHR's preliminary opinion on the safety of the use of bisphenol A in medical devices

A public consultation on this opinion was opened on the website of the Scientific Committees from 29 January 2014 to 26 March 2014. Information about the public consultation was broadly communicated to national authorities, international organisations and other stakeholders.

Fourteen organisations and companies participated in the public consultation providing input to the main scientific questions (in total 119 contributions were received). Out of the 14 organisations participating in the consultation, there were six industry associations, three private companies, two professional organisations, two national authorities and one non-governmental organization.

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 the references provided during the public consultation.

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

Comments received during the public on the SCENIHR preliminary opinion on "The safety of the use of bisphenol A in medical devices"

SUBMISSION			SCENIHR's Response
Name of individual / organisation	**Table of content to which comment refers**	**Comment**	**SCENIHRs Response**
Moussa Miranda, AESGP - Association of the European Self-Medication Industry, m.moussa@aesgp.eu, Belgium	1. BACKGROUND	Line 21-22: The sentence "Examples include implants, catheters, and most dental devices" should be rewritten so as to reflect the fact that many dental devices do not contain BPA.	The SCENIHR agrees with this comment. However, the text of the Background and Terms of reference sections is provided by the Commission as part of the mandate and cannot be changed. In the Executive summary, text has been changed to address the comment as follows 'Examples include implants, catheters, and dental devices fabricated from certain materials (eg. polycarbonate or bisGMA) that may contain and release residual BPA present in these devices.'
Stock Gregor, FIDE - European Dental Industry, g.stock@fide-online.org, Germany	1. BACKGROUND and Executive summary	Page 9, line 6 and page 18, lines 21-22 "Examples include implants, catheters, and most dental devices." Comment: The use of the term "most" is questionable as written. Many dental devices do not contain BPA. This sentence should be re-written to reflect that dental devices fabricated from certain materials (eg. polycarbonate or bisGMA) may contain and release trace amounts of BPA.	See the above response.
Sterk Thecla, Eucomed, thecla.sterk@eucomed.or, Belgium	Abstract, 4, 17	The draft opinion refers to the temporary TDI of 5 µg/kg bw/day recently proposed by EFSA (2014). The proposed t-TDI is result of a highly conservative derivation using high uncertainty factors. This led to an overall safety factor of more than 700 compared to the previous TDI derivation (EFSA, 2006) using 100. We challenge that the referred derivation of the temporary TDI is too conservative based on what the review cites:	The SCHENIR disagrees with the comment considering the TDI derivation too conservative. Indeed, some uncertainties were still present on BPA- induced effect other than the one on the liver and the kidney, so that the previous TDI (EFSA, 2006) was no more adequate. However the text has been changed accordingly

		A. Orally administered BPA is readily absorbed from the GI across species – therefore correction to parenteral routes should not need to consider oral bioavailability that is absorption limited. B. The clearance of free BPA from the circulation appeared to be quite fast with >50% of circulating BPA already conjugated 5 min after intravenous injection and showing an half-life of 0.66 hour in rats. C. In Non-Human Primates (NHP), serum half-life of free BPA is approximately 0.7 hours and >50% of the free BPA is conjugated within 5 min of infusion (P. 62). Based on half-life, all free BPA will be conjugated and / or cleared from circulation within 5 hours (assuming 7 half-lives elapsed); therefore the duration of exposure to free BPA is limited. Overall, these finding are also in line with those obtained in the rat. D. The original TDI of 50 µg/kg was based on liver effects (hypertrophy) after chronic exposure when administered orally (i.e. big dose to the liver) in a species that utilizes biliary excretion as a major elimination pathway. Given parenteral routes will dilute the dose to the liver, and that elimination in primates is primarily in the urine, the original 50 ug/kg TDI already provides a very conservative limit for a target organ that might not be clinically relevant.	throughout the document in the revised opinion, to take into account the temporary TDI as derived in the recent EFSA opinion (EFSA, 2015). The newly derived TDI takes into account a BMDL for kidney effects as PoD, derived a HED (human equivalent dose) considering kinetic differences, based on which the assessment factor is reduced to 25 then multiplied by 6 (Assessment Factor=150) to account for those effects considered as 'likely' and included in the uncertainty analysis by EFSA (2015). The SCENIHR agrees with the conclusions of EFSA based on its own evaluation, the EFSA t-TDI was used in the risk assessment of BPA in medical devices.
Sterk Thecla, Eucomed, thecla.sterk@eucomed.or, Belgium	Abstract, 5, 40	Long-term dialysis treatment is considered in detail as a relevant exposure scenario by SCENIHR. For exposure from most medical uses, including dialysis, SCENIHR estimates margins of safety (MOS) well above 100, the usual factor for definition of no risk exposure doses. The draft opinion should state more clearly, that: a) medical uses with estimated margins of safety above	The limited exposure time via medical devices is already mentioned in the opinion. However, the major point here is that info on the different exposure scenarios are very scant, the uncertainties are considerable, and therefore it is difficult at the moment to think to a refined evaluation. Some text on the relevance of MOS and lack of

		100 give no reasons for concern. b) this also applies to long-term use of medical devices as for dialysis patients.	concern is added to ABSTRACT, EX ECUTIVE SUMMARY and OPINION. An example is in the following: Considering that, with the exception of dialysis patients, the exposure via medical devices is generally of limited duration, whereas the MOS based on the uncertainty factor used for the derivation of the t-TDI by EFSA (2015), is based on long term exposure, the application of correction factors to the MOS accounting for the time of exposure (3 as used by ECHA) might indicate that MOS around 50 could be sufficiently protective, although with a high degree of uncertainties. Nevertheless scenarios relative to multiple treatment to neonates in intensive care units, prolonged medical procedures in infants and long term dialysis treatment still remains in the area of concern
Sterk Thecla, Eucomed, thecla.sterk@eucomed.or, Belgium	Executive summary	Background, 9, 40 Should "kidney" be replaced with "liver"? According to the EFSA (2014), the temporary TDI of 5 mg/Kg bw/day oral exposure is on kidney alterations as the critical effect. However, more clarification throughout document around the determination of the NOAELs which have been used to establish the t-TDI. Specifically, what species and what endpoints.	No, the t-TDI is based primarily on kidney alterations. As the TDI was derived by EFSA, this comment should be dealt with by EFSA. No need to change the text of the opinion.
Sterk Thecla, Eucomed, thecla.sterk@eucomed.or, Belgium	1. BACKGROUND		Reference refers to FDA website with information of BPA in food contact materials as indicated in the text. No need to change the text of the opinion

Jamin Marc, SABIC Innovative Plastics BV, marc.jamin@sabic-ip.com, Netherlands	Executive summary	The SCENIHR Preliminary Opinion provides a thorough summary of relevant information for evaluation of the safety of bisphenol A (BPA) in medical devices. In particular the document includes a comprehensive set of available data on exposure to BPA from medical devices, along with an appropriate recommendation for more exposure research. Overall, the conclusions of the Preliminary Opinion are overly conservative and several opportunities are available for improving the utility of the Opinion. First, the t-TDI and BMDL10 values used in the document should be refined, as previously noted in comments to EFSA. Second, the TDI for chronic/life-time exposure should be adjusted for use in evaluation of acute/short-term exposures, which is more representative of medical device applications for polycarbonate plastic. Third, the utility of the report can be extended by broader use of available polycarbonate migration data.	The SCHENIR partly disagrees with the comment, considering the evaluation too conservative. However the text has been changed in the revised opinion, to take into account the temporary TDI as derived in the recent EFSA opinion (EFSA, 2015). The newly derived TDI takes into account a refined BMDL for kidney effects as PoD, derived a HED (human equivalent dose) considering kinetic differences, based on which the assessment factor is reduced to 25 then multiplied by 6 (AF=150) to account for those effects considered as 'likely' and included in the uncertainty analysis by EFSA (2015). The SCENIHR agrees with the conclusions of EFSA based on its own evaluation, the EFSA t-TDI was used in the risk assessment of BPA in medical devices. The SCENIHR agrees with the comment regarding the exposure period. In the case Reference values derived for prolonged exposures were compared against short-term exposure for medical devices and no risk can be anticipated, there is no need to refine the evaluation. However, the major point here is that info on the different exposure scenarios are very scant, the uncertainties are considerable, and therefore it is difficult at the moment to think to a refined evaluation. Some text on the relevance of MOS and lack of concern is added to ABSTRACT, EX ECUTIVE SUMMARY and OPINION. An example is in the following: Considering that, with the exception of dialysis patients, the exposure via medical devices is generally of limited duration, whereas the MOS

			based on the uncertainty factor used for the derivation of the t-TDI by EFSA (2015), is based on long term exposure, the application of correction factors to the MOS accounting for the time of exposure (3 as used by ECHA) might indicate that MOS around 50 could be sufficiently protective, although with a high degree of uncertainties. Nevertheless scenarios relative to multiple treatment to neonates in intensive care units, prolonged medical procedures in infants and long term dialysis treatment still remains in the area of concern
Jamin Marc, SABIC Innovative Plastics, marc.jamin@sabic-ip.com, Netherlands	Executive summary	The SCENIHR Preliminary Opinion provides a thorough summary of relevant information for evaluation of the safety of bisphenol A (BPA) in medical devices. In particular the document includes a comprehensive set of available data on exposure to BPA from medical devices, along with an appropriate recommendation for more exposure research. Overall, the conclusions of the Preliminary Opinion are overly conservative and several opportunities are available for improving the utility of the Opinion. First, the t-TDI and BMDL10 values used in the document should be refined, as previously noted in comments to EFSA. Second, the TDI for chronic/life-time exposure should be adjusted for use in evaluation of acute/short-term exposures, which is more representative of medical device applications for polycarbonate plastic. Third, the utility of the report can be extended by broader use of available polycarbonate migration data. Note to the readers of our comment: Our comment was written as comprehensive consecutive text report. Our comment provided to the EFSA draft human health risk assessment also forms part of our comments to SCENIHR, as SCENIHR refers to the conclusions in the EFSA document. The EFSA online formatting restriction was 3.800 characters per comment-section. To account for the online filing format restriction of 2.500 characters in SCENIHR, our complete commenting text has been cut	See the response above.

		into smaller pieces and was then filed subsequently to the available chapters. If read altogether, they will combine back to the original scientific comment. In addition, we also file the comments and related further scientific documents as pdf under the file upload option.	
Hamelton Anne-Marie, PlasticsEurope, anne-marie.hamelton@plasticseurope.org, Belgium	1. Executive Summary	The SCENIHR Preliminary Opinion provides a thorough summary of relevant information for evaluation of the safety of bisphenol A (BPA) in medical devices. In particular the document includes a comprehensive set of available data on exposure to BPA from medical devices, along with an appropriate recommendation for more exposure research. Overall, the conclusions of the Preliminary Opinion are overly conservative and several opportunities are available for improving the utility of the Opinion. First, the t-TDI and BMDL10 values used in the document should be refined, as previously noted in comments to EFSA. Second, the TDI for chronic/life-time exposure should be adjusted for use in evaluation of acute/short-term exposures, which is more representative of medical device applications for polycarbonate plastic. Third, the utility of the report can be extended by broader use of available polycarbonate migration data. Note to the readers of our comment: Our comment was written as comprehensive consecutive text report. Our comment provided to the EFSA draft human health risk assessment also forms part of our comments to SCENIHR, as SCENIHR refers to the conclusions in the EFSA document. The EFSA online formatting restriction was 3.800 characters per comment-section. To account for the online filing format restriction of 2.500 characters in SCENIHR, our complete commenting text has been cut into smaller pieces and was then filed subsequently to the available chapters. If read altogether, they will combine back to the original scientific comment. In addition, we also file the comments and related further	See the response above.

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Fernandez Alvaro, MedPharmPlast Europe, Alvaro.fernandez@eupc.org, Belgium	Executive Summary	The SCENIHR Preliminary Opinion provides a thorough summary of relevant information for evaluation of the safety of bisphenol A (BPA) in medical devices. In particular the document includes a comprehensive set of available data on exposure to BPA from medical devices, along with an appropriate recommendation for more exposure research. Overall, the conclusions of the Preliminary Opinion are overly conservative and several opportunities are available for improving the utility of the Opinion. First, the t-TDI and BMDL10 values used in the document should be refined, as previously noted in comments to EFSA. Second, the TDI for chronic/life-time exposure should be adjusted for use in evaluation of acute/short-term exposures, which is more representative of medical device applications for polycarbonate plastic. Third, the utility of the report can be extended by broader use of available polycarbonate migration data. Note to the readers of our comment: Our comment was written as comprehensive consecutive text report. Our comment provided to the EFSA draft human health risk assessment also forms part of our comments to SCENIHR, as SCENIHR refers to the conclusions in the EFSA document. The EFSA online formatting restriction was 3.800 characters per comment-section. To account for the online filing format restriction of 2.500 characters in SCENIHR, our complete commenting text has been cut into smaller pieces and was then filed subsequently to the available chapters. If read altogether, they will combine back to the original scientific comment. In addition, we also file the comments and related further scientific documents as pdf under the file upload option.	See the response above.

Amaral Maria José, HCWH Europe, maria.jose@hcwh.org, Belgium	Executive Summary	L9 - The concept of BPA as a weak oestrogen has been challenged by several authors see for example Wozniak et al. 2005 Environmental Health Perspectives 113: 431-439.	The paper of Wozniak et al., 2005 provides a comparison between various exogenic oestrogens among which BPA. Whether BPA is a weak or strong oestrogens is not concluded in the paper. The action as a weak estrogenic compounds is not questioned by most data available. This does not mean than this has been identified as the 'critical' effect. No need to change the text of the opinion.
Jamin Marc, SABIC Innovative Plastics BV, marc.jamin@sabic-ip.com, Netherlands	3. SCIENTIFIC RATIONALE	The SCENIHR Preliminary Opinion appropriately includes sections that discuss exposure scenarios (Section 3.7), toxicokinetics (Section 3.8), and toxicity (Section 3.9). The section on exposure to BPA from medical devices (Section 3.7.2) is particularly important since the data presented in this section is used in the medical device safety assessments that follow. The exposure section appears to be comprehensive with respect to available data on medical devices and we are not aware of any missing studies or data. In contrast, the sections on toxicokinetics and toxicity are not fully comprehensive, but do not need to be since the data in these sections is not directly used in the safety assessments. Instead, the proposed t-TDI and BMDL¬10 values from EFSA's recent Draft Opinion (EFSA, 2014) are used for the assessments. In this regard, the toxicokinetics and toxicity sections are supporting overviews rather than comprehensive summaries. Since the t-TDI and BMDL¬10 values come from EFSA's Draft Opinion, it would be helpful to explicitly incorporate EFSA's Opinion, by reference, as the comprehensive source of information on toxicity and toxicokinetics. Medical device exposure data from Section 3.7.2 is used to construct and evaluate a series of six exposure scenarios in Section 3.7.3, which are evaluated in reference to EFSA's t-TDI and BMDL10 values. Given the limited amount and nature of exposure data, this overall approach is conceptually reasonable, but is overly conservative and there are several opportunities for	The main papers were in-dependently evaluated by the SCENIHR and reported in the opinion, although the two committees regularly exchanged and discussed their views. The SCENIHR therefore supports the choice of EFSA on the key studies on toxicity (Tyl et al.), and concurs with EFSA re-evaluation for the derivation of the t-TDI (EFSA 2015), following which the text has been changed accordingly. The SCENIHR has considered appropriate to refer to the thorough EFSA evaluation for the hazard assessment and characterization (common part of the two opinions-TK and toxicity part being included), and indeed the EFSA Opinion is endorsed by the SCENIHR in the SCENIHR Opinion on BPA in Medical Devices. In several locations the limited exposure time via medical devices is mentioned. The SCENIHR agrees that the info on exposure is limited and for this reason it has been stated in the Opinion that to have more data on exposure available would be highly beneficial for this risk assessment. A refinement would be possible as soon as new data on exposure will be available.

		improvement as discussed below.	
Hamelton Anne-Marie, PlasticsEurope, anne-marie.hamelton@plasticseurope.org, Belgium	3. SCIENTIFIC RATIONALE	The SCENIHR Preliminary Opinion is Thorough, but Overly Conservative and can be improved. The SCENIHR Preliminary Opinion appropriately includes sections that discuss exposure scenarios (Section 3.7), toxicokinetics (Section 3.8), and toxicity (Section 3.9). The section on exposure to BPA from medical devices (Section 3.7.2) is particularly important since the data presented in this section is used in the medical device safety assessments that follow. The exposure section appears to be comprehensive with respect to available data on medical devices and we are not aware of any missing studies or data. In contrast, the sections on toxicokinetics and toxicity are not fully comprehensive, but do not need to be since the data in these sections is not directly used in the safety assessments. Instead, the proposed t-TDI and BMDL¬10 values from EFSA's recent Draft Opinion (EFSA, 2014) are used for the assessments. In this regard, the toxicokinetics and toxicity sections are supporting overviews rather than comprehensive summaries. Since the t-TDI and BMDL¬10 values come from EFSA's Draft Opinion, it would be helpful to explicitly incorporate EFSA's Opinion, by reference, as the comprehensive source of information on toxicity and toxicokinetics. Medical device exposure data from Section 3.7.2 is used to construct and evaluate a series of six exposure scenarios in Section 3.7.3, which are evaluated in reference to EFSA's t-TDI and BMDL10 values. Given the limited amount and nature of exposure data, this overall approach is conceptually reasonable, but is overly conservative and there are several opportunities for improvement as discussed below.	The main papers were independently evaluated by the SCENIHR and reported in the opinion, although the two committees regularly exchanged and discussed their views. The SCENIHR therefore supports the choice of EFSA on the key studies on toxicity (Tyl et al.), and concurs with EFSA re-evaluation for the derivation of the t-TDI (EFSA 2015), following which the text has been changed accordingly. The SCENIHR has considered appropriate to refer to the thorough EFSA evaluation for the hazard assessment and characterization (common part of the two opinions-TK and toxicity part being included), and indeed the EFSA Opinion endorsed by the SCENIHR in the SCENIHR Opinion. In several locations the limited exposure time via medical devices is mentioned. The SCENIHR agrees that the info on exposure is limited and for this reason it has been stated in the Opinion that to have more data on exposure available would be highly beneficial for this risk assessment. A refinement would be possible as soon as new data on exposure will be available.

Fernandez Alvaro, MedPharmPlast Europe, Alvaro.fernandez@eupc.org, Belgium	3. SCIENTIFIC RATIONALE	2. The SCENIHR Preliminary Opinion is Thorough, but Overly Conservative and Can Be Improved The SCENIHR Preliminary Opinion appropriately includes sections that discuss exposure scenarios (Section 3.7), toxicokinetics (Section 3.8), and toxicity (Section 3.9). The section on exposure to BPA from medical devices (Section 3.7.2) is particularly important since the data presented in this section is used in the medical device safety assessments that follow. The exposure section appears to be comprehensive with respect to available data on medical devices and we are not aware of any missing studies or data. In contrast, the sections on toxicokinetics and toxicity are not fully comprehensive, but do not need to be since the data in these sections is not directly used in the safety assessments. Instead, the proposed t-TDI and BMDL¬10 values from EFSA's recent Draft Opinion (EFSA, 2014) are used for the assessments. In this regard, the toxicokinetics and toxicity sections are supporting overviews rather than comprehensive summaries. Since the t-TDI and BMDL¬10 values come from EFSA's Draft Opinion, it would be helpful to explicitly incorporate EFSA's Opinion, by reference, as the comprehensive source of information on toxicity and toxicokinetics. Medical device exposure data from Section 3.7.2 is used to construct and evaluate a series of six exposure scenarios in Section 3.7.3, which are evaluated in reference to EFSA's t-TDI and BMDL10 values. Given the limited amount and nature of exposure data, this overall approach is conceptually reasonable, but is overly conservative and there are several opportunities for improvement as discussed below.	See the response above.

Moussa Miranda, AESGP - Association of the European Self-Medication Industry, m.moussa@aesgp.eu, Belgium	3.1. Introduction	Lines 32-33: Most manufacturers have discontinued use of bisDMA as an intentional ingredient. This seems to be acknowledged in the text on page 46, line 43. The quoted text suggests that use of bisDMA is a standard practice; as such, it should be revised to more accurately reflect current practice. Thus the text should re-written as follows: "some dental materials are fabricated from monomers such as bisphenol A glycidyl methacrylate (Bis-GMA, Figure 1) and very few from bisphenol A dimethacrylate (Bis-DMA, Figure 1)"	The SCENIHR agrees with this comment. Text changed. Included the wording "very few".
Stock Gregor, FIDE - European Dental Industry, g.stock@fide-online.org, Germany	3.1. Introduction	Page 20, lines 32-33 "…some dental materials are fabricated from monomers such as bisphenol A glycidyl methacrylate (Bis-GMA, Figure 1) and bisphenolA dimethacrylate (Bis-DMA, Figure 1)…" Comment: Many if not all manufacturers have discontinued use of bisDMA as an intentional ingredient. This seems to be acknowledged in text elsewhere in the document (e.g. page 46, line 43). The quoted text suggests that use of bisDMA is a standard practice; as such, it should be revised to more accurately reflect current practice.	See the response above.

Jamin Marc, SABIC Innovative Plastics BV, marc.jamin@sabic-ip.com, Netherlands	3.1. Introduction	The SCENIHR Preliminary Opinion appropriately includes sections that discuss exposure scenarios (Section 3.7), toxicokinetics (Section 3.8), and toxicity (Section 3.9). The section on exposure to BPA from medical devices (Section 3.7.2) is particularly important since the data presented in this section is used in the medical device safety assessments that follow. The exposure section appears to be comprehensive with respect to available data on medical devices and we are not aware of any missing studies or data. In contrast, the sections on toxicokinetics and toxicity are not fully comprehensive, but do not need to be since the data in these sections is not directly used in the safety assessments. Instead, the proposed t-TDI and BMDL¬10 values from EFSA's recent Draft Opinion (EFSA, 2014) are used for the assessments. In this regard, the toxicokinetics and toxicity sections are supporting overviews rather than comprehensive summaries. Since the t-TDI and BMDL¬10 values come from EFSA's Draft Opinion, it would be helpful to explicitly incorporate EFSA's Opinion, by reference, as the comprehensive source of information on toxicity and toxicokinetics. Medical device exposure data from Section 3.7.2 is used to construct and evaluate a series of six exposure scenarios in Section 3.7.3, which are evaluated in reference to EFSA's t-TDI and BMDL10 values. Given the limited amount and nature of exposure data, this overall approach is conceptually reasonable, but is overly conservative and there are several opportunities for improvement as discussed below.	The main papers were in-dependently evaluated by SCENIHR and reported in the opinion, although the two committees regularly exchanged and discussed their views. The SCENIHR therefore supports the choice of EFSA on the key studies on toxicity (Tyl et al.), and concurs with EFSA re-evaluation for the derivation of the t-TDI (EFSA 2015), following which the text has been changed accordingly. The SCENIHR has considered appropriate to refer to the thorough EFSA evaluation for the hazard assessment and characterization (common part of the two opinions-TK and toxicity part being included), and indeed the EFSA Opinion endorsed by the SCENIHR in the SCENIHR Opinion. In several locations the limited exposure time via medical devices is mentioned. The SCENIHR agrees that the info on exposure is limited and for this reason it has been stated in the Opinion that to have more data on exposure available would be highly beneficial for this risk assessment. A refinement would be possible as soon as new data on exposure will be available.
Hamelton Anne-Marie, PlasticsEurope, anne-marie.hamelton@plasticseurope.org, Belgium	3.1. Introduction	3. EFSA's Proposed t-TDI and BMDL10 Should Be Refined As discussed in our comments in response to EFSA's Draft Opinion, the approach taken by EFSA to calculate a TDI is conceptually sound. The t-TDI proposed by EFSA is derived from a three step process that involves benchmark dose (BMD) analysis to calculate a BMDL10 as a point of departure, conversion of the BMDL10 to a	The EFSA approach including the HED resulted in an improved exposure estimation compared to the previous use of the NOAEL and uncertainty factors. Following some comments during the Public Consultation, EFSA carried out a further refinement, deriving a new t-TDI (EFSA, 2015), the SCENIHR supports this approach, and the text has

		human equivalent dose (HED), and adjustment of the HED with an uncertainty factor to account for remaining uncertainties. Overall the procedure is scientifically defensible and can be a superior method to calculate a point of departure and TDI when suitable data are available. However, both the BMD and HED analyses conducted by EFSA have limitations and should be refined. The result of the limitations is that the TDI calculated by EFSA is overly conservative and not well-supported by the underlying data. Additional BMD and HED analyses are presented in our comments to EFSA, with full technical details provided in reports from two expert consultants, all of which are provided as attachments to these comments. These analyses reveal that a range of scientifically defensible TDI values is possible. In contrast to the t-TDI of 5 mg/kg-bw/day proposed by EFSA, scientifically defensible TDI values range from 57 – 854 µg/kg-bw/day. Accordingly, our recommendation to EFSA is to retain the current TDI of 50 µg/kg-bw/day with a temporary designation. The t-TDI should then be re-evaluated and finalized once the results of anticipated significant studies are available. In particular, the U.S. Food and Drug Administration is conducting a chronic toxicity study on BPA and the U.S. National Toxicology Program (NTP) is conducting human pharmacokinetic studies with both oral and dermal routes of exposure. This same recommendation is appropriate for SCENIHR's purposes. In addition, we recommend that SCENIHR retain the current NOAEL of 5 mg/kg-bw/day for now rather than use the BMDL10 value calculated in the EFSA Draft Opinion.	been changed accordingly SCHENIR partly disagrees with the comment, in which the evaluation and the TDI derivation were considered too conservative. The temporary TDI as derived in the recent EFSA opinion (EFSA, 2015) takes into account a refined BMDL for kidney effects as PoD, derived a HED (human equivalent dose) considering kinetic differences, based on which the assessment factor is reduced to 25 then multiplied by 6 (AF=150) to account for those effects considered as 'likely' and included in the uncertainty analysis by EFSA (2015). The SCENIHR agrees with the conclusions of EFSA based on its own evaluation, the EFSA t-TDI was used in the risk assessment of BPA in medical devices. The SCENIHR disagrees with the comment, in which the TDI derivation is considered too conservative. Indeed, some uncertainties were still present on BPA- induced effect other than the one on the liver and the kidney, so that the previous TDI (EFSA, 2006) was no more adequate.

Belgium	3.1. Introduction	continued: 3. EFSA's Proposed t-TDI and BMDL10 Should Be Refined As discussed in our comments in response to EFSA's Draft Opinion, the approach taken by EFSA to calculate a TDI is conceptually sound. The t-TDI proposed by EFSA is derived from a three step process that involves benchmark dose (BMD) analysis to calculate a BMDL10 as a point of departure, conversion of the BMDL10 to a human equivalent dose (HED), and adjustment of the HED with an uncertainty factor to account for remaining uncertainties. Overall the procedure is scientifically defensible and can be a superior method to calculate a point of departure and TDI when suitable data are available. However, both the BMD and HED analyses conducted by EFSA have limitations and should be refined. The result of the limitations is that the TDI calculated by EFSA is overly conservative and not well-supported by the underlying data. Additional BMD and HED analyses are presented in our comments to EFSA, with full technical details provided in reports from two expert consultants, all of which are provided as attachments to these comments. These analyses reveal that a range of scientifically defensible TDI values is possible. In contrast to the t-TDI of 5 mg/kg-bw/day proposed by EFSA, scientifically defensible TDI values range from 57 – 854 µg/kg-bw/day. Accordingly, our recommendation to EFSA is to retain the current TDI of 50 µg/kg-bw/day with a temporary designation. The t-TDI should then be re-evaluated and finalized once the results of anticipated significant studies are available. In particular, the U.S. Food and Drug Administration is conducting a chronic toxicity study on BPA and the U.S. National Toxicology Program (NTP) is conducting human pharmacokinetic studies with both oral and dermal routes of exposure. This same	The SCHENIR disagrees with the comment, in which the TDI derivation is considered too conservative. Indeed, some uncertainties were still present on BPA- induced effect other than the one on the liver and the kidney, so that the previous TDI (EFSA, 2006) was no more adequate. The EFSA approach including the HED resulted in an improved exposure estimation compared to the previous use of the NOAEL and uncertainty factors. By the way, following some comments during the Public Consultation round, EFSA carried out a further refinement, deriving a new t-TDI, SCENIHR supports this approach, and the text has been changed accordingly. The SCHENIR partly disagrees with the comment, in which the evaluation and the TDI derivation were considered too conservative. The temporary TDI as derived in the recent EFSA opinion (EFSA, 2015) takes into account a refined BMDL for kidney effects as PoD, derived a HED (human equivalent dose) considering kinetic differences, based on which the assessment factor is reduced to 25 then multiplied by 6 (AF=150) to account for those effects considered as 'likely' and included in the uncertainty analysis by EFSA (2015). The SCENIHR agrees with the conclusions of EFSA based on its own evaluation, the EFSA t-TDI was used in the risk assessment of BPA in medical devices.

		recommendation is appropriate for SCENIHR's purposes. In addition, we recommend that SCENIHR retain the current NOAEL of 5 mg/kg-bw/day for now rather than use the BMDL10 value calculated in the EFSA Draft Opinion	
Amaral Maria José, HCWH Europe, maria.jose@hcwh.org, Belgium	3.10. Epidemiological studies	L50-51 The number of studies considered in the opinion is disappointing. A recent study found 91 peer-reviewed studies linking BPA to human health, 53 published during 2012 so in time to be considered in the opinion see Rochester (2013) Bisphenol A and human health: a review of the literature. Reproductive Toxicology 42: 132-155. The authors of the opinion seem overall more concerned in pointing each and every limitation in the research papers that document effects on human health of BPA exposure than of having a precautionary approach taking in account the consistency and overwhelming amount of evidence provided by many of those studies. The difficulties associated with performing epidemiological studies should not prevent that the trends observed in many studies are valid and that the precautionary principle is put in place. L7-8 Although the three studies have limitations they show consistent results in different populations and strong dose-response effects. L24 Taking in consideration the difficulty of performing human studies, animal studies can provide helpful insights. For both rodents and primates there is ample evidence that prenatal exposure to BPA can cause disruption of the mammary tissue and increased susceptibility to chemical carcinogens. L50-51 Several studies have looked into neurobehavioral effects during gestation. On the whole, the studies strongly suggest that BPA is associated with neurobehavioral problems in children. L3-L12 Many scientific studies have been carried on the	When so many studies are available not all need to be referred to, especially when they are not conclusive. Please not that Reviews are not usually cited, the SCENIHR prefers to cite papers publishing original data. To address the comment, Rochester 2013 was added to the reference list, and text added. See In the following A recent overview (Rochester 2013) did identify 91 epidemiological studies showing various associations between adverse effects in humans and environmental BPA exposure, but concluded that these studies were primarily supportive and that a causal relationship was still difficult to obtain (Rochester 2013). Page 104 L29-32 The SCENIHR is looking for scientific evidence identifying causal relationships between an exposure and an adverse effect. It also considers the strength of the evidence i.e. is a clear dose response observed. As indicated in the' methodology section' the SCENIHR uses a weight of evidence approach as indicated in the Opinion. So, the conclusions need to be science based. Regarding the precautionary approach proposed, this is a risk management tool and therefore outside the mandate of the SCENIHR.

		bases of the NHANES data, and the results of the different studies are consistent, which strengthens the association between adult BPA exposure and type 2 diabetes and coronary disease. L12-L15 The major limitation pointed to the study - spot urine sample - just implies that BPA exposure might have been in the past more reduced but also higher than the current levels. BPA exposure has been consistently associated across different population groups with different reproductive, metabolic, cardiovascular, immunological and genetic diseases. Most of these results are also supported by in vitro and in vivo animals studies, and should not be disregarded lightly. The precautionary principle clearly states than in the absence of scientific consensus that the burden of proof that it is not harmful falls on those taking action. For all the comments provided in this section please see the attached scientific paper Rochester 2013 and references there in.	
Amaral Maria José, HCWH Europe, maria.jose@hcwh.org, Belgium	3.11. Alternatives to BPA currently use	The list of current alternatives is not complete, other materials currently being used as alternatives for BPA include polymethylmetacrylate, copolyester, prolypropylene, triacetate. In the case of PVC products, several PVC free alternatives are also available in the market (see www.safermedicaldevices.org for examples of PVC free alternatives in the market and alternative materials).	The SCENIHR agrees with this comment. Indeed the examples are not exhaustive. Sofar, the toxicological information of alternative materials is limited and in general less than the information on BPA or PVC.
Jamin Marc, SABIC Innovative Plastics BV, marc.jamin@sabic-ip.com, Netherlands	3.2. Methodology	continued: 4. Use of TDI and BMDL10 Values for Chronic Toxicity Are Not Appropriate for Evaluation of Acute Exposures Most medical devices based on polycarbonate plastic are used in applications with short contact times where any exposure to BPA would essentially be acute in nature. In contrast, the SCENIHR Preliminary Opinion evaluated all types of medical devices in reference to t-TDI and BMDL10 values from EFSA that are applicable to	In several locations the limited exposure time via medical devices is already mentioned. In the case where Reference values derived for prolonged exposures were compared against short-term exposure for Med Dev and no risk can be anticipated, there is no need to refine the evaluation. However, the major point here is that info on the different exposure scenarios are very scant, the

		chronic/life-time exposures. Specifically, the t-TDI and BMDL10 values are based on kidney weight increases, as the most sensitive parameter, that occur only in long-term studies with very high doses. It's highly unlikely that increased kidney weight would occur with acute/short-term exposures at doses that are orders of magnitude lower. As noted in the Preliminary Opinion, BPA has low acute toxicity: "These data indicate that BPA is of low acute toxicity by all routes of exposure relevant to human health (EC, 2003, 2008, 2010a,b)." While a chronic/life-time TDI is appropriate for EFSA's evaluation of food safety, it is overly conservative for evaluation of medical devices with acute/short-term exposures. This is not merely an arcane technical issue since over-estimation of potential risks could have significant real-life consequences. For example, as noted by SCENIHR, "the survival of specifically these prematurely born infants often depends on the availability of the same medical devices which result in a relative high BPA exposure due to treatment." It is of significant practical importance that potential risks are accurately characterized to avoid adverse impacts on life-saving medical treatments. A more appropriate approach for medical devices could be to derive a TDI for acute/short-term exposures in addition to the chronic/life-time TDI. A more practical approach would be to adjust the TDI for chronic/life-time exposure to account for the inherently lower risk associated with acute/short-term exposures. This approach would build on the TDI established by EFSA, which is based on reliable data from multi-generation studies, by applying a series of adjustment factors.	uncertainties are considerable, and therefore it is difficult at the moment to think to a refined evaluation. Some text on the relevance of MOS and lack of concern is added to ABSTRACT, EX ECUTIVE SUMMARY and OPINION. An example is in the following: Considering that, with the exception of dialysis patients, the exposure via medical devices is generally of limited duration, whereas the MOS based on the uncertainty factor used for the derivation of the t-TDI by EFSA (2015), is based on long term exposure, the application of correction factors to the MOS accounting for the time of exposure (3 as used by ECHA) might indicate that MOS around 50 could be sufficiently protective, although with a high degree of uncertainties. Nevertheless scenarios relative to multiple treatment to neonates in intensive care units, prolonged medical procedures in infants and long term dialysis treatment still remains in the area of concern
Hamelton Anne-Marie, Plasticseurope, anne-marie.hamelton@plasticseurope.org, Belgium	3.2. Methodology	4. Use of TDI and BMDL10 Values for Chronic Toxicity Are Not Appropriate for Evaluation of Acute Exposures Most medical devices based on polycarbonate plastic are	The SCENIHR agrees with the comment regarding the exposure period. In the case where Reference values derived for

		used in applications with short contact times where any exposure to BPA would essentially be acute in nature. In contrast, the SCENIHR Preliminary Opinion evaluated all types of medical devices in reference to t-TDI and BMDL10 values from EFSA that are applicable to chronic/life-time exposures. Specifically, the t-TDI and BMDL10 values are based on kidney weight increases, as the most sensitive parameter, that occur only in long-term studies with very high doses. It's highly unlikely that increased kidney weight would occur with acute/short-term exposures at doses that are orders of magnitude lower. As noted in the Preliminary Opinion, BPA has low acute toxicity: "These data indicate that BPA is of low acute toxicity by all routes of exposure relevant to human health (EC, 2003, 2008, 2010a,b)." While a chronic/life-time TDI is appropriate for EFSA's evaluation of food safety, it is overly conservative for evaluation of medical devices with acute/short-term exposures. This is not merely an arcane technical issue since over-estimation of potential risks could have significant real-life consequences. For example, as noted by SCENIHR, "the survival of specifically these prematurely born infants often depends on the availability of the same medical devices which result in a relative high BPA exposure due to treatment." It is of significant practical importance that potential risks are accurately characterized to avoid adverse impacts on life-saving medical treatments. A more appropriate approach for medical devices could be to derive a TDI for acute/short-term exposures in addition to the chronic/life-time TDI. A more practical approach would be to adjust the TDI for chronic/life-time exposure to account for the inherently lower risk associated with acute/short-term exposures. This approach would build on the TDI established by EFSA, which is based on reliable data from multi-generation studies, by applying a series of adjustment factors.	prolonged exposures were compared against short-term exposure for Med Dev and no risk can be anticipated, there is no need to refine the evaluation. However, the major point here is that info on the different exposure scenarios are very scant, the uncertainties are considerable, and therefore it is difficult at the moment to think to a refined evaluation. Some text on the relevance of MOS and lack of concern is added to ABSTRACT, EX ECUTIVE SUMMARY and OPINION. An example is in the following: Considering that, with the exception of dialysis patients, the exposure via medical devices is generally of limited duration, whereas the MOS based on the uncertainty factor used for the derivation of the t-TDI by EFSA (2015), is based on long term exposure, the application of correction factors to the MOS accounting for the time of exposure (3 as used by ECHA) might indicate that MOS around 50 could be sufficiently protective, although with a high degree of uncertainties. Nevertheless scenarios relative to multiple treatment to neonates in intensive care units, prolonged medical procedures in infants and long term dialysis treatment still remains in the area of concern

Fernandez de Celis Alvaro, MedPharmPlast Europe, Alvaro.fernandez@eupc.org, Belgium	3.2. Methodology	continued: 4. Use of TDI and BMDL10 Values for Chronic Toxicity Are Not Appropriate for Evaluation of Acute Exposures Most medical devices based on polycarbonate plastic are used in applications with short contact times where any exposure to BPA would essentially be acute in nature. In contrast, the SCENIHR Preliminary Opinion evaluated all types of medical devices in reference to t-TDI and BMDL10 values from EFSA that are applicable to chronic/life-time exposures. Specifically, the t-TDI and BMDL10 values are based on kidney weight increases, as the most sensitive parameter, that occur only in long-term studies with very high doses. It's highly unlikely that increased kidney weight would occur with acute/short-term exposures at doses that are orders of magnitude lower. As noted in the Preliminary Opinion, BPA has low acute toxicity: "These data indicate that BPA is of low acute toxicity by all routes of exposure relevant to human health (EC, 2003, 2008, 2010a,b)." While a chronic/life-time TDI is appropriate for EFSA's evaluation of food safety, it is overly conservative for evaluation of medical devices with acute/short-term exposures. This is not merely an arcane technical issue since over-estimation of potential risks could have significant real-life consequences. For example, as noted by SCENIHR, "the survival of specifically these prematurely born infants often depends on the availability of the same medical devices which result in a relative high BPA exposure due to treatment." It is of significant practical importance that potential risks are accurately characterized to avoid adverse impacts on life-saving medical treatments. A more appropriate approach for medical devices could be to derive a TDI for acute/short-term exposures in addition to the chronic/life-time TDI. A more practical approach would be to adjust the TDI for chronic/life-time exposure to account for the inherently	See the response above.

		lower risk associated with acute/short-term exposures. This approach would build on the TDI established by EFSA, which is based on reliable data from multi-generation studies, by applying a series of adjustment factors.	
Amaral Maria José, HCWH Europe, maria.jose@hcwh.org, Belgium	3.2. Methodology	L31-33 How was SCENIHR able to assess clinical benefit of the medical devices in consideration? Clinical benefit is evaluated during the authorisation process for a specific product. It should not be taken lightly by SCENIHR, which is only a scientific consultation group.	The SCENIHR did not take the benefit lightly. In the Opinion the benefit is clearly mentioned (page 117 L28-33, Page 118 L20-24) even if these are to be considered by risk managers.
Jamin Marc, SABIC Innovative Plastics BV, marc.jamin@sabic-ip.com, Netherlands	3.3. Chemistry of BPA	continued: One way this could be done is by applying the well-established concept of time extrapolation, which is used in regulatory assessments globally to extrapolate data from studies with short exposure duration (e.g., subacute or subchronic duration) to longer term exposure scenarios. In the current situation, extrapolation would be done in reverse order from a TDI based on long-term studies to shorter term exposure scenarios. This would mean that a higher adjusted TDI would be appropriate for evaluation of acute/short-term exposures to BPA since EFSA's TDI is based on high-quality data from long-term multi-generation studies. As a specific example under REACH, extrapolation from subacute to chronic is done by using a factor of 6. Following this logic it would be sensible to use a factor of at least 10 to derive a suitable TDI for short-term BPA exposure and an even higher factor for acute BPA exposures. We recommend that the chronic/life-time TDI for BPA be adjusted upward by a factor of at least 10 for use in evaluation of medical devices based on polycarbonate plastic, in particular devices that are used only for short periods of time. Starting with the current EFSA TDI of 50 µg/kg-bw/day, a suitable TDI for short-term exposures would be in the range of 500 µg/kg-bw/day or higher. 5. Extensive Migration Data is Available to Estimate Exposure to BPA From Polycarbonate Plastic Medical	See responses above.

		Devices As noted in SCENIHR's Preliminary Opinion, only limited data are available on exposure to BPA from use of medical devices. In general, the data are of uncertain quality and it is not clear if the data are representative of medical devices on the market today. In some cases, it is not even clear what medical devices were tested, what materials were used to fabricate the medical devices, what material was the source of BPA, or the route of exposure.	
Hamelton Anne-Marie, PlasticsEurope, anne-marie.hamelton@plasticseurope.org, Belgium	3.3. Chemistry of BPA	One way this could be done is by applying the well-established concept of time extrapolation, which is used in regulatory assessments globally to extrapolate data from studies with short exposure duration (e.g., subacute or subchronic duration) to longer term exposure scenarios. In the current situation, extrapolation would be done in reverse order from a TDI based on long-term studies to shorter term exposure scenarios. This would mean that a higher adjusted TDI would be appropriate for evaluation of acute/short-term exposures to BPA since EFSA's TDI is based on high-quality data from long-term multi-generation studies. As a specific example under REACH, extrapolation from subacute to chronic is done by using a factor of 6. Following this logic it would be sensible to use a factor of at least 10 to derive a suitable TDI for short-term BPA exposure and an even higher factor for acute BPA exposures. We recommend that the chronic/life-time TDI for BPA be adjusted upward by a factor of at least 10 for use in evaluation of medical devices based on polycarbonate plastic, in particular devices that are used only for short periods of time. Starting with the current EFSA TDI of 50 µg/kg-bw/day, a suitable TDI for short-term exposures would be in the range of 500 µg/kg-bw/day or higher. 5. Extensive Migration Data is Available to Estimate Exposure to BPA From Polycarbonate Plastic Medical Devices	See responses above. Information submitted after the call for information was used, no better data were available.

		As noted in SCENIHR's Preliminary Opinion, only limited data are available on exposure to BPA from use of medical devices. In general, the data are of uncertain quality and it is not clear if the data are representative of medical devices on the market today. In some cases, it is not even clear what medical devices were tested, what materials were used to fabricate the medical devices, what material was the source of BPA, or the route of exposure.	
Fernandez de Celis Alvaro, MedPharmPlast Europe, Alvaro.fernandez@eupc.org, Belgium	3.3. Chemistry of BPA	continued: One way this could be done is by applying the well-established concept of time extrapolation, which is used in regulatory assessments globally to extrapolate data from studies with short exposure duration (e.g., subacute or subchronic duration) to longer term exposure scenarios. In the current situation, extrapolation would be done in reverse order from a TDI based on long-term studies to shorter term exposure scenarios. This would mean that a higher adjusted TDI would be appropriate for evaluation of acute/short-term exposures to BPA since EFSA's TDI is based on high-quality data from long-term multi-generation studies. As a specific example under REACH, extrapolation from subacute to chronic is done by using a factor of 6. Following this logic it would be sensible to use a factor of at least 10 to derive a suitable TDI for short-term BPA exposure and an even higher factor for acute BPA exposures. We recommend that the chronic/life-time TDI for BPA be adjusted upward by a factor of at least 10 for use in evaluation of medical devices based on polycarbonate plastic, in particular devices that are used only for short periods of time. Starting with the current EFSA TDI of 50 µg/kg-bw/day, a suitable TDI for short-term exposures would be in the range of 500 µg/kg-bw/day or higher. 5. Extensive Migration Data is Available to Estimate Exposure to BPA From Polycarbonate Plastic Medical Devices	See responses above.

		As noted in SCENIHR's Preliminary Opinion, only limited data are available on exposure to BPA from use of medical devices. In general, the data are of uncertain quality and it is not clear if the data are representative of medical devices on the market today. In some cases, it is not even clear what medical devices were tested, what materials were used to fabricate the medical devices, what material was the source of BPA, or the route of exposure.	
Jamin Marc, SABIC Innovative Plastics BV, marc.jamin@sabic-ip.com, Netherlands	3.4. Physico-Chemical Properties	continued: For example, some of the hemodialysis tubes tested by Haishima (2001) were made with polycarbonate casings and polysulfone hollow fibers, both of which could be a source of the BPA measured when the tubes were tested under simulated use conditions. As another example, a study reporting exposure to BPA of neonates in intensive care units (Calafat, 2009) did not report information on the source of BPA (i.e., devices or materials) or the route of exposure (i.e., oral or parenteral). Conclusions regarding potential risks associated with these medical devices or scenarios are of limited utility since the specific source of the exposure and potential risk is not identified. Lacking information on the route of exposure, as in the Calafat (2009) study, even the existence and degree of the potential risk is not well characterized. In both of these cases, as well as for medical devices in general, potentially more useful information could be generated by focusing on materials rather than complete devices or intensive care units In light of the limited exposure data, SCENIHR has appropriately noted that more and better exposure information is needed. However, even without more data on the source and release of BPA from medical devices in actual use conditions, SCENIHR could make more use of extensive migration data that is available for polycarbonate plastic. Although polycarbonate migration data has most commonly been generated for assessment of food-contact products, polycarbonate plastic used for	The SCENIHR agrees with this comment. However, other data were not available. That is why the SCENIHR has clearly stated that the availability of better exposure data could lead to a refinement of this risk assessment. When data on medical devices are available the SCENIHR prefers to use these data, also because the matrix food versus tissue/blood is quite different and migration is not easily comparable.

		food-contact products is chemically the same as polycarbonate used for medical devices. Accordingly, migration data generated for evaluation of food-contact products could be applied as well to evaluation of medical devices.	
Jamin Marc, SABIC Innovative Plastics BV, marc.jamin@sabic-ip.com, Netherlands	3.4. Physico-Chemical Properties	continued: For example, some of the hemodialysis tubes tested by Haishima (2001) were made with polycarbonate casings and polysulfone hollow fibers, both of which could be a source of the BPA measured when the tubes were tested under simulated use conditions. As another example, a study reporting exposure to BPA of neonates in intensive care units (Calafat, 2009) did not report information on the source of BPA (i.e., devices or materials) or the route of exposure (i.e., oral or parenteral). Conclusions regarding potential risks associated with these medical devices or scenarios are of limited utility since the specific source of the exposure and potential risk is not identified. Lacking information on the route of exposure, as in the Calafat (2009) study, even the existence and degree of the potential risk is not well characterized. In both of these cases, as well as for medical devices in general, potentially more useful information could be generated by focusing on materials rather than complete devices or intensive care units. In light of the limited exposure data, SCENIHR has appropriately noted that more and better exposure information is needed. However, even without more data on the source and release of BPA from medical devices in actual use conditions, SCENIHR could make more use of extensive migration data that is available for polycarbonate plastic(1). Although polycarbonate migration data has most commonly been generated for assessment of food-contact products, polycarbonate plastic used for food-contact products is chemically the same as polycarbonate used for medical devices. Accordingly, migration data generated for evaluation of food-contact products could be applied as well to	See the response above. The reference specifically deals with BPA release from baby bottles and food containers into food. Generally it shows that the release is below the regulatory limit in the various food simulants. Text was added to include this information at the end of section 3.7.1.2 at page 40 L11-16.

		evaluation of medical devices. (1) One source of polycarbonate migration data is the recent Draft Opinion from EFSA, which is the source of the TDI and BMDL10 values used in SCENIHR's Preliminary Opinion. Another comprehensive source is a recent review article from researchers at the Joint Research Centre of the European Commission: Hoekstra, E. J. and Simoneau, C. (2013) Release of bisphenol A from polycarbonate – A review. Critical Reviews in Food Science and Nutrition. 53:386-402.	
Hamelton Anne-Marie, PlasticsEurope, anne-marie.hamelton@plasticseurope.org, Belgium	3.4. Physico-Chemical Properties	For example, some of the hemodialysis tubes tested by Haishima (2001) were made with polycarbonate casings and polysulfone hollow fibers, both of which could be a source of the BPA measured when the tubes were tested under simulated use conditions. As another example, a study reporting exposure to BPA of neonates in intensive care units (Calafat, 2009) did not report information on the source of BPA (i.e., devices or materials) or the route of exposure (i.e., oral or parenteral). Conclusions regarding potential risks associated with these medical devices or scenarios are of limited utility since the specific source of the exposure and potential risk is not identified. Lacking information on the route of exposure, as in the Calafat (2009) study, even the existence and degree of the potential risk is not well characterized. In both of these cases, as well as for medical devices in general, potentially more useful information could be generated by focusing on materials rather than complete devices or intensive care units. In light of the limited exposure data, SCENIHR has appropriately noted that more and better exposure information is needed. However, even without more data on the source and release of BPA from medical devices in actual use conditions, SCENIHR could make more use of extensive migration data that is available for polycarbonate plastic. Although polycarbonate migration data has most commonly been generated for assessment of food-contact products, polycarbonate plastic used for food-contact products is chemically the same as	See the response above.

		polycarbonate used for medical devices. Accordingly, migration data generated for evaluation of food-contact products could be applied as well to evaluation of medical devices. One source of polycarbonate migration data is the recent Draft Opinion from EFSA, which is the source of the TDI and BMDL10 values used in SCENIHR's Preliminary Opinion. Another comprehensive source is a recent review article from researchers at the Joint Research Centre of the European Commission: Hoekstra, E. J. and Simoneau, C. (2013) Release of bisphenol A from polycarbonate – A review. Critical Reviews in Food Science and Nutrition. 53:386-402.	
Fernandez de Celis Alvaro, MedPharmPlast Europe, Alvaro.fernandez@eupc.org, Belgium	3.4. Physico-Chemical Properties	continued: For example, some of the hemodialysis tubes tested by Haishima (2001) were made with polycarbonate casings and polysulfone hollow fibers, both of which could be a source of the BPA measured when the tubes were tested under simulated use conditions. As another example, a study reporting exposure to BPA of neonates in intensive care units (Calafat, 2009) did not report information on the source of BPA (i.e., devices or materials) or the route of exposure (i.e., oral or parenteral). Conclusions regarding potential risks associated with these medical devices or scenarios are of limited utility since the specific source of the exposure and potential risk is not identified. Lacking information on the route of exposure, as in the Calafat (2009) study, even the existence and degree of the potential risk is not well characterized. In both of these cases, as well as for medical devices in general, potentially more useful information could be generated by focusing on materials rather than complete devices or intensive care units. In light of the limited exposure data, SCENIHR has appropriately noted that more and better exposure information is needed. However, even without more data on the source and release of BPA from medical devices in actual use conditions, SCENIHR could make more use of extensive migration data that is available for polycarbonate plastic. Although polycarbonate migration	See the response above.

		data has most commonly been generated for assessment of food-contact products, polycarbonate plastic used for food-contact products is chemically the same as polycarbonate used for medical devices. Accordingly, migration data generated for evaluation of food-contact products could be applied as well to evaluation of medical devices.	
Da Cortà Giuseppe, EUROM 1, giuseppe.dacorta@certottica.it, Belgium	3.5. Overview of existing assessments on BPA	Possible exposure/administration[1] -Dietary exposure was indeed estimated to contribute for more than 90% to the overall BPA-exposure for non-occupationally exposed individuals and - Exposure through dust ingestion, dental surgery and dermal absorption from thermal paper accounted for less than 5%. - Skin absorption. As a worst-case a systemic bioavailability equal to 30 % of the applied dermal dose can be used for risk assessment purposes. - Subcutaneous exposure/administration - Intravenous administration -Inhalation [1] EFSA Journal DRAFT Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs – Part: exposure assessment	The possible exposure scenarios were not included here as for medical devices it is described in the Opinion itself.
Jamin Marc, SABIC Innovative Plastics BV, marc.jamin@sabic-ip.com, Netherlands	3.5. Overview of existing assessments on BPA	continued: An example of how this might be done is already available in Section 3.7.3(iii) of SCENIHR's Preliminary Opinion, which briefly describes the evaluation of implanted devices made from polycarbonate. The first calculation in this section is based on data taken from the EFSA Draft Opinion on migration of BPA from polycarbonate baby bottles into food simulants. The same calculation could be scaled for larger or smaller medical devices as well as for contact times shorter than a full day. At least for screening purposes, calculations of this type could be useful to initially assess whether any potential risk is present for different types of polycarbonate medical	Indeed for the first exposure scenario data from EFSA were used. As for other scenarios data on medical devices themselves were available (although limited), the data of the EFSA estimations for polycarbonate tableware were not used by scaling up this calculation. Indeed, when data on medical devices are available the SCENIHR prefers to use these data, also because the matrix food versus tissue/blood is quite different and migration is not easily comparable. No need to change the text of the opinion.

		devices and whether additional, more detailed evaluations are appropriate. We encourage SCENIHR to evaluate further use of the available polycarbonate migration data to assess the safety of polycarbonate in a broader range of medical devices.	
Hamelton Anne-Marie, PlasticsEurope, anne-marie.hamelton@plasticseurope.org, Belgium	3.5. Overview of existing assessments on BPA	An example of how this might be done is already available in Section 3.7.3(iii) of SCENIHR's Preliminary Opinion, which briefly describes the evaluation of implanted devices made from polycarbonate. The first calculation in this section is based on data taken from the EFSA Draft Opinion on migration of BPA from polycarbonate baby bottles into food simulants. The same calculation could be scaled for larger or smaller medical devices as well as for contact times shorter than a full day. At least for screening purposes, calculations of this type could be useful to initially assess whether any potential risk is present for different types of polycarbonate medical devices and whether additional, more detailed evaluations are appropriate. We encourage SCENIHR to evaluate further use of the available polycarbonate migration data to assess the safety of polycarbonate in a broader range of medical devices.	See the response above.
Fernandez de Celis Alvaro, MedPharmPlast Europe, Alvaro.fernandez@eupc.org, Belgium	3.5. Overview of existing assessments on BPA	continued: An example of how this might be done is already available in Section 3.7.3(iii) of SCENIHR's Preliminary Opinion, which briefly describes the evaluation of implanted devices made from polycarbonate. The first calculation in this section is based on data taken from the EFSA Draft Opinion on migration of BPA from polycarbonate baby bottles into food simulants. The same calculation could be scaled for larger or smaller medical devices as well as for contact times shorter than a full day. At least for screening purposes, calculations of this type could be useful to initially assess whether any potential risk is present for different types of polycarbonate medical devices and whether additional, more detailed evaluations are appropriate. We encourage SCENIHR to evaluate	See response above.

		further use of the available polycarbonate migration data to assess the safety of polycarbonate in a broader range of medical devices.	
Jamin Marc, SABIC Innovative Plastics BV, marc.jamin@sabic-ip.com, Netherlands	3.5.1. Existing assessments	continued: PC/BPA Comments on EFSA's Draft Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs March 12, 2014 1. Executive Summary Overall, EFSA's Draft Opinion is comprehensive, transparent and relies on a sound Weight-of-Evidence approach. The hazard identification process is thorough and well documented; it systematically applies clear study quality criteria to all relevant studies. In particular, the approach taken by EFSA to deal with claimed low-dose effects and non-monotonic dose-response curves is data-driven, scientifically sound and consistent with the Weight-of-Evidence approach used throughout the Draft Opinion. The hazard characterization process is also scientifically sound, but its implementation can be improved in both the benchmark dose and human equivalent dose analyses. In light of the uncertainties associated with both of these analyses, the range of benchmark doses and human equivalent doses that can be calculated, and the upcoming data from ongoing studies, it is most appropriate for EFSA to leave the current TDI of 50mg/kg-bw/day unchanged at this time. It is appropriate for the TDI to be designated as temporary and EFSA should promptly re-evaluate and finalize the TDI once the results of anticipated significant studies are available.	The SCENIHR thanks for the positive comment, but partly disagrees with the statement that the evaluation (and TDI derivation) are considered too conservative. However the text has been changed in the revised opinion, to take into account the temporary TDI as derived in the recent EFSA opinion (EFSA, 2015), has been used by the SCENIHR and therefore the text has been changed accordingly throughout the document. The newly derived TDI takes into account a refined BMDL for kidney effects as PoD, derived a HED (human equivalent dose) considering kinetic differences, based on which the assessment factor is reduced to 25 then multiplied by 6 (AF=150) to account for those effects considered as 'likely' and included in the uncertainty analysis by EFSA (2015). The SCENIHR concurs with the conclusions of EFSA based on its own evaluation, the EFSA t-TDI was used in the risk assessment of BPA in medical devices.

Hamelton Anne-Marie, PlasticsEurope, anne-marie.hamelton@plasticseurope.org, Belgium	3.5.1. Existing assessments	PC/BPA Comments on EFSA's Draft Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs March 12, 2014 1. Executive Summary Overall, EFSA's Draft Opinion is comprehensive, transparent and relies on a sound Weight-of-Evidence approach. The hazard identification process is thorough and well documented; it systematically applies clear study quality criteria to all relevant studies. In particular, the approach taken by EFSA to deal with claimed low-dose effects and non-monotonic dose-response curves is data-driven, scientifically sound and consistent with the Weight-of-Evidence approach used throughout the Draft Opinion. The hazard characterization process is also scientifically sound, but its implementation can be improved in both the benchmark dose and human equivalent dose analyses. In light of the uncertainties associated with both of these analyses, the range of benchmark doses and human equivalent doses that can be calculated, and the upcoming data from ongoing studies, it is most appropriate for EFSA to leave the current TDI of 50mg/kg-bw/day unchanged at this time. It is appropriate for the TDI to be designated as temporary and EFSA should promptly re-evaluate and finalize the TDI once the results of anticipated significant studies are available	See the response above.
Fernandez de Celis Alvaro, MedPharmPlast Europe, Alvaro.fernandez@eupc.org, Belgium	3.5.1. Existing assessments	continued: PC/BPA Comments on EFSA's Draft Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs March 12, 2014 1. Executive Summary Overall, EFSA's Draft Opinion is comprehensive, transparent and relies on a sound Weight-of-Evidence approach. The hazard identification process is thorough and well documented; it systematically applies clear study quality criteria to all	See the response above.

		relevant studies. In particular, the approach taken by EFSA to deal with claimed low-dose effects and non-monotonic dose-response curves is data-driven, scientifically sound and consistent with the Weight-of-Evidence approach used throughout the Draft Opinion. The hazard characterization process is also scientifically sound, but its implementation can be improved in both the benchmark dose and human equivalent dose analyses. In light of the uncertainties associated with both of these analyses, the range of benchmark doses and human equivalent doses that can be calculated, and the upcoming data from ongoing studies, it is most appropriate for EFSA to leave the current TDI of 50mg/kg-bw/day unchanged at this time. It is appropriate for the TDI to be designated as temporary and EFSA should promptly re-evaluate and finalize the TDI once the results of anticipated significant studies are available.	
Jamin Marc, SABIC Innovative Plastics BV, marc.jamin@sabic-ip.com, Netherlands	3.5.2. Controversial issues	continued: 2. EFSA's Draft Scientific Opinion is Comprehensive, Transparent and Relies on a Sound Weight-of-Evidence Approach a. The Hazard Identification Process is Thorough and Well Documented. A complete evaluation of the potential risks of BPA to public health requires detailed knowledge of several broad areas of research: Toxicology; Toxicokinetics; and Exposure. The Draft Opinion appropriately includes extensive sections on each of these key areas and, as is evident from the risk assessment report and the preceding exposure report, BPA is one of the best studied of all substances. The process used to identify and select relevant studies (Section 2 and Appendix 1) is well-defined and resulted in a comprehensive dossier with little	This comment refers to EFSA Opinion rather than to the SCHENIR one. However, since the temporary TDI as derived in the recent EFSA opinion (EFSA, 2015), has been used by the SCENIHR is relevant as well. The newly derived TDI takes into account a refined BMDL for kidney effects as PoD, derived a HED (human equivalent dose) considering kinetic differences, based on which the assessment factor is reduced to 25 then multiplied by 6 (AF=150) to account for those effects considered as 'likely' and included in the uncertainty analysis by EFSA (2015). The SCENIHR concurs with the conclusions of EFSA based on its own evaluation. The EFSA t-TDI was used in the risk assessment of BPA in medical devices. Therefore the text has been changed accordingly

		chance of missing any significant studies. Each of the sections includes a large number of published studies, which vary substantially in size, scope, quality and relevance to human health. Many types of toxicity studies are included in the report, ranging from in vitro studies, to small-scale in vivo studies with limited scope, to large-scale multi-generational studies with broad scope. Likewise, the endpoints and findings reported cover a wide range and include positive and negative findings for many endpoints. To systematically evaluate the large number of studies and address inconsistencies, EFSA applied a sound Weight-of-Evidence (WoE) approach, as described in Section 2 and Appendix 1, to reliably identify hazards that are well supported by scientific evidence. With a large number of studies with inconsistent findings, a critical part of the hazard identification process is the detailed assessment of each individual study for strengths, weaknesses and relevance for the review. EFSA's assessment was based on separate sets of quality criteria and principles for animal and human studies as documented in Appendix 1, which were consistently applied to all studies. The quality criteria for animal and human studies appropriately included sound sets of basic study design and reporting criteria. Importantly, the criteria for animal studies also addressed controversial aspects such as route of exposure and use of dose levels relevant to human exposure.	
Hamelton Anne-Marie, PlasticsEurope, anne-marie.hamelton@plasticseurope.org, Belgium	3.5.2. Controversial issues	2. EFSA's Draft Scientific Opinion is Comprehensive, Transparent and Relies on a Sound Weight-of-Evidence Approach a. The Hazard Identification Process is Thorough and Well Documented A complete evaluation of the potential risks of BPA to public health requires detailed knowledge of several broad areas of research: Toxicology; Toxicokinetics; and Exposure.	See the response above.

		The Draft Opinion appropriately includes extensive sections on each of these key areas and, as is evident from the risk assessment report and the preceding exposure report, BPA is one of the best studied of all substances. The process used to identify and select relevant studies (Section 2 and Appendix 1) is well-defined and resulted in a comprehensive dossier with little chance of missing any significant studies. Each of the sections includes a large number of published studies, which vary substantially in size, scope, quality and relevance to human health. Many types of toxicity studies are included in the report, ranging from in vitro studies, to small-scale in vivo studies with limited scope, to large-scale multi-generational studies with broad scope. Likewise, the endpoints and findings reported cover a wide range and include positive and negative findings for many endpoints. To systematically evaluate the large number of studies and address inconsistencies, EFSA applied a sound Weight-of-Evidence (WoE) approach, as described in Section 2 and Appendix 1, to reliably identify hazards that are well supported by scientific evidence. With a large number of studies with inconsistent findings, a critical part of the hazard identification process is the detailed assessment of each individual study for strengths, weaknesses and relevance for the review. EFSA's assessment was based on separate sets of quality criteria and principles for animal and human studies as documented in Appendix 1, which were consistently applied to all studies. The quality criteria for animal and human studies appropriately included sound sets of basic study design and reporting criteria. Importantly, the criteria for animal studies also addressed controversial aspects such as route of exposure and use of dose levels relevant to human exposure.	

Fernandez de Celis Alvaro, MedPharmPlast Europe, Alvaro.fernandez@eupc.org, Belgium	3.5.2. Controversial issues	continued: 2. EFSA's Draft Scientific Opinion is Comprehensive, Transparent and Relies on a Sound Weight-of-Evidence Approach a. The Hazard Identification Process is Thorough and Well Documented A complete evaluation of the potential risks of BPA to public health requires detailed knowledge of several broad areas of research: Toxicology; Toxicokinetics; and Exposure. The Draft Opinion appropriately includes extensive sections on each of these key areas and, as is evident from the risk assessment report and the preceding exposure report, BPA is one of the best studied of all substances. The process used to identify and select relevant studies (Section 2 and Appendix 1) is well-defined and resulted in a comprehensive dossier with little chance of missing any significant studies. Each of the sections includes a large number of published studies, which vary substantially in size, scope, quality and relevance to human health. Many types of toxicity studies are included in the report, ranging from in vitro studies, to small-scale in vivo studies with limited scope, to large-scale multi-generational studies with broad scope. Likewise, the endpoints and findings reported cover a wide range and include positive and negative findings for many endpoints. To systematically evaluate the large number of studies and address inconsistencies, EFSA applied a sound Weight-of-Evidence (WoE) approach, as described in Section 2 and Appendix 1, to reliably identify hazards that are well supported by scientific evidence.With a large number of studies with inconsistent findings, a critical part of the hazard identification process is the detailed assessment of each individual study for strengths, weaknesses and relevance for the review. EFSA's assessment was based on separate sets of quality criteria and principles for animal and human studies as documented in Appendix 1, which	See the response above.

		were consistently applied to all studies. The quality criteria for animal and human studies appropriately included sound sets of basic study design and reporting criteria. Importantly, the criteria for animal studies also addressed controversial aspects such as route of exposure and use of dose levels relevant to human exposure.	
Jamin Marc, SABIC Innovative Plastics BV, marc.jamin@sabic-ip.com, Netherlands	3.5.3. Conclusion	continued: Similarly, the quality criteria EFSA used for epidemiological studies clearly addressed controversial aspects related to study design and exposure measurements, in particular the significant limitations associated with cross-sectional study designs, single exposure measurements (e.g. single urine spot samples), and measurement of BPA in blood. Although epidemiological studies can demonstrate statistically significant associations between BPA and health outcomes, as EFSA rightly noted, statistical significance does not imply a causal relationship. A particular strength of the Draft Opinion is that it includes all significant studies, including studies highlighted by some as demonstrating adverse effects from BPA, all were systematically evaluated using the same quality criteria, and all were appropriately incorporated in the WoE approach. Overall, the Draft Opinion is very well documented and transparent. This is particularly important for BPA, which is both very well studied and controversial. b. Low-Dose Effects and Non-Monotonic Dose-Response Curves Are Appropriately Addressed As noted in Section 1.3 of the Draft Opinion, the reported occurrence of low-dose effects and non-monotonic dose-response curves (NMDRCs) has been a particularly controversial aspect for BPA and other endocrine active substances. Currently there is not a scientific consensus on the existence or relevance of low-dose effects and NMDRCs in spite of numerous recent scientific reports and conferences on these topics. The approach taken by EFSA to deal with these aspects is data-driven, scientifically	See response above. A statement as this being a controversial issue is clearly made in the SCENIHR Opinion (e.g. Abstract page 4 L 44 and 5 L49)

		sound and consistent with the WoE approach used throughout the Draft Opinion. In the most comprehensive studies, in particular two multi-generation studies and a large-scale subchronic study, only monotonic dose-responses were observed and no low-dose effects were reported. Each of these studies included a wide range of doses, mostly in the low-dose range, and had high statistical power, resulting in high confidence that low-dose effects and NMDRCs did not occur. In contrast, smaller-scale studies that report low-dose effects and NMDRCs often investigate only a very limited number of doses and lack a well described dose-response curve. With statistically significant effects reported at only one or two low doses and low magnitude of effect, the reported low-dose effects and NMDRCs are not well founded and may be the result of chance.	
Hamelton Anne-Marie, PlasticsEurope, anne-marie.hamelton@plasticseurope.org, Belgium	3.5.3. Conclusion	Similarly, the quality criteria EFSA used for epidemiological studies clearly addressed controversial aspects related to study design and exposure measurements, in particular the significant limitations associated with cross-sectional study designs, single exposure measurements (e.g. single urine spot samples), and measurement of BPA in blood. Although epidemiological studies can demonstrate statistically significant associations between BPA and health outcomes, as EFSA rightly noted, statistical significance does not imply a causal relationship. A particular strength of the Draft Opinion is that it includes all significant studies, including studies highlighted by some as demonstrating adverse effects from BPA, all were systematically evaluated using the same quality criteria, and all were appropriately incorporated in the WoE approach. Overall, the Draft Opinion is very well documented and transparent. This is particularly important for BPA, which is both very well studied and controversial. b. Low-Dose Effects and Non-Monotonic Dose-Response Curves Are Appropriately Addressed As noted in Section	See the response above.

		1.3 of the Draft Opinion, the reported occurrence of low-dose effects and non-monotonic dose-response curves (NMDRCs) has been a particularly controversial aspect for BPA and other endocrine active substances. Currently there is not a scientific consensus on the existence or relevance of low-dose effects and NMDRCs in spite of numerous recent scientific reports and conferences on these topics. The approach taken by EFSA to deal with these aspects is data-driven, scientifically sound and consistent with the WoE approach used throughout the Draft Opinion. In the most comprehensive studies, in particular two multi-generation studies and a large-scale subchronic study, only monotonic dose-responses were observed and no low-dose effects were reported. Each of these studies included a wide range of doses, mostly in the low-dose range, and had high statistical power, resulting in high confidence that low-dose effects and NMDRCs did not occur. In contrast, smaller-scale studies that report low-dose effects and NMDRCs often investigate only a very limited number of doses and lack a well described dose-response curve. With statistically significant effects reported at only one or two low doses and low magnitude of effect, the reported low-dose effects and NMDRCs are not well founded and may be the result of chance.	
Fernandez de Celis Alvaro, MedPharmPlast Europe, Alvaro.fernandez@eupc.org, Belgium	3.5.3. Conclusion	continued: Similarly, the quality criteria EFSA used for epidemiological studies clearly addressed controversial aspects related to study design and exposure measurements, in particular the significant limitations associated with cross-sectional study designs, single exposure measurements (e.g. single urine spot samples), and measurement of BPA in blood. Although epidemiological studies can demonstrate statistically significant associations between BPA and health outcomes, as EFSA rightly noted, statistical significance does not imply a causal relationship. A particular strength of the Draft Opinion is that it includes all significant	See the response above.

		studies, including studies highlighted by some as demonstrating adverse effects from BPA, all were systematically evaluated using the same quality criteria, and all were appropriately incorporated in the WoE approach. Overall, the Draft Opinion is very well documented and transparent. This is particularly important for BPA, which is both very well studied and controversial. b. Low-Dose Effects and Non-Monotonic Dose-Response Curves Are Appropriately Addressed As noted in Section 1.3 of the Draft Opinion, the reported occurrence of low-dose effects and non-monotonic dose-response curves (NMDRCs) has been a particularly controversial aspect for BPA and other endocrine active substances. Currently there is not a scientific consensus on the existence or relevance of low-dose effects and NMDRCs in spite of numerous recent scientific reports and conferences on these topics. The approach taken by EFSA to deal with these aspects is data-driven, scientifically sound and consistent with the WoE approach used throughout the Draft Opinion. In the most comprehensive studies, in particular two multi-generation studies and a large-scale subchronic study, only monotonic dose-responses were observed and no low-dose effects were reported. Each of these studies included a wide range of doses, mostly in the low-dose range, and had high statistical power, resulting in high confidence that low-dose effects and NMDRCs did not occur. In contrast, smaller-scale studies that report low-dose effects and NMDRCs often investigate only a very limited number of doses and lack a well described dose-response curve. With statistically significant effects reported at only one or two low doses and low magnitude of effect, the reported low-dose effects and NMDRCs are not well founded and may be the result of chance.	

Jamin Marc, SABIC Innovative Plastics BV, marc.jamin@sabic-ip.com, Netherlands	3.6. Identification of the relevant medical devices	continued: Similarly, the quality criteria EFSA used for epidemiological studies clearly addressed controversial aspects related to study design and exposure measurements, in particular the significant limitations associated with cross-sectional study designs, single exposure measurements (e.g. single urine spot samples), and measurement of BPA in blood. Although epidemiological studies can demonstrate statistically significant associations between BPA and health outcomes, as EFSA rightly noted, statistical significance does not imply a causal relationship. A particular strength of the Draft Opinion is that it includes all significant studies, including studies highlighted by some as demonstrating adverse effects from BPA, all were systematically evaluated using the same quality criteria, and all were appropriately incorporated in the WoE approach. Overall, the Draft Opinion is very well documented and transparent. This is particularly important for BPA, which is both very well studied and controversial. b. Low-Dose Effects and Non-Monotonic Dose-Response Curves Are Appropriately Addressed As noted in Section 1.3 of the Draft Opinion, the reported occurrence of low-dose effects and non-monotonic dose-response curves (NMDRCs) has been a particularly controversial aspect for BPA and other endocrine active substances. Currently there is not a scientific consensus on the existence or relevance of low-dose effects and NMDRCs in spite of numerous recent scientific reports and conferences on these topics. The approach taken by EFSA to deal with these aspects is data-driven, scientifically sound and consistent with the WoE approach used throughout the Draft Opinion. In the most comprehensive studies, in particular two multi-generation studies and a large-scale subchronic study, only monotonic dose-responses were observed and no low-dose effects were reported. Each of these studies included a wide range of	See the response above.

		doses, mostly in the low-dose range, and had high statistical power, resulting in high confidence that low-dose effects and NMDRCs did not occur. In contrast, smaller-scale studies that report low-dose effects and NMDRCs often investigate only a very limited number of doses and lack a well described dose-response curve. With statistically significant effects reported at only one or two low doses and low magnitude of effect, the reported low-dose effects and NMDRCs are not well founded and may be the result of chance.	
Hamelton Anne-Marie, PlasticsEurope, anne-marie.hamelton@plasticseurope.org, Belgium	3.6. Identification of the relevant medical devices	Accordingly, EFSA's consideration of low-dose effects and NMDRCs is scientifically sound and appropriate. Although there is not a scientific consensus on the existence or relevance of low-dose effects and NMDRCs, EFSA's data-driven approach is consistent with other government agencies worldwide that have evaluated these aspects in general (e.g., U.S. EPA draft, 2013) and specifically for BPA (e.g., U.S. FDA). 2. Dermal Absorption and Exposure Estimates Are Adequately Conservative As outlined in Section 3.1.7 of the Draft Opinion, the dermal route of exposure is a potentially important source of exposure to BPA. Although a dermal exposure toxicokinetic study in humans is not currently available, several in vitro and in vivo studies provide sufficient information to establish a conservative upper bound estimate of dermal exposure. Based on these studies, the estimate of 10% absorption is sufficiently conservative and there is no sound scientific basis for assuming a higher value. As further noted in Section 3.1.7, this value can further be considered conservative since the likelihood of metabolism in the skin prior to systemic distribution is not considered. The conservative nature of the 10% dermal absorption estimate is validated by estimates of total BPA exposure from numerous urinary biomonitoring studies around the world. These estimates indicate that total exposure to BPA from all sources is very low. As noted in Section 3.1.7, since "dietary intake assessments alone already	See the response above. Based on its own evaluation the SCENIHR uses 10-30% as possible skin penetration, although for the evaluation of risk from medical devices releasing BPA, this route seems not to be relevant.

		exceed the urinary biomonitoring estimates," there is no indication that dermal absorption could be significantly higher than estimated by EFSA. As also noted in Section 3.1.7, the U.S. National Toxicology Program (NTP) currently has a human dermal exposure pharmacokinetic study underway with results likely to be available later in 2014. Corroborating evidence from an observational study on cashiers conducted by the U.S. National Institute of Environmental Health Sciences (NIEHS) will likely also be available later in 2014. The results of both studies will provide critical information for EFSA to refine the dermal exposure estimate with high quality in vivo human data, either before the Opinion is finalized or as a subsequent follow-up, for example when the t-TDI is re-evaluated.	
Fernandez de Celis Alvaro, MedPharmPlast Europe, Alvaro.fernandez@eupc.org, Belgium	3.6. Identification of the relevant medical devices	continued: Accordingly, EFSA's consideration of low-dose effects and NMDRCs is scientifically sound and appropriate. Although there is not a scientific consensus on the existence or relevance of low-dose effects and NMDRCs, EFSA's data-driven approach is consistent with other government agencies worldwide that have evaluated these aspects in general (e.g., U.S. EPA draft, 2013) and specifically for BPA (e.g., U.S. FDA). 2. Dermal Absorption and Exposure Estimates Are Adequately Conservative As outlined in Section 3.1.7 of the Draft Opinion, the dermal route of exposure is a potentially important source of exposure to BPA. Although a dermal exposure toxicokinetic study in humans is not currently available, several in vitro and in vivo studies provide sufficient information to establish a conservative upper bound estimate of dermal exposure. Based on these studies, the estimate of 10% absorption is sufficiently conservative and there is no sound scientific basis for assuming a higher value. As further noted in Section 3.1.7, this value can further be considered conservative since the likelihood of metabolism in the skin prior to systemic distribution is not considered.	See the response above.

		The conservative nature of the 10% dermal absorption estimate is validated by estimates of total BPA exposure from numerous urinary biomonitoring studies around the world. These estimates indicate that total exposure to BPA from all sources is very low. As noted in Section 3.1.7, since "dietary intake assessments alone already exceed the urinary biomonitoring estimates," there is no indication that dermal absorption could be significantly higher than estimated by EFSA. As also noted in Section 3.1.7, the U.S. National Toxicology Program (NTP) currently has a human dermal exposure pharmacokinetic study underway with results likely to be available later in 2014. Corroborating evidence from an observational study on cashiers conducted by the U.S. National Institute of Environmental Health Sciences (NIEHS) will likely also be available later in 2014. The results of both studies will provide critical information for EFSA to refine the dermal exposure estimate with high quality in vivo human data, either before the Opinion is finalized or as a subsequent follow-up, for example when the t-TDI is re-evaluated.	
Amaral Maria José, HCWH Europe, maria.jose@hcwh.org, Belgium	3.6. Identification of the relevant medical devices	The presence of BPA in PVC medical devices is not well addressed in the opinion. On one side, the opinion is relying exclusively in information provided by the industry, that BPA is no longer used in the production of PVC by European PVC manufacturers. This information should be verified by an independent regulatory body. For example, in the case of CMR phthalates in toys, that are regulated by EU law, the Swedish chemicals regulatory agency found several products in the market that did not comply with the law. On the other side, even accepting the claim as correct for the European PVC manufacturers, this means very little on the global medical device market. The opinion neglects that both medical devices manufacturers and medical devices procurers have suppliers outside of the European market, where PVC containing BPA can still be the norm. For example, 10 million surgical interments used each year by NHS UK are manufactured in Pakistan.	The SCENIHR agrees with this comment but has no possibilities for confirmation of such a statement other than proof published in the literature or measurements in governmental reports, which were not available. Therefore the only possibility is to report the information as received, citing the source for transparency. It is, indeed, clearly stated in the Opinion that this information comes from the European PVC manufacturers. This now more clearly expressed in the Executive Summary and Opinion. P11 and p109 The SCENIHR agrees that it is indeed a global market and this is now addressed in the document (page 19, line 48). The SCENIHR agrees about the importance of this exposure scenario, and this is the reason why, experimental data on Med Dev on

		Furthermore, many of the main European manufacturers of medical devices admit they cannot enquire their manufacturers if a certain chemical has been added or not (for further information see Green Public Procurement criteria for BPA in medical devices). The issue of PVC medical devices containing BPA is of high concern, as most of these medical devices are used to provide intravenously solutions to patients, where the problem of migration of the plastic material and leaching is greatest. Finally, BPA is also used in the production of polyacrylates used in coating of medical devices, and in polyetherimide plastics like sterilisation trays and dentist devices.	the market releasing BPA is warranted. The SCENIHR thanks for the comments pointing out the possibility that polyetherimide (used in the manufacture of some medical devices) can contain BPA. However, information on this material was not available to the WG. So, it is not mentioned in the Opinion. No information was available on the use of BPA in the production of Polyacrilate used in coating.
Amaral Maria José, HCWH Europe, maria.jose@hcwh.org, Belgium	3.6. Identification of the relevant medical devices	The presence of BPA in PVC medical devices is not well addressed in the opinion. One one side, the opinion is relying exclusively in information provided by the industry, that BPA is not longer used in the production of PVC by European PVC manufacturers. This information should be verified by an independent regulatory body. For example, in the case of CMR phthalates in toys, that are regulated by EU law, the Swedish chemicals regulatory agency found several products in the market that did not comply with the law. On the other side, even accepting the claim as correct for the European PVC manufacturers, this means very little on the global medical device market. The opinion neglects that both medical devices manufacturers and medical devices procurers have suppliers outside of the European market, where PVC containing BPA can still be the norm. For example, 10 million surgical interments used each year by NHS UK are manufactured in Pakistan. Furthermore, many of the main European manufacturers of medical devices admit they cannot enquire their manufacturers if a certain chemical has been added or not (for further information see Green Public Procurement criteria for BPA in medical devices). The issue of PVC medical devices containing BPA is of high concern, as most of these medical devices are used to	See the above response.

		provide intravenously solutions to patients, where the problem of migration of the plastic material and leaching is greatest. Finally, BPA is also used in the production of polyacrylates used in coating of medical devices, and in polyetherimide plastics like sterilisation trays and dentist devices.	
Jamin Marc, SABIC Innovative Plastics BV, marc.jamin@sabic-ip.com, Netherlands	3.6.1. Medical devices	continued: 3. The Hazard Characterization Process is Sound, But Implementation Can Be Improved a. Use of Benchmark Dose Analysis and Human Equivalent Doses is Scientifically Sound Previous assessments of BPA have relied upon traditional procedures using default uncertainty factors to calculate a Tolerable Daily Intake (TDI). With this procedure, the Point of Departure (PoD) is the no-observed-adverse-effect-level (NOAEL) for a critical effect. A TDI is then directly calculated by application of an uncertainty factor to the NOAEL. The current TDI (50 mg/kg/day) was derived with a NOAEL of 5 mg/kg/day from multi-generation studies, and an uncertainty factor of 100. In the Draft Opinion, EFSA has moved to an alternative procedure to calculate the TDI that involves a three-step procedure. In the first step, benchmark dose (BMD) analysis is used to calculate a BMDL10 for use as the PoD. As noted in the Opinion of the EFSA Scientific Committee on the use of the benchmark dose approach in risk assessment (EFSA, 2009), "the BMD approach is a scientifically more advanced method to the NOAEL approach for deriving a Reference Point, since it makes extended use of available dose-response data and it provides a quantification of the uncertainties in the dose-response data." The study used in the Draft Opinion (Tyl et al., 2008) is suitable for this purpose. The second step converts the BMDL10, which is derived from laboratory animal test data, to a human equivalent dose (HED). As implemented in the Draft Opinion, this step relies upon extensive pharmacokinetic data	This comment refers to EFSA Opinion rather than to the SCHENIR one. However, since the temporary TDI as derived in the recent EFSA opinion (EFSA, 2015), has been used by the SCENIHR is relevant as well. The EFSA approach including the HED resulted in an improved exposure estimation compared to the previous use of the NOAEL and uncertainty factors. By the way, following some comments during the Public Consultation round, EFSA carried out a further refinement, deriving a new t-TDI (EFSA, 2015), The SCENIHR supports this approach. The SCHENIR partly disagrees with the comment, in which the evaluation and the TDI derivation were considered too conservative. The temporary TDI as derived in the recent EFSA opinion (EFSA, 2015) takes into account a refined BMDL for kidney effects as PoD, derived a HED (human equivalent dose) considering kinetic differences, based on which the assessment factor is reduced to 25 then multiplied by 6 (AF=150) to account for those effects considered as 'likely' and included in the uncertainty analysis by EFSA (2015). The SCENIHR concurs with the conclusions of EFSA based on its own evaluation. The EFSA t-TDI was used in the risk assessment of BPA in medical devices and therefore the text has been changed accordingly.

		generated in recent studies conducted by the U.S. FDA. Essentially this step is a data-driven approach that takes the place of an arbitrary default uncertainty factor used in the traditional procedure to calculate a TDI. In the third step, the human equivalent dose is adjusted with an uncertainty factor to account for remaining uncertainties. Overall, this procedure is scientifically defensible and, since it relies on actual data, can be a superior method to calculate a TDI. However, the reliability of the outcome is dependent on the reliability of the data used and the appropriate use of the methodology applied. As summarized in the next sections, both the BMD analysis and the HED calculation can be improved to be more consistent with the underlying data.	
Hamelton Anne-Marie, PlasticsEurope, anne-marie.hamelton@plasticseurope.org, Belgium	3.6.1. Medical devices	3. The Hazard Characterization Process is Sound, But Implementation Can Be Improved a. Use of Benchmark Dose Analysis and Human Equivalent Doses is Scientifically Sound Previous assessments of BPA have relied upon traditional procedures using default uncertainty factors to calculate a Tolerable Daily Intake (TDI). With this procedure, the Point of Departure (PoD) is the no-observed-adverse-effect-level (NOAEL) for a critical effect. A TDI is then directly calculated by application of an uncertainty factor to the NOAEL. The current TDI (50 mg/kg/day) was derived with a NOAEL of 5 mg/kg/day from multi-generation studies, and an uncertainty factor of 100. In the Draft Opinion, EFSA has moved to an alternative procedure to calculate the TDI that involves a three-step procedure. In the first step, benchmark dose (BMD) analysis is used to calculate a BMDL10 for use as the PoD. As noted in the Opinion of the EFSA Scientific Committee on the use of the benchmark dose approach in risk assessment (EFSA, 2009), "the BMD approach is a scientifically more advanced method to the NOAEL approach for deriving a	See the response above.

		Reference Point, since it makes extended use of available dose-response data and it provides a quantification of the uncertainties in the dose-response data." The study used in the Draft Opinion (Tyl et al., 2008) is suitable for this purpose. The second step converts the BMDL10, which is derived from laboratory animal test data, to a human equivalent dose (HED). As implemented in the Draft Opinion, this step relies upon extensive pharmacokinetic data generated in recent studies conducted by the U.S. FDA. Essentially this step is a data-driven approach that takes the place of an arbitrary default uncertainty factor used in the traditional procedure to calculate a TDI. In the third step, the human equivalent dose is adjusted with an uncertainty factor to account for remaining uncertainties. Overall, this procedure is scientifically defensible and, since it relies on actual data, can be a superior method to calculate a TDI. However, the reliability of the outcome is dependent on the reliability of the data used and the appropriate use of the methodology applied. As summarized in the next sections, both the BMD analysis and the HED calculation can be improved to be more consistent with the underlying data.	
Fernandez de Celis Alvaro, MedPharmPlast Europe, Alvaro.fernandez@eupc.org, Belgium	3.6.1. Medical devices	continued: 3. The Hazard Characterization Process is Sound, But Implementation Can Be Improved a. Use of Benchmark Dose Analysis and Human Equivalent Doses is Scientifically Sound Previous assessments of BPA have relied upon traditional procedures using default uncertainty factors to calculate a Tolerable Daily Intake (TDI). With this procedure, the Point of Departure (PoD) is the no-observed-adverse-effect-level (NOAEL) for a critical effect. A TDI is then directly calculated by application of an uncertainty factor to the NOAEL. The current TDI (50 mg/kg/day) was derived with a NOAEL of 5 mg/kg/day from multi-	See the response above.

		generation studies, and an uncertainty factor of 100. In the Draft Opinion, EFSA has moved to an alternative procedure to calculate the TDI that involves a three-step procedure. In the first step, benchmark dose (BMD) analysis is used to calculate a BMDL10 for use as the PoD. As noted in the Opinion of the EFSA Scientific Committee on the use of the benchmark dose approach in risk assessment (EFSA, 2009), "the BMD approach is a scientifically more advanced method to the NOAEL approach for deriving a Reference Point, since it makes extended use of available dose-response data and it provides a quantification of the uncertainties in the dose-response data." The study used in the Draft Opinion (Tyl et al., 2008) is suitable for this purpose. The second step converts the BMDL10, which is derived from laboratory animal test data, to a human equivalent dose (HED). As implemented in the Draft Opinion, this step relies upon extensive pharmacokinetic data generated in recent studies conducted by the U.S. FDA. Essentially this step is a data-driven approach that takes the place of an arbitrary default uncertainty factor used in the traditional procedure to calculate a TDI. In the third step, the human equivalent dose is adjusted with an uncertainty factor to account for remaining uncertainties. Overall, this procedure is scientifically defensible and, since it relies on actual data, can be a superior method to calculate a TDI. However, the reliability of the outcome is dependent on the reliability of the data used and the appropriate use of the methodology applied. As summarized in the next sections, both the BMD analysis and the HED calculation can be improved to be more consistent with the underlying data.	
Da Cortà Giuseppe, EUROM 1, giuseppe.dacorta@certottica.it, Belgium	3.6.2. Presence in and release of BPA from medical devices	The possible uses of BPA in the manufacturing processes of spectacle frames and sunglasses are the following: - As monomer of polycarbonate. The production of PC is the main use for BPA, but	Optical frame and sunglasses were not specifically included.

		Polycarbonate is very rarely used to manufacture frame components, only a very small portion of ready-to-wear frames are manufactured in polycarbonate. In the ophthalmic field the main use in is to manufacture eyeglass lenses. This lead to the conclusion that there are not polycarbonate parts in direct and prolonged contact with the skin. -As monomer of epoxy resins: Epoxy resins represent the second most common use for BPA and can be used in the organic coatings of metal frames. The major factor influencing the residual amount of BPA levels is the employment of incorrect operating conditions during the processing step leading to monomer release. Metal parts of Spectacle frames and sunglasses, such as hinges, are rarely in direct and prolonged contact with the skin. - PVC is the third-most widely produced plastic. BPA has been used historically to stabilise vinyl chloride monomer; in the polymerisation of PVC plastics, and as an antioxidant in plasticisers used in PVC. According to the European Council of Vinyl Manufacturers, the use of BPA for polymerisation and as a stabiliser for storage of vinyl chloride monomer was discontinued in Europe from December 2001. In the optical business PVC is used for the injection molding of nose pads for metal frames. Compounds of PVC used for that scope are certified and the formulation and production is without Bisphenol A (BPA, DPP, 4,4'- Bisphenol A, diphenilolpropan, 2,2-bis(4-hydroxiphenil)propan.	Already appropriately addressed in Opinion. The issue of other medical devices than mentioned is indirectly discussed on page 27-28 when aspects of BPA leakage of medical devices and PC pellets is discussed.

Moussa Miranda, AESGP - Association of the European Self-Medication Industry, m.moussa@aesgp.eu, Belgium	3.6.2. Presence in and release of BPA from medical devices	Page 30, Line 18: In light of the results of SCHENIR`s preliminary opinion, which indicate that exposure to BPA originating from dental products is far below current toxicity reference values, the term "concern" should be modified. This text should be re-written to reflect that BPA exposure from dental materials containing certain ingredients (e.g. polycarbonate and bisGMA) may occur at trace levels, without implying that it is a problem. Thus we propose the sentence to read "BPA exposure from some of the dental materials are occurring, especially from ….".	The concern indicated here is the general concern in the media, not the view of the SCENIHR as in the Opinion we conclude that BPA exposure via dental materials has negligible risk. Page 17 lines 1-6, and Page 116 L31-36. As this chapter deals with presence of BPA and not the risk assessment, the word 'concern' was removed. Text on page 30 changed according to comment. BPA exposure from dental materials is occurring, especially from dental sealants …
Stock Gregor, FIDE - European Dental Industry, g.stock@fide-online.org, Germany	3.6.2. Presence in and release of BPA from medical devices	Page 30, Line 18 "BPA exposure from dental products is a concern, especially from dental sealants…BPA, as such, is not a component in dental materials…" Comment: In light of the results of the assessment, which indicate that exposure to BPA originating from dental products is far below current toxicity reference values, the use of the term "concern" seems inappropriate. In addition, the emphasis on dental sealants seems outdated, as use of BPA as an intentional ingredient in this and other categories of dental products has been discontinued. This text should be re-written to reflect that BPA exposure from dental materials containing certain ingredients (e.g. polycarbonate and bisGMA) may occur at trace levels, without use of language that implies that it is a problem.	See the response above.
Sterk Thecla, Eucomed, thecla.sterk@eucomed.org , Belgium	3.6.2. Presence in and release of BPA from medical devices	3.6.2, 27, 31-35 Regarding the synthesis of polysulfone (PSU) the draft opinion is imprecise: Contrary to chapter 3.6.2 (page 27, lines 31-35) of the draft opinion, use of 1,4-dihydroxybenzene is no alternative to use of BPA in polysulfone (PSU) synthesis, in particular because the reaction would lead to polyethersulfone (PES). In addition, the known risk profile and current legal classification (e.g. mutagen cat. 2 and carcinogen cat. 2, see Regulation EC No. 1278/2008, Annex IV) of 1,4-dihydroxybenzene is not considered in SCENIHR's discussion of potential alternatives.	1,4-dihydroxybenzene as alternative for PSU synthesis has been removed The text has been modified as follows: BPA is one of the diphenols used for PSU production. Regarding BPA classification, the new classification by ECHA has been added.

		The draft opinion should be amended accordingly.	
Jamin Marc, SABIC Innovative Plastics BV, marc.jamin@sabic-ip.com, Netherlands	3.6.2. Presence in and release of BPA from medical devices	continued: b. EFSA's Benchmark Dose Analysis Should Be Refined As described in the Draft Opinion (Section 3.2.5 and Appendix 5), the PoD was determined by BMD analysis of increased kidney weight as the critical effect from a two-generation study in mice (Tyl et al., 2008). The use of this study and the specific endpoint are appropriate. Although reporting of the methodology and results as currently available does not appear to meet the minimum reporting requirements outlined in EFSA (2009), we were able to generally replicate the results using the current version of the PROAST software. Our analysis also identified several issues that should be addressed to produce a more scientifically defensible BMDL10 value. A full report from Exponent describing these analyses will be provided separately and a synopsis of the key findings is provided below. • A significant limitation in EFSA's BMD analysis is the combined modeling of the four kidney weight datasets for F0 males, F0 females, F1 males and F1 females. Separate analysis of each dataset revealed that the F1 female data is not suitable for BMD analysis because of the lack of a dose-response to analyze. Including this data in the combined modeling likely influenced the outcomes for the other three datasets. In addition, when the F1 male data were modeled using the BMDS software package, a poor fit was observed, which is likely due to the variability in the kidney weights over the dose range. The inclusion of this dataset may also be influencing the overall fit. In this case, combined analysis results in increased uncertainty, which is contrary to the purpose of combined analysis to reduce uncertainty. A more statistically appropriate analysis is to analyze the F0 and F1 males and F0 females, without the F1 female data where there is no dose-response, or to analyze	Comment to EFSA Opinion rather than to the SCHENIR one. However, since the temporary TDI as derived in the recent EFSA opinion (EFSA, 2015), has been used by the SCENIHR is relevant as well. The EFSA approach including the HED resulted in an improved exposure estimation compared to the previous use of the NOAEL and uncertainty factors. Particularly, the use of HED considering kinetics differences between mice and humans, address the issue at best. The SCENIHR supports this approach. The temporary TDI as derived in the recent EFSA opinion (EFSA, 2015) takes into account a refined BMDL for kidney effects as PoD, derived a HED (human equivalent dose) considering kinetic differences, based on which the assessment factor is reduced to 25 then multiplied by 6 (AF=150) to account for those effects considered as 'likely' and included in the uncertainty analysis by EFSA (2015). The SCENIHR concurs with the conclusions of EFSA based on its own evaluation. The EFSA t-TDI was used in the risk assessment of BPA in medical devices. Therefore the text has been changed accordingly

		the F0 male data in a separate analysis, as the F0 male data is the driver for the PoD. • The EFSA BMD analysis relied on mean and standard deviation data from the Tyl et al., 2008 publication. As noted in EFSA (2009), "For continuous data, the individual observations should ideally serve as the input for a BMD analysis." Our analysis used the individual animal data from the full study report that supports Tyl et al. (2008). The relevant data tables from the Tyl study report will be provided separately.	
Fernandez de Celis Alvaro, MedPharmPlast Europe, Alvaro.fernandez@eupc.org, Belgium	3.6.2. Presence in and release of BPA from medical devices	continued: b. EFSA's Benchmark Dose Analysis Should Be Refined As described in the Draft Opinion (Section 3.2.5 and Appendix 5), the PoD was determined by BMD analysis of increased kidney weight as the critical effect from a two-generation study in mice (Tyl et al., 2008). The use of this study and the specific endpoint are appropriate. Although reporting of the methodology and results as currently available does not appear to meet the minimum reporting requirements outlined in EFSA (2009), we were able to generally replicate the results using the current version of the PROAST software. Our analysis also identified several issues that should be addressed to produce a more scientifically defensible BMDL10 value. A full report from Exponent describing these analyses will be provided separately and a synopsis of the key findings is provided below. • A significant limitation in EFSA's BMD analysis is the combined modeling of the four kidney weight datasets for F0 males, F0 females, F1 males and F1 females. Separate analysis of each dataset revealed that the F1 female data is not suitable for BMD analysis because of	See the response above.

		the lack of a dose-response to analyze. Including this data in the combined modeling likely influenced the outcomes for the other three datasets. In addition, when the F1 male data were modeled using the BMDS software package, a poor fit was observed, which is likely due to the variability in the kidney weights over the dose range. The inclusion of this dataset may also be influencing the overall fit. In this case, combined analysis results in increased uncertainty, which is contrary to the purpose of combined analysis to reduce uncertainty. A more statistically appropriate analysis is to analyze the F0 and F1 males and F0 females, without the F1 female data where there is no dose-response, or to analyze the F0 male data in a separate analysis, as the F0 male data is the driver for the PoD. - The EFSA BMD analysis relied on mean and standard deviation data from the Tyl et al., 2008 publication. As noted in EFSA (2009), "For continuous data, the individual observations should ideally serve as the input for a BMD analysis." Our analysis used the individual animal data from the full study report that supports Tyl et al. (2008). The relevant data tables from the Tyl study report will be provided separately.	
Hamelton Anne-Marie, PlasticsEurope, anne-marie.hamelton@plasticseurope.org, Belgium	3.6.2. Presence in and release of BPA from medical devices	b. EFSA's Benchmark Dose Analysis Should Be Refined As described in the Draft Opinion (Section 3.2.5 and Appendix 5), the PoD was determined by BMD analysis of increased kidney weight as the critical effect from a two-generation study in mice (Tyl et al., 2008). The use of this study and the specific endpoint are appropriate. Although reporting of the methodology and results as currently available does not appear to meet the minimum reporting requirements outlined in EFSA (2009), we were able to generally replicate the results using the current version of the PROAST software. Our analysis also identified several issues that should be addressed to produce a more scientifically defensible BMDL10 value. A full report from Exponent describing these analyses will be	See the response above.

		provided separately and a synopsis of the key findings is provided below. - A significant limitation in EFSA's BMD analysis is the combined modeling of the four kidney weight datasets for F0 males, F0 females, F1 males and F1 females. Separate analysis of each dataset revealed that the F1 female data is not suitable for BMD analysis because of the lack of a dose-response to analyze. Including this data in the combined modeling likely influenced the outcomes for the other three datasets. In addition, when the F1 male data were modeled using the BMDS software package, a poor fit was observed, which is likely due to the variability in the kidney weights over the dose range. The inclusion of this dataset may also be influencing the overall fit. In this case, combined analysis results in increased uncertainty, which is contrary to the purpose of combined analysis to reduce uncertainty. A more statistically appropriate analysis is to analyze the F0 and F1 males and F0 females, without the F1 female data where there is no dose-response, or to analyze the F0 male data in a separate analysis, as the F0 male data is the driver for the PoD. - The EFSA BMD analysis relied on mean and standard deviation data from the Tyl et al., 2008 publication. As noted in EFSA (2009), "For continuous data, the individual observations should ideally serve as the input for a BMD analysis." Our analysis used the individual animal data from the full study report that supports Tyl et al. (2008). The relevant data tables from the Tyl study report will be provided separately.	
Moussa Miranda, AESGP - Association of the European Self-Medication Industry, m.moussa@aesgp.eu, Belgium	3.6.3. Conclusions	Page 33 lines 24-25: The sentence "in general, there was very limited information provided to assess the reliability of available [extraction] data." is an important point that should be given more prominent discussion in the document, and should be captured in the document	The sentence have been added to the Executive Summary as well as in the opinion In general, there was very limited information provided to assess the reliability of available data.

		abstract or in the exposure section starting on page 106.	
Stock Gregor, FIDE - European Dental Industry, g.stock@fide-online.org, Germany	3.6.3. Conclusions	Page 33 lines 24-25 "in general, there was very limited information provided to assess the reliability of available [extraction] data." Comment: This is a very fundamental and important point that should be given more prominent discussion elsewhere in the document. It is not captured, for example, in the document abstract or in the exposure section starting on page 106.	See the response above.
Jamin Marc, SABIC Innovative Plastics BV, marc.jamin@sabic-ip.com, Netherlands	3.6.3. Conclusions	continued: • A potentially more biologically appropriate dataset for BMD analysis is average kidney weight adjusted for body weight rather than analysis of absolute left and right kidney weights. Although both kidneys are collected and separately weighed, there is no biological reason for a different response between the left and right kidneys. In addition, kidney weights should be evaluated on a body weight adjusted basis to account for differences in the size of the animals. Our BMD analysis used total kidney weight (combined left and right) adjusted for body weight. This analysis also requires data from the full study report, which will be provided separately. • The U.S. EPA software for BMD analysis (known as BMDS) may be preferred over PROAST due to the use in PROAST of an unconstrained parameter to model the steepness of the dose-response fit. The EFSA guidance on BMD analysis (EFSA, 2009) discusses both tools and considers both PROAST and BMDS as appropriate tools to estimate BMDs. Our analysis used both PROAST and BMDS to evaluate the effect of this issue and showed more sensible BMDL10 values in comparison to the underlying biological data. For the reasons summarized above and fully described in the Exponent report, the BMDL10 values calculated by EFSA have methodological deficiencies and should not be relied upon to establish a TDI. Suitable BMDL10 values range from 23,530–35,599 mg/kg-bw/day for F0 males, which are considered to be	Comment to EFSA Opinion rather than to the SCHENIR one. However, since the temporary TDI as derived in the recent EFSA opinion (EFSA, 2015), has been used by the SCENIHR is relevant as well. The EFSA approach including the HED resulted in an improved exposure estimation compared to the previous use of the NOAEL and uncertainty factors. Particularly, the use of HED considering kinetics differences between mice and humans, address the issue at best. The SCENIHR supports this approach. The temporary TDI as derived in the recent EFSA opinion (EFSA, 2015) takes into account a refined BMDL for kidney effects as PoD, derived a HED (human equivalent dose) considering kinetic differences, based on which the assessment factor is reduced to 25 then multiplied by 6 (AF=150) to account for those effects considered as 'likely' and included in the uncertainty analysis by EFSA (2015). The SCENIHR concurs with the conclusions of EFSA based on its own evaluation. The EFSA t-TDI was used in the risk assessment of BPA in medical devices. Therefore the text has been changed accordingly

		the most appropriate PoD values. c. More Appropriate Human Equivalent Dosimetric Factors Are Available i. Unconjugated BPA HEDF EFSA calculated the HEDF for unconjugated BPA from the Doerge et al. (2011) AUC value in mice (0.1 nmol-h/L) and the Fisher et al. (2011) estimated AUC in humans (3.6 nmol-h/L). However, as documented in an accompanying report from Summit Toxicology, the AUC value in mice is significantly underestimated. From pharmacokinetic principles, AUC is related to dose and Clearance (Clearance=Dose¸AUC). Starting with the AUC values reported by EFSA (Table 2, Section 3.1.5), Clearance values for rats (168.5 L/h-kg), monkeys (292.0 L/h-kg) and humans (121.7 L/h-kg) are reasonably consistent. These values are also in good agreement with the expected allometric relationship between Clearance and body weight. In contrast the Clearance value for mice (4,380 L/h-kg) is about 20 times higher than the other species, which is not expected based on allometry.	
Fernandez de Celis Alvaro, MedPharmPlast Europe, Alvaro.fernandez@eupc.org, Belgium	3.6.3. Conclusions	continued: • A potentially more biologically appropriate dataset for BMD analysis is average kidney weight adjusted for body weight rather than analysis of absolute left and right kidney weights. Although both kidneys are collected and separately weighed, there is no biological reason for a different response between the left and right kidneys. In addition, kidney weights should be evaluated on a body weight adjusted basis to account for differences in the size of the animals. Our BMD analysis used total kidney weight (combined left and right) adjusted for body weight. This analysis also requires data from the full study report, which will be provided separately. • The U.S. EPA software for BMD analysis (known as BMDS) may be preferred over PROAST due to the use in PROAST of an unconstrained parameter to model the steepness of the dose-response fit. The EFSA guidance on BMD analysis (EFSA, 2009) discusses both tools and	See the response above.

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Hamelton Anne-Marie, PlasticsEurope, anne-marie.hamelton@plasticseurope.org, Belgium	3.6.3. Conclusions	• A potentially more biologically appropriate dataset for BMD analysis is average kidney weight adjusted for body weight rather than analysis of absolute left and right kidney weights. Although both kidneys are collected and separately weighed, there is no biological reason for a different response between the left and right kidneys. In addition, kidney weights should be evaluated on a body weight adjusted basis to account for differences in the size of the animals. Our BMD analysis used total kidney weight (combined left and right) adjusted for body weight. This analysis also requires data from the full study report, which will be provided separately. • The U.S. EPA software for BMD analysis (known as BMDS) may be preferred over PROAST due to the use in PROAST of an unconstrained parameter to model the steepness of the dose-response fit. The EFSA guidance on BMD analysis (EFSA, 2009) discusses both tools and considers both PROAST and BMDS as appropriate tools to estimate BMDs. Our analysis used both PROAST and BMDS to evaluate the effect of this issue and showed more sensible BMDL10 values in comparison to the underlying biological data. For the reasons summarized above and fully described in the Exponent report, the BMDL10 values calculated by EFSA have methodological deficiencies and should not be relied upon to establish a TDI. Suitable BMDL10 values range from 23,530–35,599 ug/kg-bw/day for F0 males, which are considered to be the most appropriate PoD values. c. More Appropriate Human Equivalent Dosimetric Factors Are Available i. Unconjugated BPA HEDF EFSA calculated the HEDF for unconjugated BPA from the Doerge et al. (2011) AUC value in mice (0.1 nmol-h/L) and the Fisher et al. (2011) estimated AUC in humans (3.6 nmol-h/L). However, as documented in an accompanying report from Summit Toxicology, the AUC value in mice is significantly underestimated.	See the response above.

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Jamin Marc, SABIC Innovative Plastics BV, marc.jamin@sabic-ip.com, Netherlands	3.7. Exposure scenarios	continued: Additional pharmacokinetic data is available to evaluate this discrepancy. In particular Taylor et al. (2011) compared the kinetics of unconjugated and conjugated BPA in monkeys and mice following oral dosing at 400 mg/kg-bw. The AUC values for mice (16.72 ng-h/mL) and monkeys (12.36 ng-h/mL) are similar and yield Clearance values that are also very similar for mice (23.9 L/h-kg) and monkeys (32.4 L/h-kg). These values cannot be directly used in EFSA's evaluation due to study design differences compared to the studies used by EFSA, but the data indicate that the mouse is not very different from the monkey. This suggests that the AUC value for unconjugated BPA from Doerge et al. (2011) is significantly underestimated. A likely reason for the underestimated AUC was stated by Doerge et al. (2011) and in the EFSA report: "Administration of BPA (100 µg/kg bw) by gavage to adult CD-1 mice (n=12) produced levels of unconjugated BPA that were below the LOD in the preponderance of samples at all time points. Levels of unconjugated BPA that were above the LOD were observed only at the earliest three time points, and only in one or two samples of the twelve determinations each time." The Doerge et al (2011) and Taylor et al. (2011) studies reported similar half-lives of 0.63 and 0.97 hours, respectively, for the initial elimination phase, but	See the response above. The studies cited here have been already considered in the preliminary opinion in the kinetic sections.

		Doerge et al. (2011) could not observe the terminal phase due to lack of data in the relevant time period. The terminal phase half-life was reported by Taylor et al. (2011) to be 33.64 hours. Levels of unconjugated BPA in Doerge et al. (2011) were below the LOD after 2 hours. As noted below, there is good allometric agreement between species for total BPA, including the Doerge et al. (2011) study, which suggests that mice are not fundamentally different. In that regard, the Doerge et al. (2011) study is fundamentally sound, but limited by the lack of data for unconjugated BPA. Supporting evidence for the validity of the allometric agreement between species, including mice, is provided by Cho et al. (2002), which examined iv administration of BPA to mice, and Doerge et al. (2012), which examined both oral and iv administration of BPA in mice.	
Fernandez de Celis Alvaro, MedPharmPlast Europe, Alvaro.fernandez@eupc.org, Belgium	3.7. Exposure scenarios	continued: Additional pharmacokinetic data is available to evaluate this discrepancy. In particular Taylor et al. (2011) compared the kinetics of unconjugated and conjugated BPA in monkeys and mice following oral dosing at 400 mg/kg-bw. The AUC values for mice (16.72 ng-h/mL) and monkeys (12.36 ng-h/mL) are similar and yield Clearance values that are also very similar for mice (23.9 L/h-kg) and monkeys (32.4 L/h-kg). These values cannot be directly used in EFSA's evaluation due to study design differences compared to the studies used by EFSA, but the data indicate that the mouse is not very different from the monkey. This suggests that the AUC value for unconjugated BPA from Doerge et al. (2011) is significantly underestimated. A likely reason for the underestimated AUC was stated by Doerge et al. (2011) and in the EFSA report: "Administration of BPA (100 µg/kg bw) by gavage to adult CD-1 mice (n=12) produced levels of unconjugated BPA that were below the LOD in the preponderance of samples at all time points. Levels of unconjugated BPA that were above the LOD were observed only at the earliest three time points, and	See the response above.

		only in one or two samples of the twelve determinations each time." The Doerge et al (2011) and Taylor et al. (2011) studies reported similar half-lives of 0.63 and 0.97 hours, respectively, for the initial elimination phase, but Doerge et al. (2011) could not observe the terminal phase due to lack of data in the relevant time period. The terminal phase half-life was reported by Taylor et al. (2011) to be 33.64 hours. Levels of unconjugated BPA in Doerge et al. (2011) were below the LOD after 2 hours. As noted below, there is good allometric agreement between species for total BPA, including the Doerge et al. (2011) study, which suggests that mice are not fundamentally different. In that regard, the Doerge et al. (2011) study is fundamentally sound, but limited by the lack of data for unconjugated BPA. Supporting evidence for the validity of the allometric agreement between species, including mice, is provided by Cho et al. (2002), which examined iv administration of BPA to mice, and Doerge et al. (2012), which examined both oral and iv administration of BPA in mice.	
Hamelton Anne-Marie, PlasticsEurope, anne-marie.hamelton@plasticseurope.org, Belgium	3.7. Exposure scenarios	Additional pharmacokinetic data is available to evaluate this discrepancy. In particular Taylor et al. (2011) compared the kinetics of unconjugated and conjugated BPA in monkeys and mice following oral dosing at 400 mg/kg-bw. The AUC values for mice (16.72 ng-h/mL) and monkeys (12.36 ng-h/mL) are similar and yield Clearance values that are also very similar for mice (23.9 L/h-kg) and monkeys (32.4 L/h-kg). These values cannot be directly used in EFSA's evaluation due to study design differences compared to the studies used by EFSA, but the data indicate that the mouse is not very different from the monkey. This suggests that the AUC value for unconjugated BPA from Doerge et al. (2011) is significantly underestimated. A likely reason for the underestimated AUC was stated by Doerge et al. (2011) and in the EFSA report: "Administration of BPA (100 µg/kg bw) by gavage to adult CD-1 mice (n=12) produced levels of unconjugated BPA that were below the	See the response above.

		LOD in the preponderance of samples at all time points. Levels of unconjugated BPA that were above the LOD were observed only at the earliest three time points, and only in one or two samples of the twelve determinations each time." The Doerge et al (2011) and Taylor et al. (2011) studies reported similar half-lives of 0.63 and 0.97 hours, respectively, for the initial elimination phase, but Doerge et al. (2011) could not observe the terminal phase due to lack of data in the relevant time period. The terminal phase half-life was reported by Taylor et al. (2011) to be 33.64 hours. Levels of unconjugated BPA in Doerge et al. (2011) were below the LOD after 2 hours. As noted below, there is good allometric agreement between species for total BPA, including the Doerge et al. (2011) study, which suggests that mice are not fundamentally different. In that regard, the Doerge et al. (2011) study is fundamentally sound, but limited by the lack of data for unconjugated BPA. Supporting evidence for the validity of the allometric agreement between species, including mice, is provided by Cho et al. (2002), which examined iv administration of BPA to mice, and Doerge et al. (2012), which examined both oral and iv administration of BPA in mice.	
Swedish Chemical Agency, Sweden	3.7.1. Knowledge on BPA exposure	Please note that the draft exposure assessment from EFSA (2013) includes other sources to BPA than food.	The SCENIHR agrees with this comment. An indication for this is presented on page 43.
Jamin Marc, SABIC Innovative Plastics BV, marc.jamin@sabic-ip.com, Netherlands	3.7.1. Knowledge on BPA exposure	continued: Given the uncertainty in the data from Doerge et al. (2011), and related limitations to calculate an AUC, a more defensible AUC for unconjugated BPA in mice can be derived from the allometric relationship noted above. That relationship provides good agreement between the Clearance values for rats, monkeys and humans, and would be expected to provide good agreement for mice. As documented in the accompanying report, the allometric equation predicts a Clearance value for unconjugated BPA in mice of 206 L/h-kg, which equates to an AUC value of approximately 2.1 nmol-h/L (for a	This comment refers to EFSA Opinion rather than to the SCHENIR one. However, since the temporary TDI as derived in the recent EFSA opinion (EFSA, 2015), has been used by the SCENIHR is relevant as well. The EFSA approach including the HED resulted in an improved exposure estimation compared to the previous use of the NOAEL and uncertainty factors. Particularly, the use of HED considering kinetics differences between mice and humans, address the issue at best.

		dose of 100 micrograms/kg-bw). The HEDF value for unconjugated BPA is then 2.1¸3.6 (the human AUC value reported in the Draft Opinion) or 0.6.	The SCENIHR supports this approach. The temporary TDI as derived in the recent EFSA opinion (EFSA, 2015) takes into account a refined BMDL for kidney effects as PoD, derived a HED (human equivalent dose) considering kinetic differences, based on which the assessment factor is reduced to 25 then multiplied by 6 (AF=150) to account for those effects considered as 'likely' and included in the uncertainty analysis by EFSA (2015). The SCENIHR concurs with the conclusions of EFSA based on its own evaluation. The EFSA t-TDI was used in the risk assessment of BPA in medical devices. Therefore the text has been changed accordingly
Fernandez de Celis Alvaro, MedPharmPlast Europe, Alvaro.fernandez@eupc.org, Belgium	3.7.1. Knowledge on BPA exposure	continued: Given the uncertainty in the data from Doerge et al. (2011), and related limitations to calculate an AUC, a more defensible AUC for unconjugated BPA in mice can be derived from the allometric relationship noted above. That relationship provides good agreement between the Clearance values for rats, monkeys and humans, and would be expected to provide good agreement for mice. As documented in the accompanying report, the allometric equation predicts a Clearance value for unconjugated BPA in mice of 206 L/h-kg, which equates to an AUC value of approximately 2.1 nmol-h/L (for a dose of 100 micrograms/kg-bw). The HEDF value for unconjugated BPA is then 2.1¸3.6 (the human AUC value reported in the Draft Opinion) or 0.6.	See the response above.
Hamelton Anne-Marie, PlasticsEurope, anne-marie.hamelton@plasticseurope.org, Belgium	3.7.1. Knowledge on BPA exposure	Given the uncertainty in the data from Doerge et al. (2011), and related limitations to calculate an AUC, a more defensible AUC for unconjugated BPA in mice can be derived from the allometric relationship noted above. That relationship provides good agreement between the Clearance values for rats, monkeys and humans, and	See the response above.

		would be expected to provide good agreement for mice. As documented in the accompanying report, the allometric equation predicts a Clearance value for unconjugated BPA in mice of 206 L/h-kg, which equates to an AUC value of approximately 2.1 nmol-h/L (for a dose of 100 micrograms/kg-bw). The HEDF value for unconjugated BPA is then 2.1¸3.6 (the human AUC value reported in the Draft Opinion) or 0.6.	
Jamin Marc, SABIC Innovative Plastics BV, marc.jamin@sabic-ip.com, Netherlands	3.7.1.1. Methods for measurement of internal exposure in humans	continued: ii. Total BPA HEDF As noted in the Draft Opinion, it is not known whether the observed kidney weight increase is caused by conjugated or unconjugated BPA. Although experimental data is not available to definitively answer this question, the available database supports the plausibility that conjugated BPA (e.g., generally measured experimentally and referred to as total BPA) may be the more appropriate biomarker of effect. Given the low bioavailability of BPA after oral exposure, the vast majority of BPA eliminated through the kidney is conjugated BPA. It's not clear if unconjugated BPA is eliminated through the kidney but, even if so, the amount of unconjugated BPA available for elimination is less than 1% of the administered dose. The much higher level of conjugated BPA being processed by the kidney suggests that conjugated BPA is more likely to be the causative substance. Data is available to calculate an HEDF for total BPA. First, the AUC value for total BPA in mice is available from the same Doerge et al. (2011) study that is the source of the AUC value for unconjugated BPA. The value is reported as 247 nmol-h/L in Section 3.1.2 (Figure 2) of the Draft Opinion. Notably this value appears to be more reliable than the unconjugated BPA AUC from the same study since the level of total BPA is substantially higher and above the detection limit for a sufficient length of time after dosing.	See the response above.

		Although the Draft Opinion does not estimate a total BPA AUC for humans, this value can be readily calculated with experimental data from a human pharmacokinetic study (Völkel et al., 2002). This study reported a Clearance value of 0.13 L/min, which equates to 7.8 L/h. All participants received a dose of 5 mg, leading to an AUC of 0.64 mg-h/L (5 ¸ 7.8), which equates to 2807 nmol-h/L for the average dose of 69.3 mg/kg-bw. Scaling the AUC to a dose of 100 mg/kg-bw for comparison to the mouse value results in an AUC of approximately 4,000 nmol-h/L. The HEDF for conjugated BPA is then calculated as 247 ¸ 4,000 or 0.06.	
Fernandez de Celis Alvaro, MedPharmPlast Europe, Alvaro.fernandez@eupc.org, Belgium	3.7.1.1. Methods for measurement of internal exposure in humans	continued: ii. Total BPA HEDF As noted in the Draft Opinion, it is not known whether the observed kidney weight increase is caused by conjugated or unconjugated BPA. Although experimental data is not available to definitively answer this question, the available database supports the plausibility that conjugated BPA (e.g., generally measured experimentally and referred to as total BPA) may be the more appropriate biomarker of effect. Given the low bioavailability of BPA after oral exposure, the vast majority of BPA eliminated through the kidney is conjugated BPA. It's not clear if unconjugated BPA is eliminated through the kidney but, even if so, the amount of unconjugated BPA available for elimination is less than 1% of the administered dose. The much higher level of conjugated BPA being processed by the kidney suggests that conjugated BPA is more likely to be the causative substance. Data is available to calculate an HEDF for total BPA. First, the AUC value for total BPA in mice is available from the same Doerge et al. (2011) study that is the source of the AUC value for unconjugated BPA. The value is reported as 247 nmol-h/L in Section 3.1.2 (Figure 2) of the Draft Opinion. Notably this value appears to be more reliable than the unconjugated BPA AUC from the same study since the level of total BPA is substantially higher and	See the comment above.

		above the detection limit for a sufficient length of time after dosing. Although the Draft Opinion does not estimate a total BPA AUC for humans, this value can be readily calculated with experimental data from a human pharmacokinetic study (Völkel et al., 2002). This study reported a Clearance value of 0.13 L/min, which equates to 7.8 L/h. All participants received a dose of 5 mg, leading to an AUC of 0.64 mg-h/L (5 ¸ 7.8), which equates to 2807 nmol-h/L for the average dose of 69.3 mg/kg-bw. Scaling the AUC to a dose of 100 mg/kg-bw for comparison to the mouse value results in an AUC of approximately 4,000 nmol-h/L. The HEDF for conjugated BPA is then calculated as 247 ¸ 4,000 or 0.06.	
Hamelton Anne-Marie, PlasticsEurope, anne-marie.hamelton@plasticseurope.org, Belgium	3.7.1.1. Methods for measurement of internal exposure in humans	ii. Total BPA HEDF As noted in the Draft Opinion, it is not known whether the observed kidney weight increase is caused by conjugated or unconjugated BPA. Although experimental data is not available to definitively answer this question, the available database supports the plausibility that conjugated BPA (e.g., generally measured experimentally and referred to as total BPA) may be the more appropriate biomarker of effect. Given the low bioavailability of BPA after oral exposure, the vast majority of BPA eliminated through the kidney is conjugated BPA. It's not clear if unconjugated BPA is eliminated through the kidney but, even if so, the amount of unconjugated BPA available for elimination is less than 1% of the administered dose. The much higher level of conjugated BPA being processed by the kidney suggests that conjugated BPA is more likely to be the causative substance. Data is available to calculate an HEDF for total BPA. First, the AUC value for total BPA in mice is available from the same Doerge et al. (2011) study that is the source of the AUC value for unconjugated BPA. The value is reported as 247 nmol-h/L in Section 3.1.2 (Figure 2) of the Draft Opinion. Notably this value appears to be more reliable than the unconjugated BPA AUC from the same study since the level of total BPA is substantially higher and	See the comment above.

		above the detection limit for a sufficient length of time after dosing. Although the Draft Opinion does not estimate a total BPA AUC for humans, this value can be readily calculated with experimental data from a human pharmacokinetic study (Völkel et al., 2002). This study reported a Clearance value of 0.13 L/min, which equates to 7.8 L/h. All participants received a dose of 5 mg, leading to an AUC of 0.64 mg-h/L (5 / 7.8), which equates to 2807 nmol-h/L for the average dose of 69.3 mg/kg-bw. Scaling the AUC to a dose of 100 mg/kg-bw for comparison to the mouse value results in an AUC of approximately 4,000 nmol-h/L. The HEDF for conjugated BPA is then calculated as 247 / 4,000 or 0.06.	
Moussa Miranda, AESGP - Association of the European Self-Medication Industry, m.moussa@aesgp.eu, Belgium	3.7.1.2. Internal exposure to BPA in humans from all routes	Page 37 Line 20: The term 'relatively high' in the following sentence "Much of the concern for BPA exposure has come from studies reporting relatively high levels of free BPA in human body fluids/tissues …" should be defined or deleted.	The references are correct. Unless data are provided showing the contrary change is not needed. The various papers are discussed further in 3.7.1.2.
Jamin Marc, SABIC Innovative Plastics BV, marc.jamin@sabic-ip.com, Netherlands	3.7.1.2. Internal exposure to BPA in humans from all routes	continued: d. A Range of Scientifically Defensible TDI Values Are Possible Based on the BMDL¬10 and HEDF values presented above, a range of scientifically defensible TDI values are possible. All of the TDI values below are calculated with the equation shown below and an uncertainty factor of 25 as used in the Draft Opinion. (HEDF x BMDL10) ¸ 25 = TDI • (0.6 x 35,599) ¸ 25 = 854 ug/kg-bw/day • (0.6 x 23,530) ¸ 25 = 565 ug/kg-bw/day • (0.06 x 35,599) ¸ 25 = 85 ug/kg-bw/day • (0.06 x 23,530) ¸ 25 = 57 ug/kg-bw/day In comparison, EFSA calculated a TDI of 5 ug/kg-bw/day. Although the values above are all scientifically defensible, the values cover a wide range and it is apparent that there is considerable uncertainty in selection of a singular	See the responses above.

		point value for the TDI at this time.	
Fernandez de Celis Alvaro, MedPharmPlast Europe, Alvaro.fernandez@eupc.org, Belgium	3.7.1.2. Internal exposure to BPA in humans from all routes	continued: d. A Range of Scientifically Defensible TDI Values Are Possible Based on the BMDL¬10 and HEDF values presented above, a range of scientifically defensible TDI values are possible. All of the TDI values below are calculated with the equation shown below and an uncertainty factor of 25 as used in the Draft Opinion. (HEDF x BMDL10) ¸ 25 = TDI • (0.6 x 35,599) ¸ 25 = 854 mg/kg-bw/day • (0.6 x 23,530) ¸ 25 = 565 mg/kg-bw/day • (0.06 x 35,599) ¸ 25 = 85 mg/kg-bw/day • (0.06 x 23,530) ¸ 25 = 57 mg/kg-bw/day In comparison, EFSA calculated a TDI of 5 mg/kg-bw/day. Although the values above are all scientifically defensible, the values cover a wide range and it is apparent that there is considerable uncertainty in selection of a singular point value for the TDI at this time.	See the response above.
Hamelton Anne-Marie, PlasticsEurope, anne-marie.hamelton@plasticseurope.org, Belgium	3.7.1.2. Internal exposure to BPA in humans from all routes	d. A Range of Scientifically Defensible TDI Values Are Possible Based on the BMDL¬10 and HEDF values presented above, a range of scientifically defensible TDI values are possible. All of the TDI values below are calculated with the equation shown below and an uncertainty factor of 25 as used in the Draft Opinion. (HEDF x BMDL10) / 25 = TDI • (0.6 x 35,599) / 25 = 854 microgram/kg-bw/day • (0.6 x 23,530) / 25 = 565 microgram/kg-bw/day • (0.06 x 35,599) / 25 = 85 microgram/kg-bw/day • (0.06 x 23,530) / 25 = 57 microgram/kg-bw/day In comparison, EFSA calculated a TDI of 5 microgram/kg-bw/day. Although the values above are all scientifically defensible, the values cover a wide range and it is apparent that there is considerable uncertainty in	See the response above.

		selection of a singular point value for the TDI at this time.	
Jamin Marc, SABIC Innovative Plastics BV, marc.jamin@sabic-ip.com, Netherlands	3.7.1.3. Non-oral exposure routes	continued: e. EFSA Should Retain the Current TDI with a Temporary Designation As discussed above, the approach taken by EFSA to characterize hazards and establish a TDI is scientifically sound, but does not justify a revision to the TDI at the present time. Although the results of the BMD and HED analyses are presented in the Draft Opinion as singular point values, the results of both analyses are more appropriately considered as a range of values. In both analyses, choices are made on the methodology to apply and the data to analyze. These choices are not without uncertainty and other choices may be equally valid if not superior. The Draft Opinion discusses some uncertainty aspects regarding the HED analysis, but uncertainty also exists for the BMD analysis. Applying the same approach taken by EFSA, and considering uncertainties in both the BMD and HED analyses, it is possible to calculate a range of scientifically defensible TDIs, including some that are well above the current TDI of 50 ug/kg-bw/day. In addition, as noted in the Draft Opinion, significant research on BPA is underway, most notably research undertaken by the U.S. Food and Drug Administration and the U.S. National Toxicology Program. The results of these studies may further enlighten the analytical process and allow EFSA to defensibly select the most appropriate TDI from the range of available values. In light of the range of TDI's that can be calculated using the same methodologies and data sets, and the upcoming data from significant ongoing studies, it is most appropriate for EFSA to leave the current TDI of 50 mg/kg-bw/day unchanged at this time. It is appropriate for the TDI to be designated as temporary and EFSA should promptly re-evaluate and finalize the TDI once the results of anticipated significant studies are available.	See the response above.

Jamin Marc, SABIC Innovative Plastics BV, marc.jamin@sabic-ip.com, Netherlands	3.7.1.3. Non-oral exposure routes	continued: e. EFSA Should Retain the Current TDI with a Temporary Designation As discussed above, the approach taken by EFSA to characterize hazards and establish a TDI is scientifically sound, but does not justify a revision to the TDI at the present time. Although the results of the BMD and HED analyses are presented in the Draft Opinion as singular point values, the results of both analyses are more appropriately considered as a range of values. In both analyses, choices are made on the methodology to apply and the data to analyze. These choices are not without uncertainty and other choices may be equally valid if not superior. The Draft Opinion discusses some uncertainty aspects regarding the HED analysis, but uncertainty also exists for the BMD analysis. Applying the same approach taken by EFSA, and considering uncertainties in both the BMD and HED analyses, it is possible to calculate a range of scientifically defensible TDIs, including some that are well above the current TDI of 50 ug/kg-bw/day. In addition, as noted in the Draft Opinion, significant research on BPA is underway, most notably research undertaken by the U.S. Food and Drug Administration and the U.S. National Toxicology Program. The results of these studies may further enlighten the analytical process and allow EFSA to defensibly select the most appropriate TDI from the range of available values. In light of the range of TDI's that can be calculated using the same methodologies and data sets, and the upcoming data from significant ongoing studies, it is most appropriate for EFSA to leave the current TDI of 50 mg/kg-bw/day unchanged at this time. It is appropriate for the TDI to be designated as temporary and EFSA should promptly re-evaluate and finalize the TDI once the results of anticipated significant studies are available.	See the response above.

Fernandez de Celis Alvaro, MedPharmPlast Europe, Alvaro.fernandez@eupc.org, Belgium	3.7.1.3. Non-oral exposure routes	continued: e. EFSA Should Retain the Current TDI with a Temporary Designation As discussed above, the approach taken by EFSA to characterize hazards and establish a TDI is scientifically sound, but does not justify a revision to the TDI at the present time. Although the results of the BMD and HED analyses are presented in the Draft Opinion as singular point values, the results of both analyses are more appropriately considered as a range of values. In both analyses, choices are made on the methodology to apply and the data to analyze. These choices are not without uncertainty and other choices may be equally valid if not superior. The Draft Opinion discusses some uncertainty aspects regarding the HED analysis, but uncertainty also exists for the BMD analysis. Applying the same approach taken by EFSA, and considering uncertainties in both the BMD and HED analyses, it is possible to calculate a range of scientifically defensible TDIs, including some that are well above the current TDI of 50 mg/kg-bw/day. In addition, as noted in the Draft Opinion, significant research on BPA is underway, most notably research undertaken by the U.S. Food and Drug Administration and the U.S. National Toxicology Program. The results of these studies may further enlighten the analytical process and allow EFSA to defensibly select the most appropriate TDI from the range of available values. In light of the range of TDI's that can be calculated using the same methodologies and data sets, and the upcoming data from significant ongoing studies, it is most appropriate for EFSA to leave the current TDI of 50 mg/kg-bw/day unchanged at this time. It is appropriate for the TDI to be designated as temporary and EFSA should promptly re-evaluate and finalize the TDI once the results of anticipated significant studies are available.	See the response above.

Hamelton Anne-Marie, PlasticsEurope, anne-marie.hamelton@plasticseurope.org, Belgium	3.7.1.3. Non-oral exposure routes	e. EFSA Should Retain the Current TDI with a Temporary Designation As discussed above, the approach taken by EFSA to characterize hazards and establish a TDI is scientifically sound, but does not justify a revision to the TDI at the present time. Although the results of the BMD and HED analyses are presented in the Draft Opinion as singular point values, the results of both analyses are more appropriately considered as a range of values. In both analyses, choices are made on the methodology to apply and the data to analyze. These choices are not without uncertainty and other choices may be equally valid if not superior. The Draft Opinion discusses some uncertainty aspects regarding the HED analysis, but uncertainty also exists for the BMD analysis. Applying the same approach taken by EFSA, and considering uncertainties in both the BMD and HED analyses, it is possible to calculate a range of scientifically defensible TDIs, including some that are well above the current TDI of 50 microgram/kg-bw/day. In addition, as noted in the Draft Opinion, significant research on BPA is underway, most notably research undertaken by the U.S. Food and Drug Administration and the U.S. National Toxicology Program. The results of these studies may further enlighten the analytical process and allow EFSA to defensibly select the most appropriate TDI from the range of available values. In light of the range of TDI's that can be calculated using the same methodologies and data sets, and the upcoming data from significant ongoing studies, it is most appropriate for EFSA to leave the current TDI of 50 microgram/kg-bw/day unchanged at this time. It is appropriate for the TDI to be designated as temporary and EFSA should promptly re-evaluate and finalize the TDI once the results of anticipated significant studies are available.	See the response above.

Amaral Maria José, HCWH Europe, maria.jose@hcwh.org, Belgium	3.7.1.3. Non-oral exposure routes	In the opinion the SCENIHR chose to not consider gloves in the assessment. This was based on the information provided by the use of BPA in PVC products provided by European PVC manufacturers, mentioned already in a previous comment. Gloves are one of the products where low cost has driven procurers to find cheaper solutions outside of the EU. Moreover, are one of the most consumed products in healthcare that can put workers and patients under regular and intense exposure to BPA.	The SCENIHR agrees that Extra-EU imported PVC gloves could be an important source of exposure, when produced with PVC containing BPA. And indeed, they were mentioned at page 43: Sun et al. (2001) reported that BPA content in commercially available samples of PVC wrap film, PVC gloves and PVC hose to be 68±3.5 µg/g, 60.5±2.8 µg/g and 290.1 µg/g, respectively. No data is available on BPA exposure from PVC gloves, but it cannot be ruled out that small amounts of BPA may be transferred to the skin when these gloves are used. However, no other data are available on the possible level of exposure, therefore no sound risk assessment could have been possible. However in order to stress the possible relevance a sentence have been used at page 43, after the information related to the non use of BPA by EU PVC-manufacturers: However, PVC as a possible source of BPA exposure cannot be completely excluded because BPA-containing PVC may still be used in the EU due to medical devices coming from outside of the EU because of the global market for medical devices. As stated in the opinion 'Better data on exposure would be beneficial for the refinement of this risk assessment, to be carried out when new data on exposure via medical devices will be available.' Having data on gloves or any other Med Dev releasing BPA, a new risk assessment could be carried out.
Amaral Maria José, HCWH Europe, maria.jose@hcwh.org, Belgium	3.7.1.3. Non-oral exposure routes	In the opinion the SCENIHR chose to not consider gloves in the assessment. This was based on the information provided by the use of BPA in PVC products provided by European PVC manufacturers, mentioned already in a previous comment. Gloves are one of the products where low cost has driven procurers to find cheaper solutions	See the response above.

		outside of the EU. Moreover, are one of the most consumed products in healthcare that can put workers and patients under regular and intense exposure to BPA.	
Wallin Maria, KemI, Swedish Chemicals Agency, maria.wallin@kemi.se, Sweden	3.7.2. Exposure to BPA from medical devices	• In Gayrard et al. (2013), it has been observed that BPA is readily absorbed through the oral mucous membrane, evading the first-pass effect in the liver and yielding a high bioavailability (up to 100%?). In the assessment of dental materials for which there could be a very high bioavailability through the mucous membrane, the internal exposure should rather be compared to the internal t-TDI, as calculated in the draft report. The consequence would be concern for the acute dental scenario.	The SCENIHR thanks for the useful comment. Some text has been added in 3.8.2 toxicokinetics describing sublingual absorption. However, after sublingual exposure systemic bioavailability was found to be much higher (70-90% of the dose) probably due to the absence of a first pass effect (Gayrard et al., 2013). In addition it was added to Abstract, Executive summary and Opinion the evaluation due to absorption of BPA released by dental material in acute exposure in the oral cavity. For release in the oral cavity itself a different internal exposure may occur as uptake in the oral cavity can be considerable. The highest acute exposure to dental materials in the estimated exposure scenario is 200 ng/kg b.w./day If we assume 100% bioavailability in the oral cavity, this is 5-fold higher than the internal dose of the t-TDI (40 ng/kg b.w./day estimated as 1% of 4 µg/kg). However, when using a margin of safety (MOS) approach based on the BMDL10 of 8.96 mg/kg resulting in an human equivalent dose (HED) of 609 µg/kg b.w./day, and consequently an internal dose of 6 µg/kg b.w./day, the MOS of the 200 ng/kg internal exposure would be 30 , which is below the uncertainty factor or MOS of 150 as recently established by EFSA (2015). However, the calculation that 100% of the released dose is absorbed in the oral cavity is a largely exaggerated assumption, and it should be considered that the high exposure is acute (some hours) whereas the MOS based on the uncertainty factor used for the derivation of the t-TDI by EFSA (2015), is based on long term exposure. Therefore, it can be considered that the 5-fold difference can account for the differences in exposure duration and hence, the

			MOS of 30 for acute exposure to dental materials is sufficiently large.
Da Cortà Giuseppe, EUROM 1, giuseppe.dacorta@certottica.it, Belgium	3.7.2. Exposure to BPA from medical devices	Unforeseeable risks - Leaching or Mouthing by children might result in exposure to any BPA leaching into the saliva, but it has been estimated that 95% of optical frames and sunglasses (such as internal hinge construction), corresponding to the largest volume of items, are not available for mouthing [2] - migration of BPA from packaging materials might constitute a source of exposure, but studies indicate that diffusion-migration of the residual monomer is a reaction that is catalysed by hydroxide and occurs if the interface is an aqueous media. [1] Reasons for exemption - According to Council Directive 93/42/EEC, medical devices may only be placed on the market if they meet the essential requirements laid down in its Annex I. The devices must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety. Concerning BPA-exposure, Spectacle Frames and Sunglasses fulfil all these requirements. [1] EFSA Journal DRAFT Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs – Part: exposure assessment [2] rest_lead_bd_db010957-56_tc_en page 240	Optical frame and sunglasses were not specifically included. Already appropriately addressed in Opinion. The issue of other medical devices than mentioned is indirectly discussed on page 27-28 when aspects of BPA leakage of medical devices and PC pellets is discussed.

MOUSSA Miranda, AESGP - Association of the European Self-Medication Industry, m.moussa@aesgp.eu, Belgium	3.7.2. Exposure to BPA from medical devices	Line 43: The statement that "This wide range in BPA measurements reflects a continuous reduced leaching of BPA from dental materials, probably due to the reduced use of bis-DMA" should be reflected in orther parts of the document that refers to the use of bis-DMA	The SCENIHR disagrees with this comment, as the reduced use of bis_DMA was just an hypothesis, not supported by sound data. Therefore that part of the sentence was deleted, and not reported in other parts of the document.
Moussa Miranda, AESGP - Association of the European Self-Medication Industry, m.moussa@aesgp.eu, Belgium	3.7.2. Exposure to BPA from medical devices	Page 43 lines 49-52: There are quite different forms of dental materials used in clinical practice. For instance, polymerizable dental composite materials (e.g. filling materials, bondings, fissure sealants, retainer materials) do not contain BisDMA. A survey among leading dental manufacturers, that are members of the Dental Working Group (AG Dental) of German Medicines Manufacturers' Association has shown, that this compound is no longer used in dental formulations. This fact should also be mentioned in the text.	The SCENIHR agrees with this comment. However, Page 43 Lines 37-44 cite a recently published Swedish report that provides examples. So, there is no need to change the text of the Opinion.
Stock Gregor, FIDE - European Dental Industry, g.stock@fide-online.org, Germany	3.7.2. Exposure to BPA from medical devices	Page 43, lines 49-52 Comment: There are quite different forms of dental materials used in clinical practice. Polymerizable dental composite materials (e. g. filling materials, bondings, fissure sealants, retainer materials) itself do not contain BisDMA. An informal survey among leading dental manufacturers has shown, that this compound is no longer used in dental formulations. Page 46, lines 41-43 "This wide range in BPA measurements reflects a continuous reduced leaching of BPA from dental materials, probably due to the reduced use of bis-DMA." Comment: There is apparently no discussion elsewhere in the document to support this statement. On the contrary, bisDMA is referenced in several locations in the document as though it is routinely used in dental products. Please add supporting documentation for this statement and revise the document for consistency throughout in regard to current use of bisDMA as a dental product ingredient. In addition, the wide range in measured BPA concentration may also reflect variations in analytical methodology. There have been recent refinements in analytical methodology (e.g.	See the response above. The SCENIHR agrees with this comment. As the reduced use of bis_DMA was just an Hypothesis, not supported by sound data. Therefore that part of the sentence was deleted and a comment to possible influence of analytical methods included. .

		use of LC/MS/MS detection and use of d16BPA as an internal standard) that have significantly reduced misidentification of co-eluting compounds as BPA.	
Sterk Thecla, Eucomed, thecla.sterk@eucomed.org , Belgium	3.7.2. Exposure to BPA from medical devices	3.7.2, 42 -43 Although SCENIHR identified dialysis treatment as a relevant exposure scenario, only very limited information on BPA exposure from medical devices in dialysis treatment was identified in the draft opinion (see page 42-43). Since reliability, statistical significance and analytical selectivity of the named studies are questioned by SCENIHR, further independent research on actual exposure of dialysis patient is needed. Ø The (general) recommendations for research on exposure made in the draft opinion (chapter 3.12) are supported. Additionally, a clearer description of the dialysis-related gap would be appreciated: independent research on actual exposure of dialysis patient.	The SCENIHR agrees about the need for good and reliable exposure data. In section 3.12 a statement is made for need for more accurate exposure data, but the concept has been underlined also in the abstract, in the executive summary and opinion, beside in the recommendations for research.

Sanderson Susie, CED Working Group Amalgam and Other Restorative Materials, ced@eudental.eu,	3.7.2. Exposure to BPA from medical devices Check reference 7	Dear Sir or Madam, I am writing on behalf of the Council of European Dentists (CED). The CED is the representative organisation for the dental profession in the EU, representing over 340,000 practising dentists through 32 national dental associations. Established in 1961 to advise the European Commission on matters relating to the dental profession, the CED promotes high standards of oral healthcare and effective patient-safety centred and evidenced-based professional practice across Europe. The CED would like to provide a few comments on the SCENIHR preliminary opinion on 'the safety of the use of bisphenol A in medical devices'. The CED welcomes the preliminary opinion and more specifically the Committee's conclusion with regard to longterm and short-term exposure to bisphenol A (BPA) via dental materials. The CED shares the Committee's view that by itself the exposure to composite fillings/fissure sealants does not constitute a health risk due to BPA release. However, the CED is of opinion that the labelling of all dental materials should provide the details of all the contents so that dental clinicians are able to assess and ensure the safety of materials that they use (CED Resolution on Environmental Management of Dental Materials: Responsible Practice 2013 update – Statement on Alternative Materials, adopted in November 2013 – see attached).	The SCENIHR cannot answer this specific comment, since it is outside the mandate of the Scientific Committee. The proposal on labelling of medical devices regarding their content is an issue for risk managers and it is outside the mandate received by the SCHENIHR for this opinion.
Swedish Chemical Agency, Sweden	3.7.3. Exposure to BPA from medical devices under different scenarios	It is not clear whether dental splints and braces made of polycarbonate were included in the assessment of exposure from dental devices. Although these will not emit as much BPA as a dental restoration, they may contribute to overall exposure.	PC brackets were included in the Opinion on page 30 and 31.
Moussa Miranda, AESGP - Association of the European Self-Medication Industry, m.moussa@aesgp.eu, Belgium	3.7.3. Exposure to BPA from medical devices under different scenarios	"Worst-case" calculations of exposure based on the residual BPA content of bisGMA give substantially lower estimates of exposure (with resulting increased margins of exposure/safety) than do estimates based on extraction data reported by various authors and cited in the table 2 on page 45. Given the difficulty of BPA measurement in biological media and the often limited documentation of the analytical methods used, such	Since by using this 'worst case' no risk was evidenced, the SCENIHR considers any refinement unnecessary (even though the exposure estimate can be considered too high)

		theoretical calculations should be included in the risk assessment, to provide much needed context for the published data.	
Stock Gregor, FIDE - European Dental Industry, g.stock@fide-online.org, Germany	3.7.3. Exposure to BPA from medical devices under different scenarios	Page 47, lines 40 ff (scenarios) Comments: Several in-house analyses performed by dental manufacturers, as well as numerous analyses carried out by independent external laboratories, usually show BPA readings of below 1 ppm (0.02 ppm, 0.35 ppm, 0.06 ppm, 0.41 ppm,etc.) for Bis-GMA (by a range of different manufacturers). The highest ever reading taken was 2.27 ppm. Higher readings were taken for Bis-GMA derivates, normally between 1 and 2 ppm; one single maximum reading was 3.73 ppm. Despite Bis-GMA being the most commonly used dental monomer and Bis-GMA derivates being used extremely rarely, we assume a value of 4 ppm BPA contained in the Bis-GMA, thus constructing a "worst case" scenario. We first look at an extremely large filling (0.25 g - again, the worst case) of a composite material rich in Bis-GMA (15 % [by weight] Bis-GMA in relation to the overall formulation). Based on an assumed 4 ppm BPA in the raw material, the amount of BPA per filling would be 0.15 µm. If 10 large fillings were to release their total disposable BPA content in one day (absolute worst case), then the person would be exposed once to an amount of 1.5 µg. When viewing the EFSA's new and much stricter proposal (see above, e.g. in the abstract), one finds that the TDI value, using a margin of safety of the factor 25, is indicated as a tolerable daily intake of 5 µg per kg of body mass. The scenario of short-term exposure (p. 47, l. 42) states a value of 13 µg after a total of 24 h. In accordance with the measurements conducted to determine the BPA content of filling materials, however, this would require (following the above exemplary calculation) a total of 87 fillings, which together would be capable of releasing this maximum amount of BPA. The short-term scenario, however, describes the release from the crown of only one molar tooth. The scenario of long-term exposure (p.	Published data were used for the exposure calculations for dental materials. (Van Landuyt 2011, Kingman 2012, Kang 2011). SCENIRH cannot use data coming from personal communication. However, since by using this 'worst case' no risk was evidenced, the SCENIHR considers any refinement unnecessary (even though the exposure estimate can be considered too high)

		47, l. 45) is, again, in agreement with the consensus that dental materials show no further release of BPA after 24 hours.	
Stock Gregor, FIDE - European Dental Industry, g.stock@fide-online.org, Germany	3.7.3. Exposure to BPA from medical devices under different scenarios	Page 48, lines 4-10[Exposure calculations] "Worst-case" calculations of exposure based on the residual BPA content of bisGMA give substantially lower estimates of exposure (with resulting increased margins of exposure/safety) than do estimates based on extraction data reported by various authors cited in the preliminary opinion (e.g. page 45, table 2). Given the difficulty of BPA measurement in biological media and the often limited documentation of the analytical methods used, such theoretical calculations should be included in the risk assessment, to provide much needed context for the published data.	See the response above.
Björkman Lars, Uni Research Health, lars.bjorkman@uni.no, Norway	3.7.3. Exposure to BPA from medical devices under different scenarios	At page 47 (line 45) it is stated that "After 24 h, no elevation in BPA-level (saliva, urine) is found (Kingman et al., 2012; Kang et al., 2011)". This is true for saliva, but not for urine according to data from the study by Kingman et al. (2012). In the study by Kang et al. (2011) mean values for the BPA excretion via urine was increased after treatment by a factor of 4 (from 0.561 ng/mL to 2.351, 2.083 and 1.805 ng/mL after 1 day, 1 week and 1 month, respectively; see Table IV in the publication). According to the statistical method used the increase was not statistical significant, but the power of the study was limited.	Kang et al., 2011, only found a statistically difference in saliva. Kingman et al., 2012 indeed found for urine some increase statistically significant at $p<0.05$. This is corrected in the text on page 47.
Da Cortà Giuseppe, EUROM 1 , giuseppe.dacorta@certottica.it, Belgium	3.7.5. Conclusions	Conclusion: - In sum, there is both scientific and objective evidence that the risk assessment concerning the exposure to BPA due to Optical frames and Sunglasses Should not considered as a hazard.	Optical frame and sunglasses were not specifically included. No information was available to the SCENIHR The issue of other medical devices than those mentioned is indirectly discussed on page 27-28 when aspects of BPA leakage of medical devices and PC pellets is discussed.

Swedish Chemical Agency, Sweden	3.9. Toxicity	It is unfortunate that, although very well described in the draft report, it is not entirely obvious from the abstract and executive summary that the absence of conventional dose-response may be the result on non-monotonic dose-response.	This is left open as the scientific debate is going on. So, it is included in the report but not specifically emphasized in the abstract and executive summary. It is mentioned as an important issue at the end of the Opinion itself and the answers to the Commission.
Swedish Chemical Agency, Sweden	3.9.3. Carcinogenicity	It is stated in the draft report that the studies indicating effects on mammary gland development raise some concern for a possible effect after prenatal exposure to BPA. It is not entirely clear from the report as to why these effects were not considered further.	The available information is presented. As there are limitations in the papers cited and no further information was available, it was identified as a possible issue for the future when more data may become available. Recent data published (Deloclos et al., 2014 did not find convincing evidence for mammary gland hyperplasia in a well conducted dose response study this is now included. Page 80 In addition, the text related to the TDI derivation has been changed in the revised opinion, to take into account the temporary TDI as derived in the recent EFSA opinion (EFSA, 2015), used by the SCENIHR. The newly derived TDI takes into account a BMDL for kidney effects as PoD, derived a HED (human equivalent dose) considering kinetic differences, and include uncertainty related to effects which are 'likely' based on which the assessment factor is reduced to 25. The AF of 25 was then multiplied by 6 (AF=150) to account for those effects considered as 'likely' and included in the uncertainty analysis by EFSA (2015).
Swedish Chemical Agency, Sweden	3.9.8. Reproductive and developmental toxicity	BPA has a harmonized classification as Repro 2. In the draft SCENIHR report it is stated: "On the basis of the above studies, it can be concluded that BPA is essentially not a specific reproductive or developmental toxicant." Considering the legally binding classification of BPA as a reproductive toxicant, the conclusion in the draft report seems incorrect and opposing a legally binding classification. Please note that the Risk Assessment Committee under REACH (RAC) has adopted an opinion to	The SCENIHR agrees with the comment. Text has been added to indicate that BPA is a reproductive toxicant, although reproductive toxicity was not the end-point used for the risk assessment and the TDI determination. On the basis of the above studies, it can be concluded that reproductive or developmental toxicity are not the critical end-point in BPA toxicity, although it does have reproductive toxicity

		strengthen the existing harmonized classification and labelling (CLH) of BPA from a category 2 reproductive toxicant to a category 1B reproductive toxicant regarding the adverse effects on sexual function and fertility in line with a proposal from the French competent authority. RAC concluded that there were adverse effects on reproductive capacity (functional fertility) following oral exposure to BPA in a multi-generation guideline study in mice and in rats. Impaired female reproductive capacity was also observed in several supplementary non-guideline studies. In addition, toxic effects in reproductive organs were observed in several of the studies.	at doses higher than those causing liver and kidney damage. On this base it was classified as a Repro 2 toxicant (being classification an hazard-based process). More recently, The Committee for Risk Assessment (RAC) of the European Chemicals Agency (ECHA) has adopted an opinion to strengthen the existing harmonised classification and labelling (CLH) of BPA from a category 2 reproductive toxicant to a category 1B reproductive toxicant regarding the adverse effects on sexual function and fertility in line with a proposal from the French competent authority (ECHA 2014). The changes applied to all sections in the document
Moussa Miranda, AESGP - Association of the European Self-Medication Industry, m.moussa@aesgp.eu, Belgium	4. OPINION	Page 104 Lines 43-45: The following text "various dental materials are fabricated from monomers such as bisphenol A glycidyl methacrylate (Bis-GMA) and bisphenol A dimethacrylate (Bis-DMA) derived from BPA." suggests that use of bisDMA is a standard practice; as such, it should be revised to more accurately reflect current manufacturing practice.We would propose modifying the sentence as follows: "various dental materials are fabricated from monomers such as bisphenol A glycidyl methacrylate (Bis-GMA and very few from bisphenol A dimethacrylate (Bis-DMA) derived from BPA."	The SCENIHR agrees with the comment. Text has been changed accordingly. Added "very few from".
Moussa Miranda, AESGP - Association of the European Self-Medication Industry, m.moussa@aesgp.eu, Belgium	4. OPINION	Page 113, Line 19 and Page 114 Line 52: The term " relatively high" should be defined or deleted.	The SCENIHR disagrees with this comment. It indicates a contrast with the previous sentence in which the long term low exposure is mentioned. In that respect the short term exposure is "relatively high". The text has been changed for clarification (word added in italics): However, it should be realised that the benefit of medical devices should also be considered: the survival of these premature infants often depends on the availability of the same medical devices which result in a relatively high BPA exposure as compared to other exposures due to treatment with

			medical devices.
Stock Gregor, FIDE - European Dental Industry, g.stock@fide-online.org, Germany	4. OPINION	Page 104, lines 43-45 "…various dental materials are fabricated from monomers such as bisphenol A glycidyl methacrylate (Bis-GMA) and bisphenol A dimethacrylate (Bis-DMA) derived from BPA." Comment: The quoted text suggests that use of bisDMA is a standard practice; as such, it should be revised to more accurately reflect current manufacturing practice. Page 113, line 19 (and page 5, lines 16-17 and page 16, lines 33-34), "...short-term (relatively high)..." Comment: There is no frame of reference for the use of the term "relatively high". The term should be defined or deleted.	The text on bis-DMA is changed by adding "very few", to reflect current status. The SCENIHR disagrees with this comment. It indicates a contrast with the previous sentence in which the long term low exposure is mentioned. In that respect the short term exposure is "relatively high". The text has been changed for clarification (word added in italics): However, it should be realised that the benefit of medical devices should also be considered: the survival of these premature infants often depends on the availability of the same medical devices which result in a relatively high BPA exposure as compared to other exposures due to treatment with medical devices.
Lars Björkman, Uni Research Health, Lars.Bjorkman@uni.no, Norway	4. OPINION	At page 107 (line 7-11) it is stated that "Calculations based on the maximum values of BPA found in fissure sealants and in composite materials, in combinations with the actual amount of material used in clinical practice and a median 4-year life-time of a composite restoration, suggest a maximum exposure of 0.06 µg BPA/day from fissure sealants, and a maximum exposure of 0.36 µg BPA/day from composite restorations." The value 0.36 µg/day is taken from reference "Socialstyrelsen 2012". In the actual reference this value was calculated from an estimate of the maximal value for the bisphenol A content in one three surface composite filling and a constant release of the total content of bisphenol A over 4 years was assumed. It should, however, be taken into consideration that people may have more than one filling.	The SCENIHR agrees with the comment. The text suggests that dental restorations release an amount of BPA. This should be interpreted indeed as one restoration. For the short term release data from Van Landuyt et al., 2011 were used.

Sanak Aleksandra, Council of European Dentists, ced@eudental.eu,	4. OPINION Check reference 8		
Sijm Dick, RIVM, dick.sijm@rivm.nl, Netherlands	4. OPINION	We think the description of the differences between on the one hand prematurely born infants and babies and on the other hand mature people should be more extensively described, which would help to understand why effects to the prematurely born infants and babies following a higher, although temporarily exposure would cause different types of effects. Further information on the route of exposure-specific ADME (Absorption, Distribution, Metabolism and Excretion) information is needed for adults as well as for prematurely born infants and babies to further refine the assessment of BPA. Our comment to the EFSA approach on interspecies differences in toxicokinetics are relevant too for the SCENIHR opinion. EFSA has used the Human Equivalent Dose Factor (HEDF) and mentions that uncertainties in a number of effects (i.e. toxicodynamics) could be addressed by including an additional uncertainty factor in the derivation of the t-TDI. However, EFSA considers that no additional factor is needed since the HEDF for interspecies toxicokinetics may be already conservative up to a factor of 5. RIVM considers it not transparent to cover uncertainties in the toxicodynamics with a possible conservativeness in the uncertainty factor for toxicokinetics. The need for further information on alternatives to BPA, at least in some specific medical devices, seems opportune as risks to e.g. prematurely born infants by BPA cannot be excluded. As some producers as well as hospitals claim to use BPA-free medical devices, the information on those alternatives and their risk assessments need to be made transparent to avoid changing one substance that may pose a risk by another one. This would include the information on how the (new) Regulation on Medical Devices would deal with such alternatives. Which substance are used, how much do they emit from the	The SCENIHR agrees that differences in effects between adults and prematurely born infants is of interest. And indeed it is considered in the opinion for example addressing possible differences in the kinetics and focussing on the effects seen in multigeneration studies, in which the effects on F1 and F2 are taken into account. Neonates in Intensive care unit are at risk due to their exposure scenarios, the SCENIHR considers that a lengthy discussion on differences in response between the neonates/children/adults/aged people was outside the scope of the SCENIHR Opinion. The temporary TDI as derived in the recent EFSA opinion (EFSA, 2015) has been used by the SCENIHR and therefore the text has been changed accordingly throughout the document. The newly derived TDI takes into account a BMDL for kidney effects as PoD, derived a HED (human equivalent dose) considering kinetic differences, based on which the assessment factor is reduced to 25, then multiplied by 6 (AF=150) to account for those effects considered as 'likely' and included in the uncertainty analysis by EFSA (2015). The SCENIHR concurs with the conclusions of EFSA based on its own evaluation, the EFSA t-TDI was used in the risk assessment of BPA in medical devices. Regarding the alternatives, the SCENIHR had to rely on the limited information available. The SCENIHR does recognise that for many alternatives limited information is available regarding the toxicity and thus potential risk. This is addressed.

		medical devices, what is their bioavailability and ADME and what are their hazardous properties, etc? While recognizing the need for further information on alternatives, the promotion of alternatives, including a proper risk/benefit assessment could require further attention, in particular when current substances that are used in medical devices can be a risk.	
Amaral Maria José, HCWH Europe, maria.jose@hcwh.org, Belgium	4. OPINION	Health Care Without Harm Europe has been involved for many years in the promotion of safer medical devices without hazardous chemicals, as part of the solution to a non-toxic healthcare sector. Recently, we launched a fact sheet on Bisphenol A in medical devices and an online database to help healthcare staff to help identify alternatives to medical devices containing PVC or phthalates, which we hope to expand to BPA-free medical devices in the near future. HCWH Europe disagrees with the approach of the SCENIHR and asks for an interpretation of scientific uncertainty in favor of a precautionary approach rather than inaction and regulatory business as usual. In particular for vulnerable groups like premature infants and dialysis patients, which have developing or impaired organs unable to metabolise efficiently BPA into a safe metabolite. Furthermore, we are exposed to a variety of environmental toxicants on our daily life and effects of exposure to BPA cannot be looked at individually, as the substances can have cumulative and mixture effects. HCWH Europe also disagrees with the position SCENIHR takes on the benefit analysis, BPA content on PVC products, the safeness of EFSA toxicological values, the reproductive toxic effects and the overwhelming consistency of results from epidemiological studies. The benefit analysis is already performed during the market authorisation of the devices. Is not the goal of this opinion to discourse on that, as the Committee does not have enough information about the medical efficiency of each and all-medical device under scrutiny. The opinion relies on claims of European manufacturers of PVC, that BPA is	The SCENIHR thanks for the information, but did take into consideration scientific evidence as published in the open literature. When better information is available on BPA in PVC the SCENIHR will take that into consideration. However, the the SCENIHR cannot by itself investigate PVC samples for this purpose, but does recommend research in the exposure areas. Some text has been added to address the possibility that PVC products produced in extra-EU countries and containing BPA can be on the market, although the SCENIHR has no data on that issue. The precautionary principle application, being a risk management tool, is outside the mandate of the SCENIHR (in charge of risk assessment). Regarding the TDI derivation, the text has been changed in the revised opinion, to take into account the temporary TDI as derived in the recent EFSA opinion (EFSA, 2015). The newly derived TDI takes into account a BMDL for kidney effects as PoD, derived a HED (human equivalent dose) considering kinetic differences, based on which the assessment factor is reduced to 25 then multiplied by 6 (AF=150) to account for those effects considered as 'likely' and included in the uncertainty analysis by EFSA (2015). The SCENIHR concurs with the conclusions of EFSA based on its own evaluation, the EFSA t-TDI was used in the risk assessment of BPA in medical devices.

		no longer used as an additive to PVC and completely ignoring that many medical devices manufacturers and procurers obtain their raw material or products in other markets outside EU. The opinion also grossly overlooks important information from the ANSES report, that has lead to the calculation of toxicological reference values much lower than the Adult Daily Intake values defended by EFSA and to a request from France, recently adopted in an ECHA committee, to raise the CMR category of BPA to R2 due to the strong evidence of reproductive toxicity from animal studies. Finally, the opinion neglects or dismisses the consistency over different populations and age groups of epidemiological studies that have associated BPA exposure with a variety of disease conditions.	ANSES (France) used an approach for the precautionary principle as indicated above that is not the task of the SCENIHR, but for risk managers. The SCENIHR did include the remark on the recent ECHA proposal for reclassification of BPA as a class 1B reproductive toxic compound (which is a hazard based process, not a risk assessment).
Amaral Maria José, HCWH Europe, maria.jose@hcwh.org, Belgium	4. OPINION	Health Care Without Harm Europe has been involved for many years in the promotion of safer medical devices without hazardous chemicals, as part of the solution to a non-toxic healthcare sector. Recently, we launched a fact sheet on Bisphenol A in medical devices and an online database to help healthcare staff to help identify alternatives to medical devices containing PVC or phthalates, which we hope to expand to BPA-free medical devices in the near future. HCWH Europe disagrees with the approach of the SCENIHR and asks for an interpretation of scientific uncertainty in favor of a precautionary approach rather than inaction and regulatory business as usual. In particular for vulnerable groups like premature infants and dialysis patients, which have developing or impaired organs unable to metabolise efficiently BPA into a safe metabolite. Furthermore, we are exposed to a variety of environmental toxicants on our daily life and effects of exposure to BPA cannot be looked at individually, as the substances can have cumulative and mixture effects. HCWH Europe also disagrees with the position SCENIHR takes on the benefit analysis, BPA content on PVC products, the safeness of EFSA toxicological values, the reproductive toxic effects and the overwhelming	See the response above.

		consistency of results from epidemiological studies. The benefit analysis is already performed during the market authorisation of the devices. Is not the goal of this opinion to discourse on that, as the Committee does not have enough information about the medical efficiency of each and all-medical device under scrutiny. The opinion relies on claims of European manufacturers of PVC, that BPA is no longer used as an additive to PVC and completely ignoring that many medical devices manufacturers and procurers obtain their raw material or products in other markets outside EU. The opinion also grossly overlooks important information from the ANSES report, that has lead to the calculation of toxicological reference values much lower than the Adult Daily Intake values defended by EFSA and to a request from France, recently adopted in an ECHA committee, to raise the CMR category of BPA to R2 due to the strong evidence of reproductive toxicity from animal studies. Finally, the opinion neglects or dismisses the consistency over different populations and age groups of epidemiological studies that have associated BPA exposure with a variety of disease conditions.	
Ian McKay, British Dental Association, ian.mckay@bda.org, United Kingdom	4. OPINION	The opinion confirms that dental restorative materials represent a relatively small and transient contribution to overall exposure to BPA. These materials therefore do not constitute a health risk due to the release of BPA. However, it would be sensible to encourage manufacturers to provide detailed information on the composition of their materials. This would prevent materials being marketed as free from BPA when they in fact contain alternatives with significant potential biological activity. In most cases these alternatives have been less well-characterised than BPA and their presence should be made apparent to dental clinician.	The SCENIHR agrees with the comment. Regulation on labelling of products is outside the mandate of the SCENIHR.
Jamin Marc, SABIC Innovative Plastics BV, marc.jamin@sabic-ip.com, Netherlands	6. LIST OF ABBREVIATIONS	continued: 4. Reference List Crump KS (1984) A new method of determining allowable daily intakes. Fundamental and Applied Toxicology. 4:854-871. Cho CY, Shin BS, Jung JH, Kim DH, Lee KC, Han SY, Kim HS, Lee BM, Yoo SD. Pharmacokinetic scaling of bisphenol	The SCENIHR made a selection of most recent literature (as indicated in the Methodology section) Most of the literature indicated is already included in the SCENIHR Opinion.

		A by species-invariant time methods. Xenobiotica. 2002 Oct;32(10):925-34. Doerge DR, Twaddle NC, Vanlandingham M, Fisher JW. Pharmacokinetics of bisphenol A in neonatal and adult CD-1 mice: inter-species comparisons with Sprague-Dawley rats and rhesus monkeys. Toxicol Lett. 2011 Dec 15;207(3):298-305. Doerge DR, Twaddle NC, Vanlandingham M, Fisher JW. Pharmacokinetics of bisphenol A in serum and adipose tissue following intravenous administration to adult female CD-1 mice. Toxicol Lett. 2012 Jun 1;211(2):114-9. Dunnett CW (1955) A multiple comparison procedure for comparing several treatments with a control. Journal of the American Statistical Association. 50:1096-1121 EFSA (2014) Draft scientific opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs. Draft report by the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids. Fisher JW, Twaddle NC, Vanlandingham M, Doerge DR. Pharmacokinetic modeling: prediction and evaluation of route dependent dosimetry of bisphenol A in monkeys with extrapolation to humans. Toxicol Appl Pharmacol. 2011 Nov 15;257(1):122-36. Mahmood I. Theoretical versus empirical allometry: Facts behind theories and application to pharmacokinetics. J Pharm Sci. 2010 Jul;99(7):2927-33.	
Fernandez de Celis Alvaro, MedPharmPlast Europe, Alvaro.fernandez@eupc.org, Belgium	6. LIST OF ABBREVIATIONS	continued: 4. Reference List Crump KS (1984) A new method of determining allowable daily intakes. Fundamental and Applied Toxicology. 4:854-871. Cho CY, Shin BS, Jung JH, Kim DH, Lee KC, Han SY, Kim HS, Lee BM, Yoo SD. Pharmacokinetic scaling of bisphenol A by species-invariant time methods. Xenobiotica. 2002 Oct;32(10):925-34. Doerge DR, Twaddle NC, Vanlandingham M, Fisher JW. Pharmacokinetics of bisphenol A in neonatal and adult	The SCENIHR made a selection of most recent literature (as indicated in the Methodology section). Most of the literature indicated is already included in the SCENIHR Opinion

		CD-1 mice: inter-species comparisons with Sprague-Dawley rats and rhesus monkeys. Toxicol Lett. 2011 Dec 15;207(3):298-305. Doerge DR, Twaddle NC, Vanlandingham M, Fisher JW. Pharmacokinetics of bisphenol A in serum and adipose tissue following intravenous administration to adult female CD-1 mice. Toxicol Lett. 2012 Jun 1;211(2):114-9. Dunnett CW (1955) A multiple comparison procedure for comparing several treatments with a control. Journal of the American Statistical Association. 50:1096-1121 EFSA (2014) Draft scientific opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs. Draft report by the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids. Fisher JW, Twaddle NC, Vanlandingham M, Doerge DR. Pharmacokinetic modeling: prediction and evaluation of route dependent dosimetry of bisphenol A in monkeys with extrapolation to humans. Toxicol Appl Pharmacol. 2011 Nov 15;257(1):122-36. Mahmood I. Theoretical versus empirical allometry: Facts behind theories and application to pharmacokinetics. J Pharm Sci. 2010 Jul;99(7):2927-33.	
Hamelton Anne-Marie, PlasticsEurope, anne-marie.hamelton@plasticseurope.org, Belgium	6. LIST OF ABBREVIATIONS Check reference 11, 12	4. Reference List Crump KS (1984) A new method of determining allowable daily intakes. Fundamental and Applied Toxicology. 4:854-871. Cho CY, Shin BS, Jung JH, Kim DH, Lee KC, Han SY, Kim HS, Lee BM, Yoo SD. Pharmacokinetic scaling of bisphenol A by species-invariant time methods. Xenobiotica. 2002 Oct;32(10):925-34. Doerge DR, Twaddle NC, Vanlandingham M, Fisher JW. Pharmacokinetics of bisphenol A in neonatal and adult CD-1 mice: inter-species comparisons with Sprague-Dawley rats and rhesus monkeys. Toxicol Lett. 2011 Dec 15;207(3):298-305. Doerge DR, Twaddle NC, Vanlandingham M, Fisher JW.	The SCENIHR made a selection of most recent literature (as indicated in the Methodology section) Most of the literature indicated is already included in the SCENIHR Opinion

		Pharmacokinetics of bisphenol A in serum and adipose tissue following intravenous administration to adult female CD-1 mice. Toxicol Lett. 2012 Jun 1;211(2):114-9. Dunnett CW (1955) A multiple comparison procedure for comparing several treatments with a control. Journal of the American Statistical Association. 50:1096-1121 EFSA (2014) Draft scientific opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs. Draft report by the EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids. Fisher JW, Twaddle NC, Vanlandingham M, Doerge DR. Pharmacokinetic modeling: prediction and evaluation of route dependent dosimetry of bisphenol A in monkeys with extrapolation to humans. Toxicol Appl Pharmacol. 2011 Nov 15;257(1):122-36. Mahmood I. Theoretical versus empirical allometry: Facts behind theories and application to pharmacokinetics. J Pharm Sci. 2010 Jul;99(7):2927-33.	
Moussa Miranda, AESGP - Association of the European Self-Medication Industry, m.moussa@aesgp.eu, Belgium	7. REFERENCES	Delclos et al. Toxicity Evaluation of Bisphenol A Administered by Gavage to Sprague-Dawley Rats from Gestation Day 6 through Postnatal Day 90. Toxicol. Sci. kfu022 first published online February 4, 2014 doi:10.1093/toxsci/kfu022 Churchwell et al. Comparison of Lifestage-Dependent Internal Dosimetry for Bisphenol A, Ethinyl Estradiol, a Reference Estrogen, and Endogenous Estradiol to Test an Estrogenic Mode of Action in Sprague-Dawley Rats. Toxicol. Sci. kfu021 first published online February 4, 2014 doi:10.1093/toxsci/kfu021	As indicated in the Opinion there is an abundance of literature. Several papers were cited on possible effects. This literature was published after the finalisation of the SCENIHR Opinion. Both Delclos et al., 2014 and Churchwell et al., 2014 are now included in the final Opinion. The results on various parameters including reproduction and mammary gland hyperplasia are discussed in relevant sections of the Opinion.

Moussa Miranda, AESGP - Association of the European Self-Medication Industry, m.moussa@aesgp.eu, Belgium	7. REFERENCES	The following recent publications relevant to the low-dose effects of BPA should be considered in the opinion/assessment and add to the list of references: - Delclos et al. Toxicity Evaluation of Bisphenol A Administered by Gavage to Sprague-Dawley Rats from Gestation Day 6 through Postnatal Day 90. Toxicol. Sci. kfu022 first published online February 4, 2014 doi:10.1093/toxsci/kfu022 - Churchwell et al. Comparison of Lifestage-Dependent Internal Dosimetry for Bisphenol A, Ethinyl Estradiol, a Reference Estrogen, and Endogenous Estradiol to Test an Estrogenic Mode of Action in Sprague-Dawley Rats. Toxicol. Sci. kfu021 first published online February 4, 2014 doi:10.1093/toxsci/kfu021	See the response above.
Stock Gregor, FIDE - European Dental Industry, g.stock@fide-online.org, Germany	7. REFERENCES	The following recent publications relevant to the low-dose effects of BPA should be considered in the assessment: Delclos et al. Toxicity Evaluation of Bisphenol A Administered by Gavage to Sprague-Dawley Rats from Gestation Day 6 through Postnatal Day 90. Toxicol. Sci. kfu022 first published online February 4, 2014 doi:10.1093/toxsci/kfu022 Churchwell et al. Comparison of Lifestage-Dependent Internal Dosimetry for Bisphenol A, Ethinyl Estradiol, a Reference Estrogen, and Endogenous Estradiol to Test an Estrogenic Mode of Action in Sprague-Dawley Rats. Toxicol. Sci. kfu021 first published online February 4, 2014 doi:10.1093/toxsci/kfu021	See the response above.

Jamin Marc, SABIC Innovative Plastics BV, marc.jamin@sabic-ip.com, Netherlands	7. REFERENCES	continued: Shao K, Gift JS, Setzer RW (2013) Is the assumption of normality or log-normality for continuous response data critical for benchmark dose estimation? Toxicological Applied Pharmacology. 272:767-779. Slob W (2002) Dose-response modeling of continuous endpoints. Toxicological Sciences. 66:298-312. Slob W, Setzer RW (2013) Shape and steepness of toxicological dose-response relationships of continuous endpoints. Critical Reviews in Toxicology. 44:270-297. Slob W (2014) PROAST Manual. Available at http://www.rivm.nl/en/Documents_and_publications/Scientific/Models/PROAST. Taylor JA, Vom Saal FS, Welshons WV, Drury B, Rottinghaus G, Hunt PA, Toutain PL, Laffont CM, VandeVoort CA. Similarity of bisphenol A pharmacokinetics in rhesus monkeys and mice: relevance for human exposure. Environ Health Perspect. 2011 Apr;119(4):422-30. Tyl RW, Marr MC, Thomas BF, Keimowitz AR, Brine DR, Veselica MM, Fail PA, Chang TY, Seely JC, Joiner RL, Butala JH, Diamond SS, Cagan SZ, Shiotsuka RN, Stroop GD, Waechter JM. Three-generation reproductive toxicity study of dietary bisphenol A in CD Sprague-Dawley rats. Toxicological Sciences. 68:121-146. U.S. EPA (2014) BMDS user manual. Available at http://www.epa.gov/ncea/bmds/ Völkel W, Colnot T, Csanády GA, Filser JG, Dekant W. Metabolism and kinetics of bisphenol a in humans at low doses following oral administration. Chem Res Toxicol. 2002 Oct;15(10):1281-7	The SCENIHR made a selection of most recent literature (as indicated in the Methodology section) Most of the literature indicated is already included in the SCENIHR Opinion The first papers and the US EPA reference seem to deal with the EFSA approach for the calculation of the t-TDI.
Fernandez de Celis Alvaro, MedPharmPlast Europe, Alvaro.fernandez@eupc.org, Belgium	7. REFERENCES	continued: Shao K, Gift JS, Setzer RW (2013) Is the assumption of normality or log-normality for continuous response data critical for benchmark dose estimation? Toxicological Applied Pharmacology. 272:767-779. Slob W (2002) Dose-response modeling of continuous endpoints. Toxicological Sciences. 66:298-312.	See the response above.

		Slob W, Setzer RW (2013) Shape and steepness of toxicological dose-response relationships of continuous endpoints. Critical Reviews in Toxicology. 44:270-297. Slob W (2014) PROAST Manual. Available at http://www.rivm.nl/en/Documents_and_publications/Scientific/Models/PROAST. Taylor JA, Vom Saal FS, Welshons WV, Drury B, Rottinghaus G, Hunt PA, Toutain PL, Laffont CM, VandeVoort CA. Similarity of bisphenol A pharmacokinetics in rhesus monkeys and mice: relevance for human exposure. Environ Health Perspect. 2011 Apr;119(4):422-30. Tyl RW, Marr MC, Thomas BF, Keimowitz AR, Brine DR, Veselica MM, Fail PA, Chang TY, Seely JC, Joiner RL, Butala JH, Diamond SS, Cagan SZ, Shiotsuka RN, Stroop GD, Waechter JM. Three-generation reproductive toxicity study of dietary bisphenol A in CD Sprague-Dawley rats. Toxicological Sciences. 68:121-146. U.S. EPA (2014) BMDS user manual. Available at http://www.epa.gov/ncea/bmds/ Völkel W, Colnot T, Csanády GA, Filser JG, Dekant W. Metabolism and kinetics of bisphenol a in humans at low doses following oral administration. Chem Res Toxicol. 2002 Oct;15(10):1281-7	
Hamelton Anne-Marie, PlasticsEurope, anne-marie.hamelton@plasticseurope.org, Belgium	7. REFERENCES	Shao K, Gift JS, Setzer RW (2013) Is the assumption of normality or log-normality for continuous response data critical for benchmark dose estimation? Toxicological Applied Pharmacology. 272:767-779. Slob W (2002) Dose-response modeling of continuous endpoints. Toxicological Sciences. 66:298-312. Slob W, Setzer RW (2013) Shape and steepness of toxicological dose-response relationships of continuous endpoints. Critical Reviews in Toxicology. 44:270-297. Slob W (2014) PROAST Manual. Available at http://www.rivm.nl/en/Documents_and_publications/Scientific/Models/PROAST. Taylor JA, Vom Saal FS, Welshons WV, Drury B, Rottinghaus G, Hunt PA, Toutain PL, Laffont CM,	See the response above.

		VandeVoort CA. Similarity of bisphenol A pharmacokinetics in rhesus monkeys and mice: relevance for human exposure. Environ Health Perspect. 2011 Apr;119(4):422-30. Tyl RW, Marr MC, Thomas BF, Keimowitz AR, Brine DR, Veselica MM, Fail PA, Chang TY, Seely JC, Joiner RL, Butala JH, Diamond SS, Cagan SZ, Shiotsuka RN, Stroop GD, Waechter JM. Three-generation reproductive toxicity study of dietary bisphenol A in CD Sprague-Dawley rats. Toxicological Sciences. 68:121-146. U.S. EPA (2014) BMDS user manual. Available at http://www.epa.gov/ncea/bmds/ Völkel W, Colnot T, Csanády GA, Filser JG, Dekant W. Metabolism and kinetics of bisphenol a in humans at low doses following oral administration. Chem Res Toxicol. 2002 Oct;15(10):1281-7	