Results of the public consultation on SCENIHR's preliminary Opinion on the safety of dental amalgam and alternative dental restoration materials for patients and users

A public consultation on the preliminary Opinion was opened on the website of the Scientific Committees from 9 September to 16 November 2014. Information about the public consultation was broadly communicated to national authorities, international organisations and other stakeholders.

Twenty five contributors- representing industry associations, universities, professional organisations, national authorities, non-governmental organizations and individuals- participated in the public consultation providing input to the main scientific questions (in total 102 contributions were received).
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 scientific rationale and the Opinion section were clarified and strengthened.

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

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

Comments received during the public consultation on the SCENIHR preliminary opinion on the safety of dental amalgam and alternative dental restoration materials for patients and users

No	Name of individual/ organisation	Table of content to which comment refers	Comment	Scientific Committees Response
1	Rooney James, Trinity College Dublin, jrooney@rcsi.ie	ABSTRACT	Page 4, paragraph 5: "The most recent in vitro evidence provides new insight into the effects of mercury on developing neural brain cells at concentrations similar to those found in human brain. The effects of genetic polymorphism concerning mercury elimination may influence the degree of individual susceptibility in regard to mercury internal exposure and toxicity. They therefore raise some concern for possible effects on the brain of mercury originating from dental amalgam. However, so far such effects have not been documented in humans." Comment: There is evidence from epidemiological studies of numerous genetically predisposed subgroups who do suffer subtle neurobehavioural effects on exposure to mercury. This has been demonstrated in both dental workers and children partaking in amalgam trials. Key findings are summarized in recent review papers.(1,2) Page4, paragraph 6: "As with any other medical or pharmaceutical intervention, caution should be exercised when considering the placement of any dental restorative material in pregnant women." Comment: It is not clear from this statement whether mercury is contraindicated in pregnant women or not. SCENIHR should show leadership here and clearly define pregnancy as a contraindication to amalgam placement.	Concerning the two cited references, please consider that: Basu et al., 2014 is a review; no original data are presented. However, the reference it is now included in the text Ref 2 is again a review, presenting a re-evaluation of data from the Casa Pia Study (cited in the opinion). In a reply of the authors to a former re-evaluation of the Casa Pia study, the method used for re-evaluation was criticised by the authors of the Casa Pia study (DeRouen T, Woods J, Leroux B, Martin M:Critique of reanalysis of Casa Pia data on associations of porphyrins and glutathione-S-transferases with dental amalgam exposure. Hum Exp Toxicol. 2014 Jul 8.): the paper is referred to in the text. The problem of post-hoc analyses was addressed in the Opinion: "As Friedman et al. document, there are numerous examples of such post hoc findings not being confirmed in subsequent trials." The issue of polymorphism is treated in more detail in the main text of the Opinion; not too many details can be added here in the abstract. Furthermore, the issue is still controversial, since the amount of available information has grown over the last years and has not yet been well consolidated. In addition, the evidence of genetic factors impacting Hg dynamics comes from a single research team. In the specific commented paragraph, reference is made specifically to direct effects on the brain that have not been documented. To make the text clearer and in order to address

			Page4, paragraph 7: "Recent studies do not indicate that dental personnel in general, despite somewhat higher exposures, suffer from adverse effects that can be attributed to mercury exposure due to dental amalgam." Comment: In fact numerous genetically (CPOX4, BDNF, COMT etc) predisposed subgroups who do suffer subtle neurobehavioral effects on exposure to mercury have been demonstrated in dental workers.(3–6) Page 5, paragraph 2: "It is concluded that current evidence does not preclude the use of either amalgam or alternative materials in dental restorative treatment. However, the choice of material should be based on patient characteristics such as primary or permanent teeth, pregnancy, the presence of allergies to mercury or other components of the restorative materials, and presence of decreased renal clearance." Comment: It is not clear from this statement whether mercury is contraindicated in these cohorts of people. Again SCENIHR should show leadership here and clearly define these conditions as a contraindication to amalgam placement. Furthermore, I will present evidence in my further comments to argue that this list should be extended to include: children, breast-feeding mothers, and thyroid disease patients. Finally SCENIHR should provide some guidance on the maximum number of fillings that an individual patient should be exposed to. References: 1. Basu, N., Goodrich, J. M. & Head, J. Environ. Toxicol. Chem. 33, 1248–58 (2014). 2. Woods, J. S., Heyer, N. J., Russo, J. E., Martin, M. D. & Farin, F. M. Neurotoxicology 44C, 288–302 (2014). 3. Woods, J. S. et al. Toxicol. Appl. Pharmacol. 206, 113–20 (2005). 4. Heyer, N. J. et al. Toxicol. Sci. 363, 354–363 (2004). 5. Heyer, N. J., Echeverria, D., Farin, F. M. & Woods, J. S. J. Toxicol. Environ. Health. A 71, 1318–1326 (2008). 6. Heyer, N. J., Echeverria, D., Martin, M. D., Farin, F. M. &	the concern related to this point, the text in the abstract has been slightly modified as follows: "The most recent in vitro evidence provides new insight into the effects of mercury on developing neural brain cells at concentrations similar to those found in human brain. The effects of genetic polymorphism concerning mercury *kinetics* may influence the degree of individual susceptibility in regard to mercury internal exposure and *consequently* toxicity. They therefore raise some concern for possible effects on the brain of mercury originating from dental amalgam. However, so far such effects have not been *clearly demonstrated* in humans*, although some evidence on alteration of Hg dynamics have been reported.* The SCENHIR clearly stated that 'the choice of material should be based on patient characteristics' including pregnancy. Therefore there is not contraindication, but this statement is consistent with the conclusion 'current evidence does not preclude the use of either amalgam or alternative materials in dental restorative treatment': caution is requested, as for any other medical or pharmaceutical intervention. Ref 3 by Woods is already included in the text. The fact that there may be genetic variants related to mercury kinetics is discussed in the document (see page 32). Refs 4-6: studies by Heyer at al. These studies have been mentioned and are discussed in the document (see above). See also the previous answer related to the polymorphism issue. As it has been mentioned in the document, no definite conclusions can be drawn from such data, but research in this area is emphasised. (see also page 38 of the document). No data comparing amalgam to alternatives concerning these genetic markers are available. Please see response above.

			Woods, J. S. J. Toxicol. Environ. Health. A 72, 599–609 (2009).	
2	Swedish Chemicals Agency, kemi@kemi.se	ABSTRACT	6th para: See our comment on section 3.3.10. Change due to proposed change in section 3.3.10. p4, 8th para+p5 1st para: Other alternatives than those containing bisphenol A are summarized as if they are a homogenous group of materials. Especially inorganic materials are missed in the conclusion. Altogether it gives an impression that all alternatives are similar or more hazardous than the dental amalgam, although the scientific data are very limited. The text in the report needs to be rephrased	This is not correct. The text of the document is: "Release of bisphenol A (BPA) from **some** dental materials …" Glass ionomers and ceramics are mentioned in the Abstract and in the respective paragraphs. For other inorganic materials, mechanical properties are inferior (e.g. phosphate cements, calcium-silicate cements) or clinical data are missing (e.g. gionomers).
3	Lidmark Ann-Marie, Tandvårdsskadeförbudet (The Swedish Association of Dental Mercury Patients), lidmark@gmail.com	ABSTRACT	Tandvårdsskadeförbundet (The Swedish Association of Dental Mercury Patients) agree with the enumeration of mercury´s different toxic effects. In contrary with the committee our opinion is that the evidence for such effects is high according to both the background material presented and our members experience. In our opinion and according to the evidence and the precautionary principle dental amalgam should be faced out as fast as possible. There is high exposure for mercury under removal of amalgam fillings and our conclusion is that good methods for amalgam removal needs to be worked out with adequate protection for both patients and dental personnel. This has not been noticed by the committee nor yet detoxification or other effective treatements.	This is a matter of interpretation of available data. In the absence of additional data, the SCENIHR Opinion is described and justified in the document. The use of dental amalgam is rapidly decreasing. It is emphasised that information on the toxicological profile of alternative material is limited when compared to that of dental amalgam. Therefore, their adoption is not 'safer' as a default factor. The high exposure related to removal of existing filling is acknowledged in the document, SCENHIR agrees that good practices for amalgam removal need to be applied, but their definition is out of the mandate of this document. However a reference to this issue has been included in the abstract p.4. *However, exposure of both patients and dental personnel should be minimised by the use of appropriate clinical techniques.*Many aspects may deserve further investigations, but clinical data showing problems with amalgam removal under today's practices should be provided.

4	Schulze Florian, World Alliance for Mercury free Dentistry, florianschulze@hotmail.com	ABSTRACT	The report is analyzing the direct health impact of amalgam-fillings. It is proofed that mercury is constantly evaporating from the amalgam fillings and deposited in the human body. It is also proofed that under certain conditions a transformation from mercury into Methymercury can take place inside the human body. But since the inhaled amount of Mercury from amalgam fillings is very low, you are considering the burden for the general population as insignificant to cause health effects. Even though you have done exceptions for vulnerable people, you have not considered the synergetic effect of mercury with other elements like for example Lead(1). Many people do have a burden of lead, since it is diffused in the atmosphere by combustion and also by tab water due to tubes out of lead. The health impact would therefore be multiplied for a significant part of the population. Please take the attached studies into consideration for the report of direct health risks. 1) J Toxicol Environ Health. 1978 Sep-Nov;4(5-6):763-76. Combined effects in toxicology--a rapid systematic testing procedure: cadmium, mercury, and lead. Schubert J, Riley EJ, Tyler SA. http://www.ncbi.nlm.nih.gov/pubmed/731728 2)Arch Med Res. 2003 Jan-Feb;34(1):50-5. Nephrotoxic effects of mercury exposure and smoking among Egyptian workers in a fluorescent lamp factory. El-Safty IA1, Shouman AE, Amin NE. http://www.ncbi.nlm.nih.gov/pubmed/12604375 3)J Inorg Biochem. 2003 Feb 1;94(1-2):50-8. Enhanced conformational changes in DNA in the presence of mercury(II), cadmium(II) and lead(II) porphyrins. Tabata M1, Kumar Sarker A, Nyarko E. http://www.ncbi.nlm.nih.gov/pubmed/12620673 4)Biol Trace Elem Res. 2001 Winter;84(1-3):139-54. Nephrotoxicity of simultaneous exposure to mercury and uranium in comparison to individual effects of these metals in rats. Sánchez DJ1, Bellés M, Albina ML, Sirvent JJ, Domingo JL.	SCENHIR agrees that the issue can be of relevance, but the synergistic effect of mercury with other elements is outside the mandate received from the Commission. In addition the comment refers to mercury/lead combinations, but the references provided do not show clinically relevant information for amalgam or mercury derived from amalgam, nor do the authors of these articles refer to the amalgam situation. Ref 1 refers to the general issue of interactions among chemicals. However, no data are provided for mercury from amalgam. Ref 2 refers to industrial workers and mercury exposure, not to amalgam. Ref 3 refers to *in vitro* test on different metals/metal porphyrins on DNA change. No mention of amalgam, no indirect relation to the subject. Ref 4 considers that mercury and uranium interaction in rat studies are not related to the topic. Ref 5 refers to seafood methyl mercury and PCB: possible synergistic effect, but does not include dental amalgam. In addition, methyl mercury effects are different from mercury in dental amalgam.

			http://www.ncbi.nlm.nih.gov/pubmed/11817685 5) Neurotoxicol Teratol. 2001 Jul-Aug;23(4):305-17. Neurobehavioral deficits associated with PCB in 7-year-old children prenatally exposed to seafood neurotoxicants. Grandjean P1, Weihe P, Burse VW, Needham LL, Storr-Hansen E, Heinzow B, Debes F, Murata K, Simonsen H, Ellefsen P, Budtz-Jørgensen E, Keiding N, White RF. http://www.ncbi.nlm.nih.gov/pubmed/11485834	
5	Zimmerman Clinton, self-also works with consumers for dental choice, clintonzim@aol.com	3.1. Introduction	Scenihr conclusion: "The contribution of methyl mercury exposure when compared to inorganic exposure is excpected to be limited"This unsupported scientific conclsion is completely unjustified. In recent testimony at the 2010 FDA hearings, Dr. Ann Summers microbiologist, a leading expert in this field and invited expert speaker who uses newer extremely sensitive tests for methyl Hg noted-as seen in the transcripts, that Hg from amalgam "vastly boosted the levels of methyl and dimethyl Hg found in the gut". The advanced methods used by Summers and her team were shortly published thereafter. See "Discovering mercury protein modifications in whole proteomes using natural isotope distributions observed in liquid chromotraphy-tandam mass spectrometry" Purvine,Zink,Lipton,Summers Mol Cell Proteomics 2011Aug:10(8) for a description of newer methyl mercury detection methods. This finding was uncontested by the expert FDA committee who showed great interest in these results. Hardly a consensus as stated by SCENIHRthat mercury conversion from amalgam is insignificant in the human body. Therefore there is every reason to expect the contribution to be significant. The conversion of amalgam Hg to methyl and dimethyl, an extremely toxic form of Hg has also been documented by Haley in "The Relationship of the Toxic Effects of Mercury to the Exacerbation of the Medical Condition Classified as Alzhiemers Disease". SCENIHR excludes this important reference in the peer reviewed literature. There are numerous similar scientific	About the transformation of inorganic mercury to methyl mercury in the body, which is treated in the document, the comment makes reference to an open hearing, where individual Opinions could be presented. The SCENIHR recognises the importance of the outcome of FDA hearings. However, the SCENIHR can only cite definitive conclusions from such hearings when published on the FDA website. The SCENIHR cannot cite views presented at those hearings unless they are supported by scientific data in the open literature. Please take into account that the amount of methylmercury eventually formed from dental amalgam should be put into context, considering the exposure coming from the diet (especially fish). In the provided reference (Purvine et al, 2011), the topic of transformation of inorganic mercury originating from dental amalgam into methyl mercury is not mentioned. The topic of Alzheimer's and amalgam has been extensively covered. In a review paper, Mutter et al (2010) did not indicate that available data allowed judgement on an association between amalgam and Alzheimer's.

			refernces in the peer reviewed literature on this issue as given by Mutter in "Is dental amalgam safe for humans? The opinion of the scientific committee of the European Commission" where he documents many papers and gives many likely routes of methyl Hg absorption from amalgam including conversion of Hg from amalgam by Bacteria near the jawbone and direct delivery to the brain via the jawbone. The studies cited by Scenihr do not address the most likely modes of transmission, conversion in the gut, breakdown of amalgam particles in the gut (significant and also published in peer reviewed journals) and corrosion and conversion on the top surface of fillings in the jaw, however one of the two studies cited by Scenihr clearly demonstrates ready conversion of dental Hg to the methyl form by S. Mutans a common bacteria in the oral cavity. The other study does not investigate corrosion and bacterial interaction on the top unexposed surface of the filling at all, the most likely route of Hg delivery besides conversion in the gut, but takes a few bacteria scrapings from the surface of a few teeth.	
6	Begon Geoffrey, World Alliance for Mercury-Free Dentistry, beggeof@yahoo.fr	3.1. Introduction	The preliminary opinion says "Once released into saliva, inorganic mercury might be methylated by bacteria in the periodontal pocket and gastrointestinal tract, but the rate is not clear (Langendijk et al., 2001, Leistevuo et al., 2002, van der Hoeven et al., 2007). However, the contribution of this reaction when compared to the intake of methyl mercury from the food is expected to be limited." (page 13) This is beside the point. It does not matter how the amount of amalgam's methylated mercury compares to the amount of methylmercury in diet. Instead, SCENIHR needs to consider these two sources of methylmercury combined – is the total amount of methylmercury from both sources problematic? The preliminary opinion says "The alternatives for dental amalgam in dental restoration include resin based composite materials, glass ionomer cements, ceramics, gold-based and other alloys, and a variety of hybrid structures. Many of	The mandate of the SCENIHR deals with the safety of dental amalgam, therefore methyl mercury by itself was not evaluated. Only the possible additive effect due to the release of mercury or transformation to methyl mercury after release from dental amalgam as well as the transformation of methyl mercury to inorganic mercury were considered in the Opinion. Indeed, resin-based formulations (and other materials) have been studied for more than half of a century, but at the beginning for non-stress—bearing areas like front teeth. However, here we are concerned with the use of such materials in the posterior teeth. Materials for stress-bearing areas, based on resin formulations, have only been extensively tested since the 1990s. At that time, materials and bonding substances were inferior. Formulations with improved technical properties have only been clinically tested recently, during the last 10 years or so. These formulations are rapidly changed by the

			them have been in use only for a limited number of years..." (page 13) In fact, mercury-free alternatives to dental amalgam have been studied for more than half a century. Jack L Ferracane, Resin composite--state of the art, Dental Materials, Vol.27, issue 1, p.29-38 (Jan. 2011), http://www.ppgo.ufma.br/uploads/files/Dental%20materials%20official%20publication%20of%20the%20Academy%20of%20Dental%20Materials%202010%20FerracaneResin%20composite-State%20of%20the%20art.pdf	manufacturers, so that the actual information on new materials is indeed limited and certainly much less than for amalgam. The exact composition of those materials is not published – in contrast to amalgam and dental alloys.
7	Rooney James, Trinity College Dublin, jrooney@rcsi.ie	3.2. Methodology	Page 14, paragraph 2 & 3: "The SCENIHR has considered evidence derived from a wide variety of sources, including peer reviewed scientific and medical literature and published reports of institutional, professional, governmental and non-governmental organisations. In coherence with the usual practice of the SCENIHR, less weight has been given to work not freely available in the public domain. The SCENIHR has reviewed as much evidence as possible and, especially where the available data on alternatives is limited, attention has been given to some less well-controlled studies where no other information was available. During the course of the deliberations of the Working Group, a Call for Information was issued by the Commission (8 August 2012 to 10 October 2012) and all of the responses have been considered." Comment: It is surprising that this report does not include precise details on the search strategy used to identify the relevant papers from the literature and details of inclusion and exclusion criteria, other than to state that a call for information was made. Several guidelines for performing systematic reviews and reporting formats are available and are required by several journals – for example the PRISMA statement (http://www.prisma statement.org/statement.htm), or the Cochrane Handbook for Systematic Reviews of Interventions (http://handbook.cochrane.org/). This review appears to	This comment is relevant. The following text has been added under 3.2. Methodology: During the course of the deliberations of the Working Group, a Call for Information was issued by the Commission (8 August 2012 to 10 October 2012) and all of the responses have been considered. An extensive literature search was performed in 2012 (covering the period 2008-2012) by an external contractor with the following search terms: *Dental amalgams/mercury amalgams implants/fillings and:* – mercury exposure/levels/ blood/body burden/brain – leaching/ loss/release/mobilisation/stability – risk assessment/hazard/adverse effects/disorders/ neuro* effects/safety/risk benefits – removal, health effects/implications/risk/risk benefit/safety – cremation – life cycle analysis/ manufacturing/use/disposal Non –mercury/ceramic/implants/fillings and: – leaching/ loss/release/mobilisation/stability – risk assessment/hazard/adverse effects/disorders/ neuro* effects/safety/risk benefits – removal, health effects/implications/risk/risk benefit/safety – life cycle analysis/ manufacturing/use/disposal In addition, during the writing of the Opinion, additional relevant literature up to 2014 was provided by both members of the working group and of THE SCENIHR. Also literature before 2008, not included in the previous Opinion, but considered relevant, was assessed.

			have missed several important papers on mercury and amalgam that I will upload with further comments. However, as there is no clearly stated search strategy, inclusion or exclusion criteria I cannot determine if these papers were identified by the committee and rejected for some reason or were simply not identified in the first place.	Furthermore, relevant references provided via the Public Consultation have been included as well.
8	Björkman Lars, The Dental Biomaterials Adverse Reaction Unit / Uni Research AS, Norway, Lars.Bjorkman@uni.no	3.2. Methodology	In section "3.2. Methodology", generally accepted criteria for causation are mentioned. One of these is "the evidence of a dose-response relationship". In the present report two important references regarding dose – response relationships are lacking: Stenman and Grans (1997). And Weidenhammer et al (2010). These references should be considered and discussed. Without taking these references into consideration the report is not complete. A dose-response relationship between amalgam exposure and a (sub-clinical) effect was also reported in the paper by Kingman et al (2005), which is cited in the present report (section 3.3.5.2. Systemic effects, page 30). A statistically significant association was detected between amalgam exposure and the continuous vibrotactile sensation response. The findings support the hypothesis that exposure to amalgam produces sub-clinical neurological effects. REFERENCES: Kingman A, Albers JW, Arezzo JC, Garabrant DH, Michalek JE. Amalgam exposure and neurological function. Neurotoxicology. 2005;26:241-55. Stenman S, Grans L. Symptoms and differential diagnosis of patients fearing mercury toxicity from amalgam fillings. Scand J Work Environ Health. 1997;23 Suppl 3:59-63. Weidenhammer W, Bornschein S, Zilker T, Eyer F, Melchart D, Hausteiner C. Predictors of treatment outcomes after removal of amalgam fillings: associations between subjective symptoms, psychometric variables and mercury levels. Community Dent Oral Epidemiol. 2010;38:180-9.	In the study of Stenman and Grans (1997), Finnish patients with high urinary mercury levels and self-reported problems were investigated. A clear study design related to the number of amalgam fillings is missing. Also, no attempt was made to analyse other mercury sources; e.g. from food. This is especially of importance for this population, where fish consumption may play a major role. The authors write themselves: "The clinical picture of possible mercury toxicity from amalgam cannot be determined on the basis of our results" For this reason it was not considered relevant and not included in the Opinion. In the study by Ahlqwist et al. (1993), referred to in the Opinion, the "dose" (expressed as "number of amalgams") was used. No correlation of possible health symptoms for cardiovascular disease, diabetes, cancer and early death in Swedish women with the number of existing amalgam filling was found. Weidenhammer et al (2010): This evaluation is based on the patient sample from the Melchart study from 2008, which is mentioned in the document (see page 31/34). The main results are: (1) First, the main result of the trial published so far was confirmed. … (2) Prediction of symptom improvement after intervention was weak and involved baseline values with respect to psychological distress as well as mercury levels. … (3) The number of amalgam fillings (often used in the literature to estimate mercury burden) is probably a less precise measure and also usually fails to be associated with symptom scores– this was also the case in the study presented here (r = 0.13). … (4) … there may be a true association between symptoms and mercury levels in subgroups. Therefore, the question of 'amalgam sensitivity' should concentrate more on individual vulnerability, either in the form of biological (e.g. genetic) or

				psychosocial (e.g. personality, experiences, health beliefs and concerns) predisposition. This means that a dose-relation between the number of amalgam fillings and clinical symptoms was not established and that research is necessary for vulnerable subgroups. The study of Weidenhammer et al., (2010) does not add any relevant information to the issue. This statement is not correct. The Kingman study has been discussed in the document and the authors themselves do not support this statement.
9	Zimmerman Clinton, self, clintonzim@aol.com	3.3.1. Metallurgical principles and physical-chemical properties	"Scenihr is not aware of any new developments in dental metallurgy" Has Schnier conducted a thorough review of papers on mercury alloys and changes of state published in the literature? Does Scenihr consider dental metallurgy to exclude phase changes in alloys with mercury that are not exclusively used in the dental industry? It is clear that that the current understanding of amalgam properties is inadequate as noted in the 2010 FDA hearings where it was recommend that the FDA investigate updated of amalgam "material" interactions. This statement ignores the understanding in the scientific literature that amalgam changes state (phases) with time and that numerous studies such as document by Mutter above, show that as much as 50% of Hg is missing from old amalgam, that clearly Hg migrates in significant amount from the inside of the filling. Scanning electron microscope studies shows vast depletion of Hg form the surface of amalgam and the formation of droplets on the surface. Extensive corrosion and depletion of Hg from amalgam with attendant changes in amalgam phases during the life of the filling is shown and referenced to other peer reviewed work on this subject such as in Pleva (1989). It is unquestioned in the scientific community that Hg is released as a vapor from amalgam which the current "dental material models" of amalgam cannot predict or explain whatsoever. Therefore this statement "nothing new" implies that everything is understood about the physics	The SCENIHR is aware of the release of mercury from dental amalgam, such as presented by Pleva (1989), but is not aware of basically new developments in dental amalgam metallurgy. However, the issue of developments in dental metallurgy is outside the mandate received from the Commission. The SCENIHR recognises the importance of the outcome of FDA hearings. However, the SCENIHR can only cite definitive conclusions from such hearings when published on the FDA website. The SCENIHR cannot cite views presented at those hearings unless they are supported by scientific data in the open literature.

			amalgam and this is uncontested and that new findings about changes in state of mercury alloy's have not been published outside of dental journals which is unsubstantiated. In fact the opposite is true. We now know that amalgam is not stable over the long term, is volatile and loses a great portion of its Hg in liquied gas and particle form. Certainly "that has not changed". Schnier should clarify whether the models of amalgam used in the dental journals can quantitatively predict the release of vapor and loss of Hg under various easily measurable lab conditions and make satisfactory predictions about long term amalgam corrosion and breakdown.	
10	GROSMAN Marie, Non au Mercure Dentaire, mariegrosman@free.fr	3.3.1.2. Background exposure to mercury	En 2013, plusieurs travaux dans des pays européens se sont intéressés à l'exposition au mercure de l'enfant in utero. Une étude espagnole sur 1800 nouveau-nés montre que cette exposition excède les doses recommandées par l'OMS dans 24 % des cas et les niveaux préconisés par l'EPA (5,8 µg/L dans le cordon ombilical) dans 64 % des cas [Llop, 2013]. Une seconde étude espagnole sur 112 trios (père, mère et enfant) confirme le transfert placentaire et estime quant à elle que les niveaux préconisés par l'EPA sont dépassés chez 70 % des enfants [Garcias-Esquinas, 2013]. Enfin une étude polonaise sur 40 femmes met en évidence que les concentrations de mercure dans le cordon ombilical dépassent dans 75 % des cas la dose que l'EPA considère comme sûre [Kozilowska, 2013]. De nombreux enfants européens sont donc surexposés au mercure avant même leur naissance : tout doit donc être fait pour réduire leur imprégnation. Or les amalgames contribuent significativement à l'exposition du fœtus en mercure [Drasch 1994, Palkovicova 2007]. Il est donc impératif de mettre fin à leur usage. D'abord parce que l'extrême toxicité du mercure sur le cerveau en développement est pointée depuis très longtemps [ATSDR 1999, Jedrychowski 2006]. Ensuite parce que de récents travaux ont montré que les niveaux de mercure placentaire influencent fortement la longueur du	The mandate of the Opinion was to evaluate the risk coming from mercury in dental amalgam, not the risk associated with mercury in general. Please consider that in many papers, mercury exposure is expressed as total (without differentiating between organic and inorganic, making it impossible to estimate the contribution from dental amalgam). Drasch 1994, Palkovicova 2007: The topic of foetal exposure is comprehensively discussed in the document. Mercury from dental amalgam is not an issue in the studies of Al-Saleh et al., (2013, 2013b). Norouzi et al.(2012) find a correlation between the number of maternal dental amalgam fillings and the concentration of mercury in breast milk. There is a very high background level of mercury, which the authors claim cannot be due to seafood, but they did not suggest any other sources. Ask Björnberg et al. (2003) find a correlation between the number of maternal dental amalgam fillings and the concentration of mercury in cord blood. They also find a correlation between the number of maternal meals with chicken and the mercury levels in cord blood. Due to the reduction of use of dental amalgam in children, the

			cordon, la circonférence de la tête et le score d'Apgar [Al-Saleh 2013b] et que les concentrations médianes de mercure sont plus élevées dans le cas des enfants souffrant d'une anomalie du tube neural [Jin 2013]. En outre, la concentration en mercure du lait est étroitement corrélée au nombre d'amalgames maternels [Björnberg 2005], ce qui peut entraîner un dépassement de la DHTP dans de nombreux cas [Da Costa 2005, Norouzi 2012]. Une récente étude a précisément démontré pour la première fois que l'exposition au mercure du lait maternel induit du stress oxydatif chez le nourrisson [Al-Saleh 2013]. L'arrêt de l'usage des amalgames permet d'abaisser rapidement l'exposition in utero. Ainsi, la quantité de mercure inorganique dans le cordon a été divisée par deux en 3 ans entre 2000 et 2003 chez les femmes suédoises suite au déremboursement des amalgames et à leur remplacement par des alternatives [Ask Björnberg 2003]. En Allemagne, de récents travaux ont montré que l'imprégnation en mercure de la population a significativement baissé depuis que les autorités sanitaires de ce pays ne recommandent plus l'usage des amalgames dentaires [Link 2012]. Références : cf. 8 References ***English translation:*** In 2013, a number of studies in European countries focused on the in utero exposure of babies to mercury. Spanish research on 1 800 new-borns shows that this exposure exceeds the levels recommended by the WHO in 24% of cases and those advocated by the EPA (5.8 µg/L in the umbilical cord) in 64% of cases [Llop, 2013]. A second Spanish study on 112 trios (father, mother and child) confirms the placental transfer and considers that the levels recommended by the EPA have been exceeded in 70% of children [Garcias-Esquinas, 2013]. Lastly, a Polish study of 40 women shows that the concentrations of mercury in the umbilical cord exceed the dose which the EPA considers to be	mercury levels in that population have significantly decreased as indicated by a study in Germany (Link et al 2012). The section 3.3.1.3. Intake estimates for mercury from dental amalgams was amended accordingly. The SCENIHR is not aware of any recommendation made by German authorities to stop the use of dental amalgam.

			safe in 75% of cases [Kozilowska, 2013]. Many European children are therefore over-exposed to mercury before they are even born: everything must therefore be done to reduce the levels in their blood. Since amalgam contributes significantly to foetal exposure to mercury [Drasch 1994, Palkovicova 2007], it is imperative that it no longer be used: first of all because the extreme toxicity of mercury for the developing brain has long been established [ATSDR 1999, Jedrychowski 2006]; secondly, because recent research shows that placental mercury levels have a strong influence on the length of the cord, the circumference of the head and the Apgar score [Al-Saleh 2013b] and that median concentrations of mercury are higher in the case of children suffering from an anomaly of the neural tube [Jin 2013]. Furthermore, the mercury concentration in milk is closely correlated to the number of amalgams which the mother has [Björnberg 2005], which can result in the PTWI being exceeded in numerous cases [Da Costa 2005, Norouzi 2012]. For the first time, recent research has clearly shown that exposure to mercury in breast milk causes oxidative stress in infants [Al-Saleh 2013]. Stopping the use of amalgam fillings makes it possible to quickly reduce in utero exposure. The quantity of inorganic mercury in the cord has thus decreased by half over three years between 2000 and 2003 in Swedish women, following reductions in reimbursement for amalgam fillings and their replacement with alternatives [Ask Björnberg 2003]. In Germany, recent work has shown that mercury levels in the population have significantly dropped since the German health authorities stopped recommending the use of dental amalgam [Link 2012]. References: cf. 8 References	
11	Zimmerman Clinton, self,	3.3.1.2. Background	"Mercury exposure in the general population by inhalation is very low"This arbitrary statement ignores recent studies	The Richardson papers are included in the documents and have been extensively discussed.

	clintonzim@aol.com	exposure to mercury	commissioned by Health Canada by Richardson as presented in the 2010 FDA hearings and noted in the FDA 2010 hearings transcript which show that it is estimated that about half of the population exceeds safe levels of exposure through this route. These studies by Richardson are peer reviewed and published in 2010 and 2011. Numerous peer reviewed studies such as those published by Haley and Mutter show that Hg release from vapor in the lab exceeds safe levels. Scenihr should take particular note of this when reading my response in section 4.2 when Schnier recommends that "no amalgam should ever by removed". Scenihr has not provided a meaningful model which shows that blood testing can accurately estimate vapor release from amalgams. The US FDA has never provided any data or even followed it's own toxilogical standards to show that urine and blood testing are accurate measures of total body burden or recent exposure from Hg vapor and neither has any regulatory body in the European Union. Scenihr also omits this basic fact. In fact at the FDA hearings in 2010 it was noted that urine testing is not adequate, "but it's the best we can do" according one panel member. In fact numerous studies show that excretion of Hg goes down with increased exposure, that is is inversely proportional in those most toxic. For example : "Urine Mercury in Micromercurialsism: Bimodal Distribution and Diagnostic Implcations. "Bull Envirion Toxicol.63(1999) Ely. Therefore according to leading experts and numerous peer reviewed scientific articles the above arbitrary and generalized claim cannot be justified in any meaningful scientific sense. Scenihr cannot simply ignor the peer reviewed literature on this issue. Most importantly a well-balanced and scientifically honest presentation should separate the various methods of measuring Hg exposure, i.e. fecal, urine, saliva, direct measurement and note the results of each method and conflicting opinions conclusions. The	In addition the paper from Nicolae et al., 2013 is cited in the text providing more recent measurements and also criticising the calculations made by Richardson et al. 2011. SCENIHR amended section 3.3.1.3 accordingly. The problems related to mercury exposure assessment in biomonitoring studies, especially related to the source of exposure, are addressed in the document. As to the reference to the FDA hearing, please see response to comment #5. There is very likely a misunderstanding, since the Opinion does not address exposure to methylmercury, as is clearly stated in the document: 'The present Opinion reviews only the toxicology of elemental and inorganic mercury, being relevant to amalgam safety considerations' (see the abstract) 'This Opinion does not address the issues of organic mercury or methyl mercury' (see page 8 Executive Summary) 'The present Opinion will focus on this mercury species' (referring to elemental mercury; see page 13 in the introduction). In the same paragraph, the possibility that methylation can occur (although with a non-clear rate) due to bacteria is considered, but the amount is estimated as limited when compared to the diet source. Due to the study design and methodological problems, the papers of Ely et al., 1999 and Haley et al, 2007 were not considered relevant to be addressed in the Opinion.

			following significant bias exists in Scenihr evaluations. As a class Scenihr omits those types of methods which give the highest estimations including published peer reviewed measurments of amalgam release by Chew(1992) and Haley (2007) and then quotes about half a dozen studies repeatedly which as a class all use the same controversial methodologies, urine and blood testing. Scenihr cannot simply exlude major classes of Hg exposure measurement published in the peer reviewed literature and expect this to be seen as good science. Scenihr also ignores direct measurements available in the literature given by fecal and saliva testing which are in line with estimations of Haley and Chew. I will not look these up but surely anyone with a scientific background could easily locate these studies.In section 3.1 Scenihr states that the importance of methyl conversion (from amalgam Hg) is not known and will not be considered, but it then proceeds in this section to provide scientifically unjustified estimates of methyl Hg exposure which are contradicted by testimony at the 2010 FDA hearings by world class experts in microbiology such as Dr. Ann Summers and peer reviewed articles as previously explained. Scenihr should take the FDA record on the expert committee findings with the same weight it gives to the WHO panel findings. This is not in my opinion a satisfactory scientific presentation. The fact that Scenihr initially admits that there is no adequate studies on Hg methyl uptake, then proceeds later to provide an "exact estimate" which ignores the major modes of likely amalgam delivery, conversion in the gut and corrosion bacterial conversion in the oral cavity jaw-bone is inadequate, since later conclusions then methodically build on these scientifically unsubstantiated statements. Scenihr should be more transparent about it's reasoning. Also Scenihr should clearly label in its tables as stated in the introduction that "methyl uptake due to Hg omitted or unknown" or show the studies which are capable of measuring long and short term Hg conversion to methyl and dimethyl forms in the gut and oral cavity. Especially	

			since Scenihr in its question and answer section reaches the stunning conclusion that no placed amalgam should ever be removed.	
12	Rooney James, Trinity College Dublin, jrooney@rcsi.ie	3.3.1.2. Background exposure to mercury	Page 17, paragraph 1 "Mercury is normally present in amniotic fluid." Comment: It may be usual to find mercury in amniotic fluid however it is certainly not "normal". Mercury has no useful function in human biology and no known safe limit of exposure has been determined – particularly in utero. Page 17, paragraph 2: "In breast milk total mercury (expressed as inorganic plus organic mercury). The exposure to both methyl mercury and inorganic mercury was low. They concluded that the exposure to both forms of mercury is higher before birth than during the breast-feeding period, and that methyl mercury seems to contribute more than inorganic mercury to infant exposure postnatal via breast milk." Comment: However milk harvested from fish-eating mothers in Brazil did show correlation with the number of amalgams in the mother and that the amount of Hg likely to be ingested by breast-fed infants was above WHO reference values in 56.% of cases(da Costa, Malm, & Dórea, 2005). Page 17, paragraph 4: "Brain tissue obtained from 35 children below 5 years of age showed mercury concentrations up to 20 µg/kg and a significant correlation ($p < 0.05$) with the mother's number of amalgam fillings (grouped as less than 2 or more than 10 fillings), and the same correlation was found for kidney cortex samples from	The word 'normally' has been replaced with 'usually'. The calculation of this value remains unclear in the publication. The data are in contradiction to other studies. However, reference to the paper has now been made in the Opinion (paragraph 3.3.1.2.), together with the consideration of other contrasting results. '*Da Costa et al, 2005 refer in their paper to the paper of Drasch et al. 1994, who compared mercury in breast milk and in cow's-milk-based formulas and concluded that even for mothers with large numbers of dental amalgam, these fillings should pose little danger to breast-feeding infants. Indeed, during the first 2 mo, it is uncertain if any correlation between milk mercury concentrations and maternal amalgam filling exists.* *Drexler and Schaller(1998) concluded that mercury exposure in breast-fed babies from maternal amalgam is of no significance to foetal and neonatal mercury in blood.* *Stoz et al. (1995) also reported that newly made tooth fillings during pregnancy had no influence on mercury concentrations in newborns.'* The Opinion was revised, and the reference about occurrence of restoration during pregnancy is more a comment than a real conclusion from the paper. As a consequence of the revision, the paragraph has been changed as follows: Brain tissue obtained from *18 foetuses and* 35 children below 5 years of age showed mercury concentrations up to *6 and* 20 µg/kg , respectively. A significant correlation ($p < 0.05$) with the mother's number of amalgam fillings (grouped as less than 2 or more than 10 fillings), *was evident only for older children and*

			38 foetuses and 35 infants. The transfer of mercury to the foetus was apparently not due to any dental restoration during pregnancy (Drasch 1994)." Comment: This study appears to have been misinterpreted by SCENIHR. Firstly - it does not report any dental restorations during pregnancy. Secondly the study concludes: "From our results it can be concluded that infants can accumulate mercury, apparently derived from maternal amalgam fillings, in their kidneys to a similar extent as older children or adults do from their own fillings. There- fore the unrestricted application of amalgam for dental restorations in women before and during the child-bearing age should be reconsidered in analogy to the recommen- dation of the German Health Authorities from 1992 [3], which argued that because of a higher vulnerability of in- fants to mercury, amalgam cannot be further recom- mended for dental restorations for children up to 6 years and notably not during the first 3 years of life. At the very least, high numbers of amalgam fillings should be avoided for women before and during child-bearing age. In 1991, the WHO confirmed an earlier statement from 1980: "The exposure of women of child-bearing age to mercury vapour should be as low as possible" [24]. " (Drasch, Schupp, Höfl, Reinke, & Roider, 1994) References: Da Costa, S. L., Malm, O., & Dórea, J. G. (2005). Breast-milk mercury concentrations and amalgam surface in mothers from Brasília, Brazil. Biological Trace Element Research, 106(2), 145–51. doi:10.1385/BTER:106:2:145 Drasch, G., Schupp, I., Höfl, H., Reinke, R., & Roider, G. (1994). Mercury burden of human fetal and infant tissues. European Journal of Pediatrics, 153(8), 607–10. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7957411	*not for foetuses. In foetuses and older infants significantly higher mean mercury concentrations in the liver and the renal cortex were found, if the mothers had >10 teeth with dental amalgam* (Drasch et al., 1994)." .
13	Begon Geoffrey, World Alliance for	3.3.1.2. Background	Exposure to Mercury in Adults The preliminary opinion says "As described in the previous opinion, exposure to mercury	The SCENIHR agrees and the text has been amended

	Mercury-Free Dentistry, beggeof@yahoo.fr	exposure to mercury	by inhalation is very low in the general population. The major sources of mercury intake in the diet is as inorganic mercury and methyl mercury (See Table 1 and 2)." (page 15-16) This is not consistent with Table 1, which lists estimated average daily intake of mercury vapour from amalgam (i.e. inhalation) as 3900-21,000 and intake from diet as only 4200 for inorganic mercury compounds and only 2400 for methylmercury. Exposure during pregnancy and breast-feeding The following studies were not included: • La Roo (2010) examined the association between maternal amalgam fillings placed early in pregnancy and oral clefts in a case-control study of 337 infants with cleft lip with or without cleft palate and 763 controls born in 1996-2001 in Norway. Mothers who received amalgam fillings during the first two months of pregnancy were more likely to have an infant with cleft palate. • Da Costa et. al. (2005) indicate that amalgams in nursing mothers can expose breast-fed infants to levels of mercury above the World Health Organization reference. While few known adverse effects were observed throughout pregnancies and in the newborn,it should be noted that some disorders such as learning disabilities and ADHD are not diagnosed until a child is older. LA DeRoo, Maternal amalgam fillings and the risk of infant oral clefts: a population-based case control study in Norway (2010), http://www.sper.org/archive/FinalProgram2010.pdf, page 177. Da Costa, Breast-milk mercury concentrations and amalgam surface in mothers from Brasília, Brazil, Biol Trace Elem Res (2005). Pastor PN, Reuben CA., Diagnosed attention deficit hyperactivity disorder and learning disability: United States, 2004-2006, Vital Health Stat 10. 2008 Jul;(237):1-14.	accordingly. Data in the original Table 1 were more than 25 years old and likely not relevant now; The SCENIHR considers it more relevant to use the more recent estimates by EFSA, now indicated in the new Table 1. The La Roo et al. study was considered and is available as an abstract from 2010. The paper has not been published since and thus not been subjected to a peer review. Apparently, no association was found with existing fillings, but with fillings that were placed in the first two months of pregnancy. This was only true for CPO (Cleft palate only), but not for cleft lip with or without cleft palate (CLP). The SCENIHR considered the data not suitable to be cited, since as an abstract, it is not a sufficiently reliable source of information. For comments to the Da Costa paper, please see response to comment # 12 The study of Pastor and Reuben (2008) does not include data on mercury exposure and is not relevant in the present context.
14	Björkman Lars, The Dental Biomaterials	3.3.1.2. Background	"As described in the previous opinion, exposure to mercury by inhalation is very low in the general population. The major	SCENIHR agrees and the text has been amended accordingly.

	Adverse Reaction Unit / Uni Research AS, Norway , Lars.Bjorkman@uni.no	exposure to mercury	sources of mercury intake in the diet is as inorganic mercury and methyl mercury (See Table 1 and 2).” COMMENT: This is not consistent with data presented in Table 1. In addition, data regarding daily intake of inorganic mercury from dental amalgam is given an estimate of “0” in the table. This is not correct and the table should be updated. In a paper published in 1997 (Björkman et al 1997), the daily gastrointestinal exposure to mercury in saliva was estimated to between 10 and 150 nmol/day (equal to 2-30 µg/day) in a group of individuals with amalgam fillings. Using a body weight of 70 kg the weekly exposure to mercury via saliva could be estimated to between 0.2 and 3 µg/kg b.w. per week (200 to 3000 ng/kg b.w. per week). In a reference group without amalgam fillings the median concentration of mercury in saliva was less than 0.1 % of the concentration in the amalgam group. This indicates that almost all mercury in saliva originated from amalgam restorations (Björkman et al 1997). REFERENCE: Björkman L, Sandborgh-Englund G, Ekstrand J. 1997. Mercury in saliva and feces after removal of amalgam fillings. Toxicol Appl Pharmacol. 144:156-62.	Data from Björkman et al (1997)have been included in the paragraph 3.3.1.3
15	Malmström Christer, World Alliance for Mercury-Free Dentistry. , Christer.malmstroem@tele2.se	3.3.1.3. Intake estimates for mercury from dental amalgams	PUBLIC CONSULTATION on the Preliminary Opinion on The safety of dental amalgam and alternative dental restoration materials for patients and users 2. Mercury exposure from amalgam 3.3.1.3. Intake estimates for mercury from dental amalgams. Amalgam fillings always leak mercury and silver in the mouth. With no amalgam filling there is no measurable mercury vapour in the mouth. With only one amalgam filling there is always measurable mercury vapour in the mouth. It is only in the laboratory at room temperature where amalgam can be almost stable, never in the mouth. Even a small amount of amalgam under a gold crown gives a measurable amount of mercury vapour. Putting any load on	The SCENIHR thanks the contributor for the information provided, but according to the Rules of procedure only scientific peer-reviewed reports can be considered

			the amalgam increases the leakage of mercury. It suffices to drink a cup of coffee to double the leakage. Brushing increases it eight times. Dry polishing at the dentist increases the leakage one hundred (100) times. One published research paper shows that a very small amalgam filling expose children to considerable amounts of mercury. An 11-year-old girl weighing 37kg had previous to an amalgam filling a measured amount of 3 µg Hg/24 h. An amalgam filling (0.12 grams) made with extreme precautions (Rubberdam, Clean Up suction) showed after three days an exposure of 400 µg Hg/24 h., and after 35 days an exposure of 13 µg Hg/24 h. This is an initial increase of over 100 times her pre amalgam exposure. Since the child weighed only about half of an adult, it is an extreme and completely unnecessary mercury exposure to a child. During a more normal procedure a more commonly used surface filling (0.8 g) exposed a 17-year-old girl after three days with 1800 µg Hg/24 h (Sic). (http://www.misac.se/research7.html,) This can be compared with the WHO standards for maximum acceptable total intake of mercury by food ~ 45 µg Hg / 24. This is ≈ 40 times higher than the WHO limit. People without amalgam excrete 2-3 µg Hg/24 h.	
16	GROSMAN Marie, Non au mercure dentaire, mariegrosman@free.fr	3.3.1.3. Intake estimates for mercury from dental amalgams	Le SCENIHR rappelle avec justesse que les amalgames dentaires contribuent de manière majoritaire à l'apport de mercure inorganique des Européens : leur contribution va de 50 à 87 % selon que l'on porte peu ou beaucoup d'amalgames. L'EFSA (2012) relève qu'en Europe « l'inhalation du mercure élémentaire des amalgames augmente significativement l'imprégnation en mercure, pouvant conduire à dépasser la dose hebdomadaire tolérable provisoire ». Il paraît inacceptable qu'une instance sanitaire accepte cette situation. Or, les amalgames constituent l'apport le plus facile à éliminer, bien plus que l'apport alimentaire via les produits de la mer ou que l'exposition environnementale via les émissions industrielles. L'amalgame dentaire est une source d'exposition devenue	

			inutile avec l'essor des alternatives : l'interdiction est donc la seule solution acceptable. ***English translation:*** The SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks) rightly recalls that dental amalgam is the major source of inorganic mercury in Europeans: its contribution rises from 50 to 87% depending on whether the person has a few or many amalgam fillings. The EFSA (2012) points out that, in Europe, "inhaling the elementary mercury of amalgam fillings significantly increases mercury levels in the blood, which can result in the provisional tolerable weekly intake being exceeded". It seems unacceptable for a health authority to accept this situation. When amalgam fillings are the easiest source to eliminate, much easier than the intake from food products from the sea or than environmental exposure via industrial emissions. Dental amalgam is a source of exposure which has become pointless, given the increase in alternatives: its prohibition is therefore the only acceptable solution.	It is outside the remit of the SCENIHR to suggest the adoption of a risk management measure.
17	Zimmerman Clinton, self , clintonzim@aol.com	3.3.1.3. Intake estimates for mercury from dental amalgams	3.3.1.3 "Daily uptake of amalgams has been estimated to be 1- 27 ug/day. " As a high end estimate which Scenihr does not make clear this figure is completely contradicted by direct measurments of Hg release in published peer reviewed studies such as those given by Haley and urine and blood testing estimates given Richardson as I mentioned in the previous section. As an average figure it misrepresents real uptake for a large portion of the population as noted by Richardson. This scientifically unjustified generalization relies on unproven urine and blood testing methodologies and ignores the obvious and unrefuted measurements of Hg release performed directly in the laboratory such as by Haley, and such experiments have never been refuted or found to be flawed again see "The Relationship of the Toxic	Please see response above to comment # 11, referring to the Richardson papers

			Effects of Mercuy to the Exacerbation of the Medical Condition Classified as Alzhiemers Disease", Boyd Haley. Again the use of blood testing and urine testing are false indicators of Hg uptake as noted in many peer reviewed articles by Haley, Mutter, and Kazantzis and Ely such as discussed in "Mercury and the Kidney", Kazantzis G. Trans Soc Occup Med 1970 and again "Urine Mercury in Micromercurialsism: Bimodal Distribution and Diagnostic Implcations. "Bull Envirion Toxicol.63(1999) Ely. At the FDA 2010 hearings it was actively discussed by the panel members that Hg exposure is likely to occur in acute form from amalgam as a result of catastrophic corrosion and exposure to vapor from drilling in short pulses. That is the greatest release from corrosion and from drilling is likely very short lived, although this Hg will obviously be quickly absorbed into the nervous system. Why does Scenihr automatically assume that large releases of Hg from amalgam will be sustainable and measureable by blood testing as low level release is assumed to be? This is a completely arbitrary assumption. Given the fact that blood testing and urine testing are done infrequently and that Hg clears the blood and urine in hours that renders blood and urine testing as a completely arbitrary measure of greatest exposure of Hg due to amalgam based on these common sense considerations for exposure due to drilling and short and long term corrosion. Additionally no one has demonstrated or proved that mercury levels in blood are linear to exposure from amalgam as exposure is continually increased. Peer reviewed studies on high copper amalgam readily available to Scenihr such as "Corrosion products from Dental Alloys and Effects of Mercuric ions on a Neruoeffector System", Moberg Le 1985 show that corrosion of copper amalgam and release of all corrison products including mercury is exponential with time as well for example. Moberg concludes that release of corrosion products which include mercury is exponential with corrosion depth in some cases. As discussed at the 2010 FDA	The comment makes reference to an open hearing, where individual opinions could be presented. Please refer to the response to comment #5.

			hearings such exposures could be transient since a high level of Hg release from amalgam cannot be sustained without depleting the Hg. In real life mercury doesn't simply wait in the blood and urine for months after these kinds of short lived high exposures to be measured by scientists and here lies one of the key flaws in the exclusive collection of blood and urine testing studies relied upon by Scenihr. Numerous studies have shown large uptake of amalgam through fecal testing and saliva testing as documented in published peer reviewed literature by Haley and Mutter. These studies support steady state release levels of Hg found in the lab which are far greater than those quoted in this section and certainly above safe levels in the opinion of many expert scientists. Scenihr quotes recent work by Richardson (2011). It should be noted that as stated by Schnier even though this shows	
18	Rooney James, Trinity College Dublin, jrooney@rcsi.ie	3.3.1.3. Intake estimates for mercury from dental amalgams	Page 18, paragraph 2: "The total amount of mercury that must reach the brain to cause a condition commensurable with severe clinical disease or fatal poisoning would therefore be 1 mg or more." Comment: It is unclear where SCENIHR have gotten this estimate. Is it based on methy-mercury exposure or mercury vapour exposure? If it is based on the preceeding reference to (Takeuchi and Eto, 1999), SCENIHR should be aware that recent reanalysis of Minamata cases has identified long term clinical effects at lower levels of exposure than previously recognized.(Maruyama et al., 2012) References: Maruyama, K., Yorifuji, T., Tsuda, T., Sekikawa, T., Nakadaira, H., & Saito, H. (2012). Methyl mercury exposure at niigata, Japan: results of neurological examinations of 103 adults. Journal of Biomedicine & Biotechnology, 2012, 635075. doi:10.1155/2012/635075	The estimate, based on the Takeuchi and Eto study, was cited only as comparison, to put into context the data found in the cerebral cortex of individuals bearing 12 or more dental amalgam fillings (200 microgram/kg) or ≤ 3 amalgam fillings (20 microgram/kg). The estimate was associated with 'severe clinical disease or fatal poisoning'. A re-evaluation of the Takeuchi and Eto study showed evidence of neurological problems found in individuals. The text was modified according to the comments and the references included. However, the authors do not find a dose-response relationship; i.e. even with very high Hg levels in the hair (20 µg Hg/g hair), the number of neurological cases does not increase, which limits the interpretation of the obtained results (Maruyama et al., 2012)

19	Rooney James, Trinity College Dublin, jrooney@rcsi.ie	3.3.1.3. Intake estimates for mercury from dental amalgams	Page 18, paragraph 2: "The total amount of mercury that must reach the brain to cause a condition commensurable with severe clinical disease or fatal poisoning would therefore be 1 mg or more." Comment: It is unclear where SCENIHR have gotten this estimate. Is it based on methy-mercury exposure or mercury vapour exposure? If it is based on the preceeding reference to (Takeuchi and Eto, 1999), SCENIHR should be aware that recent reanalysis of Minamata cases has identified long term clinical effects at lower levels of exposure than previously recognized.(Maruyama et al., 2012) References: Maruyama, K., Yorifuji, T., Tsuda, T., Sekikawa, T., Nakadaira, H., & Saito, H. (2012). Methyl mercury exposure at niigata, Japan: results of neurological examinations of 103 adults. Journal of Biomedicine & Biotechnology, 2012, 635075. doi:10.1155/2012/635075	Please see response to comment # 20. The text was modified according to the comments and the references included.
20	McKay Ian , British Dental Association , ian.mckay@bda.org	3.3.1.4. Exposure to mercury in dental personnel	1. The following paper is relevant to the consideration of occupational exposure to mercury for dental personnel. It clearly shows the changing pattern of exposure and the impact of environmental controls. Duncan A, O'Reilly DS, McDonald EB, Watkins TR, Taylor M. (2011) Thirty-five year review of a mercury monitoring service for Scottish dental practices. Br Dent J. Feb 12; 210(3):E2. doi: 10.1038/sj.bdj.2011.4	THE SCENIHR agrees. New text was included in the Opinion: *Nevertheless, according to head hair mercury data acquired over 35 years in Scottish dental practice (Duncan et al. 2011), median concentrations were reduced from 8.6 µg/g in the period 1975-1979 to 0.5 µg/g in the period 2005-2009. The reduction was attributed to preparation techniques and increased awareness. In comparison, mean hair mercury concentration in the U.S. population of women in childbearing age is 0.20µg/g (McDowell et al. 2004).*
21	Doneus Wolfgang, Council of European Dentists, ced@eudental.eu	3.3.1.4. Exposure to mercury in dental personnel	The following paper is relevant to the consideration of occupational exposure to mercury for dental personnel. It clearly shows the changing pattern of exposure and the impact of environmental controls. Duncan A, O'Reilly DS, McDonald EB, Watkins TR, Taylor M. (2011) Thirty-five year review of a mercury monitoring service for Scottish dental practices. Br Dent J. Feb 12; 210(3):E2. doi: 10.1038/sj.bdj.2011.49.	Please see response to comment #20 which also applies to e-mail contribution no 1.

22	malmström christer, World Alliance for Mercury-Free Dentistry. , christer.malmstroem@tele2.se	3.3.1.5. Considerations on exposure	3.3.1.5. Considerations on exposure. Amalgam fillings always leak mercury and silver. With no amalgam filling there is no measurable mercury vapour in the mouth. With only one amalgam filling there is always measurable mercury vapour in the mouth. It is only in the laboratory where amalgam can be almost stable, never in the mouth. Even a small amount of amalgam under a gold crown gives a measurable amount of mercury vapour. Putting any load on the amalgam increases the leakage of mercury. It suffices to drink a cup of coffee to double the leakage. Brushing increases it eight times. Dry polishing at the dentist increases the leakage one hundred (100) times. Exposure. Exposure means how much of the substance you are TOTALLY exposed to. There is a decent correlation between inhaling mercury vapour at an industrial workplace and urine and blood tests. However, there is no scientific study that shows the same correlation between urinary and blood tests dental amalgam mercury exposure. Yet these theoretical calculations have been used as the basis for this report? Furthermore, the exposure and mercury uptake from an industrial workplace and from amalgam are completely different. In terms of industrial exposure it is only for a maximum of 8 hours a day, 5 days a week, while exposure from amalgam is always 24 hours a day 7 days a week potentially for decades. This means that there is no possibility of recovery by the amalgam exposure as there is from exposure at an industrial workplace. Mercury from an industrial site is absorbed through the lungs. In contrast, dental amalgam mercury mainly absorbed through the mucous membrane and gastrointestinal tract and only to a minor extent by the lungs. This has an adverse affect on both the digestive tract and its bacterial flora. The excreted mercury exposure from a new filling with amalgam is best measured on the third day after exposure. It means that it is first taken up by the body and then excreted. Mercury is excreted mainly in the faeces and very little in	THE SCENIHR thanks the contributor for the information provided, but according to the Rules of procedure only peer-reviewed scientific reports can be considered. The problems related to mercury exposure assessment in biomonitoring studies, especially related to the source of exposure, are already addressed in the Opinion.

			urine. Hence urine alalysis does not show the true extent of exposure and should therefore not be used as the diagnostic tool. Measuring exposure. The exposure from amalgam can only be properly measured in two ways. 1. Measurement of mercury content in amalgam of known age and composition. Metallurgical experts have shown that after 20 years, 30% of the mercury had leaked from the dental amalgam. This gives an average daily exposure of about 200 micrograms µg Hg/24h having 13 grams of amalgam in the mouth and 100 µg Hg/24h if it was 6 grams of amalgam. The results were verified by chemical analysis of the amalgam. Results: Correlation between reduction in mercury content in amalgam and age R = 0.86. The exposure matches well with studies Hanson / Pleva 1991 did and showing 120-160 µg Hg/24 h and those Skare / Engqvist 1994 did, showing up to 125 µg Hg/24 h. 2. Cycle Principle. Exposure to mercury from amalgam is ≥ than excreted mercury. Amalgam Hg ≥ faeces Hg + urine Hg + sweat Hg + absorbed Hg. At least 80% is found in the faeces, while approximately 15% is visible in urine and sweat. The other way to measure the exposure is by measuring the total excretion of mercury from people with amalgam fillings compared with excretion from people without amalgam fillings. Thus measuring faeces, urine and sweat. It turns out that approximately 80% of the mercury is excreted through faeces while only about 10% from urine. Hence, to assume that urine values gives the right exposure is completely wrong.	
23	McKay Ian , British	3.3.1.5.	2. The work of Li et al., (2013) (quoted in the text and	Agreed, this consideration is included in the Opinion to make the

	Dental Association, ian.mckay@bda.org	Considerations on exposure	references as Sherman et al., 2013) suggests that at least some of the methylmercury consumed in the diet can be excreted as inorganic mercury in the urine. It is worth noting that estimates of the mercury released from dental amalgam (for example Richardson et al., 2011) are based on the assumption that inorganic mercury detected in urine is entirely unaffected by consumption of fish. If any methylmercury is excreted in the urine as inorganic mercury it would mean that current assessments of mercury released from dental amalgam are an over-estimate.	text clearer. The same consideration is added also in 3.3.1.5 . The last paragraph then reads: Sherman et al. (2013) suggested that Hg isotopes can be used to differentiate between exposure to fish-derived inorganic mercury and elemental mercury inhaled from dental amalgams. A large part of the urinary mercury was found to be derived from methyl mercury due to fish consumption. *Demethylation of methyl mercury from seafood may also contribute to the mercuric mercury excreted in the urine.* Only for fish-consumers with more than 10 amalgam restorations did a large percentage of the mercury derive from exposure to elemental mercury.
24	Rooney James, Trinity College Dublin, jrooney@rcsi.ie	3.3.1.5. Considerations on exposure	Page 20, paragraph 2: "As a general caveat, exposure imprecision tends to bias study findings towards the null hypothesis, i.e. the dose related toxic effects may be underestimated (Grandjean 2008, Grandjean and Budtz-Jørgensen, 2010) Comment: This is a critically important point that is further complicated by the presence of genetically sensitive subpopulations (Basu, Goodrich, & Head, 2014; Woods, Heyer, Russo, Martin, & Farin, 2014). SCENIHR need to bear this point in mind when weighing the evidence, particularly with regard to sensitive groups such as children (particularly boys), pregnant and breast-feeding mothers, sensitive disease groups (chronic kidney disease, thyroid disease). Page 20, paragraph 3: "There may be differences in internal exposure since mercury excretion may differ between boys and girls 8-18 years of age, treated with dental amalgam (Woods 2007)." Comment: Indeed Woods latest paper provides more convincing evidence there are gender differences in response to mercury among genetically sensitive children(Woods et al., 2014). References: Basu, N., Goodrich, J. M., & Head, J. (2014). Ecogenetics of mercury: from genetic polymorphisms and epigenetics to risk assessment and decision-making. Environmental Toxicology and Chemistry / SETAC, 33(6), 1248–58.	The comment agrees with the text in the Opinion. It has to be underlined that the Basu et al (2014) paper is a review, not reporting any original data. It has now been included in the reference list, being cited in the paragraph specific for polymorphisms. The report of Woods et al (2014) is a summary of earlier reports from the same group and is now discussed in the text of the Opinion.

			doi:10.1002/etc.2375 Woods, J. S., Heyer, N. J., Russo, J. E., Martin, M. D., & Farin, F. M. (2014). Genetic polymorphisms affecting susceptibility to mercury neurotoxicity in children: Summary findings from the Casa Pia Children's Amalgam Clinical Trial. Neurotoxicology, 44C, 288–302. doi:10.1016/j.neuro.2014.07.010	
25	Stöckl Annegret, BBFU e. V. (Bundesverband der Beratungsstellen für Umweltgifte und Amagam), annegret.stoeckl@gmx.de	3.3.1.5. Considerations on exposure	As shown by the above-mentioned studies (to Point 3.3.1.5.), there are no precise diagnostic options indicating how much mercury is effectively saved in brain and organs of a human individual. The exact part of human genetics responsible for mercury storage is not yet known to the present day. In order to diagnose a chronic amalgam poisoning blood and urine are being tested, but that is no indication of how much mercury due to amalgam fillings has been deposited in human organs over the years. The number of allergies, autoimmune diseases and cancer has dramatically increased since 1950. At the same time amalgam has been increasingly used throughout Europe as a dental filling. New research results come to the conclusion that the proliferation of mast cells play a major role on the immune system. There are no current studies indicating how mercury affects the mast cells. A dilemma of amalgam studies in general is that there are no control groups with people without amalgam. All major studies do not take into account, that persons without teeth or other current dental fillings may have previously had fillings. J. Mutter, J. Naumann, C. Sadaghiani, H. Walsch, G. Drasch, Amalgam studies: Disregarding basic principles of mercury toxicity Inst. For Environmental Medicine and Hospital Epidemiologie, University Hospital, Freiburg, Germany, Int. J. Hyg. Environ. Healt 207 (2004), S. 392 .: "In scientific research on the toxic effects of substances, it is necessary to compare at least two samples: one that is exposed to the substance in question and one that isn't. One of the main dilemmas in so called amalgam studies is that the vast majority do not	THE SCENIHR is aware of the difficulty comparing data on amalgam exposure with adequate control groups. However, due to the reduced use of dental amalgam, it is now possible to compare amalgam vs true non-amalgam population. In both the Casa Pia study and the New England study, children with and without amalgam were compared. Children with composite restorations had NO amalgam treatment before. The data reported by Ursinyova et al (2012) are the same as those reported by Palkovikova 2008 on the positive relationship between amalgam fillings of the mothers and mercury in maternal blood and cord blood. Further data in the latest article: mothers with amalgam fillings had lower total thyroxine (T4), and free thyroxine (fT4) levels in comparison with mothers with no amalgam fillings. However, maternal fT4 levels were also reduced by THg exposure, especially in women who gave birth to a boy. However, in this study, mercury exposure of children at the age of 6 months did not correlate with the cord or maternal blood mercury level at the time of delivery. The mercury exposure status of children at the age of 6 months more likely depends on other sources than prenatal exposure. Serum T4 and fT4 levels in 6-month-old children were not related to any of the studied variables. This study shows the known and reported relation of amalgams and serum mercury level. But no increase of mercury level was

			incorporate true control groups which have genuinely not been exposed to dental amalgam. What is neglected is the possibility that non-amalgam controls may at some point in their earlier life have had dental amalgam fillings over a long period of time and may thus display a higher body mercury load." Thyroid diseases are increasing dramatically. Ursinyova et al. have investigated, that mothers with dental amalgam fillings had significantly lower T4 and fT4 levels. Moreover, fT4 in boys' mothers negatively correlated with maternal THg levels. Cf. M. Ursinyova: The relation between human exposure to mercury and thyroid hormone status in: Biol Trace Elem Res. 2012 Sep; 148(3):281-91. For an abstract, cf.: http://www.ncbi.nlm.nih.gov/pubmed/22426797.	found in the children at 6 months. The clinical consequences of lower total and free thyroxine levels have not been determined and were not discussed. It was furthermore observed that other variables also influence the thyroid status. For these reasons, THE SCENIHR considers that the article adds nothing new to the information present in the Opinion.
26	Malmström Christer, World Alliance for Mercury-Free Dentistry. , christer.malmstroem@tele2.se	3.3.1.6. Conclusions on mercury exposure from dental amalgam	The scientific basis of the preliminary opinion seems to avoid the basic facts in their report. After careful reading, I can only conclude that the report is based on wrong facts, wrong reasons and wrong assumptions, hence the conclusions will be wrong. I would like to add some real facts. If you wish more information, I stand happy to assist. One published research paper shows that a very small amalgam filling expose children to considerable amounts of mercury. An 11-year-old girl weighing 37kg had previous to an amalgam filling a measured amount of 3 µg Hg/24 h. An amalgam filling (0.12 grams) made with extreme precautions (Rubberdam, Clean Up suction) showed after three days an exposure of 400 µg Hg/24 h., and after 35 days an exposure of 13 µg Hg/24 h. This is an initial increase of over 100 times her pre amalgam exposure. Since the child weighed only about half of an adult, it is an extreme and completely unnecessary mercury exposure to a child. During a more normal procedure a more commonly used surface filling (0.8 g) exposed a 17-year-old girl after three days with 1800 µg Hg/24 h (Sic). (http://www.misac.se/research7.html,) This can be compared with the WHO standards for maximum acceptable total intake of mercury by food ~ 45 µg Hg / 24.	In order to be considered, the data have to be provided as a peer-reviewed scientific report, as mentioned in the methodology section.

			This is ≈ 40 times higher than the WHO limit. People without amalgam excrete 2-3 µg Hg/24 h. Conclusion. Exposing people to high doses of toxic mercury cannot be lege artis and therefore amalgam should be promptly banned in the EU. There are no scientific or economic facts that can defend that we do not take children's and adults' right not to be poisoned by mercury seriously.	
27	Rooney James, Trinity College Dublin, jrooney@rcsi.ie	3.3.1.6. Conclusions on mercury exposure from dental amalgam	Page 20, paragraph 6: "SCENHIR therefore performed the exposure assessment based on urinary excretion of Hg in individuals with and without amalgam fillings. Data on urinary excretion of Hg are available on a large number of subjects from several surveys. Urinary excretion of Hg is considered a suitable biomarker of systemic exposures to elemental and inorganic Hg." Comment: Urinary Hg is considered a suitable biomarker for recent (1 – 2 months) exposure to elemental and inorganic Hg. It is NOT a suitable biomarker for historical or chronic low dose exposure(Rooney, 2007), therefore it is not, in isolation, a suitable biomarker to measure mercury exposure due to amalgam. References: Rooney, J. P. K. (2007). The role of thiols, dithiols, nutritional factors and interacting ligands in the toxicology of mercury. Toxicology, 234, 145–156. doi:10.1016/j.tox.2007.02.016	It is generally accepted that hair reflects exposure to organic mercury, blood generally reflects exposure to organic mercury (though some inorganic mercury may be present in blood), and urine generally reflects exposure to inorganic mercury (though some of this may have been derived from organic mercury that was demethylated inside the body). Therefore urinary mercury is a suitable biomarker for exposure to elemental and inorganic Hg mainly reflecting recent exposure. Unfortunately no better biomarker is available to express the levels possibly accumulated in different tissues. The problems related to Hg exposure assessment in biomonitoring studies, especially related to the source of exposure are addressed in the Opinion. Data available on actual levels/estimated levels in tissues are also given, but the SCENIHR agrees that this is a still a 'grey' area. Rooney (2007) refers to the use of chelating agents. The use of chelating agents like DMPS does not provide additional diagnostic value (Vamnes et al., 2000) and chelating substances may be associated with notable side effects (Schuurs et al, 2000). This information has been included in the text of the Opinion (paragraph 3.3.1.6)

28	Zimmerman Clinton, works with consumers for dental choice, clintonzim@aol.com	3.3.1.6. Conclusions on mercury exposure from dental amalgam	Scenihr concludes "Exposure assessments based on such consideration have significant variations due to availability of Hg after inhalation and ingestion" While it's good that Scenihr acknowledges this, this extremely limited evaluation obviously ignores the major source of variation which is poor preparation of amalgam and condensing methods of the amalgam which can leave excess mercury at the surface of the filling and the drilling out of fillings which has been proven to provide tremendous exposures of Hg. Other variables include crevice corrosion , placement in wet fields and also corrosion of amalgams with zinc in wet fields, use of dissimilar materials, materials "doped" with high levels of mercury , a frequent practice in dental offices to make amalgam more workable which are prone to higher mercury release and corrosion, amalgams prepared with capsules that have faulty pillow packs, capsules with faulty alloy, amalgam barriers, capsules that have duplicate pillow packs, amalgam which is made with improper tituration settings, which is prepared with titurators which are mal functiniong and so on. Scenihr provides no evaluation of the variation in the quality of amalgam preparation and assumes that all amalgams are identical and perfectly made. All of these considerations are documented in the scientific literature and can easily be verified by contacting amalgam manufacturers, talking with dental personnel or reading texts on amalgam preparation. It also ignores that fact that most Hg is proven to pass through the GI tract. Scenihr also quotes numerous dental journal articles assuming they are properly done. However almost all of these articles are methodologically flawed. Take "Mercury Release from Dental Amalgam, an invitro study under controlled chewing and brushing in an artificial mouth"- Journal of Dental Research. I wrote a critique of this article noting the following obvious flaws:	The authors did not provide the papers to support their conclusions. The term 'low quality' or poor preparation of amalgam is not defined. THE SCENIHR assumes that the standard clinical practice should be used: it not being possible to address all the possible misuse scenarios. See also the answer to comment 27. To address this comment, please see the Methodology section.

			-the amalgam is formulated under ideal conditions -water spray applied to "simulate" saliva actually washes away excess mercury from the test chamber and the surface of the fillings, greatly reducing measured Hg release-unacceptable scientific technique -the sealed container incorrectly allows vapor equilibrium to be established unlike in the oral cavity rendering the findings meaningless -However most incredibly the actually formula for hg release given in the paper roughly agrees with Haleys results of measuremts of Hg release from capsules in water, but the final calculation used in the paper incredibly introduces a completely unjustified .oo4 "inhalation factor" to allegedly model "retention" of inhaled mercury. Thus the paper represents the results as in vitro when these assumptions are in vivo. This kind of faulty methodogly is typical of many dental journal articles quoted by Scenihr Scenihr states"Urinary excretion of Hg is considered a suitable biomarker of systematic exposures to inorganic and elemental Hg" As I stated previously this arbitrary and scienfically unjustifiable generalization would not be agreed to by many experts in the field who have published peer reviewed studies including Haley,Chew,Mutter,Ely,Kaztanzis and probably Richardson and many others. This section also blurs the distinction between methyl and dimethyl forms derived from amalgam and that derived from fish implying that all methyl exposure is from fish when as I noted previously in its introduction Scenihr implied that it wasn't going to address conversion of amalgam hg to the methyl form. A policy making reading this however would incorrectly conclude that it has been shown that no methyl exposure is derived from amalgam. If Scenihr is going to insinuate this than Schine should prove this.	There is probably a misunderstanding. We are not saying 'that no methyl exposure is derived from amalgam.' And vice versa that all the inorganic mercury is derived from amalgam. The text has been changed to make it clearer. The issue is discussed in more details in the Toxicokinetic section. As with other materials, differences in quality may also occur for dental amalgam. None of the clinical exposure studies have included an assessment the quality of the restorations, per se.

29	GROSMAN Marie, Non au Mercure Dentaire, mariegrosman@free.fr	3.3.10. Conclusions on Dental Amalgam	Le corps du rapport montre que : - Les amalgames dentaires sont de loin la première source d'exposition au mercure des Européens ; - Les amalgames sont susceptibles d'induire un dépassement des valeurs d'exposition tolérables ; - Les professionnels de la dentisterie continuent d'être contaminés en proportion du nombre d'amalgames qu'ils posent, et ils sont en moyenne bien plus intoxiqués que la population générale ; - Les femmes enceintes ou allaitantes porteuses d'amalgames intoxiquent leur bébé ; - Certains patients présentent des symptômes généraux invalidants qui s'améliorent après le retrait de leurs amalgames - Les publications montrent un effet délétère du mercure dentaire sur le système nerveux, le système immunitaire, le système endocrinien et les reins ; - Même si l'état de la science ne permet pas de trancher avec certitude, les amalgames dentaires pourraient favoriser l'autisme, la maladie d'Alzheimer, la maladie de Parkinson, la maladie de Charcot (SLA), la sclérose en plaques et des neuropathies périphériques ; - Les assistantes dentaires présentent des symptômes neurologiques plus fréquents que la population générale et des travaux mettent en lumière que les dentistes souffrent davantage de problèmes rénaux et de troubles neurocognitifs que la population générale. La conclusion rassurante du rapport est en contradiction totale avec ces éléments, qui montrent tous la nécessité d'interdire au plus tôt l'usage du mercure dentaire. ***English version:*** The body of the report shows that: - dental amalgams are by far the prime source of mercury exposure for Europeans;	THE SCENIHR disagrees. Most of the statements reported in comment 29 do not represent exactly what is reported in the preliminary Opinion, but are a personal interpretation by the commenter. In the Opinion, THE SCENIHR does not say 'pregnant or breastfeeding women with amalgams are poisoning their babies'. The comment has an inconsistency between the content in the main text and the conclusions. To indicate risk management measures is outside the mandate of the Scientific Committee.

			- amalgams are likely to result in the tolerable exposure levels being exceeded; - dentistry professionals are still being contaminated in proportion to the number of amalgams which they fit, and on average the level of poisoning is much higher than in the general population; - pregnant or breastfeeding women with amalgams are poisoning their babies; - some patients show general incapacitating symptoms which improve after their amalgams have been removed; - publications show the deleterious effect of dental mercury on the nervous system, immune system, endocrine system and kidneys; - even though the state of science does not allow for an unequivocal conclusion, dental amalgams could contribute to autism, Alzheimer's disease, Parkinson's disease, Charcot's disease (ALS), multiple sclerosis and peripheral neuropathies; - dental assistants show more frequent neurological symptoms than the general population, and studies reveal that dentists suffer more from renal problems and neurocognitive disorders than the general population. The reassuring conclusion of the report completely contradicts this information, which highlights the need to prohibit the use of dental mercury as soon as possible.	
30	Rooney James , Trinity College Dublin, jrooney@rcsi.ie	3.3.10. Conclusions on Dental Amalgam	Page 40, paragraph 1: "The existence of susceptible subpopulations due to genetic predisposition needs further research before conclusions can be drawn." Comment: There is enough evidence that there are at least a handful of relatively common polymorphisms affecting both mercury toxicokinetics and toxicodynamics (Basu, Goodrich,	THE SCENIHR agrees that a growing literature is becoming available on genetic polymorphisms possibly affecting mercury kinetics and dynamics. The paper of Basu et al (2014) is addressed in the Opinion (see the specific paragraph) Regarding kinetics, as also shown in the review cited in the

			& Head, 2014; Woods, Heyer, Russo, Martin, & Farin, 2014). Therefore the precautionary principle should be applied to protect those we suspect could be more sensitive, i.e. children, during pregnancy, breast feeding, chronic kidney disease and thyroid disease patients. Page 40, paragraph 4: "Dental restorative therapy during pregnancy, as for any other therapeutic treatment, should be limited as much as possible in order to reduce the exposure of the foetus. The choice of material should be based on patient characteristics such as primary or permanent teeth, pregnancy, the already existent number of dental amalgam fillings, presence of allergies to mercury or other components of the restorative materials, and presence of decreased renal clearance." Comment: I applaud the SCENIHR for making this statement. However I think it is somewhat non-committal in its phraseology and it would be better to show greater leadership by providing a more clear statement that amalgam is contraindicated in pregnancy, decreased renal clearance or the presence of large numbers of existent amalgam fillings. I also recommend that this list should be extended to include children, breast feeding mothers, and thyroid disease patients based on the available evidence.	comment, although many modified alleles have been shown to affect (in both ways, i.e. increasing or decreasing) the internal dose of mercury, the alteration was not sufficient to determine significant changes in health outcomes. Regarding dynamics, not all studies exploring gene–mercury interactions showed significant links with the assessed health outcomes, and the positive results come from one single research group. According to THE SCENIHR, the findings are still not robust enough; that is why we conclude: 'no prospective clinical studies clearly showing the influence of genetic variations on the occurrence of adverse effects due to mercury from dental amalgam are available' and we ask for further data in order to draw clear conclusion. The application of the precautionary principle is a risk management measure, which is outside the mandate of our Committee. SCENHIR does not clearly give a strict contraindication consistently with the conclusion 'current evidence does not preclude the use of either amalgam or alternative materials in dental restorative treatment', but as stated, caution is requested, especially in some conditions.

			Page 40, paragraph 4: "As far as dental personnel are concerned, it is recognised that they may be more exposed to mercury exposure than the general population, although the incidence and type of reported adverse effects are similar to what is observed in the general population." Comment: It is curious that SCENIHR have recommended the avoidance of amalgam restorations for patients who are pregnant or have chronic kidney disease, yet have not recommended the same for dental personnel who might be pregnant or have chronic kidney disease. Given that dental personnel are exposed to higher levels of mercury than patients this issue needs to be further addressed by SCENIHR, I would in addition urge SCENIHR to further consider the risks of exposure to dental personnel who might be breast feeding or suffer thyroid disease. References: Basu, N., Goodrich, J. M., & Head, J. (2014). Ecogenetics of mercury: from genetic polymorphisms and epigenetics to risk assessment and decision-making. Environmental Toxicology and Chemistry / SETAC, 33(6), 1248–58. doi:10.1002/etc.2375 Woods, J. S., Heyer, N. J., Russo, J. E., Martin, M. D., & Farin, F. M. (2014). Genetic polymorphisms affecting susceptibility to mercury neurotoxicity in children: Summary findings from the Casa Pia Children's Amalgam Clinical Trial. Neurotoxicology, 44C, 288–302. doi:10.1016/j.neuro.2014.07.010	Agreed. This is a good comment, and the same considerations for caution used for patients have been applied to dental personnel too. Added new text 3.3.10, last paragraph: *However, the same considerations for caution in regard to patient exposure, also apply to dental personnel.*
31	Swedish Chemicals Agency, kemi@kemi.se	3.3.10. Conclusions on Dental Amalgam	p 40, 3rd para A fundamental basis for a risk assessment is a thorough knowledge of the pharmacokinetic/toxicokinetic profile of the substance in question. It is well established that dental amalgam fillings gives rise to chronic exposure to mercury. It is also well known that this chronic exposure is related to the number of fillings in the oral cavity, and that there is a considerable inter-individual variation. However, this risk assessment report does not include important aspects on mercury pharmacokinetics. In the	THE SCENIHR consider the comments as valid and consequently the text has been changed in order to make it clearer (e.g. in the abstract: *Placement and removal results in short-time exposure to the patients compared to leaving the amalgam intact.* In the text further details are discussed, together with the suggested references (Sandborgh-Englund 1998 a and b)

			Abstract, in the Executive summary and in Section 3.3.10, it is stated that the highest exposure occurs during placement and removal of amalgam fillings. There are no scientific references supporting this statement, so the basis is unclear. It is true that in particular the removal of fillings causes additional Hg-exposure and results in a transient increase in plasma Hg levels. Notably, the actual Hg dose from amalgam placement and removal is limited compared to the chronic exposure from the fillings in place: The daily retained dose is estimated to range between 3.8 and 17 µg/day, and results in a steady-state level of Hg in body fluids. The Hg-dose from removal of 16 amalgam filled surfaces is estimated to be around 40 µg Hg (estimated based on data from Sandborgh-Englund (1998a) and Sandborgh-Englund (1998b)). This single-dose exposure is equal to the integrated chronic Hg dose from amalgam restorations over 2.3-10 days. Thus, dental amalgam gives rise to a chronic exposure of inorganic mercury due to the continuous release of Hg, and over time this is the main, important exposure. Greater plasma Hg-peaks have been shown in conjunction to amalgam removal in the studies by Molin et al (1990) and Berglund and Molin (1997), whereas later studies show plasma peaks in parity with Sandborgh-Englund et al (1998b) (Halbach et al 1998; Halbach et al 2000; Kremers et al 1999;). The number of fillings removed and the working technique (water spray, suction efficiency, rubber dam use) affects the amount of mercury released, which emphasizes the demand for knowhow in the dental team. The text in the report needs to be rephrased accordingly in the Abstract (6th para), in the Executive summary (p9, 1st para and p 10, 4th para), in Section 3.3.10 (p 40, 3rd para) and in the Opinion Section 4.1 (p.67, 1st para). References: Due to copyright restrictions some references submitted as abstracts. Two references larger than 1MB emailed. Sandborgh-Englund G, Elinder C-G, Johanson G, Lind B, Skare I, Ekstrand J. (1998a) The absorption, blood levels, and excretion of mercury after a single dose of mercury	

			vapor in humans. Toxicol Appl Pharmacol;150:146-153. Sandborgh-Englund G, Langworth S, Schütz A, Elinder C-G, Ekstrand J (1998b) Mercury in biological fluids after amalgam removal. J Dent Res 77(4):615-624. Molin M, Bergman B, Marklund SL, Schutz A, Skerfving S (1990) Mercury, selenium, and glutathione peroxidase before and after amalgam removal in man. Acta Odontol Scand 48:189-202. Berglund A and Molin M (1997) Mercury levels in plasma and urine after removal of all amalgam restorations: The effect of using rubber dams. Dent Mater 13:297-304 Halbach S, Kremers L, Willruth H, Mehl A, Welzl G, Wack FX Hickel R, Greim H (1998) Systemic transfer of mercury from amalgam fillings before and after cessation of emission. Env Res A 77;115-123. Halbach S, Welzl G, Kremers L, Willruth H, Mehl A, Wack FX, Hickel R, Greim H (2000) Steady-state transfer and depletion kinetics of mercury from amalgam fillings (2000) Sci Total Environ 259;13-21. Kremers L, Halbach S, Willsruth H, Mehl A, Welzl G Ack F-X, Hickel R, Greim H (1999) Effect of rubber dam on mercury exposure during amalgam removal. Eur J Oral Sci 107; 202-207	

32	Rooney James, Trinity College Dublin, jrooney@rcsi.ie	3.3.2.1. Toxicokinetics	Page 21, paragraph 6: "One can assume that up to 1% of the absorbed dose may be retained in the central nervous system." Comment: The 1% figure is incorrect. In fact as per Clarkson it is 7%: "Approximately 7% is deposited in the cranial region after a single exposure to non- toxic levels of the vapor. The kidney is the main depository."(Clarkson, 2002) Page 22, paragraph 2: "However, some mercury can be reabsorbed, thus contributing to the inorganic mercury circulating in the blood." Comment: This is incorrect – this mercury is reabsorbed as methyl-mercury as part of an entero-hepatic recirculation – only inorganic mercury is not reabsorbed after biliary excretion.(Clarkson, 2002) References Clarkson, T. W. (2002). The three modern faces of mercury. Environmental Health Perspectives, 110 Suppl (February), 11–23. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1241144&tool=pmcentrez&rendertype=abstract	The reference provided is a review; no original data are presented. It refers to data that are now included in the text of paragraph 3.3.2.1, referring to the original papers. 3rd para of 3.3.2.1 Human toxicokinetic data are scant: it has been reported that after a single exposure to mercury vapour the half-time of distribution to the plasma compartment is approximately 5 hr (Sandborgh-Englund et al, 1998). The amount of mercury in plasma at the time of the peak concentration was 4% of the inhaled dose (95% confidence limit, 3–5%). Approximately 7% of the initial dose is deposited in the cranial region after a single exposure to non-toxic levels of the vapour. The kidney is the main depository. When experimental toxicology data are considered it appears that in squirrel monkeys, a 4-hour exposure to mercury vapour led to a brain retention of 0.27 % of the absorbed amount. In mice, a somewhat higher immediate retention of about 1.2 % was seen, with a decrease over several days to about 0.4 % (Berlin et al., 1966). One can assume that *0.3%-7%* of the absorbed dose may be retained in the central nervous system. Thus, the daily inhalation of up to 10 µg from amalgam fillings may after almost complete absorption result in a brain retention of up to *0.03-0.7 µg per day*. Methyl mercury elimination in humans mainly occurs via the biliary route after conjugation with liver glutathione S-transferases (GSTs), which produce a stable glutathione–metal conjugate which is then eliminated mainly via faeces (Ballatori and Clarkson, 1985). However, some mercury can be reabsorbed, thus contributing to the inorganic mercury circulating in the blood. *Excretion of inorganic mercury takes place via both urine and faeces. Urinary mercury originates mainly from mercury in kidney tissue.* GSTs are highly polymorphic in humans and an association between certain GST genotypes (e.g. GSTM1*0 and GSTT1*0, *resulting in the deletion of the entire genes*) . T GST polymorphisms may be associated with methyl mercury

				detoxification (Mazzaron Barcelos et al., 2012). Demethylation of methyl mercury from seafood, *mainly by gut microflora*, may also contribute to the mercuric mercury excreted in the urine, as previously suggested *by WHO (1990)*, by population studies (Johnsson et al., 2005), and by recent studies on Hg-isotopes (Sherman et al., 2013). Indeed, species involved in environmental mercury methylation are present in the human gut (Gibson et al., 1993), and limited evidence supports the notion that human faecal and oral microorganisms can generate methyl mercury from inorganic mercury (Edwards and McBride, 1975; Leistevuo et al., 2001). However, the extent and the rate this happens and gives rise to increased methyl mercury exposure due to dental amalgam is unclear.
33	Doneus Wolfgang, Council of European Dentists, ced@eudental.eu	3.3.2.1. Toxicokinetics	The work of Li et al., (2013) (quoted in the text and references as Sherman et al., 2013) suggests that at least some of the methylmercury consumed in the diet can be excreted as inorganic mercury in the urine. It is worth noting that estimates of the mercury released from dental amalgam (for example Richardson et al., 2011) are based on the assumption that inorganic mercury detected in urine is entirely unaffected by consumption of fish. If any methylmercury is excreted in the urine as inorganic mercury it would mean that current assessments of mercury released from dental amalgam are an over-estimate.	The SCENIHR agrees with the comment's content, which is already reflected in the text.
34	GROSMAN Marie, Non au Mercure Dentaire, mariegrosman@free.fr	3.3.2.2. Toxicity of Elemental Mercury	Le SCENIHR a raison de rappeler que le mercure élémentaire est un neurotoxique, un immunotoxique, un néphrotoxique et un perturbateur endocrinien. Il faut surtout rappeler que la Commission Européenne (CE) a récemment classé le mercure élémentaire Reprotoxique de catégorie 1B (peut nuire au fœtus) ainsi qu'en Acute tox 2 (mortel par inhalation) et STOT RE1 (toxicité spécifique pour certains organes cibles à la suite d'une exposition répétée). Quant au mercure inorganique, le toxique ultime issu des amalgames,	THE SCENIHR is aware of this new EC classification of mercury but there is no need to modify the scientific Opinion, also considering that the classification is a hazard-based process, not a risk-based one. However a mention is made in a separate text box in the Opinion referring to this new classification of ECHA. It is noted that a threshold can be identified for a category 2 reprotoxin (the classification indicated by the commenter for

			il a été classé Mutagène (Susceptible d'induire des anomalies génétiques) et Reprotoxique de catégorie 2 (Susceptible de nuire à la fertilité) par la CE. Cette nouvelle classification s'ajoute aux arguments développés dans nos commentaires à la partie 3.3.1.2 : compte tenu de la durée de vie des amalgames, il est inadmissible de poser ces dispositifs médicaux sur des femmes, de leur naissance à 45 ans. Il est aussi important de rappeler les valeurs toxicologiques de référence (VTR) pour le mercure élémentaire : celles de l'US EPA et de l'ATSDR sont respectivement de 0,3 µg/m3 et de 0,2 µg/m3. Or ces VTR sont dépassées chez de nombreux porteurs d'amalgames, qui inhalent un air contenant souvent plusieurs dizaines de µg de mercure /m3, dont 80 % passeront dans le sang. Il est essentiel d'insister sur les propriétés de bioaccumulation du mercure inorganique : la demi-vie du mercure dentaire est d'environ 27 ans dans le cerveau, valeur rappelée dans le rapport du SCENIHR. Une partie du mercure qui s'échappe peu à peu des amalgames s'accumule dans le cerveau pour des décennies et s'y concentre tout au long de la vie. Enfin, il est établi qu'il n'existe pas de seuil en dessous duquel ne se produiraient pas d'effets indésirables [Kazantzis 2002 ; OMS 2005]. G. Kazantzis. Mercury exposure and early effects: an overview. Medicina del Lavoro, vol. 93, no. 3, pp. 139–147, 2002. OMS. Mercure et soins de santé. Document d'orientation stratégique, 2005. http://www.who.int/water_sanitation_health/medicalwaste/mercury/fr/ ***English translation:*** The SCENIHR is right to point out that elementary mercury is a neurotoxin, an immunotoxin, a nephrotoxin and an endocrine disruptor. It must above all be borne in mind that the European	inorganic mercury), therefore the last statement that there is no threshold is incorrect.

			Commission (EC) recently classed elementary mercury as Reprotoxic in category 1B (can harm the fœtus) and as Acute tox 2 (fatal if inhaled) and STOT RE1 (specific target organ toxicity after repeated exposure). Inorganic mercury, the last toxin released from amalgams, has been categorised by the European Commission as a mutagen (suspected of causing genetic defects) and a category 2 reprotoxin (suspected of damaging fertility). This new classification adds to the arguments set out in our comments on Section 3.3.1.2: given the duration life of amalgams, it is inadmissible to fit these medical devices in women, between birth and 45 years. It is also important to recall the toxicity reference values (TRV) for elementary mercury: those of the US EPA and the ATSDR are, respectively, 0.3 µg/m3 and 0.2 µg/m3. However, these TRVs have been exceeded in numerous wearers of amalgams who inhale air often containing several dozen µg of mercury/m3, 80% of which enters the bloodstream. Emphasis must be laid on the bioaccumulation properties of inorganic mercury: the half-life of dental mercury is around 27 years in the brain, as pointed out in the SCENIHR report. Some of the mercury which is released gradually from amalgams accumulates in the brain over decades and is concentrated there throughout the person's life. Lastly, it has been established that there is no threshold below which undesirable effects would not occur [Kazantzis 2002 ; OMS 2005]. G. Kazantzis. Mercury exposure and early effects: an overview. Medicina del Lavoro, vol. 93, no. 3, pp. 139–147, 2002. WHO. Mercury in health care. Policy paper, 2005. http://www.who.int/water_sanitation_health/medicalwaste/mercury/en/	
35	GROSMAN Marie, Non au Mercure	3.3.5. Adverse effects in	Les experts du SCENIHR persistent à considérer les études épidémiologiques bien conduites, comme les études cas-	SCENIHR agrees that epi studies can have some bias, mainly in the area of exposure; conversely, the toxicological studies also

	Dentaire, mariegrosman@free.fr	individuals with amalgam restorations	témoins ou les études de cohortes, comme des éléments de preuves centraux. Pourtant, ils reconnaissent eux-mêmes [3.3.7] que les polymorphismes génétiques expliquent que ces études trouvent des résultats contradictoires. Relevons d'autres difficultés et d'autres biais auxquels se heurte en l'occurrence l'épidémiologie : - L'ensemble de la population européenne est exposée au mercure : il n'existe pas de véritables témoins non exposés. - L'exposition au mercure dentaire ne dépend qu'en partie du nombre d'amalgames : elle dépend aussi d'autres métaux en bouche, du bruxisme, de la consommation de chewing-gum, etc. - Une fois absorbé, le mercure sous sa forme oxydée a de multiples effets sur les cellules à l'origine d'une myriade de symptômes et de maladies : le mercure est un toxique ubiquiste et polymorphe. Il se lie aux liaisons thiols des protéines fonctionnelles ou de structure. Il va alors perturber des voies de signalisation, des neurotransmetteurs, des systèmes enzymatiques, se lier à des récepteurs membranaires ce qui altère la perméabilité membranaire, accroître l'agression oxydante et la peroxydation, entraîner une dysfonction mitochondriale, engendrer une inflammation, etc. - Comme pour la plupart des affections d'origine environnementale, les effets délétères d'une exposition sont décalés dans le temps. - La période d'exposition est importante, et pas seulement la dose (« Time is poison ») : ainsi le système nerveux en développement est très vulnérable. - L'organisme est exposé à plusieurs toxiques (effets cocktails) entre lesquels existent des synergies ; il existe de même des synergies entre méthylmercure et mercure inorganique. Ainsi, les bases classiques de la « médecine basée sur le niveau de preuve », s'appuyant sur des études épidémiologiques (si possible de cohortes), apparaissent totalement inadaptées aux expositions environnementales.	have uncertainties due to species-to-species extrapolation and to the high to low dose, since in order to limit the number of animals, doses administered are necessarily quite high compared to the human exposure actual conditions. Therefore, both type of studies were looked at, using a WoE approach. What is noted in the comment for mercury exposure is true for many other chemicals, which are ubiquitous and cause more than one effect by different mechanisms in specific vulnerability windows of exposure; the polymorphisms relevant for mercury kinetics (e.g. GST deletion) are present in a large part of the Caucasian population (40-50% are GSTM1 null; around 30% are GSTT1 null, to make an example) therefore the number of enrolled individuals should not be extremely high to see their effect, if any. No changes in the Opinion needed. This statement that *there is no level of exposure which we can deem to be "safe"* is not scientifically based. Elimination of the exposure through a ban is a risk management measure, which is outside the remit of THE SCENIHR

			Par exemple, la plus vaste étude épidémiologique rétrospective, l'étude de Bates [2004], qui grâce à sa puissance (cohorte de 20 000 personnes) a pu mettre en évidence une relation entre la présence d'amalgames et la survenue d'une sclérose en plaques (SEP), reste à la limite de la significativité car seuls 7 cas de SEP ont été dénombrés. Mais qui réalisera des études de cohortes encore plus puissantes ? Personne, assurément, compte tenu du coût élevé de ce type d'études. Cela prouve bien que ce parti pris mène à une impasse. Il est donc nécessaire de se concentrer sur les études toxicologiques et, à l'appui de ce que celles-ci nous apprennent du mercure – à savoir qu'il n'y a aucun niveau d'exposition que l'on puise considérer comme « sûr » – d'éliminer toutes les sources d'exposition évitables. ***English translation:*** The SCENIHR experts still consider properly conducted epidemiological research, such as the case/control studies or the cohort studies, to be elements of central proof. However, they themselves recognise [3.3.7] that the genetic polymorphisms explain why the results of these studies are contradictory. Other difficulties and biases facing epidemiology should be pointed out, in particular: - the entire European population is exposed to mercury: there are no real unexposed control subjects; - exposure to dental mercury depends only in part on the number of amalgams: it also depends on other metals in the mouth, bruxism, the consumption of chewing gum, etc.; - once absorbed, mercury in its oxidised form has multiple effects on cells at the origin of a myriad of symptoms and diseases: mercury is a ubiquitous and polymorphous toxin. It joins to the thiol bonds of functional or structural proteins. It	

			will then disrupt signalling pathways, neurotransmitters, enzyme systems, bind to membrane receptors, which alters the membrane permeability, increase oxidising stress and peroxidation, lead to a mitochondrial dysfunction, create inflammation, etc.; - as for the majority of diseases of environmental origin, the deleterious effects of exposure are staggered over time; - the exposure period is important, and not only the dose ("Time is poison"): for instance, the developing nervous system is very vulnerable. - The organism is exposed to a number of toxins (cocktail effects) between which synergies exist; synergies even exist between methylmercury and inorganic mercury. For instance, the classic bases of "evidence-based medicine", drawing on epidemiological studies (of cohorts where possible), appear to be totally unsuited to environmental exposure. For example, the largest retrospective epidemiological study, the Bates study [2004] which, thanks to its scale (cohort of 20 000 persons) revealed a relationship between the presence of amalgams and the onset of multiple sclerosis (MS), has only borderline significance because it covers only seven cases of MS. But who will perform cohort studies on an even wider scale? Most certainly no one, given the high cost of this type of study. Consequently, this standpoint simply results in a deadlock. It is therefore necessary to focus on the toxicological studies and, based on what they teach us about mercury – namely that there is no level of exposure which we can deem to be "safe"– to eliminate all avoidable sources of exposure	
36	GROSMAN Marie, Non au Mercure Dentaire, mariegrosman@free.	3.3.5.1. Localized mucosal reactions	Bibliographie relative à la question « mercure dentaire et antibiorésistance » (voir 3.3.5.2) Ball MM et al. Mercury resistance in bacterial strains isolated from tailing ponds in a gold mining area near El Callao (Bolívar State, Venezuela).Curr Microbiol. 2007 Feb;54(2):149-54.	The problem of antibiotic resistance induced by mercury from amalgam and other sources is important. However, this is discussed extensively in the recent Opinion published in 2014 by the Scientific Committee on Health and Environmental Risks (SCHER). The Opinion of SCHER is mentioned in the introduction

	fr		Caballero-Flores GG et al. Chromate-resistance genes in plasmids from antibiotic-resistant nosocomial enterobacterial isolates. FEMS Microbiol Lett. 2012 Feb;327(2):148-54. Dyke KG et al. Occurrence of various types of penicillinase plasmid among 'hospital' staphylococci. J Clin Pathol. 1967 Jan;20(1):75-9. Edlund C et al. Resistance of the normal human microflora to mercury and antimicrobials after exposure to mercury from dental amalgam fillings. Clin Infect Dis. 1996 Jun;22(6):944-50. Ferreira da Silva M et al. Antimicrobial resistance patterns in Enterobacteriaceae isolated from an urban wastewater treatment plant. FEMS Microbiol Ecol. 2007 Apr;60(1):166-76. Grewal JS et al. Resistance to antibiotics, metals, hydrophobicity and klebocinogeny of Klebsiella pneumoniae isolated from foods. Cytobios. 1999;98(388):113-23. Hall BM. Distribution of mercury resistance among Staphylococcus aureus isolated from a hospital community. J Hyg (Lond). 1970 Mar;68(1):111-9. Joly B et al. [The role of heavy metals and their derivatives in the selection of antibiotics resistant gram-negative rods]. Ann Microbiol (Paris). 1975 Jul-Aug;126B(1):51-61. Makino S et al. Change of drug resistance patterns and genetic properties of R plasmids in Salmonella typhimurium of bovine origin isolated from 1970 to 1979 in northern Japan. J Hyg (Lond). 1981 Oct;87(2):257-69. McArthur JV et al. Spatial patterns in antibiotic resistance among stream bacteria: effects of industrial pollution. Appl Environ Microbiol. 2000 Sep;66(9):3722-6. Meredith MM et al. Concomitant antibiotic and mercury resistance among gastrointestinal microflora of feral brook trout, Salvelinus fontinalis. Curr Microbiol. 2012 Nov;65(5):575-82. Nakahara H et al. Survey of resistance to metals and antibiotics in clinical isolates of Klebsiella pneumoniae in Japan. Zentralbl Bakteriol Orig A. 1978 Jan;240(1):22-9. Nakahara H et al. Survey of resistance to metals and volatilization activity of Hg-resistant R plasmids in	of the SCENIHR Opinion. The SCENIHR Opinion addresses direct health effects from the use of dental amalgam on patients and users and not risks for the environment, which are covered by the SCHER Opinion New text and relevant references added in the 'Other effects paragraph': *The earlier, now banned use of mercury as antimicrobial agent was demonstrated to induce antibiotic resistance. (Hall et al 1970, Joly et al. 1975 and Poiata et al, 2000). For the induction of antibiotic resistance in relation to the use of dental amalgam, contradictory studies were reported (Summers et al 1993, Ready et al. 2007, Roberts et al 2008). However, in the positive studies the increase in antibiotic resistance did not seem to influence the health of the individual patients. In general the intestinal exposure to mercury from dental amalgam seems to be extremely low, so an effect on intestinal flora is not anticipated.*

			Citrobacter isolated from clinical lesions in Japan. Zentralbl Bakteriol Mikrobiol Hyg A. 1984 Aug;257(3):400-8. Poiată A et al. Mercury resistance among clinical isolates of Escherichia coli. Roum Arch Microbiol Immunol. 2000 Jan-Jun;59(1-2):71-9. Rasmussen LD et al. The effect of longterm exposure to mercury on the bacterial community in marine sediment. Curr Microbiol. 1998 May;36(5):291-7. Ready D et al. The effect of amalgam exposure on mercury-and antibiotic-resistant bacteria. Int J Antimicrob Agents. 2007 Jul;30(1):34-9. Resende JA et al. Multidrug-resistance and toxic metal tolerance of medically important bacteria isolated from an aquaculture system. Microbes Environ. 2012;27(4):449-55. Skurnik D et al. Is exposure to mercury a driving force for the carriage of antibiotic resistance genes? J Med Microbiol. 2010 Jul;59(Pt 7):804-7. Summers AO et al. Mercury released from dental "silver" fillings provokes an increase in mercury- and antibiotic-resistant bacteria in oral and intestinal floras of primates. Antimicrob Agents Chemother. 1993 Apr;37(4):825-34. Timoney JF et al. Heavy-metal and antibiotic resistance in the bacterial flora of sediments of New York Bight. Appl Environ Microbiol. 1978 Sep;36(3):465-72. Wireman J et al. Association of mercury resistance with antibiotic resistance in the gram-negative fecal bacteria of primates. Appl Environ Microbiol. 1997 Nov;63(11):4494-503. ***English translation:*** Bibliography on the issue "dental mercury and antibiotic resistance" (see 3.3.5.2). Ball MM et al. Mercury resistance in bacterial strains isolated from tailing ponds in a gold mining area near El Callao (Bolívar State, Venezuela).Curr Microbiol. 2007	

Feb;54(2):149-54.

Caballero-Flores GG et al. Chromate-resistance genes in plasmids from antibiotic-resistant nosocomial enterobacterial isolates. FEMS Microbiol Lett. 2012 Feb;327(2):148-54.

Dyke KG et al. Occurrence of various types of penicillinase plasmid among 'hospital' staphylococci. J Clin Pathol. 1967 Jan;20(1):75-9.

Edlund C et al. Resistance of the normal human microflora to mercury and antimicrobials after exposure to mercury from dental amalgam fillings. Clin Infect Dis. 1996 Jun;22(6):944-50.

Ferreira da Silva M et al. Antimicrobial resistance patterns in Enterobacteriaceae isolated from an urban wastewater treatment plant. FEMS Microbiol Ecol. 2007 Apr;60(1):166-76.

Grewal JS et al. Resistance to antibiotics, metals, hydrophobicity and klebocinogeny of Klebsiella pneumoniae isolated from foods. Cytobios. 1999;98(388):113-23.

Hall BM. Distribution of mercury resistance among Staphylococcus aureus isolated from a hospital community. J Hyg (Lond). 1970 Mar;68(1):111-9.

Joly B et al. [The role of heavy metals and their derivatives in the selection of antibiotics resistant gram-negative rods]. Ann Microbiol (Paris). 1975 Jul-Aug;126B(1):51-61.

Makino S et al. Change of drug resistance patterns and genetic properties of R plasmids in Salmonella typhimurium of bovine origin isolated from 1970 to 1979 in northern Japan. J Hyg (Lond). 1981 Oct;87(2):257-69.

McArthur JV et al. Spatial patterns in antibiotic resistance among stream bacteria: effects of industrial pollution. Appl

			Environ Microbiol. 2000 Sep;66(9):3722-6. Meredith MM et al. Concomitant antibiotic and mercury resistance among gastrointestinal microflora of feral brook trout, Salvelinus fontinalis. Curr Microbiol. 2012 Nov;65(5):575-82. Nakahara H et al. Survey of resistance to metals and antibiotics in clinical isolates of Klebsiella pneumoniae in Japan. Zentralbl Bakteriol Orig A. 1978 Jan;240(1):22-9. Nakahara H et al. Survey of resistance to metals and volatilization activity of Hg-resistant R plasmids in Citrobacter isolated from clinical lesions in Japan. Zentralbl Bakteriol Mikrobiol Hyg A. 1984 Aug;257(3):400-8. Poiată A et al. Mercury resistance among clinical isolates of Escherichia coli. Roum Arch Microbiol Immunol. 2000 Jan-Jun;59(1-2):71-9. Rasmussen LD et al. The effect of longterm exposure to mercury on the bacterial community in marine sediment. Curr Microbiol. 1998 May;36(5):291-7. Ready D et al. The effect of amalgam exposure on mercury- and antibiotic-resistant bacteria. Int J Antimicrob Agents. 2007 Jul;30(1):34-9. Resende JA et al. Multidrug-resistance and toxic metal tolerance of medically important bacteria isolated from an aquaculture system. Microbes Environ. 2012;27(4):449-55. Skurnik D et al. Is exposure to mercury a driving force for the carriage of antibiotic resistance genes? J Med Microbiol. 2010 Jul;59(Pt 7):804-7. Summers AO et al. Mercury released from dental "silver" fillings provokes an increase in mercury- and antibiotic-resistant bacteria in oral and intestinal floras of primates.	

			Antimicrob Agents Chemother. 1993 Apr;37(4):825-34. Timoney JF et al. Heavy-metal and antibiotic resistance in the bacterial flora of sediments of New York Bight. Appl Environ Microbiol. 1978 Sep;36(3):465-72. Wireman J et al. Association of mercury resistance with antibiotic resistance in the gram-negative fecal bacteria of primates. Appl Environ Microbiol. 1997 Nov;63(11):4494-503.	
37	McKay Ian , British Dental Association, ian.mckay@bda.org	3.3.5.2. Systemic effects	There is undue significance placed on the work of Geier et al., (2009) where the conclusion that mercury exposure during pregnancy from amalgam restorations is associated with elevated risk of severe autism appears flawed. The relationship between mercury exposure (particularly in the form of thimerosal) and the development of autism is highly contentious. Despite extensive research there has been no clear evidence to support a relationship between mercury and autism. The conclusions of the paper rely entirely on the mothers knowing how many amalgam restorations they had present when pregnant 10 years earlier. No details are provided as to how this information was obtained and validated. Neither is there any indication if the mothers have other non-amalgam restorations or teeth lost due to decay. More problematic is that the study fails to adjust for confounding effects of socio-economic factors and diet. Clearly the number of dental restorations are strongly correlated with diet and socio-economic status. This study can at best provide evidence of a correlation between amalgams and severity of autism. It cannot in any way be used as evidence of causation. The conclusions of the paper that elevated mercury levels during pregnancy is associated with the severity of autism goes far beyond anything that can be concluded from the available information.	The article of Geier et al (2009) does not indicate how information on the number of amalgam fillings is recovered. It is indicated, however, that the children included had not been exposed to mercury-containing drugs (including thimerosal). Adjustment for age, gender, age and region was made, but not for diet and socio-economic status. In the SCENIHR Opinion it is stated that: "Patients whose mother had 6 or more amalgam fillings had 3.2 times greater risk of having a severe autism compared to patients with mild autism where the mother had 5 or less amalgam fillings. In conclusion, the available data do not show a correlation between autism and blood mercury levels in small children. However, one paper indicated an association between the severity of autism in autistic children and the number of dental amalgam fillings in their mothers during pregnancy, thus suggesting a need for further research. " The Opinion does thus not conclude that elevated mercury levels during pregnancy is associated with the severity of autism. Likewise, there is no mention of causation. A new sentence has now been included in the Opinion concerning the limitations in the methodology used in the study.

38	McKay Ian , British Dental Association, ian.mckay@bda.org	3.3.5.2. Systemic effects	The paper of Julvez et al., 2013 represents probably the most comprehensive analysis of possible interactions of mercury with gene polymorphisms. This study examines the influence of 40 different polymorphisms and it would be helpful to note that these include polymorphisms reported in several other studies. In particular this study suggests that polymorphisms in CPOX appear unrelated to cognitive development.	The paper is already cited in the Opinion. It evaluates the effect of prenatal methylmercury exposure on cognitive defects at the age of 8 years depending on genetic predisposition. The exposure was generally at a low level and the lack of influence of CPOX4 polymorphism on cognitive development at 8 years does not invalidate the report by Woods et al (2012) which showed an effect of the CPOX4 polymorphism on neurobehavioral functions in boys exposed chronically to mercury due to presence of amalgam fillings (the Casa Pia study).
39	GROSMAN Marie, Non au Mercure Dentaire, mariegrosman@free.fr	3.3.5.2. Systemic effects	Le SCENIHR ne tient pas compte d'un problème de santé publique majeur, en partie induit par la pollution d'origine dentaire : la résistance aux antibiotiques. L'OMS (mai 2013) rappelle que les résistances aux antimicrobiens augmentent la morbidité comme la mortalité et qu'elles élèvent en conséquence le coût des dépenses de santé. On observe aujourd'hui une augmentation extrêmement préoccupante de ces résistances : 3,7 % des nouveaux cas de tuberculose sont multirésistants ; de nombreuses infections nosocomiales sont provoquées par des bactéries hautement résistantes telles que S. aureus résistant à la méthicilline ou des bactéries Gram négatives communes (P. aeruginosa, A. baumanii) multirésistantes. En France, l'Inserm estime que le cas le plus préoccupant, en ville comme à l'hôpital, est celui des entérobactéries productrices de bêta-lactamases à spectre étendu (E. coli ou K. pneumoniae). Le mercure est identifié depuis plus de 50 ans comme un vecteur de l'antibiorésistance et l'on compte aujourd'hui de nombreuses références dans Medline sur ce sujet. On a commencé à s'intéresser dans les années 1960 à la résistance de S. aureus à la fois à certains antibiotiques et au mercure, en milieu hospitalier [Dyke 1967]. Cette résistance multiple a bientôt été rencontrée dans d'autres milieux et pour d'autres espèces de bactéries : E. coli	Please see the answer to comment #36

			[Grewal 1999], Citrobacter [Nakahara 1984], K. pneumoniae [Nakahara 1978], S. typhimurium [Makino 1981] et d'autres espèces encore [Ferreira da Silva 2007, Cabarello-Flores 2012, Resende 2012]. Assez vite, on a avancé puis confirmé l'hypothèse selon laquelle c'est l'utilisation du mercure comme antimicrobien qui induit l'antibiorésistance [Hall 1970, Joly 1975, Poiata 2000]. Selon le rapport BIOIS (2012), en Europe, le mercure dentaire contamine chaque année : - l'air (19 tonnes), l'eau (3 tonnes), - le sol et les eaux souterraines (20,5 tonnes) Or l'induction de l'antibiorésistance dans l'environnement par la pollution au mercure a été clairement mise en évidence [Timoney 1978, Rasmussen 1998, McArthur 2000, Ball 2007]. Deux récentes études doivent à cet égard aiguiser notre vigilance : 1) Meredith et al. [2012] ont montré que la bioaccumulation de mercure dans les poissons (telle que celle induite par le mercure dentaire selon l'expertise du SCHER) peut conduire à une accumulation de bactéries résistantes au mercure et aux antibiotiques, même en l'absence de source d'émission de mercure ponctuelle. 2) Même si la part d'antibiorésistance induite par le mercure est inquantifiable, il faut se garder d'imaginer que le phénomène resterait marginal. Skurmik et al. [2010] ont comparé une population française métropolitaine (exposée aux antibiotiques et sans exposition importante au mercure) à une population amérindienne de Guyane française (peu exposée aux antibiotiques, très exposée au mercure) : c'est la flore bactérienne des Amérindiens qui contient le plus d'e. coli résistantes aux antibiotiques. L'amalgame dentaire pourrait également induire une résistance aux antibiotiques dans la flore intestinale du porteur ; de solides travaux soutiennent cette hypothèse [Summers 1993, Edlund 1996, Wireman 1997, Ready 2007]. On dispose donc aujourd'hui d'éléments concordants pour affirmer que le mercure dentaire constitue un danger, facilement éliminable, du point de vue de la résistance aux	

			antibiotiques. Références bibliographiques : voir 8. references ***English translation:*** The SCENIHR fails to take into account one major public health problem, partly caused by pollution of dental origin: resistance to antibiotics. The WHO (May 2013) points out that resistance to antimicrobials increases morbidity and mortality and that it consequently adds to health expenditure. Today, an extremely worrying increase in such resistance can be observed: 3.7 % of new cases of tuberculosis are multi-drug-resistant; numerous nosocomial infections are caused by highly resistant bacteria such as S. aureus resistant to methicillin or multi-drug-resistant common Gram-negative bacteria (P. aeruginosa, A. baumanii). In France, the Inserm considers that the most worrying case, in both towns and hospitals, is that of the extended-spectrum beta-lactamase-producing enterobacteriaceae (E. coli or K. pneumoniae). Mercury was identified over 50 years ago as a vector of antibiotic resistance, and numerous references to this subject can be found today in Medline. In the 1960s, we started to take an interest in the resistance of S. aureus both to certain antibiotics and to mercury, in the hospital environment [Dyke 1967]. This multiple resistance was soon encountered in other environments and for other species of bacteria: E. coli [Grewal 1999], Citrobacter [Nakahara 1984], K. pneumoniae [Nakahara 1978], S. typhimurium [Makino 1981] and other species [Ferreira da Silva 2007, Cabarello-Flores 2012, Resende 2012]. Rather quickly, the assumption was put forward and then confirmed that it is the use of mercury as an antimicrobial which creates antibiotic resistance [Hall 1970, Joly 1975, Poiata 2000]. According to the BIOIS report (2012), in Europe, contamination each year by dental mercury is as follows:- air (19 tonnes), - water (3 tonnes), - soil and groundwater (20.5 tonnes).	

			Antibiotic resistance in the environment caused by mercury pollution has been clearly highlighted [Timoney 1978, Rasmussen 1998, McArthur 2000, Ball 2007]. In this respect, two recent studies should make us more vigilant: 1) Meredith et al. [2012] have shown that the bioaccumulation of mercury in fish (like that caused by dental mercury according to the SCHER assessment) can lead to an accumulation of bacteria resistant to mercury and antibiotics, even where there is no source of mercury emission. 2) Even if some of the antibiotic resistance caused by mercury is unquantifiable, we would be well advised not to assume that it is negligible. Skurmik et al. [2010] compared a metropolitan French population (exposed to antibiotics and less exposed to mercury) with an Amerindian population in French Guyana (little exposure to antibiotics, very exposed to mercury): it is the bacterial flora of the Amerindians which contains the most antibiotic-resistant e. coli. Dental amalgam could also lead to antibiotic resistance in the carrier's intestinal flora; solid research supports this hypothesis [Summers 1993, Edlund 1996, Wireman 1997, Ready 2007]. Today , we therefore have corroborating evidence that dental mercury poses a danger, which can easily be eliminated, as regards resistance to antibiotics. Bibliographical references: see 8. references	
40	GROSMAN Marie, Non au Mercure Dentaire, mariegrosman@free.fr	3.3.5.2. Systemic effects	Le SCENIHR ne tient pas compte d'un problème de santé publique majeur, en partie induit par la pollution d'origine dentaire : la résistance aux antibiotiques. L'OMS (mai 2013) rappelle que les résistances aux antimicrobiens augmentent la morbidité et la mortalité, et élèvent donc le coût des dépenses de santé. Or on observe une augmentation	Please see response to comment #36

			extrêmement préoccupante de ces résistances : 3,7 % des nouveaux cas de tuberculose sont multirésistants ; de nombreuses infections nosocomiales sont provoquées par des bactéries hautement résistantes telles que S. aureus résistant à la méthicilline ou des bactéries Gram négatives communes (P. aeruginosa, A. baumanii) multirésistantes. En France, l'Inserm estime que le cas le plus préoccupant, en ville comme à l'hôpital, est celui des entérobactéries productrices de bêta-lactamases à spectre étendu (E. coli ou K. pneumoniae). Le mercure est identifié depuis plus de 50 ans comme un vecteur de l'antibiorésistance (nombreuses références dans Medline). On a commencé à s'intéresser dans les années 1960 à la résistance de S. aureus à la fois à certains antibiotiques et au mercure, en milieu hospitalier [Dyke 1967]. Cette résistance multiple a bientôt été rencontrée dans d'autres milieux et pour d'autres espèces de bactéries : E. coli [Grewal 1999], Citrobacter [Nakahara 1984], K. pneumoniae [Nakahara 1978], S. typhimurium [Makino 1981] et d'autres espèces encore [Ferreira da Silva 2007, Cabarello-Flores 2012, Resende 2012]. Assez vite, on a avancé puis confirmé l'hypothèse selon laquelle c'est l'utilisation du mercure comme antimicrobien qui induit l'antibiorésistance [Hall 1970, Joly 1975, Poiata 2000]. Selon le rapport BIOIS (2012), en Europe, le mercure dentaire contamine chaque année l'air (19 tonnes), l'eau (3 tonnes), le sol et les eaux souterraines (20,5 tonnes). Or l'induction de l'antibiorésistance dans l'environnement par la pollution au mercure a été clairement mise en évidence [Timoney 1978, Rasmussen 1998, McArthur 2000, Ball 2007]. Deux récentes études doivent à cet égard aiguiser notre vigilance : 1) Meredith et al. [2012] ont montré que la bioaccumulation de mercure dans les poissons (telle que celle induite par le mercure dentaire selon l'expertise du SCHER) peut conduire à une accumulation de bactéries résistantes au mercure et aux antibiotiques, même en l'absence de source d'émission de mercure ponctuelle. 2) Même si la part d'antibiorésistance induite par le mercure	

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			we started to take an interest in the resistance of S. aureus both to certain antibiotics and to mercury, in the hospital environment [Dyke 1967]. This multiple resistance was soon encountered in other environments and for other species of bacteria: E. coli [Grewal 1999], Citrobacter [Nakahara 1984], K. pneumoniae [Nakahara 1978], S. typhimurium [Makino 1981] and other species [Ferreira da Silva 2007, Cabarello-Flores 2012, Resende 2012]. Rather quickly, the assumption was put forward and then confirmed that it is the use of mercury as an antimicrobial which creates antibiotic resistance [Hall 1970, Joly 1975, Poiata 2000]. According to the BIOIS report (2012), contamination each year by dental mercury is as follows: air (19 tonnes), water (3 tonnes), soil and underground water (20.5 tonnes). Antibiotic resistance in the environment caused by mercury pollution has been clearly highlighted [Timoney 1978, Rasmussen 1998, McArthur 2000, Ball 2007]. In this respect, two recent studies should make us more vigilant: 1) Meredith et al. [2012] have shown that the bioaccumulation of mercury in fish (like that caused by dental mercury according to the SCHER assessment) can lead to an accumulation of bacteria resistant to mercury and antibiotics, even where there is no source of mercury emission. 2) Even if some of the antibiotic resistance caused by mercury is unquantifiable, we would be well advised not to assume that it is negligible. Skurmik et al. [2010] compared a metropolitan French population (exposed to antibiotics and less exposed to mercury) with an Amerindian population in French Guyana (little exposure to antibiotics, very exposed to mercury): it is the bacterial flora of the Guyanese which contains the most antibiotic-resistant e. coli. Dental amalgam could also lead to antibiotic resistance in the carrier's intestinal flora [Summers 1993, Edlund 1996, Wireman 1997, Ready 2007]. Today , we therefore have	

			corroborating evidence that dental mercury poses a danger, which can easily be eliminated, as regards resistance to antibiotics. We have carried over the bibliographical references of this section in our comment to Part 3.3.5.1. due to a lack of space.	
41	Würkner Gerald, privat, g.wuerkner@web.de	3.3.5.2. Systemic effects	Please have a look at the file "mercury-amalgam-chlorophyll-heme_1-2.pdf". It contains two relevant and brand-knew articles regarding the amalgam topic. The first article reveals toxic interactions thus the toxic effect of amalgam can be understood from a new point of view. The second analyses why mercury from dental amalgam is considered to be non-hazardous. Here the abstracts: Chlorophyll and Heme: Toxic Interactions at Subclinical Porphyria and Heavy Metal Poison-ing. In the treatment of suspected chronic heavy metal poisoning such as from amalgam by Chlorella spp. following the therapeutic approach of Dr. Klinghardt it has been repeatedly observed that high oral doses of chlorophyll, as found in this popular algae products, are toxic under certain conditions, whereby the symptoms suggest parallels with defects in heme metabolism. On the basis of two different cases an attempt is made to isolate the relevant factors and to relate them to known processes. Several theories are discussed, characterized by the model that under certain conditions the chemical similarity of chlorophyll and heme metabolism burdens the same resources, resulting in porphy-rinopathies in case of overload. In connection with common weaknesses and strains of heme metabolism, such as by genetic predispositions and heavy metal contamination, it is suspected that subclinical, chronic, acquired porphyrias are relatively common and for the current lack of detection parameters are proposed and required. Key words: Chlorophyll, heme, porphyria, pyrrole, chlorella, heavy metal poisoning, mercury On the Methodological Problem of Verification of Low-Threshold Chronic Intoxication, Especially of Neurotoxins,	The question relates to toxicokinetics rather than to systemic effects However, the abstract considers linking two case reports to a possible similarity between chlorophyll and Heme metabolism. As there are no studies indicating an effect of mercury on heme metabolism available in the public literature, this was not further considered by THE SCENIHR. Also regarding the frequency of porphyria, this could not be substantiated.

			Using the Example of Mercury from Amalgam By the conclusions of the article "Chlorophyll and Heme: Toxic Interactions at Subclinical Porphyria and Heavy Metal Poisoning" in umwelt•medizin•gesellschaft 4/2014, concerning chronic mercury intoxication cause porphyria and therefore are likely more widespread in subclinical form than previously thought, the potential significance of mercury from dental amalgam was focused again. It is worked out, how it does happen, that mercury from dental amalgam is considered by many as non-hazardous. Methodological errors are addressed as well as methodological problems with neu-rotoxins and methodological problems of environmental medicine. Finally proposals are made, by which approaches more clarity could be brought into the discussion to dental amalgam. Key words: Amalgam, mercury, chronic intoxication, Neurotoxins, methodological problems With kind regards Mag. Gerald Würkner	
42	Rooney James, Trinity College Dublin, jrooney@rcsi.ie	3.3.5.2. Systemic effects	Page 30, paragraph 1:Comment: However, subsequent genetics studies on the Casa Pia cohort determined that there were several subgroups of children with genetic sensitivities to mercury who experience neurobehavioral symptoms on exposure to mercury – particularly boys(Woods, Heyer, Russo, Martin, & Farin, 2014) Page 30, paragraph 7 – Page 30, paragraph 6: Heading: "Neurobehavioural functions" Comment: I have reservations about this entire section. First, although it is titled "Neurobehavioural functions" many of the symptoms/conditions discussed, i.e. muscle and joint pains, Th1 cytokine levels are not neurobehavioural in nature. Second, I have ethical and experimental design concerns around studies that recruit people based on complaints 'attributed to amalgams'. This is not a clear inclusion/exclusion criteria and is likely to be heavily	The article by Woods et al (2014) belongs to a series of previous articles from the same group on genetic polymorphisms and mercury neurotoxicity in the Casa Pia study. The main effects have already been described on page 32 in the preliminary Opinion, citing all the original studies. The 2014 paper is now also cited in the opinion. The section on neurobehavioral functions describe studies that address heterogeneous symptoms. Indeed the same patients who have neurobehavioral symptoms also often describe muscle and joint pains. Elevated Th1 cytokine level is a possible mechanism for the induction of the symptoms. The Th1 cytokine levels are also discussed in the section on the Immune system, page 33. Concerning the design of the studies reported, it is true that selection bias is probably present. But THE SCENIHR did not design these studies and is obliged to evaluate the existing

			influenced by individual patient beliefs and individual physician beliefs. Thus, these studies are likely to suffer severe selection bias – regardless of findings pro or against amalgam safety. I do not believe these studies provide useful evidence on "neurobehavioural functions". However, there are numerous studies that do provide evidence of the effects of largely amalgam derived mercury on subgroups of the population that are genetically sensitive, that have not been considered in this section. Genetic-mercury interaction effects on neurobehavioural functions have been identified amongst dentists (Heyer et al., 2004; Heyer, Echeverria, Farin, & Woods, 2008; Heyer, Echeverria, Martin, Farin, & Woods, 2009; Woods et al., 2005) and also amongst children(Woods, Heyer, Russo, Martin, & Farin, 2014). It is noteworthy that some of these polymorphisms have now been associated with gene-mercury effects on neurobehavioural functions in both adults and children. Page 32, paragraph 5: "In conclusion, there is no evidence that amalgam negatively influences the neuropsychological development of children." Comment: In light of the studies on genetic polymorphisms interacting with mercury exposure in children, and the fact that the two large amalgam trials were not powered to detect such subgroups in the intervention arms, this statement is not reassuring. There is evidence both in children and in dentists that low level mercury exposure in the range of blood mercury levels consistent with having amalgams is associated with neurobehavioural deficits in those with the relevant genes(Heyer et al., 2004, 2008, 2009; Woods et al., 2005)(Woods, Heyer, Russo, Martin, & Farin, 2014). Neither amalgam trial was designed to detect such subgroups in those receiving amalgam. References Heyer, N. J., Echeverria, D., Bittner, A. C., Farin, F. M., Garabedian, C. C., & Woods, J. S. (2004). Toxicological Sciences, 363, 354–363. doi:10.1093/toxsci/kfh220 Heyer, N. J., Echeverria, D., Farin, F. M., & Woods, J. S.	reports in an objective way. This possibility has been included to make the text clearer. The influence of genetic polymorphisms in dentists and in children on susceptibility to mercury toxicity is described in section 3.3.7. and the most recent reference from Woods et al (2014) is included in the section. The two large amalgam trials in children did not show a negative influence on the neuropsychological development of children in the first analyses and only post-hoc analyses on children with certain genetic polymorphisms showed deficits that could be attributed to mercury toxicity. It is true that the design of the studies was not optimal to detect such effects. The text has been changed to take into account the genetic polymorphisms issue (also described in details in the specific paragraph 3.3.7).

			(2008). Journal of Toxicology and Environmental Health. Part A, 71(19), 1318–1326. doi:10.1080/15287390802240850 Heyer, N. J., Echeverria, D., Martin, M. D., Farin, F. M., & Woods, J. S. (2009). Journal of Toxicology and Environmental Health. Part A, 72(9), 599–609. doi:10.1080/15287390802706405 Woods, J. S., Echeverria, D., Heyer, N. J., Simmonds, P. L., Wilkerson, J., & Farin, F. M. (2005). Toxicology and Applied Pharmacology, 206(2), 113–20. doi:10.1016/j.taap.2004.12.016 Woods, J. S., Heyer, N. J., Russo, J. E., Martin, M. D., & Farin, F. M. (2014). Neurotoxicology, 44C, 288–302. doi:10.1016/j.neuro.2014.07.010	
43	Rooney James, Trinity College Dublin, jrooney@rcsi.ie	3.3.5.2. Systemic effects	Page 31, paragraph 9 & Page 32, paragraph 1: Comment: Both the New England and Casa Pia trials were not designed, nor sufficiently powered, to detect subgroups carrying genetic polymorphisms that sensitize the carriers to mercury in the intervention arm only - particularly if multiple subgroups of possibly interacting polymorphisms were present (likely given that these polymorphisms are not rare)(1). Indeed, the New England trial was powered to detect a 3 point IQ change over 5 years with 80% power with an effective alpha of 0.045 and power calculations implying a sample size of 186 per children per group(2). If we use the same parameters and wish to detect an effect in a subgroup exposed to amalgams with heterozygous or homozygous CPOX4 carriage compared to those not exposed to amalgams we would need a sample size of 492 at 80%, or 654 at 90% power in the amalgam group only. (see uploaded sample size calculations for the workings.) Of course in reality we would need more than this as we would like to also detect the difference between the heterozygous and homozygous groups. This example is for one polymorphism and we know there are many others of potential importance, therefore samples sizes well into the thousands are required. Page 32, paragraph 3:	THE SCENIHR agrees that the studies were not primarily designed to detect genetically susceptible subgroups. In order to prove such associations, larger studies would be required, although this is not valid for all the involved genes (depending on their frequency among the population). For a number of reasons, it is unlikely that such large studies would be planned nowadays. THE SCENIHR modified the section 3.3.7. to take these comments into account.

			"It is important to note that the three articles by Woods et al do not compare amalgam versus alternative treatment, but evaluate the association between mercury levels in urine and outcome of the neurobehavioral tests. The authors estimate that only about 17 % of the urinary mercury level variation was due to amalgam (15 % in girls), indicating considerable background mercury exposure unrelated to dental amalgam. They therefore conclude that the findings do not support an association between mercury in dental amalgam and adverse neurobehavioral outcome observed (Woods et al 2013)." Comment: However, as demonstrated by the above power calculations, the Casa Pia trial was not sufficiently powered to detect gene-mercury effects in the amalgam group of the trial only. Furthermore, the gene-mercury interaction effects of CPOX4, COMT, 5-HTTLPR, BDNF were originally discovered in a cohort of dentists occupationally exposed to mercury(3–6), and thus there is evidence for these effects in two independent cohorts, one of which has occupational exposure to mercury from amalgam. Thus the evidence is considerably stronger than the SCENIHR is recognizing here. References: 1. Woods, J. S., Heyer, N. J., Russo, J. E., Martin, M. D. & Farin, F. M. Genetic polymorphisms affecting susceptibility to mercury neurotoxicity in children: Summary findings from the Casa Pia Children's Amalgam Clinical Trial. Neurotoxicology 44C, 288–302 (2014). 2. The Children's Amalgam Trial Study Group. The Children's Amalgam Trial: design and methods. Control. Clin. Trials 24, 795–814 (2003). 3. Woods, J. S. et al. The association between genetic polymorphisms of coproporphyrinogen oxidase and an atypical porphyrinogenic response to mercury exposure in humans. Toxicol. Appl. Pharmacol. 206, 113–20 (2005). 4. Heyer, N. J., Echeverria, D., Martin, M. D., Farin, F. M. & Woods, J. S. Catechol O-methyltransferase (COMT) VAL158MET functional polymorphism, dental mercury	

			exposure, and self-reported symptoms and mood. J. Toxicol. Environ. Health. A 72, 599–609 (2009). 5. Heyer, N. J. et al. Chronic Low-Level Mercury Exposure , BDNF Polymorphism , and Associations with Self-Reported Symptoms and Mood. Toxicol. Sci. 363, 354–363 (2004). 6. Heyer, N. J., Echeverria, D., Farin, F. M. & Woods, J. S. The association between serotonin transporter gene promoter polymorphism (5-HTTLPR), self-reported symptoms, and dental mercury exposure. J. Toxicol. Environ. Health. A 71, 1318–1326 (2008).	
44	Rooney James, Trinity College Dublin, jrooney@rcsi.ie	3.3.5.2. Systemic effects	Page 31, paragraph 9 & Page 32, paragraph 1: Comment: Both the New England and Casa Pia trials were not designed, nor sufficiently powered, to detect subgroups carrying genetic polymorphisms that sensitize the carriers to mercury in the intervention arm only - particularly if multiple subgroups of possibly interacting polymorphisms were present (likely given that these polymorphisms are not rare)(1). Indeed, the New England trial was powered to detect a 3 point IQ change over 5 years with 80% power with an effective alpha of 0.045 and power calculations implying a sample size of 186 per children per group(2). If we use the same parameters and wish to detect an effect in a subgroup exposed to amalgams with heterozygous or homozygous CPOX4 carriage compared to those not exposed to amalgams we would need a sample size of 492 at 80%, or 654 at 90% power in the amalgam group only. (see uploaded sample size calculations for the workings.) Of course in reality we would need more than this as we would like to also detect the difference between the heterozygous and homozygous groups. This example is for one polymorphism and we know there are many others of potential importance, therefore samples sizes well into the thousands are required. Page 32, paragraph 3: "It is important to note that the three articles by Woods et al do not compare amalgam versus alternative treatment, but	Please see response to comment #43

			evaluate the association between mercury levels in urine and outcome of the neurobehavioral tests. The authors estimate that only about 17 % of the urinary mercury level variation was due to amalgam (15 % in girls), indicating considerable background mercury exposure unrelated to dental amalgam. They therefore conclude that the findings do not support an association between mercury in dental amalgam and adverse neurobehavioral outcome observed (Woods et al 2013)." Comment: However, as demonstrated by the above power calculations, the Casa Pia trial was not sufficiently powered to detect gene-mercury effects in the amalgam group of the trial only. Furthermore, the gene-mercury interaction effects of CPOX4, COMT, 5-HTTLPR, BDNF were originally discovered in a cohort of dentists occupationally exposed to mercury(3–6), and thus there is evidence for these effects in two independent cohorts, one of which has occupational exposure to mercury from amalgam. Thus the evidence is considerably stronger than the SCENIHR is recognizing here. References: 1. Woods, J. S., Heyer, N. J., Russo, J. E., Martin, M. D. & Farin, F. M. Genetic polymorphisms affecting susceptibility to mercury neurotoxicity in children: Summary findings from the Casa Pia Children's Amalgam Clinical Trial. Neurotoxicology 44C, 288–302 (2014). 2. The Children's Amalgam Trial Study Group. The Children's Amalgam Trial: design and methods. Control. Clin. Trials 24, 795–814 (2003). 3. Woods, J. S. et al. The association between genetic polymorphisms of coproporphyrinogen oxidase and an atypical porphyrinogenic response to mercury exposure in humans. Toxicol. Appl. Pharmacol. 206, 113–20 (2005). 4. Heyer, N. J., Echeverria, D., Martin, M. D., Farin, F. M. & Woods, J. S. Catechol O-methyltransferase (COMT) VAL158MET functional polymorphism, dental mercury exposure, and self-reported symptoms and mood. J. Toxicol. Environ. Health. A 72, 599–609 (2009).	

			5. Heyer, N. J. et al. Chronic Low-Level Mercury Exposure , BDNF Polymorphism , and Associations with Self-Reported Symptoms and Mood. Toxicol. Sci. 363, 354–363 (2004). 6. Heyer, N. J., Echeverria, D., Farin, F. M. & Woods, J. S. The association between serotonin transporter gene promoter polymorphism (5-HTTLPR), self-reported symptoms, and dental mercury exposure. J. Toxicol. Environ. Health. A 71, 1318–1326 (2008).	
45	Rooney James, Trinity College Dublin, jrooney@rcsi.ie	3.3.5.2. Systemic effects	Page 33, paragraph 5: "Other Effects A study of 75 mother-child pairs from Slovakia showed that exposure to mercury from amalgam and the environment influences thyroid hormone status with e.g. lower thyroxine levels in the mothers. This was correlated to a higher level of thyroid-stimulating hormone in the blood of the newborn children (Ursinyova et al 2012). Although the findings appear meaningful, the clinical implications are not clear." Comment: The SCENIHR have not mentioned several other important findings with regard to mercury, amalgam and thyroid hormones. A 2006 controlled trial (n=39) from the Czech republic found that the removal of dental amalgam was associated with a significant decrease in anti-TPO (p=0.0007) and anti-Tg (p=0.001) autoantibodies in patients with autoimmune thyroiditis(Sterzl et al., 2006). In addition, several large-scale cross-sectional surveys have reported associations between blood mercury levels and thyroid hormones and thyroid auto-antibodies. Gallagher and Meliker used data from the 2007 - 2008 US NHANES dataset to examine associations between thyroid autoantibodies in women and blood mercury levels(Gallagher & Meliker, 2012). After exclusions they included 2,047 women aged 20 – 80 years in their analysis and found an odds ratio of 2.24 (95% CI = 1.22 – 4.12, Ptrend=0.032) for thyroid peroxidase antibody positivity between the highest blood mercury quintile relative to the lowest quintile(Gallagher & Meliker, 2012). More recently, two independent analyses of the 2007 – 2008 US NHANES dataset found negative associations	Concerning other studies evoked by Dr Rooney, they have been evaluated carefully by THE SCENIHR. The report by Sterzl et al. (2006) showed that only patients with mercury hypersensitivity as measured by the Melisa test, had a decrease of autoimmune antibodies after removal of dental amalgam. No change was seen in patients without hypersensitivity. As mentioned by Dr Rooney, several analyses of the National Health and Nutrition Examination Survey (NHANES) showed a negative correlation between blood mercury levels and thyroid hormones. One analysis (Gallagher & Meliker, 2012) also indicated a higher frequency of autoantibodies towards thyroglobulin (but not towards thyroid peroxidase) in women with the highest blood mercury level. However, the NHANES dataset did not take into account the presence of dental amalgam and it is unknown to which degree mercury from dental amalgam has contributed to the mercury levels in blood. These references have been included in the revised Opinion.

			between thyroid hormones and blood mercury(Chen, Kim, Chung, & Dietrich, 2013; Yorita Christensen, 2013). Chen et al analyzed data for 5,418 people after exclusions, and including 1,009 aged 12 – 19 who were separately analyzed. Statistically significant negative associations were found between total blood mercury and total T4 and Free T3 in adolescents, and between both total blood mercury and organic blood mercury, and total T4, total T3, and Free T3 in adults (a subgroup analysis in women of reproductive age also found associations between blood mercury and thyroid hormones)(Chen et al., 2013). The findings were robust to inclusion of cadmium and lead in models. The study by Christensen included 1,587 adults after exclusions blood mercury was associated with reduced T3(total and free) and T4 and on univariate regression, and after multivariate regression including other metals(Yorita Christensen, 2013). Therefore there is considerable evidence that mercury, whether amalgam derived or not, may be important in thyroid dysfunction. References: Chen, A., Kim, S. S., Chung, E., & Dietrich, K. N. (2013). Thyroid Hormones in Relation to Lead , Mercury , and Cadmium Exposure in the National Health and Nutrition Examination Survey , 2007 – 2008, 121(2), 2007–2008. Gallagher, C. M., & Meliker, J. R. (2012). Mercury and thyroid autoantibodies in U.S. women, NHANES 2007-2008. Environment International, 40, 39–43. doi:10.1016/j.envint.2011.11.014 Sterzl, I., Prochazkova, J., Hrda, P., Matucha, P., Bartova, J., & Stejskal, V. (2006). Removal of dental amalgam decreases anti-TPO and anti-Tg autoantibodies in patients with autoimmune thyroiditis. Neuro Endocrinology Letters, 27 Suppl 1, 25–30. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16804512 Yorita Christensen, K. L. (2013). Metals in blood and urine, and thyroid function among adults in the United States 2007-2008. International Journal of Hygiene and Environmental	

			Health, 216(6), 624–32. doi:10.1016/j.ijheh.2012.08.005	
46	Begon Geoffrey, World Alliance for Mercury-Free Dentistry, beggeof@yahoo.fr	3.3.5.2. Systemic effects	Urinary system The following studies were not included: • Trachtenberg et. al. (2007) found the first signs of kidney damage, microalbuminuria, in children after only five years of exposure to amalgam. Mortada et. al. (2002), in a study of 101 healthy adults,urinary excretion of NAG, gammaGT and albumin was significantly higher in persons with dental amalgam than those without. In the amalgam group, urinary excretion of NAG and albumin significantly correlated with the number of fillings. Albuminuria significantly correlated with blood and urine Hg.In these exposure conditions, renal damage is possible. Neurological System Neurological function tests The preliminary opinion says "In a further post-hoc analysis of these data exposure to bisGMA-based dental composite restorations was associated with impaired psychosocial function in children in comparison to amalgam (Maserejian et al. 2012)." This unqualified statement does not take into consideration the many weaknesses of the Maserejian study, including: • the researchers relied on self-reports instead of actual testing • no measure of BPA was even taken – in fact, there is no indication that BPA was detected at all, much less that it caused any problems • the researchers did not control for all possible confounding factors (most significantly, exposure from canned food and beverages) • the researchers themselves exposed study participants to dental sealants (a potential source of BPA exposure) placed during the course of the study • the study was not blind (both participants and researchers could see what material was used in their mouths) • in a later study, researchers did a battery of neuropsychological testing that failed to find even a statistically significant association between composites and	The article by Trachtenberg et. al. (2007) concerning a secondary analysis of the New England Children's amalgam study does not mention a correlation between amalgam treatment and kidney damage. A new paragraph was included in the Opinion, Urinary system: *Mortada et al (2002) investigated 49 healthy individuals with amalgam fillings and 51 matched controls. The mercury concentration in urine was correlated to the number of amalgam fillings. In the amalgam group, urinary excretion of NAG and albumin correlated with the number of fillings and albuminuria with blood and urine mercury levels. Other kidney biomarkers were not affected.* The article cited by Dr Geoffrey (Maserejian et al. 2012) was written by the follow-up group of the New England Children's amalgam study and concerned the Neuropsychological Development. Insignificant associations were found in favour of amalgam treatment. Another article was published the same year: Maserejian et al.. 2012. This article is cited in the Opinion and it showed significant association between bisGMA based dental composite restoration and impaired psychosocial function in the children. It is true that BPA was not measured. A more recent analysis (Maserejian et al., 2014) showed that use of sealants (containing BPA) or preventive resin restorations were not associated with behavioral, neuropsychological, or physical development in the children. No strong association or consistent dose-response relationship was observed between exposure to chemical agents in dental work and the risk of miscarriage. A slightly increased risk was found for exposure to mercury amalgam, some acrylate compounds, solvents and disinfectants. These findings indicate that the possibility of a weak association between exposure to these agents and an increased risk of miscarriage cannot be excluded (Lindbohm et al., 2007)

			test scores – much less any connection to BPA Reproductive system The preliminary opinion says "There is no evidence of any association between amalgam restorations and either male of female fertility or obstetric parameters." (page 33) But there is evidence that amalgam is associated with infertility, including the following studies: • Women with more amalgam fillings or increased mercury levels in urine had a higher incidence of infertility (Gerhard et. al. 1992; Gerhard et. al. 1998). • Female dental assistants exposed to amalgam showed a higher rate of infertility (Rowland et. al. 1994). • Exposure to mercury has also been linked to decreased male fertility (Sheiner et. al. 2003). Trachtenberg F, Barregård L: The effect of age, sex, and race on urinary markers of kidney damage in children. Am J Kidney Dis 2007, 50:938-945. Wael I. Mortada, Mercury in dental restoration: Is there a risk of nephrotoxicity, J. Nephrol (2002), Maserejian et. al., Dental Composite Restorations and Neuropsychological Development in Children: Treatment Level Analysis from a Randomized Clinical Trial, Neurotoxicology (Oct. 2012). Gerhard I, Runnebaum B: The limits of hormone substitution in pollutant exposure and fertility disorders. ZentralblGynaekol 1992, 114:593-602. Gerhard I, Waibel S, Daniel V, Runnebaum B: Impact of heavy metals on hormonal and immunological factors in women with repeated miscarriages. Hum Reprod Update 1998, 4:301-309. Rowland A, Baird D, Weinberg C, Shore D, Shy C, Wilcox A: The effect of occupational exposure to the mercury vapour on the fertility of female dental assistants. Occup Environ Med 1994, 51:28-34.	Gerhard & Runnebaum (1992) is a review on a number of pollutants. It is in German. The abstract does not mention a specific influence of dental amalgam on fertility. Gerhard et al (1998) evaluated the concentration of a number of heavy metals in a material of women with repeated miscarraiges. The level of urinary mercury was correlated to number of amalgam fillings. There was a borderline (p=0.05) inverse association between mercury load and level of different hormones, but the authors state that this could well be due to the large number of parameters tested. Based on telephone interviews Rowland et al (1994) (title: The effect of occupational exposure to mercury vapour on the fertility of female dental assistants) shows that female dental assistants that were most exposed to mercury due to amalgam preparation were less fertile than a control group of female dental assistants not exposed to amalgam. But the same group was also more exposed to nitrous oxide, x rays, methyl methacrylate, and ethylene oxide (gas sterilisation. Curiously, female dental assistants with low exposure were more fertile than the control group without exposure to mercury. Sheiner et al (2003) is a review of the literature on the effect of occupational exposure on male infertility. Although the abstract indicates a significant association between mercury exposure and infertility, there is no mention of such an association in the text or tables of the article. Therefore SCENIR does not consider the papers relevant.
47	Doneus Wolfgang, Council of European	3.3.5.2. Systemic	There is undue significance placed on the work of Geier et al., (2009) where the conclusion that mercury exposure	Please see the response to comment #37

	Dentists, ced@eudental.eu	effects	during pregnancy from amalgam restorations is associated with elevated risk of severe autism appears flawed. The relationship between mercury exposure (particularly in the form of thimerosal) and the development of autism is highly contentious. Despite extensive research there has been no clear evidence to support a relationship between mercury and autism. The conclusions of the paper rely entirely on the mothers knowing how many amalgam restorations they had present when pregnant 10 years earlier. No details are provided as to how this information was obtained and validated. Neither is there any indication if the mothers have other non-amalgam restorations or teeth lost due to decay. More problematic is that the study fails to adjust for confounding effects of socio-economic factors and diet. Clearly the number of dental restorations is strongly correlated with diet and socio-economic status. This study can at best provide evidence of a correlation between amalgams and severity of autism. It cannot in any way be used as evidence of causation. The conclusions of the paper that elevated mercury levels during pregnancy is associated with the severity of autism goes far beyond anything that can be concluded from the available information.	
48	GROSMAN Marie, Non au Mercure Dentaire, mariegrosman@free.fr	3.3.6. Epidemiological and clinical evidence concerning adverse effects of dental amalgam in dental personnel	L'exposition professionnelle est un enjeu crucial – d'autant que, comme le relève le SCENIHR, les nouveaux dispositifs (capsules, récupérateurs) n'ont pas réussi à faire disparaître ce problème [3.3.1.4]. En effet, le risque d'absorption du mercure par les professionnels ne tient pas seulement au nombre d'obturations nouvelles pour lesquelles ils utilisent des amalgames, mais aussi aux conditions dans lesquelles ils travaillent sur les amalgames préexistants : une majorité de professionnels ne prennent malheureusement pas de protections suffisantes [Colson 2012, Warwick 2013]. Il nous paraît essentiel d'insister sur différents phénomènes de surmorbidités observées dans les professions dentaires, qui peuvent toutes être imputées, au moins partiellement, à l'exposition au mercure.	THE SCENIHR agrees to add a new paragraph in chapter 3.3.1.4 Exposure to mercury in dental personnel: *In a more recent study in Canada it was observed that mercury vapour exposure during dental training on amalgam removal remained below occupational exposure limits (Warwick et al., 2013).'* THE SCENIHR agreed to add a new paragraph in the paragraph on Reproductive system, under the heading Systemic Effects: *The fecundability of 558 female dental surgeons vs. 450 high school teachers. Dentists were occupationally exposed to mercury, chloroform, ethanol, benzene. Occupational exposure had no clear adverse effects on fertility among female dental*

			Plusieurs travaux ont montré que l'exposition au mercure des dentistes est associée à une augmentation de la prévalence de nombreux symptômes généraux [Neghab 2011, Ritchie 2002]. En particulier, de nombreuses études concordantes relèvent des troubles sensoriels, cognitifs, neurologiques et psychosomatiques chez les dentistes [Schach 2003, Ritchie 1995, Langworth 1997, Ngim 1992, Uzzell 1986, Shapiro 1982, Bittner 1998, Aydin 2003, Canto-Pereira 2005], et plus encore chez les assistantes dentaires [Moen 2008 , Hilt 2009]. Des publications observent une proportion de suicides augmentée chez les dentistes hommes [Arnetz 1987, Meltzer 2008, Petersen 2008], d'autres constatent des problèmes rénaux augmentés chez les dentistes [Verschoor 1988, Samir 2011], et certains risques de cancers sont augmentés chez les dentistes [Simning 2007], notamment les cancers du cerveau [Acien 2002, , Ahlbom 1986], du système reproducteur (sein ou testicule) [Eriksson 1998, Rix 1996] et de la peau [Linet 1995, Vagero 1990]. Les assistantes dentaires et les femmes dentistes risquent des troubles de la reproduction [Jones 2007, Rowland 1994, Lindbohm 2007] et l'on sait que l'exposition professionnelle au mercure augmente significativement les risques d'hypertension pour la femme enceinte ainsi que de petit poids à la naissance, de malformations de l'enfant, d'anomalies du tube neural et de bébés mort nés [Pan 2007, Figà-Talamanca 2006]. [Par manque de place, nous avons mis les références bibliographiques dans les commentaires à la section 3.3.7.] ***English translation:*** Occupational exposure is a crucial issue – especially since, as pointed out by the SCENIHR, new devices (capsules, regenerators) have not managed to make this problem disappear [3.3.1.4]. Indeed, the risk of mercury absorption	*surgeons, except for a possible effect in the last pregnancy of multiparous dental surgeons* (Dahl et al, 1999). New reference: Dahl JE, Sundby J, Hensten-Pettersen A, Jacobsen N. Dental workplace exposure and fertility. Scand J environ Health, 1999, 25,285-90. Samir and Aref (2011) and Warwick R et al. 2013. these are already cited in the Opinion THE SCENIHR considers that the additional studies/papers do not provide sufficient quantitative data on exposure to be used for risk estimates. Shapiro IM et al. (1982).The results of this study indicate a relation between tissue mercury level and peripheral nerve dysfunction. 30% of the group with raised tissue mercury levels had electrophysiological evidence of a subclinical polyneuropathy. Polyneuropathies were not found in dentists without tissue mercury accumulation. Simning A et al. (2007).The evidence for an increased mortality or cancer incidence risk among dentists must be interpreted in light of methodological limitations of published studies. Future studies of dentists would benefit from the assessment of specific occupational exposures rather than relying on job title alone. Uzzell BP et al. (1986). 13 female dental auxiliary workers with elevated head mercury levels (as measured by an X-ray fluorescence technique) were compared with 13 workers with no measurable mercury levels. Chronic subtoxic levels of inorganic mercury appear to produce mild changes in short-term nonverbal recall and heightened distress generally, and particularly in categories of obsessive compulsion, anxiety and psychoticism, without alterations in general intellectual functioning, attention, verbal recall, and motor skills. Vågerô et al. (1990). Combining the data from cutaneous

			by professionals is not only linked to the number of new fillings for which amalgams are used, but also to the conditions in which they work on pre-existing amalgams: unfortunately, the majority of professionals do not take enough protective measures [Colson 2012, Warwick 2013]. We think it is essential to draw attention to a number of cases of excessive morbidity observed in the dental professions, which can all be attributed at least partially to mercury exposure. A number of studies have shown that the exposure of dentists to mercury is associated with an increase in the prevalence of numerous general symptoms [Neghab 2011, Ritchie 2002]. In particular, numerous corroborating studies show sensorial, cognitive, neurological and psychosomatic disorders in dentists [Schach 2003, Ritchie 1995, Langworth 1997, Ngim 1992, Uzzell 1986, Shapiro 1982, Bittner 1998, Aydin 2003, Canto-Pereira 2005], and even more in dental assistants [Moen 2008 , Hilt 2009]. Publications note a higher percentage of suicides in male dentists [Arnetz 1987, Meltzer 2008, Petersen 2008], while others observe increased renal problems in dentists [Verschoor 1988, Samir 2011], and certain cancer risks are higher in dentists [Simning 2007], particularly cancer of the brain [Acien 2002, , Ahlbom 1986], the reproductive system (breast or testicle) [Eriksson 1998, Rix 1996] and skin [Linet 1995, Vagero 1990]. Dental assistants and female dentists are at risk of reproductive disorders [Jones 2007, Rowland 1994, Lindbohm 2007] and we know that occupational exposure to mercury significantly increases the risks of hypertension for pregnant women and of low birth weight, malformations in children, neural tube defects and stillborn babies [Pan 2007, Figà-Talamanca 2006]. [Due to a lack of space, we have inserted the bibliographical references in the comments on section 3.3.7.]	malignant melanoma over both sexes and both registries the occupations with the highest incidence ratios (expressed as a percentage) were: airline pilots, finance and insurance brokers, professional accountants, dentists, inspectors and supervisors in transport, pharmacists, professionals not elsewhere classified, judges; doctors, university teachers and chemists. No particular exposure in the workplace seemed to link these groups and only a few worked in high technology environments. Many of the highest risk groups have in common a high level of education. In England and Wales and in Sweden this might correlate particularly when foreign travel abroad was more unusual than it is now, but evidence on present and past exposure to the sun by occupation is needed to clarify the reasons for the association. Verschoor MA et al. (1988).Mercury exposure and renal function parameters were examined in 68 dentists and 64 dental assistants. The levels of mercury in urine were low: only three individuals exceeded 20 ug/1. Increased excretion of urinary proteins and increased activity of urinary enzymes were observed. This enhanced prevalence of renal function changes appeared to be unrelated to the mercury urine level, age, sex, or smoking and drinking habits. Only in men was a positive relation between the level of mercury in urine and the activity of p-galactosidase found. The proteinuria may be due to one or more potential nephrotoxic agents used in dental practice.
49	Begon Geoffrey, World Alliance for	3.3.6. Epidemiologic	The preliminary opinion says "The life span of dentists was shown to be three years greater than that for a control	No strong association or consistent dose-response relationship was observed between exposure to chemical agents in dental

	Mercury-Free Dentistry, beggeof@yahoo.fr	al and clinical evidence concerning adverse effects of dental amalgam in dental personnel	nondentist group. The same type of effect was seen with many other parameters, indicating that the general health of dentists is good (McComb 1997). The data do not allow for appropriate adjustment for beneficial factors associated with the dental profession, but these factors at least appear to exceed any perceived disadvantageous effects due to mercury exposure." (page 35) Of course, the beneficial factor that the opinion does not mention is that dentists are a very wealthy profession. The fact that they live longer only indicates that they can afford better health care, not that mercury is safe. Also it is not an indication that these dentists are living well even f they are living longer. A recent study found that dentists are much more likely than the control group to receive physician prescribed health medications that are used to treat neurological, neuropsychological, respiratory, and cardiac diseases (Duplinsky et. al. 2012). The following studies appear to have been excluded from this discussion: • Ritchie et al. (2002) found that dentists were significantly more likely than non-dentist control subjects to have had disorders of the kidney and memory disturbance. • Torres et. al. (2000) found skeletal muscle abnormalities in dental personnel with chronic mercury exposure. • Echeverria et.al. (2005) found statistically significant adverse associations with HgU for nine measures among dentists (Digit Span (Forward), Digit and Spatial Span(Backward), Visual Reproduction, Finger Tapping(Dominant, Alternate, and Alternate Partialed), Hand Steadiness, and Tracking), and eight measures among dental assistants (Digit Span(Forward), Visual Reproduction, Pattern Discrimination(Rate), Symbol Digit(Rate), Trailmaking B, Finger Tapping(Dominant and Alternate Partialed), and Hand Steadiness). The BDNF polymorphism was associated with four measures in dentists and three measures in dental assistants.	work and the risk of miscarriage. A slightly increased risk was found for exposure to mercury amalgam, some acrylate compounds, solvents and disinfectants. These findings indicate that the possibility of a weak association between exposure to these agents and an increased risk of miscarriage cannot be excluded (Lindbohm et al.,2007).

			• Jones (2007) compared dental nurses to controls and differences were found in current health symptom experience and reproductive health, especially early hysterectomy experience. Unfavorable reproductive outcomes for the exposed group were reported at more than twice the rate for the controls. • Lindbohm et al. (2007) found a two-fold increased risk for miscarriage through occupational exposure to mercury (OR 2,0; 95% CI 1,0- 4,1). The effect from mercury exposure was stronger than from exposure to acrylate compounds, disinfectants, or organic solvents. • Rowland et. al. (1994) studied 418 dental assistant who had been pregnant in the previous four years. Dental assistants not working with amalgam served as unexposed controls. Women with high occupational exposure to mercury were less fertile than unexposed controls. The fecundability (probability of conception each menstrual cycle) of women who prepared 30 or more amalgams per week and who had five or more poor mercury hygiene factors was only 63% of that for unexposed women (95% CI 42%-96%) after controlling for covariates. [see : "8. References" for the bibliography]	
50	Rooney James, Trinity College Dublin, jrooney@rcsi.ie	3.3.6. Epidemiological and clinical evidence concerning adverse effects of dental amalgam in dental personnel	Page 36, paragraph 4:"A US study of dentists and dental assistants suggested that an increased prevalence of symptoms of depression, anxiety, and memory was associated with two genetic polymorphisms thought to convey hypersusceptibility to mercury vapour toxicity (Heyer et al 2009)." Comment: This is but one of a series of studies identifying several genetic polymorphisms that predispose dentists to adverse neurobehavioural reactions (Heyer et al., 2004; Heyer, Echeverria, Farin, & Woods, 2008; Heyer, Echeverria, Martin, Farin, & Woods, 2009; Woods et al., 2005). Findings that are replicated in children (Woods, Heyer, Russo, Martin, & Farin, 2014; Woods et al., 2012, 2013; Woods, Heyer, Russo, Martin, Pillai, et al., 2014). SCENIHR should consider all of these studies together, not	All of the references cited here have been evaluated and the relevant ones included in the Opinion.

			simply the Heyer 2009 paper. References Heyer, N. J., Echeverria, D., Bittner, A. C., Farin, F. M., Garabedian, C. C., & Woods, J. S. (2004). Chronic Low-Level Mercury Exposure , BDNF Polymorphism , and Associations with Self-Reported Symptoms and Mood. Toxicological Sciences, 363, 354–363. doi:10.1093/toxsci/kfh220 Heyer, N. J., Echeverria, D., Farin, F. M., & Woods, J. S. (2008). The association between serotonin transporter gene promoter polymorphism (5-HTTLPR), self-reported symptoms, and dental mercury exposure. Journal of Toxicology and Environmental Health. Part A, 71(19), 1318–1326. doi:10.1080/15287390802240850 Heyer, N. J., Echeverria, D., Martin, M. D., Farin, F. M., & Woods, J. S. (2009). Catechol O-methyltransferase (COMT) VAL158MET functional polymorphism, dental mercury exposure, and self-reported symptoms and mood. Journal of Toxicology and Environmental Health. Part A, 72(9), 599–609. doi:10.1080/15287390802706405 Woods, J. S., Echeverria, D., Heyer, N. J., Simmonds, P. L., Wilkerson, J., & Farin, F. M. (2005). The association between genetic polymorphisms of coproporphyrinogen oxidase and an atypical porphyrinogenic response to mercury exposure in humans. Toxicology and Applied Pharmacology, 206(2), 113–20. doi:10.1016/j.taap.2004.12.016 Woods, J. S., Heyer, N. J., Echeverria, D., Russo, J. E., Martin, M. D., Bernardo, M. F., … Farin, F. M. (2012). Modification of neurobehavioral effects of mercury by a genetic polymorphism of coproporphyrinogen oxidase in children. Neurotoxicology and Teratology, 34(5), 513–521. doi:10.1016/j.ntt.2012.06.004 Woods, J. S., Heyer, N. J., Russo, J. E., Martin, M. D., & Farin, F. M. (2014). Genetic polymorphisms affecting susceptibility to mercury neurotoxicity in children: Summary findings from the Casa Pia Children's Amalgam Clinical Trial. Neurotoxicology, 44C, 288–302. doi:10.1016/j.neuro.2014.07.010	

			Woods, J. S., Heyer, N. J., Russo, J. E., Martin, M. D., Pillai, P. B., Bammler, T. K., & Farin, F. M. (2014). Genetic polymorphisms of catechol-o-methyltransferase modify the neurobehavioral effects of mercury in children. Journal of Toxicology and Environmental Health. Part A, 77(6), 293–312. doi:10.1080/15287394.2014.867210 Woods, J. S., Heyer, N. J., Russo, J. E., Martin, M. D., Pillai, P. B., & Farin, F. M. (2013). Modification of neurobehavioral effects of mercury by genetic polymorphisms of metallothionein in children. Neurotoxicology and Teratology, 39, 36–44. doi:10.1016/j.ntt.2013.06.004	
51	Woods James, University of Washington, jwoods@uw.edu	3.3.7. Genetic predisposition of individuals and subpopulations Line 7	Following release of the SCENIHR Preliminary opinion on "The safety of dental amalgam and alternative dental restoration materials for patients and users" on 26 August, 2014, Woods et al. published comprehensive summary findings from the Casa Pia Children's Amalgam Clinical Trial (NeuroToxicology 44:288-302, 2014). These findings describe significant impairment of multiple neurobehavioral functions in relation to low-level Hg exposure (mean urinary [Hg] ~1.3-2.8 μg/L) among adolescent and teen-aged children, particularly boys, genotyped as having 26 common variants of 12 of 13 genes that are known to affect Hg handling and/or neurologic functions. Many of these variants are highly prevalent within the general population (MAFs = 20 to 40%), implying a substantial at-risk population from Hg exposures that are well below the WHO safety thresholds. Quantitative estimates of Hg effects on neurobehavioral functions in relation to genotype can be derived from these analyses by considering the difference between the calculated correlation coefficients for the associations between Hg exposure and scores for individual tests among boys genotyped as WT versus those genotyped as variant for specific genes. In this regard, we note, for example, that boys genotyped as heterozygous or mutant for	In the main body of the opinion, the publication by Woods et al (2014) has been reported and cited in paragraph 3.3.7 and discussed in detail, also in relation to another paper reporting different results (Julvez et al., 2013). The resulting data were taken as a basis for generating hypotheses of possible susceptibility to mercury toxicity linked to genetic variants. Genetic risk factors are indeed considered an important topic for further research – not only for mercury compounds but also for alternative restorative materials. In his comment Dr Woods again summarised the results of the study, which do not contradict the description given by SCENIHR. Regarding the request to change the final paragraph of section 3.3.7, the SCENIHR is of the opinion that his study is a *post-hoc* analysis and not a prospective study *per se* as was the original Casa Pia study. In addition, paragraph 3.3.7 refers to studies in which mercury exposure can be clearly attributed to dental amalgam, which was not the case in Dr Woods analysis of the Casa Pia study where he refers to mercury exposure from any source. Indeed, in the article by Woods et al (2013), the last sentence of the abstract states: 'We note that because urinary mercury reflects a composite exposure index that cannot be attributed to a specific source, these findings do not support an association between mercury in dental amalgams specifically and the adverse neurobehavioral outcomes observed'.

			coproporphyrinogen oxidase rs1131857 (CPOX4) are 12.9 times more sensitive to Hg on overall tests of Attention, 25.1 times more sensitive on tests of Visual-Spatial acuity, 5.8 times more sensitive on tests of Learning & Memory, and 7.2 times more sensitive on tests of Motor Function, compared with boys genotyped as wildtype (WT) for this gene. Similarly, boys genotyped as mutant for catechol-O-methyl transferase (COMT) rs4680 are 4.4 times more sensitive to Hg on overall tests of Attention, and 10.5 times more sensitive on tests of Learning & Memory, compared with boys genotyped as WT for COMT. Similar computations can be made for all 26 variants of the 12 genes for which significant differences between WT and variant genotypes in terms of Hg effects on neurobehavioral test performance were found in these studies. In contrast to the statement made in the final paragraph of section 3.3.7, page 39, these analyses are derived from prospective clinical studies clearly showing the likely influence of genetic variants on the occurrence of adverse neurobehavioral effects due to Hg exposure, largely from amalgam, in boys. Moreover, we view that quantitative estimates of the relative sensitivity to Hg, such as those depicted here in relation to genotype, could and should serve as a scientific basis to account for inter-individual differences in deriving health-based reference Hg exposure limits, particularly for children, replacing the non-scientific default factor of 10 that has been employed heretofore in the absence of biologically relevant data. We recommend that this paragraph be amended accordingly.	Concerning the last remark by Dr Woods about correction of the default factor of 10 for mercury toxicity, this is already discussed in the paragraph in relation to publications by EFSA (2012) and Basu et al (2014).
52	GROSMAN Marie, Non au Mercure Dentaire, mariegrosman@free.fr	3.3.7. Genetic predisposition of individuals and subpopulation	Bibliographie sur l'exposition professionnelle du paragraphe 3.3.6. (ne sont signalés que les articles non-inclus dans l'expertise du SCENIHR) Acien A, Pollan M, Gustavsson P. et al Occupation, exposure to chemicals and risk of gliomas and meningiomas in	All of these references have been evaluated. THE SCENIHR considers that these additional studies/papers do not provide sufficient quantitative data on exposure to be used for risk estimates. THE SCENIHR added a new paragraph, chapter 3.3.1.4 Exposure

		s	Sweden. Am J Ind Med 2002. 42214–227.227. Ahlbom A et al. Dentists, dental nurses, and brain tumours. BMJ (Clin Res Ed) 1986. 292662. Arnetz BB et al. Suicide among Swedish dentists. A ten-year follow-up study. Scand J Soc Med. 1987;15(4):243-6. Aydin N et al. Neuropsychological effects of low mercury exposure in dental staff in Erzurum, Turkey. Int Dent J. 2003 Apr;53(2):85-91. Bittner ACJ et al. Behavioral effects of low-level exposure to Hg0 among dental professional: a cross-study evaluation of psychomotor effects. Neuortoxicol Teratol 1998, 17:161-168. Canto-Pereira LH et al. Visual impairment on dentists related to occupational mercury exposure. Environ Toxicol Pharmacol. 2005 May;19(3):517-22. Colson DG. A safe protocol for amalgam removal. J Environ Public Health. 2012;2012:517391. Eriksson M et al Increased cancer incidence in physicians, dentists, and health care workers. Oncol Rep 1998. 51413–1418.1418. Figà-Talamanca I. Occupational risk factors and reproductive health of women. Occup Med (Lond). 2006 Dec;56(8):521-31. Langworth S et al. Exposure to mercury vapor and impact on health in the dental profession in Sweden. J Dent Res. 1997 Jul;76(7):1397-404. Linet MS et al Occupational risks for cutaneous melanoma among men in Sweden. J Occup Environ Med 1995. 371127–1135.1135. Meltzer H et al. Patterns of suicide by occupation in England and Wales: 2001-2005. Br J Psychiatry. 2008 Jul;193(1):73-6 Neghab M et al. Symptoms of intoxication in dentists associated with exposure to low levels of mercury. Ind Health. 2011;49(2):249-54. Pan J et al. Reproductive effects of occupational exposure to mercury on female workers in China: a meta-analysis. Zhonghua Liu Xing Bing Xue Za Zhi. 2007 Dec;28(12):1215-	to mercury in dental personnel: In a more recent study in Canada it was observed that mercury vapour exposure during dental training on amalgam removal remained below occupational exposure limits (Warwick et al., 2013).' The fecundability of 558 female dental surgeons vs. 450 high school teachers. Dentists were occupationally exposed to mercury, chloroform, ethanol, benzene. Occupational exposure had no clear adverse effects on fertility among female dental surgeons, except for a possible effect in the last pregnancy of multiparous dental surgeons (Dahl et al., 1999).

			8. Petersen MR, Burnett CA. The suicide mortality of working physicians and dentists. Occup Med (Lond). 2008 Jan;58(1):25-9. Ritchie K et al. A pilot study of the effect of low level exposure to mercury on the health of dental surgeons. J Occup Environ Med 1995 , 52:813-817. Rix BA, Lynge E. Cancer incidence in Danish health care workers. Scand J Soc Med 1996. 24114–120.120. Rowland AS et al. The effect of occupational exposure to mercury vapour on the fertility of female dental assistants. Occup Environ Med. 1994 Jan;51(1):28-34. Samir AM, Aref WM. Impact of occupational exposure to elemental mercury on some antioxidative enzymes among dental staff. Toxicol Ind Health. 2011 Oct;27(9):779-86. Schach V et al. Le risque mercuriel dans les cabinets dentaires : histoire ancienne ou futur proche ? INRS, 2003 Shapiro IM et al. Neurophysiological and neuropsychological function in mercury-exposed dentists. Lancet. 1982 May 22;1(8282):1147-50. Simning A et al. Literature review of cancer mortality and incidence among dentists. Occup Environ Med. 2007 Jul;64(7):432-8. Uzzell BP et al. Chronic low-level mercury exposure and neuropsychological functioning. J Clin Exp Neuropsychol. 1986 Oct;8(5):581-93. Vagero D et al. Occupation and malignant melanoma: a study based on cancer registration data in England and Wales and in Sweden. Br J Ind Med 1990. 47317–324.324. Verschoor MA et al. Urinary mercury levels and early changes in kidney function in dentists and dental assistants. Community Dent Oral Epidemiol. 1988 Jun;16(3):148-52. Warwick R et al. Mercury vapour exposure during dental student training in amalgam removal. J Occup Med Toxicol. 2013 Oct 3;8(1):27.	

			English version: Bibliography on occupational exposure, paragraph 3.3.6. (only the articles not included in the SCENIHR report are listed). Acien A, Pollan M, Gustavsson P. et al Occupation, exposure to chemicals and risk of gliomas and meningiomas in Sweden. Am J Ind Med 2002. 42214–227.227. Ahlbom A et al. Dentists, dental nurses, and brain tumours. BMJ (Clin Res Ed) 1986. 292662. Arnetz BB et al. Suicide among Swedish dentists. A ten-year follow-up study. Scand J Soc Med. 1987;15(4):243-6. Aydin N et al. Neuropsychological effects of low mercury exposure in dental staff in Erzurum, Turkey. Int Dent J. 2003 Apr;53(2):85-91. Bittner ACJ et al. Behavioral effects of low-level exposure to Hg0 among dental professional: a cross-study evaluation of psychomotor effects. Neuortoxicol Teratol 1998, 17:161-168. Canto-Pereira LH et al. Visual impairment on dentists related to occupational mercury exposure. Environ Toxicol Pharmacol. 2005 May;19(3):517-22. Colson DG. A safe protocol for amalgam removal. J Environ Public Health. 2012;2012:517391. Eriksson M et al Increased cancer incidence in physicians, dentists, and health care workers. Oncol Rep 1998. 51413–1418.1418. Figà-Talamanca I. Occupational risk factors and reproductive health of women. Occup Med (Lond). 2006 Dec;56(8):521-31.	

			Langworth S et al. Exposure to mercury vapor and impact on health in the dental profession in Sweden. J Dent Res. 1997 Jul;76(7):1397-404. Linet MS et al Occupational risks for cutaneous melanoma among men in Sweden. J Occup Environ Med 1995. 371127–1135.1135. Meltzer H et al. Patterns of suicide by occupation in England and Wales: 2001-2005. Br J Psychiatry. 2008 Jul;193(1):73-6 Neghab M et al. Symptoms of intoxication in dentists associated with exposure to low levels of mercury. Ind Health. 2011;49(2):249-54. Pan J et al. Reproductive effects of occupational exposure to mercury on female workers in China: a meta-analysis. Zhonghua Liu Xing Bing Xue Za Zhi. 2007 Dec;28(12):1215-8. Petersen MR, Burnett CA. The suicide mortality of working physicians and dentists. Occup Med (Lond). 2008 Jan;58(1):25-9. Ritchie K et al. A pilot study of the effect of low level exposure to mercury on the health of dental surgeons. J Occup Environ Med 1995 , 52:813-817. Rix BA, Lynge E. Cancer incidence in Danish health care workers. Scand J Soc Med 1996. 24114–120.120. Rowland AS et al. The effect of occupational exposure to mercury vapour on the fertility of female dental assistants. Occup Environ Med. 1994 Jan;51(1):28-34. Samir AM, Aref WM. Impact of occupational exposure to elemental mercury on some antioxidative enzymes among	

			dental staff. Toxicol Ind Health. 2011 Oct;27(9):779-86. Schach V et al. Le risque mercuriel dans les cabinets dentaires : histoire ancienne ou futur proche ? INRS, 2003 Shapiro IM et al. Neurophysiological and neuropsychological function in mercury-exposed dentists. Lancet. 1982 May 22;1(8282):1147-50. Simning A et al. Literature review of cancer mortality and incidence among dentists. Occup Environ Med. 2007 Jul;64(7):432-8. Uzzell BP et al. Chronic low-level mercury exposure and neuropsychological functioning. J Clin Exp Neuropsychol. 1986 Oct;8(5):581-93. Vagero D et al. Occupation and malignant melanoma: a study based on cancer registration data in England and Wales and in Sweden. Br J Ind Med 1990. 47317–324.324. Verschoor MA et al. Urinary mercury levels and early changes in kidney function in dentists and dental assistants. Community Dent Oral Epidemiol. 1988 Jun;16(3):148-52. Warwick R et al. Mercury vapour exposure during dental student training in amalgam removal. J Occup Med Toxicol. 2013 Oct 3;8(1):27.	
53	Doneus Wolfgang, Council of European Dentists, ced@eudental.eu	3.3.7. Genetic predisposition of individuals and subpopulations	The paper of Julvez et al., 2013 represents probably the most comprehensive analysis of possible interactions of mercury with gene polymorphisms. This study examines the influence of 40 different polymorphisms and it would be helpful to note that these include polymorphisms reported in several other studies. In particular this study suggests that polymorphisms in CPOX appear unrelated to cognitive development.	The paper is already cited in the Opinion, where it is described in more detail. See answer to comment #38

54	Rooney James, Trinity College Dublin, jrooney@rcsi.ie	3.3.7. Genetic predisposition of individuals and subpopulations	Page 38, paragraph 8: "In this regard, the epidemiological studies generally had sufficient power only to detect interactions of fairly common variants, and none of those mentioned can be considered rare." Comment: This is only true if the effect size of the given metal – polymorphism interaction is also large enough to be detected. Page 38, paragraph 9: "The EFSA (2012) did not consider the possible impact of genetic predisposition to mercury toxicity sufficient to modify the default factor of 10 accounting for inter individual differences in deriving the health-based reference value. Considering the multiple factors affecting mercury excretion, the variability related to Hg kinetics reported so far can be considered as covered by the used default factor, unless new data will be produced on the issue, indicating larger variation." Comment: The decision to maintain a default factor of 10 is indefensible given our growing knowledge of genetic heterogeneity in response to mercury exposure. This point has been illustrated in an important 2013 paper not covered by the SCENIHR draft Opinion. In this paper, Basu et al review the growing field of mercury toxicogenetics and consider the implications for risk assessment and decision making(Basu, Goodrich, & Head, 2014). They directly addressed the uncertainty factor of 10 in the setting of methyl-mercury exposure due to fish eating via the example in the following quote: "For example, the NAS/NRC used a cord blood Hg value of 58mg/L as their benchmark dose lower limit. After the application of a 10-fold uncertainty factor, the benchmark value dropped to 5.8mg/L. Although 58mg/L is a value few would exhibit, 5.7% of women of child bearing age (16–49 yr) in the United States have blood Hg levels that exceed 5.8mg/L, with percentages being higher in certain subpopulations (e.g., 16.6% of those self-identified as Asian, Pacific Islander, Native American, or multiracial [86]), according to the NHANES 1999 2002 survey." Finally,	The paragraph 3.3.7 was changed to account for the new references that have been included

			they call for refinement of uncertainty factors so that risk assessments can be improved(Basu et al., 2014). Although the previous example relates to methylmercury due to fish consumption, the polymorphisms found to be mercury sensitizing amongst participants in the Casa Pia amalgam trial were recently summarized by Professor Woods(Woods, Heyer, Russo, Martin, & Farin, 2014). Notably, children were found to be more susceptible than adults to genetic modification of Hg neurotoxicity, and boys were found to more susceptible still than girls(Woods et al., 2014). Given these findings and the considerations raised by Basu, the use of a single uncertainty factor can no longer be considered adequate. Page 39, paragraph 1: "However, no prospective clinical studies clearly showing the influence of genetic variations on the occurrence of adverse effects due to mercury from dental amalgam are available. Therefore, especially in this area further research is needed before clinical conclusions could be drawn." Comment: Given that a) it is well established that number of amalgams corresponds with blood mercury and b) there are likely several subgroups sensitive to mercury – performing a prospective trial as suggested here would seem unethical. Larger confirmatory cross-sectional studies are warranted, but with our present knowledge there is enough evidence to warrant caution in potentially sensitive groups – i.e. children, during pregnancy, breast feeding, chronic kidney disease, thyroid disease and possibly multiple sclerosis patients.	
55	Malmström Christer, World Alliance for Mercury-Free Dentistry. , christer.malmstroem@tele2.se	3.3.9. General Observations on Amalgam Efficacy	3.3.9. General Observations on Amalgam Efficacy. The scientific basis of the preliminary opinion seems to avoid the basic facts in their report. After careful reading, I can only conclude that the report is based on wrong facts, wrong reasons and wrong assumptions, hence the conclusions will be wrong. I would like to add some real facts. If you wish more information, I stand happy to assist.	THE SCENIHR has evaluated the scientific evidence available between 2008-2014 and based on this information THE SCENIHR cannot conclude that dental amalgam is a low quality dental restorative material.

			Scientific rationale. I'm just going to focus on two important errors; it would be too much to go through all of them. 1. Amalgam from a technical perspective. 1. Amalgam is a bad material in long term. Amalgam corrodes, expands and cracks the tooth. All metals and alloys that corrode, expands, amalgam is no exception. This means that it is often necessary to redesign or do more extensive crown therapy possibly root canal treatment. As seen from the patient perspective, treatment is expensive. It is easy to distinguish fractures caused by violence/force from those caused by amalgam corrosion by studying the fracture surface. When a tooth is exposed to violence/force and fractures the surface is of pure dentin. A rupture caused by corrosion fracture surface is covered with corrosion products to a greater or lesser part. All dental clinicians with some experience have observed cracks in a tooth around an amalgam filling, even small buccal fillings. These cracks are not detected with composite or gold fillings. Ref. 1 and 2. Viken November 9, 2014. Christer Malmström	
56	Stock Gregor, FIDE - Federation of the European Dental Industry, g.stock@fide-online.org	3.4.1. Classification of alternatives according to chemical composition	Page 41, "Nanofill in the range of 5-10nm" Due to the discussion on the definition of the term "nanomaterial" we think the chosen range is not common practice.	THE SCENIHR agrees and a new paragraph has been added on page 41: More recently the European Commission has published a recommendation of the definition of nanomaterial that mentions for nanomaterials a size range of 1-100 nm (Commission Recommendation 2011/696/EU, EC 2011).
57	Swedish Chemicals Agency, kemi@kemi.se	3.4.1. Classification of alternatives according to chemical composition	The description of indirect restorations is incomplete: The substructures for metalceramic crowns and bridges are mainly manufactured in cobalt-chromium alloys or in titanium, at least in Sweden. Gold alloys are very rarely used, due to the high cost of gold. Modern manufacturing methods, i.e. CNC milling and laser sintering methods, have increased the use of base metals and alloys for fixed restorations. Corrections in the text are needed in section	Apparently, there are differences in the use of different alloys for such purposes in different countries. Original text on **page 40** with correction: "Dental alloys can be gold-based, but contain many other metals to improve the mechanical and corrosion properties. These metals can be silver, copper, palladium, platinum and others. For crowns, nickel-based alloys are also described. Recently other metals, like

			3.4.1 (p. 40 6th para), Section 3.4.5.1 (p. 52, 5th para) and in the Opinion (p. 69, 1st para). References: Sandborgh-Englund G, personal communication with KemI, October 2014	titanium/titanium alloys are used as well as cobalt-chromium alloy; e.g. for CNC milling or laser sintering." Original text on **page 52** with proposed correction: "It must be noted that there are other alternatives to amalgams in addition to these resin- and cement-, based materials. These primarily include a variety of different alloys and ceramics used for indirect restorations. These, however, do not represent clinically relevant options for the treatment of the vast majority of teeth and are only used when direct restorations are contra-indicated. Although idiosyncratic responses may be encountered with most materials (Ahlgren et al.2002), and there may be exposure even to gold from such restorations (Ahlgren et al. 2007), there are very few indications that such materials have the potential for adverse effects with the exception of allergies towards metals like nickel, cobalt, palladium and even gold (Schmalz and Arenholt-Bindslev, 2009)." Original text on **page 69** with proposed correction: "It is noted that indirect restorative techniques involving the use of a variety of different alloys and ceramics may also be used when direct restorations are contra-indicated. Their use, which is both time-consuming and expensive, has remained at a comparatively low level in recent years. This use is not seen as a health concern with the exception of allergies to some metals."
58	Lennros Hans, Upadek AB (dental clinic) , hans.lennros@gmail.com	3.4.10. Conclusions on Alternatives	3.4.11. Comments on costs. It is not the material itself that is costly (only if benchmarked with amalgam), but the time it takes to put it into place (usually in a predrilled cavity). Secondly, its longevity in regard of its lifetime functioning in the mouth (e.g. years of clinical performance in the oral environment) must be calculated. That has significantly changed just in the last few couple of years. I am attaching an example of this, it is only ONE of several similar alternatives. The file is too big so please find it here: http://www.ivoclarvivadent.se/zoolu-website/media/document/24318/Adhese+Universal	It is correct that the costs are dependent upon the factors (1) material, (2) time for placement and (2) longevity. This has been stated in the document. The text of the document is based on available data on costs in the literature. In this comment (No. 58), no further information is provided on that topic. The website given here is the information provided by one manufacturer. I could not find any cost calculation here compared to amalgam. On page 65, a second paragraph has been added after the sentence: "In a recently published report from Norway

			CONCLUSION: the factor of more expensive alternative materials to amalgam, and their generally assumed higher cost of clinical usage, may now be taken out of the equation. Dr Hans Lennros of Halmstad, Sweden	(Skjelvikand Schou Grytli, 2012) a price increase for a resin-composite filling compared to an amalgam filling in the range of €48 to €72 was reported, which means an increase of between 33 and 50 percent." This is in line with data reported for the US (52$ increase per restoration) (Beazoglu (2007) Beazoglou T1, Eklund S, Heffley D, Meiers J, Brown LJ, Bailit H.: Economic impact of regulating the use of amalgam restorations. Public Health Rep. 2007 Sep-Oct;122(5):657-63.).
59	Begon Geoffrey, World Alliance for Mercury-Free Dentistry, beggeof@yahoo.fr	3.4.11. Comments on costs	The preliminary opinion says "It can be concluded that even taking the more indirect costs for amalgam into consideration the costs for treatment of cavities with resin composites will increase the costs compared to amalgam fillings." (page 65) In making this statement, SCENIHR failed to take into consideration all of the external environmental costs associated with amalgam as explained in detail in Concorde East West, The Real Cost of Dental Mercury (2012). SCENIHR's conclusion is contrary to researchers who recognized amalgam as "more expensive than most, possibly all, other fillings when including environmental costs." It also conflicts with BIOIS, which found that ensuring separator installation and proper maintenance alone would take approximately 35,000 hours annually in the EU-27 and 1 million euros per year in labor cost for public authorities – not to mention all of the costs associated with dental mercury that does reach the environment. SCENIHR does not have the expertise to determine environmental costs, it did it engage in the detailed study that would be required to support its comments on environmental costs, and the public was not given the opportunity to submit environmental cost studies to SCENIHR (as SCENIHR was not charged with making environmental opinions). Therefore these unsupportable remarks should be struck from SCENIHR's opinion.	The statement is based on the references given in this paragraph. Costs are related to comparing the costs for single fillings, based on what is published in the literature. Other costs, as mentioned in this comment, are difficult to estimate (e.g. costs for public authorities). But taking the BIOIS numbers, the following calculations can be performed: the numbers from BIOIS (35 000 hours) refer to all dentists in the EU (310 500 according to the BIOIS report) for a whole year, which then amounts to 0.11 hours per dentist and year (= 7 minutes). According to BIOIS 125 Mio amalgams are placed annually. This means that the admin costs (1 Mio) are less than 1 cent per filling. Original text 3.4.11 and proposed changes:" …It can be concluded that even taking the more indirect costs for amalgam – as described here -into consideration the costs for treatment of cavities with resin composites will increase the costs compared to amalgam fillings. Here it says: "Given the average costs for the maintenance of separators and the management of hazardous waste (see Section2.6.3.2), the additional cost for dentists is estimated to range between EUR 5 to 32 million per year at the EU level"

			Concorde East West, The Real Cost of Dental Mercury (March 2012). Lars D. Hylander & Michael E. Goodsite, Environmental Costs of Mercury Pollution, Science of the Total Environment 368 (2006) 352-370. BIO Intelligence Service (2012), Study on the potential for reducing mercury pollution from dental amalgam and batteries, Final report prepared for the European Commission-DG ENV, p.89.	Again, per amalgam filling this is: 0.04€ to 0.25 € per filling. This means that our calculations are fairly realistic.
60	Swedish Chemicals Agency, kemi@kemi.se	3.4.11. Comments on costs	It is true that the costs for dental patients will increase if the use of dental amalgam is discontinued. However, the report overestimates the costs for using alternative filling materials. The references used are outdated. As stated in the report by Mudgal et al (2012), there will be a progressive decrease in the price difference between amalgam and the alternative filling materials. The main decrease will take place due to i) the improved skills of dentists learning how to efficiently carry out restorations in alternative materials, ii) the improvements of the alternative materials per se (i.e. the introduction of bulk fill composites and self-adhesive bonding system), and iii) improved longevity of alternative fillings. Recent studies indicate that the longevity of composite fillings is high, with an annual failure rate of around 2% (Opdam et al 2014). The caries activity of the patient affects the longevity. In a recent Cochrane Collaboration systematic review, Rasines Alcaraz et al (2014) reported randomized controlled clinical trials that compared posterior resin composite fillings with amalgam fillings in permanent teeth. The main results presented were obtained from two parallel group studies performed in children. The authors concluded that there was low-quality evidence to suggest that resin composites lead to higher failure rates and higher risk of secondary caries than amalgam restorations. However, as commented on by Rasines Alcaraz et al (2014), there is a high risk for performance and detection bias in studies comparing resin composite and amalgam longevity. In addition, the risk for allocation bias is high in studies with parallel group design. The major factor contributing to	This is the BIOIS report; the decrease of costs is an Opinion expressed for the future. No hard data This is one study and even there, amalgam in large cavities and high caries is rate is better. Rasines Alcaraz et al (2014) is a very important reference and should be included in the paragraph on the longevity. It states that amalgam is superior to comp resins re longevity. Due to technical problems, there are risks for bias, but we have no other data. On page 39 of the document under 3.3.9 after the para ending with "From such perspectives, dental amalgam may still be the material of choice with many dental practitioners e.g. for large restorations and the replacement of large restorations." The following sentence is added: "In a recent Cochrane systematic review on the comparative longevity of resin-based composites and amalgams, it is stated that the parallel group trials indicated that resin restorations had a significantly higher risk of failure than amalgam restorations and increased risk of secondary caries. The results from the split-mouth trials were consistent with those of the parallel group trials. More data with higher levels of evidence are warranted". This is the BIOIS report and was mentioned earlier. No comparison with amalgam

			treatment time is the dentist's experience. The major factors contributing to filling survival and longevity are the caries activity of the patient and the skills of the operator, which highlights the importance of caries prevention programs and the training of dentists. Corrections in the text are needed in section 3.4.11 (p. 65) References: Due to copyright restrictions some of the references are only submitted as abstracts. One reference larger than 1MB emailed. Mudgal S, Van Long L, Mitsios A, Phal S, De Toni A, Hylander L 2012. Study on the potential for reducing mercury pollution from dental amalgam and batteries http://ec.europa.eu/environment/chemicals/mercury/pdf/final_report_110712.pdf Opdam NJM, van de Sande FH, Bronkhorst E, Cenci MS, Bottenberg P, Pallesen U, Gaengler P, Lindberg A, Huysmans MCDNJM, van Dijken JW (2014) Longevity of posterior composite restorations. A systemativ review and meta-analysis. J Dent Res 93: 943-949. Rasines Alcaraz MG, Veitz-Keenan A, Sahrmann P, Schmidlin PR, Davis D, Iheozor-Ejiofor Z. (2014). Direct composite resin fillings versus amalgam fillings for permanent or adult posterior teeth (Review). The Cochrane Collaboration, John Wiley & Sons, Ltd .The Cochrane Library, Issue 3	See above
61	Stock Gregor, FIDE - Federation of the European Dental Industry, g.stock@fide-online.org	3.4.2.1. Resin composites	Page 42 "Dental resin composites are composed of a wide variety of components with different chemical composition (O'Brien 2002, Powers and Wataha 2007, Roeters and de Kloet 1998). Chemicals described in the literature as possible constituents of resin based composites are summarized in Annex 1. There is inadequate data on the composition and leachables of these materials, which is sometimes reflected in the Material Safety Data Sheets (MSDS) (Henriks-Eckerman and Kanerva, 1997, Fleisch et al., 2010). Manufacturers are required to generate and submit data on product composition and chemical characterization (e.g. ,	Text reflects the reality and is correct. The last sentence proposed by Comment No. 61 was added: According to information from the manufacturers, the dental business environment is highly competitive, and, therefore, data on product composition and chemical characterisation are presently treated as confidential business information and are not typically available to the public.

			determination of extractables) for global product registration. International standards (e.g., ISO 10993 and ISO 7405) and occasionally national guidance are used to guide this process. This information is submitted to government agencies during the product registration process for the purpose of protecting public health. Therefore, the statement that "There is inadequate data on the composition and leachables of these materials…" is misleading. Suggested text: Dental manufacturers are required to submit data on product composition and chemical characterization to government agencies as part of the global product registration process. Because the dental business environment is highly competitive, these data are treated as confidential business information and are not typically available to the public.	
62	Stock Gregor, FIDE - Federation of the European Dental Industry, g.stock@fide-online.org	3.4.3.4 Toxicity of resin composite monomers	The following publications should be cited in this section: 1. LH Moilanen, JK Dahms and A Hoberman. 2014. Reproductive toxicity evaluation of the resin monomer triethylene glycol dimethacrylate (TEGDMA) in mice. Int. J. Toxicol. 33(2):106-15. 2. LH Moilanen, JK Dahms and A Hoberman. 2013. Reproductive toxicity evaluation of the resin monomer BisGMA in mice. Int. J. Toxicol. 32(6):415-25. Suggested text: No adverse effects were noted in reproductive toxicity studies of BisGMA (Moilanen et al. 2014) or TEGDMA (Moilanen et al. 2013) conducted in mice, at doses at least 100-fold higher than estimated clinical exposure from use of composite restoratives.	Added to text: No adverse effects were noted in reproductive toxicity studies of BisGMA (Moilanen et al. 2014) or TEGDMA (Moilanen et al. 2013) conducted in mice, at doses at least 100-fold higher than estimated clinical exposure from use of composite restoratives.
63	Stock Gregor, FIDE - Feration of the European Dental Industry, g.stock@fide-online.org	3.4.4. Exposure	Page 51, discussion on Bisphenol A The following publications should be considered for addition to the opinion: 2014. Determination of Bisphenol A Released from Resin-Based Dental Composite Restoratives. ADA Professional Product Review 9(3). page 51, discussion on nanoparticles	The following text with the reference is included in 3.4.4 A study performed by the American Dental Association (2014) shows that bis-GMA-based dental restorative materials have the potential to release BPA at a detectable level. Furthermore, bis-DMA and bis-EDMA also demonstrated a high potential to release BPA. All sources of raw bis-GMA had detectable levels of

			The following publication should be cited in this section: Van Landuyt et al. 2014. Nanoparticle release from dental composites. Acta Biomaterialia 10(1):365–374 Suggested text: Exposure measurements of dust in a dental clinic revealed high peak concentrations of nanoparticles in the breathing zone of both dentist and patient, especially during aesthetic treatments or treatments of worn teeth with composite build-ups (Van Landuyt et al. 2014). Analysis of the particles generated by abrasive procedures confirmed that all tested composites, including both conventional and nano- composites, released airborne nanoscale particles.	BPA. However, all of the tested dental restorative composites released BPA at levels that are far below the daily exposure limits set by the U.S. Environmental Protection Agency and the European Food Safety Authority. Determination of Bisphenol A Released from Resin-Based Dental Composite Restoratives. ADA Professional Product Review 9(3). New text at the end of the para dealing with nano-particles: "Exposure measurements of dust in a dental clinic revealed high peak concentrations of nanoparticles in the breathing zone of both dentist and patient, especially during aesthetic treatments or treatments of worn teeth with composite build-ups (Van Landuyt et al. 2014). Analysis of the particles generated by abrasive procedures confirmed that all tested composites, including both conventional and nano- composites, released airborne nanoscale particles.
64	Swedish Chemicals Agency, kemi@kemi.se	3.4.5.1. General	p. 52, 5th para See our comment on section 3.4. 1. Change due to proposed change in section 3.4.1.	Done
65	Zimmerman Clinton, , clintonzim@aol.com	3.4.6.2. Reports from adverse reaction registry units	report states: "The US Food and Drug administration has active reporting systems for adverse reactions of all types including dental materials and manufacturer mandatory reporting" The US Food and Drug administration has received well over 2 thousand reports of Hg poisoning from dental amalgam in just one year. The US Food and Drug administration has never tested amalgam for safety, nor has the US Food and Drug Adminstration every required any manufacturer to provide any data on Hg release/safety from amalgam. Amalgam manufacturers most assuredly do not report adverse reactions from mercury release from amalgam to the FDA. In fact they have not even attended FDA's two advisory committee meetings. More generally Scenihr omits the following point. No manufacturer has every had to prove the safety of amalgam	GS: no data submitted

			in the US or the European Union. No medical or dental group such as the BDA, AMA,ADA etc has every even set what the criterion is for mercury poisoning especially micromecurialism which is relevant to Hg exposure form amalgam. Scenihr which represents itself as an expert in this matters should plainly state what the criteria are for a "diagnosis" of Hg from amalgam from the BDA,AMA,ADA,FDA,etc or plainly state that none exists. That is Scenihr's job. Clearly if no criteria exists according to these organizations then no adverse event report will be made in the majority of cases by a physician, especially if the accumulation of Hg occurs gradually many years after replacement. In the European model of healthcare which places more emphasis on field reports of adverse reactions it is striking that Scenihr fails to explain that among medical groups no agreed upon criteria exist for diagnosing low level Hg toxicity from amalgam, therefore in most circumstances none can officially be made. Assuming that it is the job of some study to compile case reports and comprehensive diagnosis for large groups of people misrepresents the facts or at the ery least makes faulty assumptions. This is not indicative of a scientifically credible report.It also assumes that adverse reporting norms should be different for amalgam than all other products since no "studies" have every compiled official "diagnosis" for cigarettes, faulty medial devices, dangerous drugs etc.	
66	Björkman Lars, The Dental Biomaterials Adverse Reaction Unit / Uni Research AS, Norway, Lars.Bjorkman@uni.no	3.4.6.2. Reports from adverse reaction registry units	"The Dental Biomaterials Adverse Reaction Unit is a permanent activity funded by the Norwegian Government and located at the University of Bergen, Department of Dental Biomaterials." COMMENT: The correct location is "…at the Department of Clinical Dentistry, University of Bergen."	Corrected
67	Begon Geoffrey, World Alliance for	3.4.9. General Observations	The preliminary opinion says "It is recognized that their use is technique sensitive and that the procedures for their	Data have been provided in the cost para, 3.4.11. Furthermore, it is general knowledge: the fact that that resin composite

	Mercury-Free Dentistry, beggeof@yahoo.fr	on Efficacy of Alternatives	placement take longer and therefore be more expensive." (page 63) This remark – which lacks a reference – is inconsistent with the BIOIS report, which found that "it has been shown that the time needed to carry out a Hg-free [mercury-free] restoration has reduced significantly as dentists have gained more experience in the handling of Hg-free materials, so that there is currently no (or minor) time difference to perform Hg-free restorations compared to amalgam." The preliminary opinion says "It is also true that they may be more susceptible to secondary caries." (page 63). But they can also help prevent caries. For example, glass ionomers release fluoride, which can help prevent tooth decay. Composite placement can also incorporate preventive measures, including sealing of adjacent pits and tooth fissures. BIO Intelligence Service (2012), Study on the potential for reducing mercury pollution from dental amalgam and batteries, Final report prepared for the European Commission-DG ENV, p.67. Mandari GJ, Mandari GJ, Frencken JE, Frencken JE, van't Hof MA, Six-Year Success Rates of Occlusal Amalgam and Glass-Ionomer Restorations Placed Using Three Minimal Intervention Approaches. Caries Res 2003;37:246-253. Lynch et. al., Managing the phase-down of amalgam: part I. Educational and training issues, Br Dent J. (Aug. 2013).	technology is technique sensitive can be found in every textbook on Operative Dentistry. See above Cochrane report (3.4.11). Longevity of glass ionomers in stress-bearing areas with more than one surface is not acceptable (Frencken JE, Leal SC, Navarro MF. Twenty-five-year a traumatic restorative treatment (ART) approach: a comprehensive overview. Clin Oral Investig. 2012 Oct;16(5):1337-46 No data provided
68	GROSMAN Marie, Non au Mercure Denrtaire, mariegrosman@free.fr	4.1. The scientific and clinical evidence	Si le SCENIHR ne recommande pas l'interdiction du mercure dentaire, il doit au moins préciser les informations que le praticien aura l'obligation de transmettre au patient dans le cadre du « consentement éclairé » : - obligation de dire aux filles et aux femmes (de 0 à 45 ans) que le mercure est un reprotoxique avéré ; - obligation de dire à tout patient qu'il y a un risque de dépassement de la VTR du mercure en raison des amalgames ; - obligation d'expliquer que l'amalgame relargue du mercure en permanence ;	All materials continuously release potentially toxic substances No data

			- obligation de préciser que le mercure est un neurotoxique, un néphrotoxique, un cardiotoxique, un reprotoxique, un perturbateur endocrinien, un immunotoxique et un génotoxique avéré, classé Cancérogène, Mutagène et Reprotoxique (CMR2) et Persistant Bioaccumulable Toxique (PBT). ***English version:*** While the SCENIHR does not recommend prohibiting dental mercury, it must at least specify the information which the practitioner will be required to give the patient with a view to "informed consent": - obligation to inform girls and women (aged 0 to 45 years) that mercury is a proven reprotoxic; - obligation to inform all patients that there is a risk of the TRV being exceeded due to amalgams; - obligation to explain that the amalgam continually releases mercury; - obligation to specify that mercury is a neurotoxin, a nephrotoxin, a cardiotoxin, a reprotoxin, an endocrine disruptor, an immunotoxin and a proven genotoxin, classed as carcinogenic, mutagenic, reprotoxic (CMR2) and persistent, bioaccumulative and toxic (PBT).	
69	Zimmerman Clinton, works with consumers for dental choice, clintonzim@aol.com	4.1. The scientific and clinical evidence	Scenihr states "Dietary mercury exposure in the general population of Europe does not exceed the TWI for methyl and inorganic mercury except for heavy fish consumers " The term general population is vague. The term dietary exposure is vague. As stated before recent work by Richardson proves otherwise. Once again Scenihr implies though does not explicitly state that methyl mercury exposure from amalgam and all other sources is directly measureable which it is not, for example hair testing can only indirectly assess some	Please see previous answers to similar comments

			forms of recent methyl exposure. Nor does Scenihr provide any methodology in the bulk of the paper which proves this before reaching this general conclusion. It ignores the fact as given by expert testimony at the 2010 FDA hearings that amalgam exposure greatly boosts methyl exposure in the gut. This is not the consensus of the scientific community! Scenihr once again breaks its promise in the introduction that it will not seriously addess methyl exposure/conversion from dental Hg and in the final sentences of its conclusion produces sweeping unjustified conclusions about cumulative inorganic and organic exposure in "most people". Scenihr states "The peak exposure to amalgam vapor will occurring during placement or removal of fillings" While it is good that Schnier acknowledges the danger of Hg exposure during drilling although this alarming fact is ignored throughout the paper , the conclusion that peak exposure occurs during placement otherwise is a sweeping unjustified statement unsubstantiated in the bluk of the document which relies almost exclusively on fautly urine testing methodologies. For one thing as noted before many studies site long term corrosion as a major source of exposure see"Corrosion products from Dental Alloys and Effects of Mercuric ions on a Neruoeffector System", Moberg Le 1985 and Pleva (1989). Pleva even contains pictures of severely corroded amalgams and finds that Hg concentration in some regions of corroded amalgam was zero! Also as noted at the FDA dental hearings and in the FDA official position statement no long term data exists on exposure to dental Hg. In "The Relationship of the Toxic Effects of Mercuy to the Exacerbation of the Medical Condition Classified as Alzhiemers Disease", Boyd Haley one can read the raw data for mercury release into water for individual amalgams and see that in most cases Hg release is not the greatest at placement. Where does Scenihr draw these conclusions from? Additionally there are no long term studies on corrosion, galvanic breakdown etc of amalgam. Most studies	

			are 3months to a year and I have not seen any over two years. This is an especially important consideration, omitted by Scenihr in its report especially for poorly placed fillings since the dental industry itself estimates the lifetime of an amalgam to be 10 years, which means significant corrosion is likely to occur after this time period. Published studies convincingly demonstrate corrosion of amalgam placed under a gold crown. Therefore this statement obviously cannot be justified in any meaningful scientific sense and is not reflective of the totality of the scientific literature and the opinions of those in the scientific community outside of the Scenihr panel and dental groups. Also short term lab test of corriosion certainly cannot recreate the conditions in the oral cavity most likely to cause corrosion such as changes in PH, galvanism, and bacterial action as noted in the scientific literature. Consider the paper by DP Dewald et al, Baylor College or Dentistry; Journal of Denitry 1992; 20: 121-127 "Evaluation of the interactions between amalgam, cement and gold castings". "If you read the full paper, you will learn that even though the crown and amalgam metals did not directly touch physically, there was corrosion in the amalgam core even in the controls that sat dry at room temperature on the shelf. The experimental groups washed with electrolytic solution, pH and temparture cycled to simnulate conditions in the human mouth, produced far worse corrosion—even though the bonding agents in all specimens wre meticulously applied to keep the metals separated at all times." (courtesy Jeff Clark),. Scenihr should acknowledge that no studies exist on long term Hg release due to corrions > 2 years, and that studies under 2 years do not all show a decrease in Hg release and further do not simulate the most likely causes of filling corrosion rather than implying that it has studies proving a decrease in Hg release/vapor for the lifetime of all amalgam fillings. Note on methyl Hg conversion: Studies on amalgam Hg-	

			methyl Hg conversion can be very difficult to find. The FDA 2010 panel included difficult to find expert testimony on this topic as mention in the comments by Dr. Anne Summers and her group at the University of Georgia. Accessing the official FDA record and summaries can be cumbersome, however this rare testimony on cutting edge amalgam-methyl Hg conversion testing can be found at (beginning on pg 69): http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/DentalProductsPanel/UCM242357.pdf	
70	Stock Gregor, FIDE - Federation of the European Dental Industry, g.stock@fide-online.org	4.1. The scientific and clinical evidence	page 68, paragraph 5 "…caution should be exercised when considering the (re-)placement of any dental restorative materials in pregnant women." What is the factual basis for this statement in relation to alternative materials? Also, see Comment 1 above (executice summary).	The factual basis for this statement is that dental treatment is always associated with the exposure of the (female) patient and thus the foetus to a variety of chemicals from the filling materials (amalgam as well as composites resins/adhesives) or due to the application e.g. of disinfecting chemicals, anaesthetics and other substances. X-rays for diagnosis or treatment control is extremely restricted, if not impossible. Furthermore, the dental treatment situation as such is often regarded very stressful. As for each single one of these exposure scenarios, no adverse effect on the foetus has been established: nothing is known on the accumulation of effects. Furthermore, pregnancy is a situation limited in time. Due to these reasons, some years ago it was recommended in Germany (ref in the document) to discourage dental treatment during pregnancy with the exception of emergency treatment. For more than 15 years this regulation has been in effect and there have been no published complaints.
71	Rooney James, Trinity College Dublin, jrooney@rcsi.ie	4.1. The scientific and clinical evidence	Page 66, paragraph 5: "The accumulated concentrations in brain tissue may reach values that are similar to those inducing neurochemical changes in experimental models. Such effects have not been convincingly demonstrated in humans and so far, studies in children of school age did not demonstrate amalgam-associated neuropsychological deficits."	The study by Woods et al., 2014 is discussed in detail in the text.

			Comment: However numerous genetically sensitive subgroups have been shown to exhibit neurobehavioural sensitivity(Woods, Heyer, Russo, Martin, & Farin, 2014) and prospective amalgam trials were not designed nor powered to detect such subgroups amongst those receiving amalgam as I have pointed out in my comments on section 3.3.5.2. References: Woods, J. S., Heyer, N. J., Russo, J. E., Martin, M. D., & Farin, F. M. (2014). Genetic polymorphisms affecting susceptibility to mercury neurotoxicity in children: Summary findings from the Casa Pia Children's Amalgam Clinical Trial. Neurotoxicology, 44C, 288–302. doi:10.1016/j.neuro.2014.07.010	
72	Swedish Chemiclas Agency, kemi@kemi.se	4.1. The scientific and clinical evidence	p.67, 1st para See our comment on section 3.3.10. Change due to proposed change in section 3.3.10. p. 69, 1st para See our comment on section 3.4. 1. Change due to proposed change in section 3.4.1.	The relevant changes have been made.
73	Björkman Lars, The Dental Biomaterials Adverse Reaction Unit / Uni Research AS, Norway, Lars.Bjorkman@uni.no	4.1. The scientific and clinical evidence	"The SCENIHR recognises that dental amalgam, for the general population, is a safe and effective restorative material." COMMENT: The sentence needs to be revised and the word "safe" should be defined somewhere in the document. Dental amalgam is probably relatively "safe" for most people. However, mercury released from amalgam fillings contributes to the individual's total mercury exposure and it cannot be excluded that the additional exposure to mercury from dental amalgam fillings in some cases could cause an increased daily uptake of mercury to levels that are not safe and may cause adverse effects (other than local contact allergy). REFERENCES: Ahlqwist M, Bengtsson C, Furunes B, Hollender L, Lapidus L. 1988. Number of amalgam tooth fillings in relation to subjectively experienced symptoms in a study of swedish women. Community Dent Oral Epidemiol 16:227-231.	The word "safe" has been deleted in 4.1. The references are included in the text.

			Ahlqwist M, Bengtsson C, Lapidus L. 1993. Number of amalgam fillings in relation to cardiovascular disease, diabetes, cancer and early death in swedish women. Community Dent Oral Epidemiol 21:40-44. Barregård L, Sällsten G, Järvholm B. 1995. People with high mercury uptake from their own dental amalgam fillings. Occup Environ Med 52:124-128. Barregård L. 2005. Mercury from dental amalgam: Looking beyond the average. Occup Environ Med 62:352-353. Björkman L, Pedersen NL, Lichtenstein P. 1996. Physical and mental health related to dental amalgam fillings in Swedish twins. Community Dent Oral Epidemiol 24:260-267. EFSA CONTAM Panel. 2012. Scientific Opinion on the risk for public health related to the presence of mercury and methylmercury in food. EFSA Journal 10:2985. doi:10.2903/j.efsa.2012.2985	
74	Rooney James, Trinity College Dublin, jrooney@rcsi.ie	4.2.1. Question 1	Page 69, paragraph 5: "The effects of genetic polymorphism concerning mercury elimination may influence the degree of individual susceptibility in regard to internal exposure to mercury. There is some concern for possible effects on the brain of mercury originating from dental amalgam. However, so far such effects have not been documented in humans." Comment: The summarized findings from genetic studies of the Casa Pia amalgam trial indicate that children are more susceptible to adverse neurobehavioural effects from mercury exposure than adults, and that boys are more susceptible than girls(Woods, Heyer, Russo, Martin, & Farin, 2014). The above statement by SCENIHR does not reflect the full findings of genetic studies. References: Woods, J. S., Heyer, N. J., Russo, J. E., Martin, M. D., & Farin, F. M. (2014). Genetic polymorphisms affecting susceptibility to mercury neurotoxicity in children: Summary findings from the Casa Pia Children's Amalgam Clinical Trial. Neurotoxicology, 44C, 288–302. doi:10.1016/j.neuro.2014.07.010	Please see the response to similar previous comments concerning the study of Woods et al., 2014.

75	Lidmark Ann-Marie, Tandvårdsskadeförbundet (The Swedish Association of Dental Mercury Patients), lidmark@gmail.com	4.2.1. Question 1	The conclusions are not in line with the Committee's own findings in the descriptive text. For example, it´s written on page 19 that mercury from amalgam fillings is 50-87% of the total mercury uptake in humans. And in Section 3.3.1.5 reports genetic differences making a group of people more sensitive to mercury exposure. Both studies appear in the reference list and there is a recently published report (1) that mercury affects the epigenome and DNA methylation. The scientific committee should therefor expand the discussion about epigenetic effects and Mercury in this report. In the descriptive text presented fetuses are more sensitive than adults and the same with people allergic to mercury. Thus, there are many health reasons to apply the precautionary principle and advocate other dental materials than amalgam. Taking into account the precautionary principle, the conclusion "so far such effects have not been documented in humans" need to be changed. Reading the Committee's documentation the natural conclusion would have been that levels of mercury from dental amalgam are sufficient to affect susceptible individuals and fetus and therefore should be phased out from dentistry with reference to the precautionary principle. 1. Goodrich, JM, Basu, N, Franzblau, A, and Dolinoy, DC (2013) Mercury Biomarkers and DNA Metylation among Michigan Dental Professonals. Environ Mol Mutagen; 54(3):195-203	This issue was considered in the revised version of para 3.3.7. The Opinion has been carefully checked for consistency.
76	GROSMAN Marie, Non au Mercure Dentaire, mariegrosman@free.fr	4.2.2. Question 2	L'opinion ne correspond pas à ce qui a été mis en évidence dans le corps du texte – voir nos commentaires à la section 3.3.10. ***English translation:*** The opinion does not correspond to what was highlighted in the body of the text– see our comments on section 3.3.10.	The Opinion has been carefully checked for consistency.
77	Zimmerman Clinton, works with consumers for	4.2.2. Question 2	Report conclusion: "Dental amalgam already in place is not considered a health risk. Pre-existing amagam restorations should not be removed as this intervention would result in a	Modified new text : Dental amalgam already in place is not considered as a health

	dental choice, clintonzim@aol.com		greater exposure to mercury" Two committes conviened by the FDA disagreed. The FDA now has warnings about amalgam for children 6 and under mandated by court settlement and expert committe findings. This statement is groundless from a scientific standpoint. This statement does not represent any consensus in the scientific community as implied by Scenihr. Many studies show corrosion of amalgam and release of Hg can greatly increase Hg exposure and Scenihr admits it will not address the issue of dental Hg conversion to methyl forms in the oral cavity or the gut the routes of greatest potential exposure. Richardson who is quoted by Scenihr in sworn testimony to the FDA stated that many people exceeed safe levels of exposure from amalgam. Therefore by what logic can Schnier leap to this scientifically unsubstianted conclusion? This statement relies on a simple discredited model in the dental community that amalgam doesn't corrode, doesn't under go galvanic reaction, is always prepared in a safe manner and never comes into contact with dissimilar material , all dental amalgams are the same and emit a small dose of Hg for the lifetime of the filling which is directly measureable. All these assumptions though believed by the dental community for years have since been demonstrated not to be true. All these assumptions have been meticulously scientifically discredited as I explained in my resonse in the previous sections and shown to be false. Though it is a historically fact that in previous decades dental organizations presented this as fact. This conclusion/informationIt appears to be derived primarily from a dental association manual since two expert committes at the FDA found that amalgam is not proven safe and FDA currently recommends amalgam not be used in those under 6. Again Schnier does not cite one credible long term study > 10 years on amalgam corrosion in poorly made high copper fillings and Hg release. Therefore how can it be asserted that no amalgam should ever be removed in a population of billions of amalgam bearers, especially when the FDA 2010 expert panel recommend that "I would restrict	risk. The highest exposure to mercury in individuals with amalgam restorations occurs during placement or removal of the fillings. The transient mercury release during placement and removal results in increased short-time exposure to the patients compared to leaving the amalgam intact. There appears to be no general justification for unnecessarily removing clinically satisfactory amalgam restorations, except in those patients diagnosed as having allergic reactions to one of the amalgam constituents. Pre-existing amalgam restorations should not be removed, as this intervention would result in a greater transient exposure to mercury.

			amalgam significantly in children under six and for pregnant women"? Sceniher should read the transcripts of FDA testimony in 2006 and 2010 to see that it cannot be reasonably stated that there is a scientific consensus on the safety of amalgam. Just the opposite, there is one that it is not safe.	
78	Stock Gregor, FIDE - Federation of the European Dental Industry, g.stock@fide-online.org	4.2.2. Question 2	"… caution should be exercised when considering the placement of any dental restorative material in pregnant women." What is the factual basis for this statement in relation to alternative materials? Also, see Comment 1 above (executive summary).	See comment above
79	Rooney James, Trinity College Dublin, jrooney@rcsi.ie	4.2.2. Question 2	Page 69, paragraph 8 & 9: "The choice of material should be based on patient characteristics. The use of amalgam restorations is not indicated in primary teeth, in patients with mercury allergies, and persons with chronic kidney diseases. As with any other medical or pharmaceutical intervention, caution should be exercised when considering the placement of any dental restorative material in pregnant women." Comment: This list of contraindications should be extended to include children, breast feeding mothers, and thyroid disease patients in line with a precautionary approach considering the evidence. Page 70, paragraph 2: "As far as dental personnel are concerned, it is recognised that they may be at greater risk with respect to mercury exposure than the general population, although the incidence and type of reported adverse effects are similar to what is observed in the general population." Comment: Whilst I recognize that each individual dentist will exercise their own judgment regarding personal exposures in their personal work environment, other workers such as dental nurses and dental assistants may not have that same control over their environment. SCENIHR should recommend the same list of contraindications for dental workers as for patients, given that those workers are generally exposed to higher levels of	Added text: However, the same considerations for caution in regard to patient exposure also apply to dental personnel.

			mercury.	
80	Lidmark Ann-Marie, Tandvårdsskadeförbundet (The Swedish Association of Dental Mercury Patients), lidmark@gmail.com	4.2.2. Question 2	See also answer to question 1. The Committee draw the conclusion there are sensitive individuals or groups of individuals who should not have amalgam as there are risk for adverse effects. The Committee has not discussed the precautionary princple nor clearly specified how people sensitive to dental amalgam should be handled in dentistry. The conclusion should rather be that as long as there are individuals who may become disabled by mercury dental amalgam should not be used. In addition we also want to point out that genetic susceptible people should be recommended to remove the amalgam fillings safely. If people for instance have reduced capability to detoxify mercury they need to take the fillings out before levels become high enough to cause disease. This is in accordance with the descriptive text. Tandvårdsskadeförbundet´s experience is that a majority decrease their symptoms after amalgam removal and many of them recover completely (2)´but it often takes more than one year. 2. Lidmark, A-M & Wikmans, T (2008) Are They Really Sick? A Report on Persons Who Are Electrosensitive and/or Injured by Dental Material in Sweden. J Orthomol Med 23(3); 153-160	THE SCENIHR reviewed these papers and concluded that there are some limitations precluding their consideration in the Opinion. The issue of genetic susceptibility is addressed in the Opinion.
81	Mickenautsch Steffen, University of the Witwatersrand, Johannesburg, South Africa / Faculty of Health Sciences, neem@global.co.za	4.2.3. Question 3	Referring to the statement of page 71: "Due to reported mediocre mechanical properties and clinical failures, glass ionomer cements can only be used in small, one-surface cavities", kindly note: [a] Clinical trial evidence in support of inferiority claims concerning high-viscosity glass-ionomers below that of amalgam restorations are found to be generally based on uncontrolled clinical longitudinal studies. Such study design has been proven to yield unreliable and misleading results, particularly in regard to the failure rate of high-viscosity glass-ionomers versus amalgam [1] [b] In addition to uncontrolled clinical longitudinal studies, laboratory trials indicate low clinical efficacy of glass-	Glass ionomer cements have also been used with the ART technique. They can be used to restore single-surface cavities both in primary and in permanent posterior teeth, but their quality in restoring multiple surfaces in primary posterior teeth cavities need to be improved. Insufficient information is available regarding the quality of ART restorations in multiple surfaces in permanent anterior and posterior teeth (Frencken JE, Leal SC, Navarro MF., Twenty-five-year a traumatic restorative treatment (ART) approach: a comprehensive overview. Clin Oral Investig. 2012 Oct;16(5):1337-46.). Other authors claim better clinical performance of high viscosity glass ionomer materials in primary teeth, but data are comparatively scarce (Mickenautsch

			ionomers. However, a consistent lack of correlation between laboratory and clinical outcomes has been shown in the dental literature [2-6]. [c] In contrast to the observations to above points [a] and [b], systematic review results appraised from clinical randomised control trials are not in support of inferiority claims concerning the failure rate of single- and multiple surface tooth restorations placed using high-viscosity glass-ionomers in load bearing posterior permanent and primary teeth below that of restorations placed with amalgam [7,8]. References: [1] Mickenautsch S, Yengopal V. Direct contra naïve-indirect comparison of clinical failure rates between high-viscosity GIC and conventional amalgam restorations. An empirical study. PLOS One 2013; 8: e78397. [2] Papagiannoulis L, Kakaboura A, Eliades G. In vivo vs in vitro anticariogenic behavior of glass-ionomer and resin composite restorative materials. Dent Mater 2002; 18: 561-9. [3] Purk JH, Dusevich V, Glaros A, Spencer P, Eick JD. In vivo versus in vitro microtensile bond strength of axial versus gingival cavity preparation walls in Class II resin-based composite restorations. J Am Dent Assoc 2004; 135: 185-93. [4] Heintze SD. Systematic reviews: I. The correlation between laboratory tests on marginal quality and bond strength. II. The correlation between marginal quality and clinical outcome. J Adhes Dent 2007; 9 Suppl 1: 77-106. Erratum in: J Adhes Dent 2007; 9: 546. [5] Heintze SD, Cavalleri A. Retention loss of class v restorations after artificial aging. J Adhes Dent 2010; 12: 443-9. [6] Heintze SD, Zimmerli B. Relevance of in vitro tests of adhesive and composite dental materials. A review in 3 parts. Part 3: in vitro tests of adhesive systems. Schweiz Monatsschr Zahnmed 2011; 121: 1024-40. [7] Mickenautsch S, Yengopal V, Banerjee A. Atraumatic	S, Yengopal V, Banerjee A. Atraumatic restorative treatment versus amalgam restoration longevity: a systematic review. Clin Oral Investig 2010; 14: 233-40).

			restorative treatment versus amalgam restoration longevity: a systematic review. Clin Oral Investig 2010; 14: 233-40. [8] Mickenautsch S, Yengopal V. Failure rate of high-viscosity GIC based ART compared to that of conventional amalgam restorations - evidence from a systematic review update. S Afr Dent J 2012; 67: 329-31.	
82	Swedish Chemicals Agency, kemi@kemi.se	4.2.3. Question 3	P 70, 2nd para. It is stated that in the SCENIHR preliminary opinion that placement of alternative fillings takes more time than for amalgam. Mudgal (2012) refers e.g that experience from Sweden show that the time difference is less than 10% for different categories of treatment and that there are only minimal differences in time use assessments on dental treatments from various parts of Sweden. A clarification including a realistic time difference when dental amalgam is compared with alternative materials is recommended. References: Reference larger than 1MB emailed. Mudgal S, Van Long L, Mitsios A, Phal S, De Toni A, Hylander L 2012. Study on the potential for reducing mercury pollution from dental amalgam and batteries http://ec.europa.eu/environment/chemicals/mercury/pdf/final_report_110712.pdf	This is the BIOIS report; the decrease of costs is an opinion expressed for the future. No hard data.
83	Rooney James, Trinity College Dublin, jrooney@rcsi.ie	4.2.4. Question 4	Page 71, 4.2.4 Question 4 Comment: SCENIHR in section 4.2.2 noted that ". The use of amalgam restorations is not indicated in primary teeth, in patients with mercury allergies, and persons with chronic kidney diseases." Therefore section 4.2.4 should recommend that amalgam should not be used in all these groups. This list of contraindications should be extended to include children, breast-feeding mothers, and thyroid disease patients based on reviewed evidence. Furthermore, in section 3.3.10 Conclusions on Dental Amalgam the SCENIHR stated: ". The choice of material should be based on patient characteristics such as primary or permanent teeth, pregnancy, the already existent number of dental amalgam fillings,". In light of this statement the	Section 4.2.4 concerns the use of alternative materials Section 4.2.2 now reads: The choice of material should be based on patient characteristics. The use of amalgam restorations is not indicated in primary teeth, in patients with mercury allergies, and persons with chronic kidney diseases with decreased renal clearance. As with any other medical or pharmaceutical intervention, caution should be taken when considering the placement of any dental restorative material in pregnant women. A decision to perform dental treatment during pregnancy should take into account the dental therapeutic needs of the patient and balance any potential risks (including the use of anaesthetics, along with

			SCENIHR should be able to offer to dentists and patients alike some guidelines as to what a sensible limit of amalgams per patient should be based on estimates of daily mercury outgassing discussed in section 3.3.1.3.	all dental materials) against therapeutic benefits to the patient. Generally, extensive dental treatment during pregnancy is discouraged. The reviewed evidence does not support the inclusion of breast-feeding mothers and thyroid disease patients as contraindications. Response to comment about section 3.3.1.3: Due to large differences in study design and exposure estimates, the current evidence is not of sufficient quality to introduce health-based limits on the numbers of amalgam fillings per patient.
84	van der Waals Herman G., ,a3kgys@kpnplanet.nl	4.2.5. Question 5	I have difficulty in finding my way in this system. The only thing I want to say is that in my opinion this opportunity must be seized to phase out dental amalgam completely; and that the use of mercury in any form, either in vaccines or in drinking water or whatever, destined to enter the body, must be prohibited.	Thank you for the comment. However, this comment is not related to risk assessment and therefore non relevant to the THE SCENIHR mandate.
85	LIdmark Ann-Marie, Tandvårdsskadeförbundet (The Swedish Association of Dental Mercury Patients), lidmark@gmail.com	4.2.5. Question 5	Some important areas for further research have been forgotten and Tandvårdsskadeförbundet propose following additions: 1. Develop methods for safe removal of amalgam fillings 2. Develop treatment including mercury detoxification for people allergic to mercury and / or with high mercury levels (measured after chelation) 3. Develop methods to choose well tolerated dental materials for sensitive people We are also concerned about risks for dental personell; better information is needed about the risks of amalgam as well as information about the necessary protective equipment as good ventilation and air respirators.	1. Several national guidelines describe procedures to minimise exposure to mercury during amalgam placement and removal. 2. The use of chelating agents or other medical or pharmaceutical intervention for mercury detoxification is outside the remit of the SCENIHR. 3. This is mentioned in the list as: International networks for Centres advising patients who claim health problems from dental materials should be established.
86	GROSMAN Marie, Non au Mercure Dentaire, mariegrosman@free.	8. REFERENCES	Bibliographie sur l'exposition professionnelle (ne sont signalés que les articles non-inclus dans l'expertise du SCENIHR) Acien A, Pollan M, Gustavsson P. et al Occupation, exposure	Canto-Pereira LH et al. Visual impairment on dentists related to occupational mercury exposure. Environ Toxicol Pharmacol. 2005 May;19(3):517-22

	fr		to chemicals and risk of gliomas and meningiomas in Sweden. Am J Ind Med 2002. 42214–227.227. Ahlbom A et al. Dentists, dental nurses, and brain tumours. BMJ (Clin Res Ed) 1986. 292662. Arnetz BB et al. Suicide among Swedish dentists. A ten-year follow-up study. Scand J Soc Med. 1987;15(4):243-6. Aydin N et al. Neuropsychological effects of low mercury exposure in dental staff in Erzurum, Turkey. Int Dent J. 2003 Apr;53(2):85-91. Bittner ACJ et al. Behavioral effects of low-level exposure to Hg0 among dental professional: a cross-study evaluation of psychomotor effects. Neuortoxicol Teratol 1998, 17:161-168. Canto-Pereira LH et al. Visual impairment on dentists related to occupational mercury exposure. Environ Toxicol Pharmacol. 2005 May;19(3):517-22. Colson DG. A safe protocol for amalgam removal. J Environ Public Health. 2012;2012:517391. Eriksson M et al Increased cancer incidence in physicians, dentists, and health care workers. Oncol Rep 1998. 51413–1418.1418. Figà-Talamanca I. Occupational risk factors and reproductive health of women. Occup Med (Lond). 2006 Dec;56(8):521-31. Langworth S et al. Exposure to mercury vapor and impact on health in the dental profession in Sweden. J Dent Res. 1997 Jul;76(7):1397-404. Linet MS et al Occupational risks for cutaneous melanoma among men in Sweden. J Occup Environ Med 1995. 371127–1135.1135. Meltzer H et al. Patterns of suicide by occupation in England and Wales: 2001-2005. Br J Psychiatry. 2008 Jul;193(1):73-6 Neghab M et al. Symptoms of intoxication in dentists associated with exposure to low levels of mercury. Ind Health. 2011;49(2):249-54. Pan J et al. Reproductive effects of occupational exposure to mercury on female workers in China: a meta-analysis. Zhonghua Liu Xing Bing Xue Za Zhi. 2007 Dec;28(12):1215-8. Petersen MR, Burnett CA. The suicide mortality of working	This study has a low number of subjects, many confounders and is a single study, not repeated by other research groups. Visual impairments appear at higher concentrations of mercury that the ones reported in the paper

			physicians and dentists. Occup Med (Lond). 2008 Jan;58(1):25-9. Ritchie K et al. A pilot study of the effect of low level exposure to mercury on the health of dental surgeons. J Occup Environ Med 1995 , 52:813-817. Rix BA, Lynge E. Cancer incidence in Danish health care workers. Scand J Soc Med 1996. 24114–120.120. Rowland AS et al. The effect of occupational exposure to mercury vapour on the fertility of female dental assistants. Occup Environ Med. 1994 Jan;51(1):28-34. Samir AM, Aref WM. Impact of occupational exposure to elemental mercury on some antioxidative enzymes among dental staff. Toxicol Ind Health. 2011 Oct;27(9):779-86. Schach V et al. Le risque mercuriel dans les cabinets dentaires : histoire ancienne ou futur proche ? INRS, 2003 Shapiro IM et al. Neurophysiological and neuropsychological function in mercury-exposed dentists. Lancet. 1982 May 22;1(8282):1147-50. Simning A et al. Literature review of cancer mortality and incidence among dentists. Occup Environ Med. 2007 Jul;64(7):432-8. Uzzell BP et al. Chronic low-level mercury exposure and neuropsychological functioning. J Clin Exp Neuropsychol. 1986 Oct;8(5):581-93. Vagero D et al. Occupation and malignant melanoma: a study based on cancer registration data in England and Wales and in Sweden. Br J Ind Med 1990. 47317–324.324. Verschoor MA et al. Urinary mercury levels and early changes in kidney function in dentists and dental assistants. Community Dent Oral Epidemiol. 1988 Jun;16(3):148-52. Warwick R et al. Mercury vapour exposure during dental student training in amalgam removal. J Occup Med Toxicol. 2013 Oct 3;8(1):27.	
87	Begon Geoffrey, World Alliance for Mercury-Free	8. REFERENCES	Thomas G. Duplinsky& Domenic V. Cicchetti, The Health Status of Dentists Exposed to Mercury from Silver Amalgam Tooth Restorations, International Journal of Statistics in	

	Dentistry, beggeof@yahoo.fr		Medical Research (2012). Ritchie KA, Gilmour WH, Macdonald EB, Burke FJ, McGowan DA, Dale IM, Hammersley R, Hamilton RM, Binnie V, Collington D (2002) Health and neuropsychological functioning of dentists exposed to mercury. Occup Environ Med 59: 287–293. Nadorfy-Lopez E, Torres SH, Finol H, Mendez M, Bello B: Skeletal muscle abnormalities associated with occupational exposure to mercury vapors. HistHistopath 2000, 15:673-682. Echeverria D, Woods JS, Heyer N, Rohlman DS,Farin FM, Bittner AC Jr, Li T, Garabedian C: Chronic low-level mercury exposure, BDNF polymorphismand associations with cognitive and motor function. NeurotoxicolTeratol2005, 27:781-796. Linda Jones et. al., A 30-year follow-up of residual effects on New Zealand School Dental Nurses, from occupational mercury exposure, Human and Experimental Toxicology (2007). Lindbohm ML, Ylöstalo P, Sallmen M: Occupational exposure in dentistryand miscarriage. Occup Environ Med 2007, 64:127-133. Rowland A, Baird D, Weinberg C, Shore D, Shy C, Wilcox A: The effect of occupational exposure to the mercury vapour on the fertility of female dental assistants. Occup Environ Med 1994, 51:28-34.	
88	Stock Gregor, FIDE - Federation of the European Dental Industry, g.stock@fide-online.org	8. REFERENCES	Additional literature to orcomers, page 42f. 1) S.H. Mahmoud, A.E. El-Embaby, A.M. AbdAllah; Clinical performance of ormocer, nanofilled, and nanoceramic resin composites in Class I and Class II restorations: a three-year evaluation; Operative Dentistry 39(1), 2014, 32-42: ”The ormocer, nanofilled, and nanoceramic composites provided acceptable clinical performance over a three-year period” 2) F. Beck, N. Dumitrescu, F. König, A. Graf, P. Bauer, W. Sperr, A. Moritz, A. Schedle; One-year evaluation of two	These studies are of merit, but the general outline of the text is not influenced, because in the text only the study with the longest observation period has been cited. Many other studies are available with shorter observation times, but this does not provide further relevant information.

			hybrid composites placed in a randomized-controlled clinical trial; Dental Materials 30(8), 2014, 824-38 "In a group of ClassI/II restorations (including cuspal-coverage), there was no significant difference in failure rates between ormocer-based and bis-GMA-based restorative systems after one year." 3) K.S. Kumar, C. H. Rao, K.B. Reddy, S. Chidambaram, H. Girish, S. Murgod; Flowable composite an alternative orthodontic bonding adhesive: an in vitro study; The Journal of Contemporary Dental Practice 14(5), 2013, 883-6 "The in vitro study showed that flowable Ormocer can be a good alternative to commonly used BisGMA based adhesives." 4) S. Kalra, A. Singh, M. Gupta, V. Chadha; Ormocer: An aesthetic direct restorative material; an in vitro study comparing the marginal sealing ability of organically modified ceramics and a hybrid composite using an ormocer-based bonding agent and a conventional fifth-generation bonding agent; Contemporary Clinical Dentistry 3(1), 2012, 48-53 "An ormocer-system showed the minimum marginal leakage and samples with no microleakage at all." 5) S. Sharma, B.K.Padda, V. Choudhary; Comparative evaluation of residual monomer content and polymerization shrinkage of a packable composite and an ormocer; Journal of Conservative Dentistry 15(2), 2012, 161-5 "The ormocer may be considered more biocompatible than other composites due to the lower residual monomer content, while being comparable with regards to their polymerization shrinkage." 6) D. Manojlovic, M. Radisic, T. Vailjevic, S. Zirkovic, M. Lausevic, V. Miletic; Monomer elution from nanohybrid and ormocer-based composites cured with different light sources; Dental Materials 27(4), 2011, 371-8 "Two conventional composites eluted ore cross-linking monomers than the ormocer." 7) H.Y. Marghalani, D.C. Watts; Vsicoelastic stability of resin-composites aged in food-simulating solvents; Dental Materials 29(9), 2913, 963-70	

			"The viscoelastic stability of an ormocer was closely matched by a high-filled dimethacrylate material." 8) C. Guler, Y. Yilmaz; A two-year clinical evaluation of glass ionomer and ormocer based fissure sealants; The Journal of Clinical Peadiatric Dentistry 37(3), 2013, 263-7 "The glass ionomer and the ormocer based fissure sealant exhibited similar retention and marginal integrity during 24 months."	
89	LIdmark Ann-Marie, Tandvårdsskadeförbundet (The Swedish Association of Dental Mercury Patients), lidmark@gmail.com	8. REFERENCES	Additional references 1. Goodrich, JM, Basu, N, Franzblau, A, and Dolinoy, DC (2013) Mercury Biomarkers and DNA Metylation among Michigan Dental Professonals. Environ Mol Mutagen; 54(3):195-203 2. Lidmark, A-M & Wikmans, T (2008) Are They Really Sick? A Report on Persons Who Are Electrosensitive and/or Injured by Dental Material in Sweden. J Orthomol Med 23(3); 153-160 3. Mutter, J (2011) Is dental amalgam safe for humans? The opinion of the scientific committee of the European Commission. JOMT 6:2	1. Goodrich et al. (2013) find an association between hair mercury levels and DNA methylation. No significant relationships between urine Hg and DNA methylation were observed. 2. Lidmark, A-M & Wikmans, T (2008): This study is based on case reports from a selected group of persons. It is not considered suitable for evaluation in the present context. 3. Mutter (2011): This is an Opinion paper.
90	McKay Ian , British Dental Association, ian.mckay@bda.org	EXECUTIVE SUMMARY	It would useful if the opinion could explicitly consider if the evidence related to amalgam provides any justification for the removal of amalgam in the absence of a specific allergic reaction.	The present text in the Abstract, page 4, is almost explicit: There appears to be no general justification for unnecessarily removing clinically satisfactory amalgam restorations, except in those patients diagnosed as having allergic reactions to one of the amalgam constituents.
91	Rooney James, Trinity College Dublin, jrooney@rcsi.ie	EXECUTIVE SUMMARY	Page8, paragraph 9: "So far, studies in children of school age did not demonstrate amalgam-associated neuropsychological deficits. However, genetic polymorphisms in relevant genes may cause increased accumulation of mercury and susceptibility to adverse effects in vulnerable subpopulations." Comment: The New England and Casa Pia amalgam trials were not designed, nor powered to detect genetically sensitive subpopulations amongst those children in the arms of those trails exposed to amalgam fillings. Nevertheless, analysis of the combined intervention + control arms of the Casa Pia trail did have enough statistical power to determine	The studies 1-5 are discussed in the text, where appropriate.

			several genetic polymorphisms of relevance – recently summarized by Woods et al 1. Page 9, paragraph 1: "Studies on large patient collectives did not show any correlation of health effects with the number of dental amalgam restorations" Comment: This ignores occupational studies from dentists and the Casa Pia amalgam trial showing that subpopulations with specific genotypes experience subtle neurobehavioral symptoms on exposure to low levels of mercury 1–5. Therefore one should not expect such studies on patients to find associations with the number of amalgam fillings if those studies have not included genetic analysis to identify sensitive individuals. Page 10, paragraph 5: "As far as dental personnel are concerned, it is recognised that they may be at greater risk with respect to higher mercury exposure from dental amalgam than the general population, although the incidence of reported adverse effects seems to be in the same order of magnitude." Comment: SCENIHR has made the recommendation that pregnancy and chronic kidney disease in patients should be born in mind when deciding which restoration material to use. Surely this warning should be extended to dental staff working with amalgams? Whilst I recognize that each individual dentist will exercise their own judgment regarding personal exposures in their personal work environment, other workers such as dental nurses and dental assistants may not have that same control over their environment. SCENIHR should recommend the same list of contraindications for dental workers as for patients, given that those workers are generally exposed to higher levels of mercury. Page 10, paragraph 8: "The choice of material should be based on patient characteristics such as primary or permanent teeth, pregnancy, presence of allergies to mercury or other components of the restorative materials, and presence of decreased renal clearance." Comment: I applaud SCENIHR for making this statement. However I think it is somewhat non-committal in its	

			phraseology and it would be better to show greater leadership by providing a more clear statement that amalgam should be avoided in pregnancy, decreased renal clearance and primary/non-permanent teeth. I also recommend that this list should be extended to include children, breast-feeding mothers and thyroid disease patients based on the available evidence. References: 1. Woods, J. S., Heyer, N. J., Russo, J. E., Martin, M. D. & Farin, F. M. Neurotoxicology 44C, 288–302 (2014). 2. Heyer, N. J. et al. Toxicol. Sci. 363, 354–363 (2004). 3. Woods, J. S. et al. Toxicol. Appl. Pharmacol. 206, 113–20 (2005). 4. Heyer, N. J., Echeverria, D., Martin, M. D., Farin, F. M. & Woods, J. S. J. Toxicol. Environ. Health. A 72, 599–609 (2009). 5. Heyer, N. J., Echeverria, D., Farin, F. M. & Woods, J. S. J. Toxicol. Environ. Health. A 71, 1318–1326 (2008).	
92	Doneus Wolfgang, Council of European Dentists, ced@eudental.eu	EXECUTIVE SUMMARY	The SCENIHR report demonstrates a comprehensive investigation of the evidence in relation to dental amalgam and other restorative materials. It should be commended for its thoroughness and should be welcomed by the dental profession which has at its heart the responsibility and will to act in patients' best interests. We make minor comments on the text.	Thank you for the comments.
93	Stock Gregor, FIDE - Federation of the European Dental Industry, g.stock@fide-online.org	EXECUTIVE SUMMARY	Page 9, Paragraph 2 "Similar to treatment with dental amalgam, the use of these materials in pregnant women is discouraged." What is the factual basis for this statement in regard to alternative materials? Supporting information should be cited. Also, see further comments (4.1. and 4.2.2), which refer to text that states that caution should be used, vs. discouraging treatment as expressed on page 9. Suggested text: Based on current information, dental composites do not pose unacceptable risks to pregnant	Added text in 4.2.4. Question 4 Based on current information, dental composites do not pose unacceptable risks to pregnant patients. A decision to perform dental treatment during pregnancy should take into account the dental therapeutic needs of the patient and balance any potential risks (including the use of anaesthetic, along with all dental materials) against therapeutic benefits to the patient.

			patients. A decision to perform dental treatment during pregnancy should take into account the dental therapeutic needs of the patient and balance any potential risks (including the use of anesthetic, along with all dental materials) against therapeutic benefits to the patient.	
94	Stock Gregor, FIDE - Federation of the European Dental Industry, g.stock@fide-online.org	EXECUTIVE SUMMARY	General Comment: Relatively little text in the opinion addresses use of glass ionomers as an alternative to use of amalgam and composite materials. It would be worthwhile for the document to emphasize that conventional glass ionomers are a class of materials that do not contain or release monomers. High viscosity glass ionomers have mechanical properties that allow their use in certain clinical indications. Other glass ionomers can be used as luting materials in indirect restorations (e.g. of ceramics) without use of monomer containing products. This combined use has the advantage of being a monomer-free alternative.	Thank you for the comment. This information is part of the text concerning alternative materials already. The present Opinion is primarily concerned with health risks and does not address all details that would be beneficial for each clinical situation.
95	Swedish Chemicals Agency, kemi@kemi.se	EXECUTIVE SUMMARY	p9, 1st para and p 10, 4th para See our comment on section 3.3.10. Change due to proposed change in section 3.3.10. p9, 2nd para The SCENIHR describes the uncertainties about toxicological risks in alternative dental materials. Regarding materials containing bisphenol A the SCENIHR concludes in another recent SCENIHR Opinion in 2014 that "Release of bisphenol A (BPA) from some dental materials has been evaluated and gave rise to negligible risk". Followed by the statement: "Therefore, nonmercury containing alternatives are not free from any concerns about adverse effects." Since bisphenol A release give rise to negligible risk, the referred opinion about BPA cannot be a reason to not recommend such alternatives to dental amalgam. Logically the sentence starting with "Therefore non mercury …" should be moved, probably to a position earlier in that para.	Agreed. The text will be clarified. A text that was also in the abstract is missing between the sentence cited in the comment and will be added: *A similar extensive risk assessment has not been performed for other compounds released from alternative dental materials. Some of the monomers used are cytotoxic to pulp and gingival cells* in vitro*. There is* in vitro *evidence that some of these alternatives are also mutagenic although long-term health consequences are unclear.*
96	Eaton Kenneth, Platform for Better Oral Health in	EXECUTIVE SUMMARY	The Platform for Better Oral Health in Europe is a joint initiative of the Association for Dental Education in Europe (ADEE), the Council of European Chief Dental Officers	Thank you for the information.

	Europe, secretariat@oralhealthplatform.eu		(CECDO), the European Association of Dental Public Health (EADPH) and the European Dental Health Foundation (EDHF). Its work is supported by the Wrigley Oral Healthcare Program and GlaxoSmithKline. The Platform seeks a common European approach towards education, prevention and access to better oral health in Europe. The Platform welcomes the opportunity to comment on the preliminary opinion on the safety of dental amalgam and alternative dental restoration materials for patients and users. Overall, the Platform believes that this opinion constitutes an excellent document which reviewed the current scientific evidence on the topic in a fair and objective manner and made very sensible recommendations. We would like in particular to stress the importance of moving away from relying extensively on restoration into national and international objectives towards prevention of oral diseases and oral health promotion that will help reducing disease rates and addressing oral health inequalities. Whilst we do continue to highlight the safety of amalgam use in dentistry, at the same time, we also identify the need for the dental profession and the dental research community to gradually move towards alternative forms of restorative materials, in order to partly account for the broader implications on the provision of affordable dental care. In this respect, we fully support the Committee's recommendation that 'equal or more research emphasis should be placed on the further development and implementation of new caries management concepts like early intervention and of new tools for caries prevention in risk groups'. The Platform applauds the work of the Scientific Committee on Emerging and Newly Identified Health Risks, and look forward to continue to engage with the Scientific Committee in the future. Oral diseases can be kept at bay with simple yet effective daily hygiene routines, and with good habits that start early and continue throughout life. About the Platform for Better Oral Health in	

			Europe The Platform for Better Oral Health in Europe is a joint initiative of the Association for Dental Education in Europe (ADEE), the Council of European Chief Dental Officers (CECDO), the European Association of Dental Public Health (EADPH) and the European Dental Health Foundation (EDHF). Its work is supported by the Wrigley Oral Healthcare Program and GlaxoSmithKline. The Platform has been created to respond to the Call to Action for Better Oral Health in Europe handed over to former Health Commissioner Dalli by several Members of the European Parliament in 2010. The mission of the Platform is to promote oral health and the cost-effective prevention of oral diseases in Europe. It seeks a common European approach towards education, prevention and access to better oral health in Europe. The Platform is a collaborating partner to the European Commission's Joint Actions on Health Workforce Planning and Forecasting, and on Chronic Diseases and Promoting Healthy Ageing across the Life-Cycle.	
97	Lidmark Ann-Marie, Tandvårdsskadeförbudet (The Swedish Association of Dental Mercury Patients), lidmark@gmail.com	EXECUTIVE SUMMARY	Tandvårdsskadeförbundet (The Swedish Association of Dental Mercury Patients) do agree with SCENIHR pointing out the need of further research related to genetic susceptibility related to all restorative materials. We also agree that amalgam and mercury is toxic, our conclusion is, however, that amalgam is not needed in dental care and therefore should as soon as possible be phased out. Sweden and Norway are examples of countries where dental amalgam is banned and it works fine. There are many great options just as durable as dental amalgam and often better. Many reasons exist to phase out amalgam from dentistry among them the precautionary principle. SCENIHR:s working group has not stated any sustainable reason to keep dental amalgam on the market and there is no discussion at all about the precautionary principle. We call for a clearer statement with reference to mercury toxicity as reported in the background chapters and the precautionary principle. Se	No action needed. The comment agrees with the Opinion The phasing out of any chemical is a risk management measure, therefore outside the mandate of the Committee.

			also óur comments on the abstract	
98	Laupie Julien, French Union of Oral Health (UFSBD), julienlaupie@ufsbd.fr, France	Abstract	 Position UFSBD SCENIHR.doc	the SCENIHR took note of the contribution and no change in the Opinion is needed
99	Munro-Hall Graeme International Academy of Oral Medicine &Toxicology-Europeiaomt-europe@steeps.net, United Kingdom	3.3.9. 3.4.9. 3.4.11. Executive summary		These sections are addressed above.

Contributions received via email

No	Name of individual/ organisation	Comment	Scientific Committees Response
1.	Council of Dentists Europe	'Council of European Dentists' Subject: CED response to the public consultation on the preliminary opinion on the safety of use of dental amalgam and alternative materials Importance: High Dear Sir/Madam, Please see attached CED response to the public consultation on the preliminary opinion on the safety of use of dental amalgam and alternative materials and respective article that we wish to submit (Duncan A, O'Reilly DS, McDonald EB, Watkins TR, Taylor M. (2011) Thirty-five year review of a mercury monitoring service for Scottish dental practices. Br Dent J. Feb 12; 210(3):E2. doi: 10.1038/sj.bdj.2011.49.). The online questionnaire did not confirm that the annexed file had been uploaded. For this reason, we submit our complete response by email. As a general comment to this specific online questionnaire, please note that the individual submission of comments was quite inefficient as you had to repeat the same general information several times. Furthermore, you do not receive at the end your complete response. Instead, you receive five documents with your different submissions. Kind regards,	Please see responses to comments to 20 and 21 New text added in the Opinion: Nevertheless, according to head hair mercury data acquired over 35 years in Scottish dental practice (Duncan et al., 2011) median concentrations were reduced from 8.6 µg/g in the period 1975-1979 to 0.5 µg/g in the period 2005-2009. The reduction was attributed to improved preparation techniques and increased awareness. In comparison, mean hair mercury concentration in the U.S. population of women in childbearing age is 0.20 µg/g (McDowell et al. 2004).

		35 year mercury_BDJ.PDF CED response to SCENIHR preliminary	
2.	Dr Graeme Munro-Hall	At our recent meeting in Luxembourg you asked for comments on the preliminary report from SCENIHR. I have attached my comments which I would like to have placed on record. This process has to be open and clear unlike the previous ones as the world is watching. I had a very interesting meeting at INC6 Minimata Convention in Bangkok. A large number of developing countries have asked to have programmes to transition away from amalgam. If they recognise the risks and with limited resources can make the transition, why not the EU which already has the Nordic example to follow? The Commission is deeply unpopular with EU citizens, to maintain the use of amalgam when the rest of the world is going to transition out of using amalgam is hardly likely to restore the credibility of the Commission in the eyes of its citizens. As I said at our meeting, this is a critical time and feet will be held to the fire if the process is flawed. Thank you for the time and courtesy extended to me SCENIHR 14-11-14.docx	The responses to comments to 3.3.9, 3.4.9, 3.4.11 have been addressed above.
3.	French Government	14-12-02 [ITEC-1088] Consulta Contribution Dental Amalgam.PDF Translation_1.rtf Translations:	1. Review substituted with Examination 2. This issue is included in the Recommendations for research, 4.2.5 Question 5 3. There is unfortunately no nomenclature that defines "large restorations". However, "large" in the present context implies that a major part of the tooth structure is replaced with a restoration. 4. The indications and restrictions of the use of dental materials are described in textbooks in restorative dentistry. In the present Opinion, the materials are

		1. To avoid any possible confusion with the auditing process, the word 'review' on the last line of page 9 in 'the certification process does not include review of the design dossier' should be replaced with 'examination'. 2. Among the elements used to evaluate toxicity, the new hypothesis of a genetic predisposition to individual susceptibility to mercury toxicity would need to be studied in greater depth through new research; 3. The concept of 'large restorations' would need to be clarified; 4. Indications and restrictions on the use of dental amalgams and their alternatives are dotted around in different paragraphs. It would be preferable to include all of them in the opinion and in the abstract.	described in the context of Risk Assessment, which may seem irregular, but is useful for the evaluation of their toxicological properties.