22/06/2017

2nd List of First Safe Dilutions

Overview of comments received on draft document

"2nd List of First Safe Dilutions"

as released for public consultation on the HMA website until 16 May 2017

Deadline for public consultation	16 May 2017
Discussion in the FSD-Subgroup	2 June – 8 June 2017
Adoption by the FSD-Subgroup	8 June 2017
Discussion and Adoption by HMPWG for publication on HMA-website	26 – 27 June 2017

Overview of comments received

Table 1: Organisations and/or individuals that commented on the draft document

2nd List of First Safe Dilutions as released for public consultation on 15 February 2017 until 16 May 2017

	Organisations and/or individuals
1	AESGP
2	BPI
3	ECH
4	ECHAMP

Table 2: Discussion of comments

GENERAL COMMENTS		
Interested party	**Comment and Rationale**	**Outcome**
AESGP	AESGP welcomes the intention of the 2nd list of first safe dilutions (FSD) to provide harmonised guidance in order to facilitate consistent assessment by the competent authorities. Nevertheless, we would like to express our concerns that calculations from safety assessments of non-homeopathic medicines are 1:1 transposed to homeopathic medicinal products. This results in an increasing limitation of safe dilutions beyond or far beyond D4. We therefore strongly plead for sufficiently taking into account the particularities of homeopathic medicinal products, in particular the safety criterion of D4 laid down in Directive 2001/83/EC as well as the fact that homeopathic preparations of D4 and above did not show any relevant safety problems during their long presence in the market.	See http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/HMPWG/2016_11_Overview_comments_Preamble_First_List_FSD.pdf
AESGP	In the Q3D-Guideline (Guideline for Elemental Impurities) the following is stated in the Introduction: "Since elemental impurities do not provide any therapeutic benefit to the patient, element impurity should be controlled within acceptable limits in the drug product. (…) The PDEs established in this guideline are considered to be protective of public health for all patient populations." We do not agree with the body weight adjustment in the PDE calculation in cases where the ICH Q3D-Guideline is used as reference. It is shown below in several examples, that if the Q3D-values are taken without weight adjustment, these values are confirmed by calculating the respective FSD on the base of drinking water and food regulations. Moreover, these are the intended calculation principles for FSDs. See also specific comments. This is also in line with the calculations presented for Barium carbonicum, Barium chloratum, Baryta carbonica, Minium, Plumbum aceticum and Pyromorphite. The FSD calculation proposed is based on the worst case scenario that one whole unit (10 ml or 10 g) is taken daily during life-time exposure with a lifelong bodyweight of 3 kg (which corresponds to the bodyweight of neonates). This is highly unrealistic.	See http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/HMPWG/2016_11_Overview_comments_Preamble_First_List_FSD.pdf Usually, the PDE is calculated by multiplying the POD (point of departure, e.g. NOAEL mg/kg/day) with 50 (kg body weight) and if necessary subsequently by dividing by the product of the uncertainty factors F1- F5. This calculation finally results in a limit value given as mg/day. Unless otherwise indicated, the PDE is related to the body weight considered in the calculation/derivation. **Example: Arsenic** Arsenic PDE– Oral Exposure: The oral PDE is based on the chronic effects of As to skin and sets the limit at 15 µg/day based on ATSDR MRL and EPA IRIS limit of 0.0003 mg/kg/d. Quotation from ICH Q3D: "The oral PDE is based on the chronic effects of arsenic to skin

GENERAL COMMENTS		
		and sets the limit at 15 µg/day based on Agency for Toxic Substances and Disease Registry (ATSDR) MRL and US EPA limit of 0.0003 mg/kg/day (ATSDR, 2007; US EPA 2007; EU EFSA, 2009). The PDE calculated based on the ATSDR MRL is consistent with drinking water standards (WHO, 2011). PDE = 0.0003 mg/kg/d **x 50 kg** = 0.015 mg/d = 15 µg/day." In this case, the MRL as the POD (point of departure) is given in mg/kg/d and, for FSD calculation, this value is to be multiplied by 3 (kg bw neonate) to ensure a first safe dilution for all population groups. In the **special case of Lead** the POD (point of departure) represents a value established for children, hence, an adjustment is deemed dispensable. Quotation from ICH Q3D: "According to the US EPA model (Integrated Exposure Uptake Biokinetic (IEUBK) Model, 1994) (100% absorption, no other sources of lead), oral intake of 5 µg/day translates into a blood level of 1-2 µg/dL for children age 0-7 years (0-82 months) (US EPA, 2007, 2009). PDE = 5.0 µg/day." In cases where the POD (e.g. NOAEL) is multiplied by 50 and subsequently divided by F1-F5, calculation of FSD should refer to the primary literature POD, usually expressed as a value mg/kg/day. Dividing by uncertainty factors F1-F5 would lead to a limit value in mg/kg/day, which is reasonably multiplied by 3 (kg bw neonate) to result in an FSD.

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		In the following passage from ICH Q3D : "The mass adjustment assumes an arbitrary adult human body mass for either sex of 50 kg. This relatively low mass provides an additional safety factor against the standard masses of 60 kg or 70 kg that are often used in this type of calculation. It is recognized that some patients weigh less than 50 kg; these patients are considered to be accommodated by the built-in safety factors used to determine a PDE and that lifetime studies were often used. **For lead, the pediatric population is considered the most sensitive population, and data from this population were used to set the PDE. Therefore, the PDEs are considered appropriate for pharmaceuticals intended for pediatric populations."** should be read in the way, that the term in yellow font refers to the different ways of administration of lead only: oral, parenteral and inhalation. This does not refer to all other PDEs in ICH Q3D.
AESGP	According to the decision tree of the HMPWG PtC on non-clinical safety of homeopathic medicinal products of botanical, mineral and chemical origin (in the following called PtC), substances allowed as food or constituents of food have to be assessed according to Regulation 178/2002/EC modified by 1642/2003/EC and all related directives and Food supplements 2002/46/EC. This also includes drinking water regulations. The correct approach for the evaluation of the pure metals would therefore be to use the limit values from the food sector. See also Specific Comments.	The HMPWG agrees to this approach. As the FSD should include all patient groups that possibly may be treated with a homeopathic medicinal product, the limit values for children have to be taken into account. In the “Points to consider on non-clinical safety of homeopathic medicinal products of botanical, mineral and chemical origin” of HMPWG, the derivation of a FSD from nutrition recommendations is not further specified. The cited regulation documents (178/2002/EC modified by 1642/2003/EC and all related directives, Food supplements 2002/46/EC) deal with the establishment of the EFSA and general principles and requirements of food law and the regulation of food supplements. In the opinion of HMPWG, it should be differentiated between nutrition recommendations for essential constituents of food that pose no serious harm on the one hand and limit values in EU regulation for impurities with a potential risk to human health on the other hand. In particular for the latter, the most conservative and suitable option should be chosen if different approaches of assessment are possible.
AESGP	As a general remark, we would like to ask that the documents on FSD (assessment reports)	On the HMA website, all documents of importance will be

GENERAL COMMENTS		
	remain permanently available on the HMA website and not only during the consultation phase. A further level of transparency and the availability of meeting reports, working documents and details on the adopted entries would definitely be of advantage.	available long term; meeting reports are and will be published on the website too. All relevant information needed for assessment is included in the list. The new approach avoids redundant information; the list entries must be read in connection with the underlying pharmacopoeial monograph and the source in the column "Reference(s)" for the derivation of FSD. If the chosen way of assessment is not self-explaining, an explanation is included in the column "Remarks".
BPI e.V.	For transparency reasons please publish the assessment reports of First Safe Dilutions	See above
BPI e.V.	ICH Q3D states: "PDEs established in this guideline are considered to be protective of public health for all patient populations". This means that also neonates are already covered, hence no further body weight adjustment is foreseen. As the PDEs are given in µg/day, a body weight-adjusted calculation is explicitly not necessary to establish the FSD. See also Specific Comments This is also in line with the calculations presented for Barium carbonicum, Barium chloratum, Baryta carbonica, Minium, Plumbum aceticum, Pyromorphite We do not agree with the body weight adjustment in the PDE calculation. Indeed PDE approach already includes safety factors (F1, F2, F3, F4, F5). Additionally the FSD calculation proposed here is based on the worst case scenario that one whole unit (10 ml or 10 g) is taken daily by a neonate with 3 kg body weight, which is highly unrealistic. It is important to say that the dosage of homeopathic medicinal products is proportional to the age groups. Therefore the dosage is adapted to the age, and is reduced in younger patient. Such a calculation leads to a disproportionate accumulation of safety factors, and finally to very high FSD. In the following specific comments, take in account the FSD calculated with 50 kg (and not with 3 kg).	See http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/HMPWG/2016_11_Overview_comments_Preamble_First_List_FSD.pdf
BPI e.V.	According to the decision tree of the HMPWG PtC on non-clinical safety of homeopathic medicinal products of botanical, mineral and chemical origin (in the following called PtC), substances allowed as food or constituents of food have to be assessed according to Regulation 178/2002/EC modified by 1642/2003/EC and all related directives and Food	See answer to the third comment from AESGP.

GENERAL COMMENTS		
	supplements 2002/46/EC. This also includes drinking water regulations. The correct approach for the evaluation of the pure metals would therefore be to use the limit values from the food sector. Concerning the calculation of substances allowed in drinking water the example of Barium should be used accordingly. See also Specific Comments.	
ECH	(no comments)	
ECHAMP	In the Q3D-Guideline (Guideline for Elemental Impurities!) the following is stated in the Introduction: "Since elemental impurities do not provide any therapeutic benefit to the patient, element impurity should be controlled within acceptable limits in the drug product. (…) The PDEs established in this guideline are considered to be protective of public health for all patient populations." We do not agree with the body weight adjustment in the PDE calculation in cases where the ICH Q3D-Guideline is used as reference. It is shown below in several examples, that if the Q3D-values are taken without weight adjustment, these values are confirmed by calculating the respective FSD on the base of drinking water and food regulations. Moreover, these are the intended calculation principles for FSDs. See also specific comments. The FSD calculation proposed is based on the worst case scenario that one whole unit (10 ml or 10 g) is taken daily during life-time exposure with a lifelong bodyweight of 3 kg (which corresponds to the bodyweight of neonates). This is highly unrealistic.	See http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/HMPWG/2016_11_Overview_comments_Preamble_First_List_FSD.pdf
ECHAMP	Please publish the assessment reports of First Safe Dilutions	See answer to first comment from BPI.
ECHAMP	According to the decision tree of the HMPWG PtC on non-clinical safety of homeopathic medicinal products of botanical, mineral and chemical origin (in the following called PtC), substances allowed as food or constituents of food have to be assessed according to Regulation 178/2002/EC modified by 1642/2003/EC and all related directives and Food supplements 2002/46/EC. This also includes drinking water regulations. The correct approach for the evaluation of the pure metals would therefore be to use the limit values from the food sector. We suggest to use the same kind of calculation for substances regulated by the drinking water regulations as done in the case of Barium salts. See also Specific Comments.	See answer to the third comment from AESGP.
ECHAMP	Please note, that calculations performed are always considering the worst case of (pharmacopoeial) analytical requirements.	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
Antimonite Sb_2S_3 HAB	AESGP	No weight adjustment necessary. PDE = 1200 µg Sb/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 753 µg Sb > **FSD = D4** According to the PtC decision tree substances allowed as food or constituents of food have to be assessed according to the limit values from the food sector. According to the publication "Antimony in Drinking-water" by the WHO *(WHO 2003)*, **the TDI value** (tolerable daily intake) is considered to be **360 µg antimony** as potassium antimony (III) oxide tartrate for a person with a body weight of 60 kg (calculated from a study on subacute toxicity). Assuming that approximately 60 µg antimony (range 10-70 µg) are ingested with the diet, this leaves a remaining 300 µg that could be taken in in other ways. Assuming an absorption rate of 10 % for antimony trisulphide in comparison with antimony potassium tartrate, this leads to a TDA for antimonite of 4.18 mg. This assumption is based on the factor of about 10 between the oral LD_{50} values on rats and on the fact that an absorption rate of 15 % was reported for antimony potassium tartrate and 1.5 % for antimony trisulphide. This is in accordance with the data reported by the *WHO (2003)*. The *WHO (2003)* mentioned that although quantitative information on the absorption of antimony is not available for all forms, 10 % for antimony potassium tartrate and 1 % for all other forms of antimony have been recommended as reference values for gastrointestinal absorption in humans. Summarising the data, the **total daily amount** (TDA) which could be administered and **which could be assessed as being safe**, is assumed to be **3,000 µg antimony (used as antimonite),** corresponding to **4,180 µg antimonite** (with 71.7 % antimony in antimonite): **FSD = D4** 10 g of the D4 trituration contains 1,000 µg antimonite and is therefore safe.	**Not agreed.** Concerning the weight adjustment of PDE values see answer on second comment from AESGP under general comments. Concerning the approach of assessment see answer on third comment from AESGP under general comments. In the EU Drinking Water Directive (98/83/EC) the intake of **5.0 µg antimony/L** is given as a limit value per day. Considering the daily consumption of water in the first half-year of life as outlined by EFSA ("Nutrient requirements and dietary intakes of infants and young children in the EU", EFSA Journal 2013; 11(10):3408; reference value for water = 700-1000 ml/day), the intake of antimony for this patient group lies in a range of 3.5-5 µg antimony/day. This would correspond to a FSD of D7 (10 g Antimonite D7 contains 0.753 µg Sb; FSD Antimonite in the 2nd list of FSD = D6). Taking into account the tolerable daily intake (TDI) for antimony = 6 µg/kg body weight, on which the WHO Drinking Water Guideline value for antimony is based (Antimony in Drinking-water - Background document for development of WHO Guidelines for Drinking-water Quality WHO/SDE/WSH/03.04/74, WHO 2003), the acceptable amount for a new-born child would be **18 µg antimony/day**. Supporting information for **WHO TDI value**: The suggested NOAEL (Lynch et al., 1999) in the subchronic drinking-water study in rats conducted by Poon et al. (1998) of 6.0 mg/kg of body weight per day was based on decreased body weight gain and reduced food and water intake. By applying an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for the use of a subchronic study), a TDI of 6 µg/kg of body weight could be determined. Supporting information for **PDE value**: "*Reevaluating the data of Poon et al. (1998), Lynch et al.*

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Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
Antimonite Sb_2S_3 HAB	BPI e.V.	No weight adjustment necessary PDE = 1200 µg Sb/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 753 µg Sb > **FSD = D4** According to the PtC decision tree substances allowed as food or constituents of food have to be assessed according to the limit values from the food sector. According to the publication "Antimony in Drinking-water" by the WHO *(WHO 2003)*, **the TDI value** (tolerable daily intake) is considered to be **360 µg antimony** as potassium antimony (III) oxide tartrate for a person with a body weight of 60 kg (calculated from a study on subacute toxicity). Assuming that approximately 60 µg antimony (range 10-70 µg) are ingested with the diet, this leaves a remaining 300 µg that could be taken in in other ways. Assuming an absorption rate of 10 % for antimony trisulphide in comparison with antimony potassium tartrate, this leads to a TDA for antimonite of 4.18 mg. This assumption is based on the factor of about 10 between the oral LD_{50} values on rats and on the fact that an absorption rate of 15 % was reported for antimony potassium tartrate and 1.5 % for antimony trisulphide. This is in accordance with the data reported by the *WHO (2003)*. The *WHO (2003)* mentioned that although quantitative information on the absorption of antimony is not available for all forms, 10 % for antimony potassium tartrate and 1 % for all other forms of antimony have been recommended as reference values for gastrointestinal absorption in humans. Summarising the data, the **total daily amount** (TDA) which could be administered and **which could be assessed as being safe**, is assumed to be **3,000 µg antimony (used as antimonite),** corresponding to **4,180 µg antimonite** (with 71.7 % antimony in antimonite): **FSD = D4** 10 g of the D4 trituration contains 1,000 µg antimonite and is therefore safe.	*concluded that a NOAEL from a 90 day drinking water study in rats using 0.5 to 500 ppm APT was 50 ppm based on lower mean body weight and reduced food consumption at the highest dose (Lynch et al., 1999). This finding is consistent with the earlier reports from Schroeder et al. (1970). Thus, the PDE for oral exposure was determined on the basis of the lowest NOAEL, i.e., 50 ppm (equivalent to 6.0 mg Sb/kg/day)."* (ICHQ3D) Conclusion: The WHO Drinking Water Guideline value of 20 µg/L lies in the same range as the weight adjusted PDE for antimony (24 µg/kg/d; for neonates: **72 µg Sb/day**) and leads to the same FSD. Notably, both limit values go back to the same POD (point of departure = NOAEL of Lynch et al., 1999). Regarding kinetics: Indeed, quantitative information on the absorption of potassium antimony tartrate (APT, $KSbOC_4H_4O_6$) is available: "*Examination of four persons after involuntary acute intoxication with APT revealed an absorption rate of 5% (Iffland & Bösche, 1987; Lauwers et al., 1990)." (*WHO 2003). In the absence of substance specific kinetic data for Sb_2S_3 per se and applying the principle of prudence, the assumed absorption rate of 10 % (value merely transferred to antimony trisulphide) and any further pharmacokinetic considerations may be addressed in a submitted Module 4.
Antimonite	ECHAMP	No weight adjustment necessary	

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Sb_2S_3 HAB		PDE = 1200 µg Sb/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 753 µg Sb > **FSD = D4** According to the PtC decision tree substances allowed as food or constituents of food have to be assessed according to the limit values from the food sector. According to the publication "Antimony in Drinking-water" by the WHO *(WHO 2003)*, **the TDI value** (tolerable daily intake) is considered to be **360 µg antimony** as potassium antimony (III) oxide tartrate for a person with a body weight of 60 kg (calculated from a study on subacute toxicity). Assuming that approximately 60 µg antimony (range 10-70 µg) are ingested with the diet, this leaves a remaining 300 µg that could be taken in in other ways. Assuming an absorption rate of 10 % for antimony trisulphide in comparison with antimony potassium tartrate, this leads to a TDA for antimonite of 4.18 mg. This assumption is based on the factor of about 10 between the oral LD_{50} values on rats and on the fact that an absorption rate of 15 % was reported for antimony potassium tartrate and 1.5 % for antimony trisulphide. This is in accordance with the data reported by the *WHO (2003)*. The *WHO (2003)* mentioned that although quantitative information on the absorption of antimony is not available for all forms, 10 % for antimony potassium tartrate and 1 % for all other forms of antimony have been recommended as reference values for gastrointestinal absorption in humans. Summarising the data, the **total daily amount** (TDA) which could be administered and **which could be assessed as being safe**, is assumed to be **3,000 µg antimony (used as antimonite),** corresponding to **4,180 µg antimonite** (with 71.7 % antimony in antimonite): **FSD = D4** 10 g of the D4 trituration contains 1,000 µg antimonite and is therefore safe.	
Antimonium	AESGP	No weight adjustment necessary.	**Not agreed.**

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crudum Sb_2S_3 Ph.Franç.		PDE = 1200 µg Sb/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 731 µg Sb > **FSD = D4**	See answer to the comments on Antimonite.
Antimonium crudum Sb_2S_3 Ph.Franç.	BPI e.V.	No weight adjustment necessary PDE = 1200 µg Sb/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 731 µg Sb > **FSD = D4**	
Antimonium crudum Sb_2S_3 Ph.Franç.	ECHAMP	No weight adjustment necessary PDE = 1200 µg Sb/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 731 µg Sb > **FSD = D4**	
Argentite Ag_2S HAB	AESGP	No weight adjustment necessary. PDE = 167 Ag/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 91.4 µg Ag > **FSD = D5**	**Not agreed.** See answer to the second comment from AESGP under general comments.
Argentite Ag_2S HAB	BPI e.V.	No weight adjustment necessary PDE = 167 Ag/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 91.4 µg Ag > **FSD = D5**	
Argentite Ag_2S HAB	ECHAMP	No weight adjustment necessary PDE = 167 Ag/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 91.4 µg Ag > **FSD = D5**	
Argentum colloidale	AESGP	No weight adjustment necessary.	**Not agreed.**

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Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
Ag HAB		PDE = 167 µg Ag/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 78 µg Ag > **FSD = D5**	See answer to the second comment from AESGP under general comments. Concerning the approach of assessment see answer on third comment from AESGP under general comments. It cannot be assumed, that a newborn consumes 2 litre drinking water per day. For the recommended feeding quantities in product information for breast milk substitutes, about 700 ml drinking water is needed to prepare the daily quantity for a 2 month old baby. Additional fluid intake is not necessary according to EFSA Journal 2013; 11(10):3408. Regarding the presented values (BfR, WHO): The values of 0.08 mg/L (BfR) and 0,1 mg/L (WHO) apply for silver salts used as chemicals applied in water treatment to maintain the bacteriological quality of drinking-water. Both represent a concentration that gives a total dose over 70 years with 2 L/d of purified/treated water (i.e. the maximum admissible concentrations may be exceeded after 70 years) and are based on the fact that silver occurs in drinking-water at concentrations above 5 µg/L (or in water treated with silver for disinfection at concentrations above 50 µg/L). In view of the above presented data basis for the cited/claimed values of 0.08 mg/L (BfR) and 0,1 mg/L (WHO), still the evaluation basis with reference to the sound POD used for PDE (ICHQ3D) is deemed appropriate. Furthermore, the FSD calculated via PDE approach is consistent with the oral RfD (reference dose) of **5 µg/kg/day** (for supporting information see below; US EPA, 2003; Integrated Risk Information System, IRIS, 1991). Supporting information for Ag **PDE** (ICHQ3D): POD = LOAEL mouse = 32.14 mg/kg silver nitrate; 64% Ag → 20 mg/kg Ag (*Ref LOAEL [Rungby J, Danscher G.*
Argentum colloidale Ag HAB	BPI e.V.	No weight adjustment necessary PDE = 167 µg Ag/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 78 µg Ag; **FSD = D5** According to the PtC decision tree substances which are constituents of food have to be assessed according the limit values from the food sector. Colloidal silver and silver ions are used for disinfection of drinking water. In drinking water 0.1 mg Ag/l is allowed (WHO 2006), this results in 0.2 mg/day (2 litre drinking water). This is consistent with the BfR-value of 0.08 mg/l (intake of 2 litre drinking water per day) and the value of 0.08 mg/l of the German Additive Regulation (Zusatzsstoff-Zulassungsverordnung (Anlage 6a (zu § 6a); Zusatzstoffe, die für Trinkwasser zugelassen sind) (https://www.gesetze-im-internet.de/zzulv_1998/anlage_6a.html http://www.bfr.bund.de/cm/343/bfr_raet_von_nanosilber_in_lebensmitteln_und_produkten_des_taeglichen_bedarfs_ab.pdf) The amount of 2 litre drinking water applies to all age groups; this is also in line with the calculation of PDE/ FSD for Barium (see Q3D Guideline: Summary of PDE for Barium)	
Argentum colloidale Ag HAB	ECH	**We do not agree with the derivation of the FSD D6 for Argentum colloidale.** Rationale: According to the PtC decision tree substances which are constituents of food have to be assessed according the limit values from the food sector. Colloidal silver and silver ions are used for disinfection of drinking water. In drinking water 0.1 mg Ag/l is allowed (WHO), this results in 0.2 mg/day (2 litre drinking water).	

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		See: http://www.who.int/water_sanitation_health/dwq/chemicals/silver.pdf On the basis of present epidemiological and pharmacokinetic knowledge, a total lifetime oral intake of about 10 g of silver can be considered as the human NOAEL. As the contribution of drinking-water to this NOAEL will normally be negligible, the establishment of a health-based guideline value is not deemed necessary. On the other hand, special situations may exist where silver salts are used to maintain the bacteriological quality of drinking-water. Higher levels of silver, up to 0.1 mg/litre (a concentration that gives a total dose over 70 years of half the human NOAEL of 10 g), could then be tolerated without risk to health. This is in line with the BfR-value of 0.08 mg/l (intake of 2 litre drinking water per day) and the value of 0.08 mg/l of the German Additive Regulation (Zusatzstoff-Zulassungsverordnung (Anlage 6a (zu § 6a); Zusatzstoffe, die für Trinkwasser zugelassen sind) (https://www.gesetze-im-internet.de/zzulv_1998/anlage_6a.html http://www.bfr.bund.de/cm/343/bfr_raet_von_nanosilber_in_lebensmitteln_und_produkten_des_taeglichen_bedarfs_ab.pdf) The amount of 2 litre drinking water applies to all age groups. (This is in line with the calculation of PDE for Barium Salts; see Guideline for Elemental impurities; Summary of PDE for Barium; No weight adaption) Allowed would be at least 160 µg/ d (BfR value) for all groups including neonates 10 g D5 = 78 µg Ag; **FSD = D5**	*Hypoactivity in silver exposed mice. Acta Pharmacol Toxicol 1984;55:398-401; referenced in ICHQ3D document])* LOAEL = 20 mg/kg Ag divided by UF → **0,0033 mg/kg/d** = **3,3 µg/kg/d Ag** x 3 kg bw neonate → 0,0099 mg/d Ag = 9,9 µg/d Ag Additional remark under consideration of calculation based on the cited/claimed drinking-water values: It should be noted,that in the German Additive Regulation (Zusatzsstoff-Zulassungsverordnung (Anlage 6a (zu § 6a); Zusatzstoffe, die für Trinkwasser zugelassen sind), no difference is made between elemental silver and silver salts. The limit value of Silver (E 174) 0.08 mg/L has the restriction in column 3 "*Konservierung, nur bei nicht systematischem Gebrauch*" (conservation, not for systematic use, i.e. for discontinuous, need-based application only). Even if the FSD calculation would consider an acceptable amount of approximately **56 µg/day** [adjustment to neonate drinking water volume necessary; 0.08 mg/L ≅ 0.16 mg/d (2 L/d) adult; 0,056 mg/700 ml/d neonate; EFSA "Nutrient requirements and dietary intakes of infants and young children in the EU", EFSA Journal 2013; 11(10):3408)], the FSD outcome remained unchanged (D6).
Argentum colloidale Ag HAB	ECHAMP	No weight adjustment necessary PDE = 167 µg Ag/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 78 µg Ag > **FSD = D5** According to the PtC decision tree substances which are constituents of food have to be assessed according the limit values from the food sector. Colloidal silver and silver ions are used for disinfection of drinking water. In drinking water 0.1 mg Ag/l is allowed (WHO 2006), this results in 0.2 mg/day (2 litre drinking water).	

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Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
		This is consistent with the BfR-value of 0.08 mg/l (intake of 2 litre drinking water per day) and the value of 0.08 mg/l of the German Additive Regulation (Zusatzstoff-Zulassungsverordnung (Anlage 6a (zu § 6a); Zusatzstoffe, die für Trinkwasser zugelassen sind) (https://www.gesetze-im-internet.de/zzulv_1998/anlage_6a.html http://www.bfr.bund.de/cm/343/bfr_raet_von_nanosilber_in_lebensmitteln_und_produkten_des_taeglichen_bedarfs_ab.pdf) The amount of 2 litre drinking water applies to all age groups; this is also in line with the calculation of PDE/ FSD for Barium (see Q3D Guideline: Summary of PDE for Barium) 10 g D5 = 78 µg Ag; **FSD = D5**	
Argentum metallicum Ag HAB	AESGP	No weight adjustment necessary. PDE = 167 µg Ag/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 106 µg Ag > **FSD = D5** According to the PtC decision tree substances allowed as food or constituents of food have to be assessed according to the limit values from the food sector. In drinking water are 0.1 mg Ag/l allowed (WHO 2006), this are 0.2 mg/day (2 litre drinking water). 10 g D5 = 106 µg Ag > **FSD = D5**	**Not agreed.** See answer to comment on Argentum colloidale.
Argentum metallicum Ag Ph.Franç.	AESGP	No weight adjustment necessary. PDE = 167 µg Ag/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 100.5 µg Ag > **FSD = D5**	
Argentum metallicum	BPI e.V.	No weight adjustment necessary PDE = 167 µg Ag/day (for all patient populations according to ICH	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
Ag HAB/ FP		guideline Q3D on elemental impurities) 10 g D5 = 106 µg Ag (HAB) > **FSD = D5** 10 g D5 = 100,5 µg Ag(FP) > **FSD = D5** According to the PtC decision tree substances which are constituents of food have to be assesses according the limit values from the food sector. Elemental silver is used in the food sector for coloring of food (E174); e.g. decoration of sweets, pralines and liquors; quantum satis See German Zusatzsstoff-Zulassungsverordnung: https://www.gesetze-im-internet.de/bundesrecht/zzulv_1998/gesamt.pdf or Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02008R1333-20140414&from=DE and Commission Regulation (EU) No 1129/2011 of 11 November 2011 amending Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02008R1333-20140414&from=DE There is no ADI for elemental silver (**E174**, typing error in the cited source, Hagers Handbuch, below) due to the fact that elemental silver is insoluble and only toxic after intake in the gram-range. See Hagers Handbuch 1995 Folgeband 1; S. 80	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
		Silber E 175 Dieses Pigment wird in Form des reinen Metalls in sehr geringen Mengen verwendet. Silber kann vom Darm resorbiert und in Geweben abgelagert werden. Vergiftungen treten erst nach Verzehr von Grammengen auf. Die Zulassung ist auf Oberflächen- und dekorative Färbung beschränkt. Die Toxikologie der Silbersalze ist für die Bewertung dieser Farbstoffanwendung nicht relevant. Wegen der Unlöslichkeit bestehen weder toxikologische noch gesundheitliche Bedenken[9, 29, 45] (→ Bd. 7, 293). The resorption of elemental silver is not comparable with the resorption of Ag^+, therefore an ADI for elemental Ag, calculated on base of oral intake of silver nitrate is not applicable. Due to the fact there is no ADI for elemental silver in food, the WHO value for drinking water can be used: See: http://www.who.int/water_sanitation_health/dwq/chemicals/silver.pdf On the basis of present epidemiological and pharmacokinetic knowledge, a total lifetime oral intake of about 10 g of silver can be considered as the human NOAEL. As the contribution of drinking-water to this NOAEL will normally be negligible, the establishment of a health-based guideline value is not deemed necessary. On the other hand, special situations may exist where silver salts are used to maintain the bacteriological quality of drinking-water. Higher levels of silver, up to 0.1 mg/litre (a concentration that gives a total dose over 70 years of half the human NOAEL of 10 g), could then be tolerated without risk to health. In drinking water 0.1 mg Ag/l is allowed (WHO 2006), this results in 0.2 mg/day (2 litre drinking water). This is consistent with the BfR-value of 0.08 mg/l and the assumed intake of 2 l water per day as well as the value of 0.08 mg/l of the German Zusatzsstoff-Zulassungsverordnung.	

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Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
		(https://www.gesetze-im-internet.de/zzulv_1998/anlage_6a.html http://www.bfr.bund.de/cm/343/bfr_raet_von_nanosilber_in_lebensmitteln_und_produkten_des_taeglichen_bedarfs_ab.pdf)	
Argentum metallicum Ag HAB	ECH	**We do not agree with the derivation of the FSD D7 for Argentum metallicum.** Rationale: According to the PtC decision tree substances which are constituents of food have to be assesses according the limit values from the food sector. Elemental silver is used in the food sector for coloring of food (E174); e.g. decoration of sweets, pralines and liquors; quantum satis References: German Zusatzstoff-Zulassungsverordnung: https://www.gesetze-im-internet.de/bundesrecht/zzulv_1998/gesamt.pdf or Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02008R1333-20140414&from=DE and Commission Regulation (EU) No 1129/2011 of 11 November 2011 amending Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02008R1333-20140414&from=DE There is no ADI for elemental silver (E174) due to the fact that elemental silver is insoluble and only toxic after intake in the gram-range. References: Hagers Handbuch 1995 Folgeband 1; S. 80 (Attachement) The resorption of elemental silver is not comparable with the resorption of Ag^+, therefore an ADI for elemental Ag, calculated on base of oral intake of silver nitrate is not applicable.	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
		Due to the fact there is no ADI for elemental silver in food, the WHO value for drinking water can be used: See: http://www.who.int/water_sanitation_health/dwq/chemicals/silver.pdf On the basis of present epidemiological and pharmacokinetic knowledge, a total lifetime oral intake of about 10 g of silver can be considered as the human NOAEL. As the contribution of drinking-water to this NOAEL will normally be negligible, the establishment of a health-based guideline value is not deemed necessary. On the other hand, special situations may exist where silver salts are used to maintain the bacteriological quality of drinking-water. Higher levels of silver, up to 0.1 mg/litre (a concentration that gives a total dose over 70 years of half the human NOAEL of 10 g), could then be tolerated without risk to health. In drinking water 0.1 mg Ag/l is allowed (WHO 2006), this results in 0.2 mg/day (2 litre drinking water). This is consistent with the BfR-value of 0.08 mg/l and the assumed intake of 2 l water per day as well as the value of 0.08 mg/l of the German Zusatzstoff-Zulassungsverordnung. (https://www.gesetze-im-internet.de/zzulv_1998/anlage_6a.html http://www.bfr.bund.de/cm/343/bfr_raet_von_nanosilber_in_lebensmitteln_und_produkten_des_taeglichen_bedarfs_ab.pdf) Allowed would be at least 160 µg/ d (BfR value) for all groups including neonates 10 g D5 = 106 µg Ag; **FSD = D5**	
Argentum metallicum Ag FP	ECH	**We do not agree with the derivation of the FSD D7 for Argentum metallicum.** Rationale: Comments see under Argentum metallicum Ag (HAB) Allowed would be at least 160 µg/ d (BfR value) for all groups including neonates 10 g D5 = 100,5 µg Ag; **FSD = D5**	
Argentum	ECHAMP	No weight adjustment necessary	

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Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
metallicum Ag HAB		PDE = 167 µg Ag/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 106 µg Ag > **FSD = D5** According to the PtC decision tree substances allowed as food or constituents of food have to be assessed according to the limit values from the food sector. In drinking water are 0.1 mg Ag/l allowed (WHO 2006), this are 0.2 mg/day (2 litre drinking water). 10 g D5 = 106 µg Ag > **FSD = D5**	
Argentum metallicum Ag HAB/ Ph. Franc.	*ECHAMP*	According to the PtC decision tree substances which are constituents of food have to be assesses according the limit values from the food sector. Elemental silver is used in the food sector for coloring of food (E174); e.g. decoration of sweets, pralines and liquors; quantum satis See German Zusatzstoff-Zulassungsverordnung: https://www.gesetze-im-internet.de/bundesrecht/zzulv_1998/gesamt.pdf or Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02008R1333-20140414&from=DE and Commission Regulation (EU) No 1129/2011 of 11 November 2011 amending Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02008R1333-20140414&from=DE There is no ADI for elemental silver (E174) due to the fact that elemental silver is insoluble and only toxic after intake in the gram-range. See Hagers Handbuch 1995 Folgeband 1; S. 80	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
		Silber E 175 Dieses Pigment wird in Form des reinen Metalls in sehr geringen Mengen verwendet. Silber kann vom Darm resorbiert und in Geweben abgelagert werden. Vergiftungen treten erst nach Verzehr von Grammengen auf. Die Zulassung ist auf Oberflächen- und dekorative Färbung beschränkt. Die Toxikologie der Silbersalze ist für die Bewertung dieser Farbstoffanwendung nicht relevant. Wegen der Unlöslichkeit bestehen weder toxikologische noch gesundheitliche Bedenken[9, 29, 45] (→ Bd. 7, 293). (Remark: "E 175" is a mistake in the cited literature source. Silver is E 174!) The resorption of elemental silver is not comparable with the resorption of Ag^+, therefore an ADI for elemental Ag, calculated on base of oral intake of silver nitrate is not applicable. Due to the fact there is no ADI for elemental silver in food, the WHO value for drinking water can be used: See: http://www.who.int/water_sanitation_health/dwq/chemicals/silver.pdf On the basis of present epidemiological and pharmacokinetic knowledge, a total lifetime oral intake of about 10 g of silver can be considered as the human NOAEL. As the contribution of drinking-water to this NOAEL will normally be negligible, the establishment of a health-based guideline value is not deemed necessary. On the other hand, special situations may exist where silver salts are used to maintain the bacteriological quality of drinking-water. Higher levels of silver, up to 0.1 mg/litre (a concentration that gives a total dose over 70 years of half the human NOAEL of 10 g), could then be tolerated without risk to health. In drinking water 0.1 mg Ag/l is allowed (WHO 2006), this results in 0.2 mg/day (2 litre drinking water). This is consistent with the BfR-value of 0.08 mg/l and the assumed	

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Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
		intake of 2 l water per day as well as the value of 0.08 mg/l of the German Zusatzstoff-Zulassungsverordnung. (https://www.gesetze-im-internet.de/zzulv_1998/anlage_6a.html http://www.bfr.bund.de/cm/343/bfr_raet_von_nanosilber_in_lebensmitteln_und_produkten_des_taeglichen_bedarfs_ab.pdf) 10 g D5 = 106 µg Ag(HAB); **FSD = D5** 10 g D5 = 100,5 µg Ag(Ph. Franc.); **FSD = D5**	
Argentum metallicum Ag Ph.Franç.	*ECHAMP*	No weight adjustment necessary PDE = 167 µg Ag/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 100.5 µg Ag > **FSD = D5**	
Argentum nitricum $AgNO_3$ HAB	AESGP	No weight adjustment necessary. PDE = 167 µg Ag/day (for all patient populations according to ICH guideline Q3D on elemental impurities) ADI for nitrate = 3.7 mg/kg b.w., expressed as nitrate ion (according to WHO Food Additives Series: 50 nitrate) 10 g D5 = 67.3 µg Ag and 38.7 µg nitrate > **FSD = D5**	**Not agreed.** See answer to comment on Argentum colloidale.
Argentum nitricum $AgNO_3$ Ph.Franç.	AESGP	No weight adjustment necessary. PDE = 167 µg Ag/day (for all patient populations according to ICH guideline Q3D on elemental impurities) ADI for nitrate = 3.7 mg nitrate/kg b.w., expressed as nitrate ion (according to WHO Food Additives Series: 50 nitrate) 10 g D5 = 63.8 µg A and 36.7 µg nitrate > **FSD = D5**	
Argentum nitricum $AgNO_3$ HAB/ FP	BPI e.V.	No weight adjustment necessary PDE = 167 µg Ag/day (for all patient populations according to ICH guideline Q3D on elemental impurities) ADI for nitrate = 3.7 mg/kg b.w., expressed as nitrate ion (according to	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
		WHO Food Additives Series: 50 nitrate) 10 g D5 = 67.3 µg Ag and 38.7 µg nitrate (HAB)> **FSD = D5** 10 g D5 = 63.8 µg A and 36.7 µg nitrate (FP) > **FSD = D5** According to the PtC decision tree substances which are constituents of food have to be assessed according the limit values from the food sector. Silver ions (including silver nitrate) are used for disinfection of drinking water. In drinking water 0.1 mg Ag/l is allowed (WHO 2006), this results in 0.2 mg/day (2 litre drinking water). This is consistent with the BfR-value of 0.08 mg/l (intake of 2 litre drinking water per day) and the value of 0.08 mg/l of the German Additive Regulation (Zusatzsstoff-Zulassungsverordnung (Anlage 6a (zu § 6a); Zusatzstoffe, die für Trinkwasser zugelassen sind) (https://www.gesetze-im-internet.de/zzulv_1998/anlage_6a.html http://www.bfr.bund.de/cm/343/bfr_raet_von_nanosilber_in_lebensmitteln_und_produkten_des_taeglichen_bedarfs_ab.pdf) The amount of 2 litre drinking water applies to all age groups; this is also in line with the calculation of PDE/ FSD for Barium (see Q3D Guideline: Summary of PDE for Barium)	
Argentum nitricum $AgNO_3$ HAB	ECH	**We do not agree with the derivation of the FSD D6 for Argentum nitricum.** Rationale: According to the PtC decision tree substances which are constituents of food have to be assessed according the limit values from the food sector. Silver ions (including silver nitrate) are used for disinfection of drinking water. In drinking water 0.1 mg Ag/l is allowed (WHO 2006), this results in 0.2 mg/day (2 litre drinking water). This is in line with the BfR-value of 0.08 mg/l (intake of 2 litre drinking water per day) and the value of 0.08 mg/l of the German Additive Regulation (Zusatzstoff-Zulassungsverordnung (Anlage 6a (zu § 6a);	

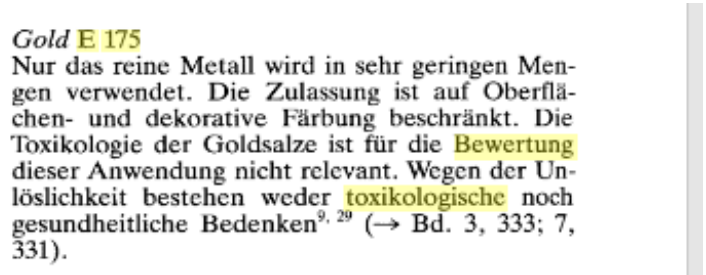
SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
		Zusatzstoffe, die für Trinkwasser zugelassen sind) (https://www.gesetze-im-internet.de/zzulv_1998/anlage_6a.html The amount of 2 litre drinking water applies to all age groups. (This is in line with the calculation of PDE for Barium Salts; see Guideline for Elemental impurities; Summary of PDE for Barium; No weight adaption) Allowed would be at least 160 µg/ d (BfR value) for all groups including neonates 10 g D5 = 67,3 µg Ag; **FSD = D5**	
Argentum nitricum $AgNO_3$ FP	ECH	**We do not agree with the derivation of the FSD D6 for Argentum nitricum**. Rationale: Comments see under Argentum nitricum Ag NO_3 (HAB) Allowed would be at least 160 µg/ d (BfR value) for all groups including neonates 10 g D5 = 63,8 µg Ag; **FSD = D5**	
Argentum nitricum $AgNO_3$ HAB	*ECHAMP*	No weight adjustment necessary PDE = 167 µg Ag/day (for all patient populations according to ICH guideline Q3D on elemental impurities) ADI for nitrate = 3.7 mg/kg b.w., expressed as nitrate ion (according to WHO Food Additives Series: 50 nitrate) 10 g D5 = 67.3 µg Ag and 38.7 µg nitrate > **FSD = D5** According to the PtC decision tree substances which are constituents of food have to be assessed according the limit values from the food sector. Silver ions (including silver nitrate) are used for disinfection of drinking water. In drinking water 0.1 mg Ag/l is allowed (WHO 2006), this results in 0.2 mg/day (2 litre drinking water). This is consistent with the BfR-value of 0.08 mg/l (intake of 2 litre drinking water per day) and the value of 0.08 mg/l of the German Additive Regulation (Zusatzstoff-Zulassungsverordnung (Anlage 6a (zu	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
		§ 6a); Zusatzstoffe, die für Trinkwasser zugelassen sind) (https://www.gesetze-im-internet.de/zzulv_1998/anlage_6a.html http://www.bfr.bund.de/cm/343/bfr_raet_von_nanosilber_in_lebensmitteln_und_produkten_des_taeglichen_bedarfs_ab.pdf) The amount of 2 litre drinking water applies to all age groups; this is also in line with the calculation of PDE/ FSD for Barium (see Q3D Guideline: Summary of PDE for Barium) 10 g D5 = 67,3 µg Ag; **FSD = D5**	
Argentum nitricum $AgNO_3$ Ph.Franç.	*ECHAMP*	No weight adjustment necessary PDE = 167 µg Ag/day (for all patient populations according to ICH guideline Q3D on elemental impurities) ADI for nitrate = 3.7 mg nitrate/kg b.w., expressed as nitrate ion (according to WHO Food Additives Series: 50 nitrate) 10 g D5 = 63.8 µg Ag and 36.7 µg nitrate > **FSD = D5**	
Auri solutio colloidalis Au HAB	AESGP	No weight adjustment necessary. PDE = 134 µg Au/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 51 µg Au > **FSD = D5** The oral FSD mentioned by the ICH Q3D on elemental impurities, is derived from a study with a differing route of administration and with a differing oxidation state of Au. In contrast, a 2 year pilot study in humans with colloidal gold is available showing no toxicity (Abraham, 1997) with a PDE = 30 mg gold/day (adults 50 kg b.w.) PDE/100= 6 µg/kg bw/day in all age groups with 18 µg Au/day in neonates (3 kg b.w.) 10 g D6 = 10.5 µg gold > **FSD = D6**	**(Partly) agreed.** Assessment based on POD from clinical study [GUY E. ABRAHAM PETER B. HIMMEL (1997) Management of Rheumatoid Arthritis: Rationale for the Use of Colloidal Metallic Gold, Journal of Nutritional & Environmental Medicine, 7:4, 295-305]: LHRD 30 mg/day (24 weeks, human study, no clinical evidence of toxicity in patients): LHRD/100 = 0,3 mg/d LHRD/100:60 kg bw = 5 µg/kg = 15 µg/neonate/d (present list entry “10 g D7 = 1.05 µg Au” → would change to suggested list entry “10 g D6 = 10.5 µg Au”) We would like to remark that the study duration is 24 weeks (30 mg/d) instead of the 2 years cited by AESGP.

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
Auri solutio colloidalis Au HAB	BPI e.V.	No weight adjustment necessary PDE = 134 Au/day (for all patient populations according to ICH guideline Q3D on elemental impurities)	
Auri solutio colloidalis Au HAB	ECH	**We do not agree with the derivation of the FSD D7 for Auri solution colloidalis.** Rationale: The basis for FSD derivation is an animal study in mice with intraperitoneally applied Au(3+). As mentioned by the ICH Q3D on elemental impurities, the toxicity of Au(3+) is thought to be higher in comparison to the here discussed colloidal metallic gold (Au). The oral FSD is thus derived from a study with a differing route of administration and with a differing oxidation state of Au. In contrast, a 2 year pilot study in humans with colloidal gold is available showing no toxicity (Abraham, 1997). Using the more relevant human oral study for derivation of a FSD this would result in the following PDE-calculation: PDE = 30 mg gold/day / uncertainty factors (F1-F5 = 1 x 10 x 10 x 1 x 1) = 30 mg gold/day / 100 = 300 µg gold/day = **6 µg/kg bw/day** F1 = 1 for human data F2 = 10 A factor to account for variability between individuals F3 = 10 A factor to account for less than lifetime exposure F4 = 1 No toxicity was observed in the study F5 = 1 Because a NOAEL was used Thus, the acceptable amount for neonates with 3 kg bw is **18 µg gold/day.** Considering the maximum daily dose of 10 g of a homeopathic product;	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
		10.5 µg gold are contained in 10 g D6 Auri solutio colloidalis and are thus below the acceptable amount for neonates. **FSD = D6** References Abraham GE, Himmel PB. Management of rheumatoid arthritis: rationale for the use of colloidal metallic gold. J Nutr Environ Med 1997;7:295-305.	
Auri solutio colloidalis Au HAB	*ECHAMP*	No weight adjustment necessary PDE = 134 µg Au/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 51 µg Au > **FSD = D5**	
Aurum chloratum $H[AuCl_4] \cdot 3\ H_2O$ HAB	AESGP	No weight adjustment necessary. PDE = 134 µg Au/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 51 µg Au > **FSD = D5** Please add the French homeopathic traditional name: Aurum muriaticum	**Not agreed.** See answer to the second comment from AESGP under general comments. The French homeopathic traditional name “Aurum muriaticum” is included under the column “remarks”.
Aurum chloratum $H[AuCl_4] \cdot 3\ H_2O$ HAB	BPI e.V.	No weight adjustment necessary PDE = 134 µg Au/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 51 µg Au > **FSD = D5**	
Aurum chloratum $H[AuCl_4] \cdot 3\ H_2O$ HAB	*ECHAMP*	No weight adjustment necessary PDE = 134 µg Au/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 51 µg Au > **FSD = D5**	
Aurum metallicum	AESGP	No weight adjustment necessary. PDE = 134 µg Au/day (for all patient populations according to ICH	**Partly agreed.** Due to the current evaluation of the EFSA in 2016 [EFSA

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
Au HAB		guideline Q3D on elemental impurities) 10 g D5 = 105 µg Au > **FSD = D5**	Journal 2016; 14(1):4362: Scientific Opinion on the re-evaluation of gold (E 175) as a food additive: "… The Panel concluded that, despite the absence of toxicity data, but taking into account the low solubility of elemental gold, systemic availability and thus systemic effects of elemental gold would not be expected. .."] the following FSD is determined: **FSD = D1** (the first possible homeopathic preparation according to the monograph) **10 g D1 = 1050 mg Au**
Aurum metallicum Au Ph.Franç.	AESGP	No weight adjustment necessary. PDE = 134 µg Au/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 101 µg Au > **FSD = D5**	
Aurum metallicum Au HAB/ FP	BPI e.V.	No weight adjustment necessary PDE = 134 µg Au/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 105 µg Au (HAB) > **FSD = D5** 10 g D5 = 101 µg Au (FP) > **FSD = D5** Elementary gold is used in the food sector for coloring of food (E175); e.g. decoration of sweets, pralines and liquors; quantum satis Addition regarding "quantum satis": See German Zusatzsstoff-Zulassungsverordnung: https://www.gesetze-im-internet.de/bundesrecht/zzulv_1998/gesamt.pdf or Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02008R1333-20140414&from=DE and Commission Regulation (EU) No 1129/2011 of 11 November 2011 amending Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02008R1333-20140414&from=DE	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
		According to manufacturers the addition of about 0.05g (50 mg) of gold (E 175; 22-23 Karat) per bottle of liquid (liqueur, sparkling wine) is recommended to get a good result. Hagers Handbuch 1995 Folgeband 1; S. 80 The toxicology of gold salts is not relevant for the assessment of elemental gold. Because of the insolubility there are neither toxicological nor health concerns concerning elementary gold.  *Gold* E 175 Nur das reine Metall wird in sehr geringen Mengen verwendet. Die Zulassung ist auf Oberflächen- und dekorative Färbung beschränkt. Die Toxikologie der Goldsalze ist für die Bewertung dieser Anwendung nicht relevant. Wegen der Unlöslichkeit bestehen weder toxikologische noch gesundheitliche Bedenken[9, 29] (→ Bd. 3, 333; 7, 331). "Elemental gold is poorly absorbed and consequently is not considered as biologically active" (ICH guideline Q3D on elemental impurities) Therefore a PDE for Au^{3+}, calculated on base of parenteral (intraperitoneal) application is not applicable for the calculation of FSD for the oral intake of elemental gold. This is contrary the principles of the factors considered in the safety assessment for establishing the PDE: - The likely oxidation state of the element in the drug product - Route of administration (Guideline for Elemental impurities; 3.1. Principles of the Safety Assessment of Elemental Impurities for Oral, Parenteral and Inhalation Routes of Administration; Page 2) Due to the fact, that elemental gold is insoluble, poorly absorbed and used in food, Article 14 of 2001/83 EC subparagraph 1 should be used for	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
		calculation of FSD: - there is a sufficient degree of dilution to guarantee the safety of the medicinal product; in particular, the medicinal product may not contain either more than one part per 10 000 of the mother tincture or more than 1/100th of the smallest dose used in allopathy with regard to active substances whose presence in an allopathic medicinal product results in the obligation to submit a doctor's prescription.	
Aurum metallicum Au HAB	ECH	**We do not agree with the derivation of the FSD D7 for Aurum metallicum.** Rationale: The basis for FSD derivation for elemental Gold is an animal study in mice with intraperitoneally applied Au^{3+}. This is contrary the principles of the factors considered in the safety assessment for establishing the PDE: - The likely oxidation state of the element in the drug product (The toxicity of Au^{3+} is not comparable with Au(o)) - Route of administration (Guideline for Elemental impurities; 3.1. Principles of the Safety Assessment of Elemental Impurities for Oral, Parenteral and Inhalation Routes of Administration; Page 2) “Elemental gold is poorly absorbed and consequently is not considered as biologically active” (ICH guideline Q3D on elemental impurities) According to the PtC decision tree substances which are constituents of food have to be assesses according the limit values from the food sector.	

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Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
		Elementary gold is used in the food sector for coloring of food (E175); e.g. decoration of sweets, pralines and liquors; quantum satis References: German Zusatzstoff-Zulassungsverordnung: https://www.gesetze-im-internet.de/bundesrecht/zzulv_1998/gesamt.pdf or Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02008R1333-20140414&from=DE and Commission Regulation (EU) No 1129/2011 of 11 November 2011 amending Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02008R1333-20140414&from=DE Hagers Handbuch 1995 Folgeband 1; S. 80 (see attachement) *Gold* E 175 Nur das reine Metall wird in sehr geringen Mengen verwendet. Die Zulassung ist auf Oberflächen- und dekorative Färbung beschränkt. Die Toxikologie der Goldsalze ist für die Bewertung dieser Anwendung nicht relevant. Wegen der Unlöslichkeit bestehen weder toxikologische noch gesundheitliche Bedenken[9, 29] (→ Bd. 3, 333; 7, 331). The toxicology of gold salts is not relevant for the assessment of elemental gold. Because of the insolubility there are neither toxicological nor health concerns concerning elementary gold.	

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Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
		Therefore there are no limit values for usage of elemental gold (E 175) in food. Addition regarding “quantum satis”: According to manufacturers the addition of about 0.05g (50 mg) of gold (E 175; 22-23 Karat) per bottle of liquid (liqueur, sparkling wine) is recommended to get a good result. The exact content of gold is not declared. Own experiments with 8 bottles of “Sekt Gold Cuvee von Goldhand” (Mixture of Sparkling wine with gold liqueur) showed an average content of 20 mg gold (22-23 Karat) per 200 ml bottle. Due to the fact, that elemental gold is insoluble, poorly absorbed and used in food, Article 14 of 2001/83 EC subparagraph 1 should be used for deriviation of FSD: - there is a sufficient degree of dilution to guarantee the safety of the medicinal product; in particular, the medicinal product may not contain either more than one part per 10 000 of the mother tincture or more than 1/100th of the smallest dose used in allopathy with regard to active substances whose presence in an allopathic medicinal product results in the obligation to submit a doctor's prescription. **FSD = D4; 10 g D4 contain 1,05 mg Au** This value is less (factor more than 1 :10) than some amounts usually used for coloring of food (example sparkling wine).	
Aurum metallicum Au	ECH	**We do not agree with the derivation of the FSD D7 for Aurum metallicum.** Rationale:	

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Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
FP		Comments see under Aurum metallicum Au (HAB) **FSD = D4; 10 g D4 contain 1,01 mg Au**	
Aurum metallicum Au HAB	*ECHAMP*	No weight adjustment necessary PDE = 134 µg Au/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 105 µg Au > **FSD = D5**	
Aurum metallicum Au HAB/ Ph. Franc.	*ECHAMP*	Elementary gold is used in the food sector for coloring of food (E175); e.g. decoration of sweets, pralines and liquors; quantum satis Addition regarding "quantum satis": See German Zusatzstoff-Zulassungsverordnung: https://www.gesetze-im-internet.de/bundesrecht/zzulv_1998/gesamt.pdf or Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02008R1333-20140414&from=DE and Commission Regulation (EU) No 1129/2011 of 11 November 2011 amending Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02008R1333-20140414&from=DE According to manufacturers the addition of about 0.05g (50 mg) of gold (E 175; 22-23 Karat) per bottle of liquid (liqueur, sparkling wine) is recommended to get a good result. Hagers Handbuch 1995 Folgeband 1; S. 80 The toxicology of gold salts is not relevant for the assessment of elemental gold. Because of the insolubility there are neither toxicological	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
		nor health concerns concerning elementary gold. *Gold* E 175 Nur das reine Metall wird in sehr geringen Mengen verwendet. Die Zulassung ist auf Oberflächen- und dekorative Färbung beschränkt. Die Toxikologie der Goldsalze ist für die Bewertung dieser Anwendung nicht relevant. Wegen der Unlöslichkeit bestehen weder toxikologische noch gesundheitliche Bedenken[9, 29] (→ Bd. 3, 333; 7, 331). "Elemental gold is poorly absorbed and consequently is not considered as biologically active" (ICH guideline Q3D on elemental impurities) Therefore a PDE for Au^{3+}, calculated on base of parenteral (intraperitoneal) application is not applicable for the calculation of FSD for the oral intake of elemental gold. This is contrary the principles of the factors considered in the safety assessment for establishing the PDE: - The likely oxidation state of the element in the drug product - Route of administration (Guideline for Elemental impurities; 3.1. Principles of the Safety Assessment of Elemental Impurities for Oral, Parenteral and Inhalation Routes of Administration; Page 2) Due to the fact, that elemental gold is insoluble, poorly absorbed and used in food, Article 14 of 2001/83 EC subparagraph 1 should be used for calculation of FSD:	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
		- there is a sufficient degree of dilution to guarantee the safety of the medicinal product; in particular, the medicinal product may not contain either more than one part per 10 000 of the mother tincture or more than 1/100th of the smallest dose used in allopathy with regard to active substances whose presence in an allopathic medicinal product results in the obligation to submit a doctor's prescription. **FSD = D4;** **10 g D4 contain 1,05 mg Au (HAB) or 1,01 mg (Ph. Franc.)**	
Aurum metallicum Au Ph.Franç.	*ECHAMP*	No weight adjustment necessary PDE = 134 µg Au/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 101 µg Au > **FSD = D5**	
Barium chloratum BaCl2 · 2H2O HAB/Ph. Eur.	AESGP	Please add the French homeopathic traditional name: Baryta muriatica	**Agreed.** The French homeopathic traditional name “Baryta muriatica” is included under the column “remarks”.
Cadmium sulfuricum $CdSO_4$ * 8/3 H_2O Ph.Eur. / HAB	AESGP	No weight adjustment necessary. PDE = 5 µg Cd/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D6 = 4.69 µg Cd > **FSD = D6**	**Not agreed.** See answer to the second comment from AESGP under general comments.

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
Cadmium sulfuricum $CdSO_4 \cdot 8/3\ H_2O$ Ph.Eur. / HAB	BPI e.V.	No weight adjustment necessary PDE = 5 µg Cd/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D6 = 4.69 µg Cd > **FSD = D6**	
Cadmium sulfuricum $CdSO_4 \cdot 8/3\ H_2O$ Ph.Eur. / HAB	*ECHAMP*	No weight adjustment necessary PDE = 5 µg Cd/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D6 = 4.69 µg Cd > **FSD = D6**	
Calcium stibiato-sulfuratum HAB	AESGP	No weight adjustment necessary. PDE = 1200 µg Sb/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D3 = 1200 µg Sb/day > **FSD = D3** Please add the French homeopathic traditional name: Calcarea sulfurata stibiata	**Not agreed.** See answer to the second comment from AESGP under general comments and to the comments on Antimonite. The French homeopathic traditional name “Calcarea sulfurata” is included under the column “remarks”.
Calcium stibiato-sulfuratum HAB	BPI e.V.	No weight adjustment necessary PDE = 1200 µg Sb/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D3 = 1200 µg Sb/day > **FSD = D3**	
Calcium stibiato-sulfuratum HAB	*ECHAMP*	No weight adjustment necessary PDE = 1200 µg Sb/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D3 = 1200 µg Sb/day > **FSD = D3**	
Chalcosine Cu_2S	AESGP	No weight adjustment necessary. PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities)	See answer to the second comment from AESGP under general comments. **Partly agreed.**

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
HAB		10 g D4 = 798.4 µg Cu > **FSD = D4** Please add the French homeopathic traditional name: Cuprum sulfuratum	The evaluation based on food regulation is possible for copper, as recommendations for the daily intake for infants exist: In "Nutrient requirements and dietary intakes of infants and young children in the EU" EFSA Journal 2013; 11(10):3408, the intake of 0.3 mg copper/day is deemed adequate for the majority of infants in the first half-year of life. If 300 µg/day are taken as acceptable amount, the FSD for Chalcosine still will be D5 (10 g Chalcosine D5 = 79.84 µg Cu). The French homeopathic traditional name "Cuprum sulfuratum" is included under the column "remarks".
Chalcosine Cu_2S HAB	BPI e.V.	No weight adjustment necessary PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 798.4 µg Cu > **FSD = D4**	
Chalcosine Cu_2S HAB	ECHAMP	No weight adjustment necessary PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 798.4 µg Cu > FSD = D4	
Chininum arsenicosum $C_{20}H_{24}N_2O_2$ + As_2O_3 HAB	AESGP	No weight adjustment necessary. PDE = 15 µg As/day (for all patient populations according to ICH guideline Q3D on elemental impurities) LHRD quinine = 81 mg quinine/day (neonate) 10 g D5 = 7.5 µg As and 97 µg quinine > **FSD = D5**	**Not agreed.** See answer to the second comment from AESGP under general comments.
Chininum arsenicosum $C_{20}H_{24}N_2O_2$ + As_2O_3 HAB	BPI e.V.	No weight adjustment necessary PDE = 15 µg As/day (for all patient populations according to ICH guideline Q3D on elemental impurities) LHRD quinine = 81 mg quinine/day (neonate) 10 g D5 = 7.5 µg As and 97 µg quinine > **FSD = D5**	
Chininum arsenicosum $C_{20}H_{24}N_2O_2$ + As_2O_3 HAB	*ECHAMP*	No weight adjustment necessary PDE = 15 µg As/day (for all patient populations according to ICH guideline Q3D on elemental impurities) LHRD quinine = 81 mg quinine/day (neonate)	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
		10 g D5 = 7.5 µg As and 97 µg quinine > **FSD = D5**	
Cobaltum metallicum Co HAB	AESGP	No weight adjustment necessary. PDE = 50 µg Co/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D6 = 10.6 µg Co > **FSD = D6**	**Not agreed.** See answer to the second comment from AESGP under general comments.
Cobaltum metallicum Co HAB	BPI e.V.	No weight adjustment necessary PDE = 50 µg Co/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D6 = 10.6 µg Co > **FSD = D6**	
Cobaltum metallicum Co HAB	*ECHAMP*	No weight adjustment necessary PDE = 50 µg Co/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D6 = 10.6 µg Co > **FSD = D6**	
Cuprite Cu_2O HAB	AESGP	No weight adjustment necessary. PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 932.6 µg Cu > **FSD = D4**	See answer to the second comment from AESGP under general comments. **Partly agreed.** The evaluation based on food regulation is possible for copper, as recommendations for the daily intake for infants exist: In “Nutrient requirements and dietary intakes of infants and young children in the EU” EFSA Journal 2013; 11(10):3408, the intake of 0.3 mg copper/day is deemed adequate for the majority of infants in the first half-year of life. If 300 µg/day are taken as acceptable amount, the FSD for Cuprite still will be D5 (10 g Cuprite D5 = 93.26 µg Cu).
Cuprite Cu_2O HAB	BPI e.V.	No weight adjustment necessary PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 932.6 µg Cu > **FSD = D4**	
Cuprite Cu_2O HAB	*ECHAMP*	No weight adjustment necessary PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities)	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
		10 g D4 = 932.6 µg Cu > **FSD = D4**	
Cuprum aceticum $Cu[C_2H_3O_2]_2 \cdot H_2O$ Ph. Eur. / HAB	AESGP	No weight adjustment necessary. PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D3 = 3373 µg Cu > **FSD = D3** According to the PtC decision tree substances allowed as food or constituents of food have to be assessed according to the limit values from the food sector. In drinking water are 2 mg Cu/l allowed (98/83/EC; TWVO 2001; WHO 2006), this are 4 mg/day (2 litre drinking water). 10 g D3 = 3.4 mg Cu > **FSD = D3**	See answer to the second comment from AESGP under general comments. Concerning the approach of assessment see answer on third comment from AESGP under general comments. **Partly agreed.** The evaluation based on food regulation is possible for copper, as recommendations for the daily intake for infants exist: In "Nutrient requirements and dietary intakes of infants and young children in the EU" EFSA Journal 2013; 11(10):3408, the intake of 0.3 mg copper/day is deemed adequate for the majority of infants in the first half-year of life. If 300 µg/day are taken as acceptable amount, the FSD for Cuprum aceticum still will be D5 (10 g Cuprum aceticum D5 = 33.73 µg Cu).
Cuprum aceticum $Cu[C_2H_3O_2]_2 \cdot H_2O$ Ph. Eur. / HAB	BPI e.V.	No weight adjustment necessary PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D3 = 3373 µg Cu > **FSD = D3** Please add the Pharmacopoeia According to the PtC decision tree substances allowed as food or constituents of food have to be assessed according to the limit values from the food sector. In drinking water are 2 mg Cu/l allowed (98/83/EC; TWVO 2001; WHO 2006), this are 4 mg/day (2 litre drinking water).	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
Cuprum aceticum $Cu[C_2H_3O_2]_2 \cdot H_2O$ Ph. Eur. / HAB	*ECHAMP*	No weight adjustment necessary PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D3 = 3373 µg Cu > **FSD = D3** According to the PtC decision tree substances allowed as food or constituents of food have to be assessed according to the limit values from the food sector. In drinking water are 2 mg Cu/l allowed (98/83/EC; TWVO 2001; WHO 2006), this are 4 mg/day (2 litre drinking water). 10 g D3 = 3.4 mg Cu > **FSD = D3**	
Cuprum arsenicosum HAB	AESGP	No weight adjustment necessary. PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities) PDE = 15 µg As/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D6 = 4.3 µg Cu and 3.4 µg As > **FSD = D6**	**Not agreed.** See answer to the second comment from AESGP under general comments.
Cuprum arsenicosum HAB	BPI e.V.	No weight adjustment necessary PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities) PDE = 15 µg As/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D6 = 4.3 µg Cu and 3.4 µg As > **FSD = D6**	
Cuprum arsenicosum HAB	*ECHAMP*	No weight adjustment necessary PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities) PDE = 15 µg As/day (for all patient populations according to ICH guideline Q3D on elemental impurities)	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
		10 g D6 = 4.3 µg Cu and 3.4 µg As > **FSD = D6**	
Cuprum metallicum Cu Ph.Eur. / HAB	AESGP	No weight adjustment necessary. PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 1050 µg Cu > **FSD = D4**	See answer to the second comment from AESGP under general comments. Concerning the approach of assessment see answer on third comment from AESGP under general comments. **Partly agreed.** The evaluation based on food regulation is possible for copper, as recommendations for the daily intake for infants exist: In "Nutrient requirements and dietary intakes of infants and young children in the EU" EFSA Journal 2013; 11(10):3408, the intake of 0.3 mg copper/day is deemed adequate for the majority of infants in the first half-year of life. If 300 µg/day are taken as acceptable amount, the FSD for Cuprum metallicum still will be D5 (10 g Cuprum metallicum D5 = 105.0 µg Cu).
Cuprum metallicum Cu Ph.Eur. / HAB	BPI e.V.	No weight adjustment necessary PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 1050 µg Cu > **FSD = D4** According to the PtC decision tree substances allowed as food or constituents of food have to be assessed according to the limit values from the food sector. In drinking water 2 mg Cu/l are allowed (98/83/EC; TWVO 2001; WHO 2006), this are 4 mg/day (2 litre drinking water).	
Cuprum metallicum Cu Ph. Eur. / HAB	*ECHAMP*	No weight adjustment necessary PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 1050 µg Cu > **FSD = D4** According to the PtC decision tree substances allowed as food or constituents of food have to be assessed according to the limit values from the food sector. In drinking water 2 mg Cu/l are allowed (98/83/EC; TWVO 2001; WHO 2006), this are 4 mg/day (2 litre drinking water). 10 g D4 = 1,05 mg Cu; **FSD =D4**	
Cuprum oxydatum	AESGP	No weight adjustment necessary. PDE = 3400 µg Cu/day (for all patient populations according to ICH	See answer to the second comment from AESGP under general comments.

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
nigrum CuO HAB		guideline Q3D on elemental impurities) 10 g D4 = 846.7 µg Cu > **FSD = D4**	Concerning the approach of assessment see answer on third comment from AESGP under general comments. **Partly agreed.** The evaluation based on food regulation is possible for copper, as recommendations for the daily intake for infants exist: In "Nutrient requirements and dietary intakes of infants and young children in the EU" EFSA Journal 2013; 11(10):3408, the intake of 0.3 mg copper/day is deemed adequate for the majority of infants in the first half-year of life. If 300 µg/day are taken as acceptable amount, the FSD for Cuprum oxydatum nigrum still will be D5 (10 g Cuprum oxydatum nigrum D5 = 33.73 µg Cu).
Cuprum oxydatum nigrum CuO HAB	BPI e.V.	No weight adjustment necessary PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 846.7 µg Cu > **FSD = D4** According to the PtC decision tree substances allowed as food or constituents of food have to be assessed according to the limit values from the food sector. In drinking water 2 mg Cu/l are allowed (98/83/EC; TWVO 2001; WHO 2006), this are 4 mg/day (2 litre drinking water).	
Cuprum oxydatum nigrum CuO HAB	*ECHAMP*	No weight adjustment necessary PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 846.7 µg Cu > **FSD = D4** According to the PtC decision tree substances allowed as food or constituents of food have to be assessed according to the limit values from the food sector. In drinking water 2 mg Cu/l are allowed (98/83/EC; TWVO 2001; WHO 2006), this are 4 mg/day (2 litre drinking water). 10 g D4 = 846.7 µg Cu; **FSD = D4**	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
Cuprum sulfuricum $CuSO_4 \cdot 5\ H_2O$ HAB	AESGP	No weight adjustment necessary. PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D3 = 2698 µg Cu > **FSD = D3** According to the PtC decision tree substances allowed as food or constituents of food have to be assessed according to the limit values from the food sector. In drinking water are 2 mg Cu/l allowed (98/83/EC; TWVO 2001; WHO 2006), this are 4 mg/day (2 litre drinking water). 10 g D3 = 2.7 mg Cu > **FSD = D3**	See answer to the second comment from AESGP under general comments. Concerning the approach of assessment see answer on third comment from AESGP under general comments. **Partly agreed.** The evaluation based on food regulation is possible for copper, as recommendations for the daily intake for infants exist: In "Nutrient requirements and dietary intakes of infants and young children in the EU" EFSA Journal 2013; 11(10):3408, the intake of 0.3 mg copper/day is deemed adequate for the majority of infants in the first half-year of life. If 300 µg/day are taken as acceptable amount, the FSD for Cuprum sulfuricum is D4 instead of D5 (10 g Cuprum sulfuricum D4 = 269.8 µg Cu).
Cuprum sulfuricum $CuSO_4 \cdot 5\ H_2O$ HAB	BPI e.V.	No weight adjustment necessary PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D3 = 2698 µg Cu > **FSD = D3** According to the PtC decision tree substances allowed as food or constituents of food have to be assessed according to the limit values from the food sector. In drinking water are 2 mg Cu/l allowed (98/83/EC; TWVO 2001; WHO 2006), this are 4 mg/day (2 litre drinking water).	
Cuprum sulfuricum $CuSO_4 \cdot 5\ H_2O$ HAB	*ECHAMP*	No weight adjustment necessary PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D3 = 2698 µg Cu > **FSD = D3** According to the PtC decision tree substances allowed as food or constituents of food have to be assessed according to the limit values from the food sector. In drinking water are 2 mg Cu/l allowed (98/83/EC; TWVO 2001; WHO 2006), this are 4 mg/day (2 litre drinking water).	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
		10 g D3 = 2.7 mg Cu > **FSD = D3**	
Dioptase $Cu_6(Si_6O_{18}) \cdot 6 H_2O$ HAB	AESGP	No weight adjustment necessary. PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 423.2 µg Cu > **FSD = D4**	See answer to the second comment from AESGP under general comments. Concerning the approach of assessment see answer on third comment from AESGP under general comments. **Partly agreed.** The evaluation based on food regulation is possible for copper, as recommendations for the daily intake for infants exist: In "Nutrient requirements and dietary intakes of infants and young children in the EU" EFSA Journal 2013; 11(10):3408, the intake of 0.3 mg copper/day is deemed adequate for the majority of infants in the first half-year of life. If 300 µg/day are taken as acceptable amount, the FSD for Dioptase still will be D5 (10 g Dioptase D5 = 42.32 µg Cu).
Dioptase $Cu_6(Si_6O_{18}) \cdot 6 H_2O$ HAB	BPI e.V.	No weight adjustment necessary PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 423.2 µg Cu > **FSD = D4**	
Dioptase $Cu_6(Si_6O_{18}) \cdot 6 H_2O$ HAB	*ECHAMP*	No weight adjustment necessary PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 423.2 µg Cu > **FSD = D4**	
Dyscrasite Ag_3Sb HAB	AESGP	No weight adjustment necessary. PDE = 167 µg Ag/day (for all patient populations according to ICH guideline Q3D on elemental impurities) PDE = 1200 µg Sb/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 81 µg Ag and 28 µg Sb > **FSD = D5**	**Not agreed.** See answer to the second comment from AESGP under general comments and the assessment of Argentum colloidale.
Dyscrasite Ag_3Sb HAB	BPI e.V.	No weight adjustment necessary PDE = 167 µg Ag/day (for all patient populations according to ICH guideline Q3D on elemental impurities) PDE = 1200 µg Sb/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 81 µg Ag and 28 µg Sb > **FSD = D5**	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
Dyscrasite Ag_3Sb HAB	*ECHAMP*	No weight adjustment necessary PDE = 167 µg Ag/day (for all patient populations according to ICH guideline Q3D on elemental impurities) PDE = 1200 µg Sb/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 81 µg Ag and 28 µg Sb > **FSD = D5**	
Lithium carbonicum Li_2CO_3 HAB	AESGP	No weight adjustment necessary. PDE = 560 µg Li/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 199.2 µg Li > **FSD = D4**	**Not agreed.** See answer to the second comment from AESGP under general comments. According to Buchholzer et al. 2014, the lowest adult daily dose will lead to an acceptable amount of the substance in question for adults. On page 194, concerning the assessment for children, is written: *"Regarding the use in pediatric patients the lowest existing LHRD for the relevant age group is recommended. If pediatric posologies are lacking, assessment might be based on considerations such as: (1) the lowest adult daily dose may be adapted to the average body weight (bw) of the neonate age group (adult LHRD in terms of mg/kg/d, divided by 100, multiplied with 3 kg for neonates bw, unless there is special concern, particular severity or justified exclusion, or (2) assessment considering TTC principles i.e. threshold of 0.15 g/person per day (related to 60 kg bw; according to Kroes et al., 2004; European Food Safety Authority, EFSA, 2012; see Section 2.1.3 in this publication)."* In the Merck Manual, for children 6-12 years old, a dosage recommendation of 15-60 mg lithium carbonate/kg/day (off-label-use) is given. The dose of 45 mg lithium carbonate for a newborn contains 8.45 mg lithium ÷ 100 = 84.5 µg lithium as acceptable amount. The FSD for Lithium carbonicum (HAB and FP) will not change (HAB: 10 g Lithium carbonicum D5 = 19.92 µg Li; FP: 10 g Lithium carbonicum D5 = 18.88 µg Li). In the Merck Manual, dosage recommendations for adults include a daily dose of 300 mg lithium carbonate (off-label use
Lithium carbonicum Li_2CO_3 Ph. Franç.	AESGP	No weight adjustment necessary. PDE = 560 µg Li/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 188.8 µg Li > **FSD = D4**	
Lithium carbonicum Li_2CO_3 HAB/ FP	BPI e.V.	No weight adjustment necessary PDE = 560 µg Li/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 199.2 µg Li (HAB)> **FSD = D4** 10 g D4 = 188.8 µg Li (FP) > **FSD = D4**	
Lithium carbonicum Li_2CO_3 HAB/ FP	ECH	**We do not agree with the derivation of the FSD D5 for Lithium carbonicum.** Rationale: The FSD in the HMPWG list is derived from an allopathic single dose of Lithium carbonate. Based on this single-dose, the LHRD/100-approach is applied for FSD derivation *"300 mg Li-carbonate equiv. to 56 mg Li, representing one-third of the recommended daily adult dose".* In contrast, the LHRD/100-approach is based on the **adult daily dose**	

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Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
		(Buchholzer et al., 2014). Furthermore, for treatment of manic episodes in bipolar I disorder, the dosage recommendation in adults is 600 mg lithium carbonate, up to three times daily (US FDA, 2016). Following the LHRD/100-approach this results in: 600 mg lithium carbonate (50 kg) x 3 times daily = 112 mg lithium (50 kg) x 3 times = 336 mg lithium daily (50 kg) = 67.2 µg/kg bw Li/day Thus, the acceptable amount for neonates with 3 kg bw is **201.6 µg Li/day.** Considering the maximum daily dose of 10 g of a homeopathic product; **199.2 µg Li are contained in 10 g D4 Lithium carbonicum and are thus below the acceptable amount for neonates.** Furthermore, in addition to the applied safety factor of 100 when using the LHRD/100-approach, the recommended allopathic daily dose already includes inherent safety factors. Thus, the above presented calculation considers the inherent safety factors of the allopathic medicinal product recommendation and the additional safety factor of 100 from the LHRD/100-concept **Thus, the D4 potency**, derived from the adult daily dosage recommendations in manic episodes in bipolar I disorder, **is safe in all age groups.** **FSD=D4**	depression). Always the *lowest* human recommended dose has to be considered. In BNF for children, the lowest recommended dose for children up to 12-17 years is 300-400 mg lithium carbonate/day; this dosage corresponds to that used for derivation of the FSD for Lithium carbonicum.
Lithium carbonicum Li_2CO_3 HAB	*ECHAMP*	No weight adjustment necessary PDE = 560 µg Li/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 199.2 µg Li > **FSD = D4**	
Lithium carboncium Li_2CO_3 Ph. Franç.	*ECHAMP*	No weight adjustment necessary PDE = 560 µg Li/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 188.8 µg Li > **FSD = D4**	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
Lithium citricum $C_6H_5Li_3O_7$ HAB	AESGP	No weight adjustment necessary. PDE = 560 µg Li/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 59.8 µg Li > **FSD = D4**	**Not agreed.** See answer to the second comment from AESGP under general comments and to the comment on Lithium carbonicum.
Lithium citricum $C_6H_5Li_3O_7$ HAB	BPI e.V.	No weight adjustment necessary PDE = 560 µg Li/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 59.8 µg Li > **FSD = D4**	
Lithium citricum $C_6H_5Li_3O_7$ HAB	*ECHAMP*	No weight adjustment necessary PDE = 560 µg Li/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 59.8 µg Li > **FSD = D4**	
Malchite $Cu(OH)_2 \cdot CuCO_3$ HAB	AESGP	No weight adjustment necessary. PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 603.5 µg Cu > **FSD D4**	See answer to the second comment from AESGP under general comments. Concerning the approach of assessment see answer on third comment from AESGP under general comments. **Partly agreed.** The evaluation based on food regulation is possible for copper, as recommendations for the daily intake for infants exist: In “Nutrient requirements and dietary intakes of infants and young children in the EU” EFSA Journal 2013; 11(10):3408, the intake of 0.3 mg copper/day is deemed adequate for the majority of infants in the first half-year of life. If 300 µg/day are taken as acceptable amount, the FSD for Malachite still will be D5 (10 g Malachite D5 = 60.35 µg Cu).
Malchite $Cu(OH)_2 \cdot CuCO_3$ HAB	BPI e.V.	No weight adjustment necessary PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 603.5 µg Cu > **FSD D4**	
Malchite $Cu(OH)_2 \cdot CuCO_3$ HAB	*ECHAMP*	No weight adjustment necessary PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 603.5 µg Cu > **FSD D4**	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
Natrium tetrachloroauratum $Na[AuCl_4] \cdot 2 H_2O$ Ph.Eur./HAB	AESGP	No weight adjustment necessary. PDE = 134 µg Au/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 51.9 µg Au > **FSD = D5** Please add the French homeopathic traditional name: Aurum muriaticum natronatum	**Not agreed.** See answer to the second comment from AESGP under general comments. The French homeopathic traditional name “Aurum muriaticum natronatum” is included under the column “remarks”.
Natrium tetrachloro-auratum $Na[AuCl_4] \cdot 2 H_2O$ Ph.Eur. / HAB	BPI e.V.	No weight adjustment necessary PDE = 134 µg Au/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 51.9 µg Au > **FSD = D5**	
Natrium tetrachloroauratum $Na[AuCl_4] \cdot 2 H_2O$ Ph.Eur./HAB	*ECHAMP*	No weight adjustment necessary PDE = 134 µg Au/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 51.9 µg Au > **FSD = D5**	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
Olivenite $Cu_2(OH)AsO_4$ HAB	AESGP	No weight adjustment necessary. PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities) PDE = 15 µg As/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D6 = 4.72 µg Cu and 2.78 µg As > **FSD = D6** According to the PtC decision tree substances allowed as food or constituents of food have to be assessed according to the limit values from the food sector. In drinking water are 10 µg As/l allowed (98/83/EC; WHO 2006), this are 20 µg/day (2 litre drinking water). 10 g D6 = 2.78 µg As > **FSD = D6**	See answer to the second comment from AESGP under general comments. Concerning the approach of assessment see answer on third comment from AESGP under general comments. **Partly agreed.** The evaluation based on food regulation is possible for copper, as recommendations for the daily intake for infants exist: In "Nutrient requirements and dietary intakes of infants and young children in the EU" EFSA Journal 2013; 11(10):3408, the intake 0.3 mg copper/day is deemed adequate for the majority of infants in the first half-year of life. Since Olivenite contains arsenic as the more toxic component, the PDE of arsenic is the relevant limit value for FSD assessment.
Olivenite $Cu_2(OH)AsO_4$ HAB	BPI e.V.	No weight adjustment necessary PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities) PDE = 15 µg As/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D6 = 4.72 µg Cu and 2.78 µg As > **FSD = D6** According to the PtC decision tree substances allowed as food or constituents of food have to be assessed according to the limit values from the food sector. In drinking water are 10 µg As/l allowed (98/83/EC; WHO 2006), this are 20 µg/day (2 litre drinking water). 10 g D6 = 2.78 µg As > **FSD = D6**	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
Olivenite $Cu_2(OH)AsO_4$ HAB	*ECHAMP*	No weight adjustment necessary PDE = 3400 µg Cu/day (for all patient populations according to ICH guideline Q3D on elemental impurities) PDE = 15 µg As/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D6 = 4.72 µg Cu and 2.78 µg As > **FSD = D6** According to the PtC decision tree substances allowed as food or constituents of food have to be assessed according to the limit values from the food sector. In drinking water are 10 µg As/l allowed (98/83/EC; WHO 2006), this are 20 µg/day (2 litre drinking water). 10 g D6 = 2.78 µg As > **FSD = D6**	
Platinum metallicum Pt HAB	AESGP	No weight adjustment necessary. PDE = 108 µg Pt/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 106.0 µg Pt > **FSD = D5** Please add the French homeopathic traditional name: Platina	**Not agreed.** See answer to the second comment from AESGP under general comments. The French homeopathic traditional name “Platina” is included under the column “remarks”.
Platinum metallicum Pt HAB	BPI e.V.	No weight adjustment necessary PDE = 108 µg Pt/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 106.0 µg Pt > **FSD = D5**	
Platinum metallicum Pt HAB	*ECHAMP*	No weight adjustment necessary PDE = 108 µg Pt/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 106.0 µg Pt > **FSD = D5**	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
Scorodite $Fe^{3+}[AsO_4] \cdot 2 H_2O$ HAB	AESGP	No weight adjustment necessary. PDE = 15 µg As/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D6 = 3.7 µg As > **FSD = D6** According to the PtC decision tree substances allowed as food or constituents of food have to be assessed according to the limit values from the food sector. In drinking water are 10 µg As/l allowed (98/83/EC; WHO 2006), this are 20 µg/day (2 litre drinking water). 10 g D6 = 3.7 µg As > **FSD = D6**	**Not agreed.** See answer to the second comment from AESGP under general comments. Concerning the approach of assessment see answer on third comment from AESGP under general comments.
Scorodite $Fe^{3+}[AsO_4] \cdot$ $2 H_2O$ HAB	BPI e.V.	No weight adjustment necessary PDE = 15 µg As/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D6 = 3.7 µg As > **FSD = D6** According to the PtC decision tree substances allowed as food or constituents of food have to be assessed according to the limit values from the food sector. In drinking water are 10 µg As/l allowed (98/83/EC; WHO 2006), this are 20 µg/day (2 litre drinking water).	
Scorodite $Fe^{3+}[AsO_4] \cdot 2 H_2O$ HAB	*ECHAMP*	No weight adjustment necessary PDE = 15 µg As/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D6 = 3.7 µg As > **FSD = D6** According to the PtC decision tree substances allowed as food or constituents of food have to be assessed according to the limit values from the food sector. In drinking water are 10 µg As/l allowed (98/83/EC; WHO 2006), this are 20 µg/day (2 litre drinking water).	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
		10 g D6 = 3.7 µg As > **FSD = D6**	
Selenium Se HAB	AESGP	No weight adjustment necessary. PDE = 170 µg Se/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 106 µg Se > **FSD = D5**	See answer to the second comment from AESGP under general comments. Concerning the approach of assessment see answer on third comment from AESGP under general comments. **Partly agreed.** The evaluation based on food regulation is possible for selenium, as recommendations for the daily intake for infants exist: In "Nutrient requirements and dietary intakes of infants and young children in the EU" EFSA Journal 2013; 11(10):3408, the intake of 12.5 µg selenium/day is deemed adequate for the majority of infants in the first half-year of life. If 12.5 µg selenium/day are taken as acceptable amount, the FSD for Selenium will be **D6 instead of D7** (10 g Selenium D6 = 10.6 µg Se). The acceptable amount based on nutrient requirements lies in the same range as the MRL for selenium for chronic oral exposure adjusted to a body weight of 3 kg.
Selenium Se HAB	BPI e.V.	According to the general given comments for Selen are two ways of argumentation and calculation possible. In this case both give different results, whereas the calculation based on alternative 2) results in an actual concentration, which lies between a D5 and D6. Therefore the proposal of HAMPWG for the FSD should be lowered in any case. 1) No weight adjustment necessary PDE = 170 µg Se/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 106 µg Se > **FSD = D5** 2) According to the decision tree of the HMPWG PtC, substances allowed as food or constituents of food have to be assessed according to Regulation 178/2002/EC modified by 1642/2003/EC and all related directives and Food supplements 2002/46/EC. This also includes drinking water regulations. The allowed Selen value for drinking water is 10 µg/l, this results in 20 µg /day (2 litre drinking water). http://www.who.int/water_sanitation_health/dwq/chemicals/selenium.pdf 10 g D6 = 10,6 µg Selen; **FSD = D6**	
Selenium	ECH	**We do not agree with the derivation of the FSD D7 for Selenium.**	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
Se HAB		Rationale: The official MRL value of 5 µg/ kg/ day for Se, calculated by Agency for Toxic Substances and Disease Registry (ATSDR) should be used for calculation of FSD. [MRL: Minimal Risk Level: An estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk. (ATSDR)] Reference: ATSDR. Toxicological profile for selenium https://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=153&tid=28 An MRL of 0.005 mg/kg/day (5 µg/kg/day) has been derived for chronic oral exposure (>365 days) to selenium. The chronic oral MRL is based on a NOAEL of 819 µg/day (0.015 mg/kg/day) for disappearance of symptoms of selenosis in recovering individuals (Yang and Zhou 1994) and uses an uncertainty factor of 3 for human variability. An uncertainty factor of 3 was considered appropriate because the individuals in this study were sensitive individuals drawn from a larger population and because of supporting studies, as discussed in Appendix A. The NOAEL used to derive the MRL is consistent with NOAELs observed for other human populations (Longnecker et al. 1991). The MRL is about 2.5–5 times higher than normal selenium intake levels of 71–152 µg/day (approximately 0.001–0.002 mg/kg/day) (DHHS 2002; FDA 1982a; Levander 1987; Pennington et al. 1989; Schrauzer and White 1978; Schubert et al. 1987; Welsh et al. 1981), and approximately 6 times greater than the RDA for selenium of 55 µg/day (~0.0008 mg/kg/day) (NAS 2000). The MRL does not represent a threshold for toxicity, but a daily intake that ATSDR considers to be safe for all populations. The exact point above the MRL at which effects might occur in sensitive individuals is uncertain. For neonates with 3 kg body weight 15 µg Se/ d are allowed. 10 g D6 = 10,6 µg Selen. This is in the same range with the Selen value in drinking water of 10 µg/ l, this are 20 µg /day (2 litre drinking water).	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
		http://www.who.int/water_sanitation_health/dwq/chemicals/selenium.pdf **FSD=D6**	
Selenium Se HAB	*ECHAMP*	In the literature there are several data to evaluate the safety, which can lead to different values that are considered safe. In the case of selenium, this results in different FSDs. Following the approach 1) (used in the Draft of the 2nd list of FSD), the PDE from the Q3D is the basis for the FSD. In approach 2) the drinking water regulation is the basis for the calculation and a different value results. 1) No weight adjustment necessary PDE = 170 µg Se/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D5 = 106 µg Se > **FSD = D5** 2) According to the decision tree of the HMPWG PtC, substances allowed as food or constituents of food have to be assessed according to Regulation 178/2002/EC modified by 1642/2003/EC and all related directives and Food supplements 2002/46/EC. This also includes drinking water regulations. The allowed Selen value in drinking water is 10 µg/l, this results in 20 µg /day (2 litre drinking water). http://www.who.int/water_sanitation_health/dwq/chemicals/selenium.pdf 10 g D6 = 10,6 µg Selen; **FSD=D6**	
Stannum metallicum Sn HAB	AESGP	No weight adjustment necessary. PDE = 6400 µg Sn/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 1060 µg Sn > **FSD = D4**	**Not agreed.** See answer to the second comment from AESGP under general comments.
Stannum	BPI e.V.	No weight adjustment necessary	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
metallicum Sn HAB		PDE = 6400 µg Sn/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 1060 µg Sn > **FSD = D4**	
Stannum metallicum Sn HAB	*ECHAMP*	No weight adjustment necessary PDE = 6400 µg Sn/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 1060 µg Sn > **FSD = D4**	
Stibium arsenicosum Sb HAB	AESGP	According to the PtC decision tree substances allowed as food or constituents of food have to be assessed according to the limit values from the food sector. In drinking water are 10 µg As/l allowed (98/83/EC page 18; WHO 2006 page 306-309), this are 20 µg/day for adults (2 litre drinking water a day). D6 (4.1 µg As/10 g) is safe. **FSD = D6** Please add the French homeopathic traditional name: Antimonium arsenicosum	**Not agreed.** Concerning the approach of assessment see answer on third comment from AESGP under general comments. The French homeopathic traditional name “Antimonium arsenicosum” is included under the column “remarks”.
Stibium arsenicosum Sb HAB	BPI e.V.	According to the PtC decision tree substances allowed as food or constituents of food have to be assessed according to the limit values from the food sector. In drinking water are 10 µg As/l allowed (98/83/EC page 18; WHO 2006 page 306-309), this are 20 µg/day for adults (2 litre drinking water a day), for infants 5 µg/day (assumed consumption of 0.5 litre drinking water a day). D6 (4.1 µg As/10 g) is safe. **FSD = D6**	
Stibium arsenicosum Sb HAB	*ECHAMP*	According to the PtC decision tree substances allowed as food or constituents of food have to be assessed according to the limit values from the food sector. In drinking water are 10 µg As/l allowed (98/83/EC page 18; WHO 2006 page 306-309), this are 20 µg/day for adults (2 litre drinking water a day), D6 (4.1 µg As/10 g) is safe. **FSD = D6**	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
Stibium metallicum Sb HAB	AESGP	No weight adjustment necessary. PDE = 1200 µg Sb/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 1060 µg Sb > **FSD = D4** Please add the French homeopathic traditional name: Antimonium metallicum	**Not agreed.** See answer to the second comment from AESGP under general comments and to the comments on Antimonite. The French homeopathic traditional name “Antimonium metallicum” is included under the column “remarks”.
Stibium metallicum Sb HAB	BPI e.V.	No weight adjustment necessary PDE = 1200 µg Sb/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 1060 µg Sb > **FSD = D4**	
Stibium metallicum Sb HAB	*ECHAMP*	No weight adjustment necessary PDE = 1200 µg Sb/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 1060 µg Sb > **FSD = D4**	
Stibium sulfuratum aurantiacum HAB	AESGP	No weight adjustment necessary. PDE = 1200 µg Sb/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D4 = 759 µg Sb > **FSD = D4** Please add the French homeopathic traditional name: Antimonium sulfuratum aureum	**Not agreed.** See answer to the second comment from AESGP under general comments and to the comments on Antimonite. The French homeopathic traditional name “Antimonium sulfuratum aureum” is included under the column “remarks”.
Stibium sulfuratum aurantiacum HAB	BPI e.V.	No weight adjustment necessary PDE = 1200 µg Sb/day (for all patient populations according to ICH guidelein Q3D on elemetal impurities) 10 g D4 = 759 µg Sb > **FSD = D4**	
Stibium sulfuratum aurantiacum	*ECHAMP*	No weight adjustment necessary PDE = 1200 µg Sb/day (for all patient populations according to ICH	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
HAB		guideline Q3D on elemental impurities) 10 g D4 = 759 µg Sb > **FSD = D4**	
Thallium aceticum oxydulatum $C_2H_3O_2Tl$ HAB	AESGP	No weight adjustment necessary. PDE = 8 µg Tl/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D7 = 0.82 µg Tl > **FSD = D7**	**Not agreed.** See answer to the second comment from AESGP under general comments.
Thallium aceticum oxydulatum $C_2H_3O_2Tl$ HAB	BPI e.V.	No weight adjustment necessary PDE = 8 µg Tl/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D7 = 0.82 µg Tl > **FSD = D7**	
Thallium aceticum oxydulatum $C_2H_3O_2Tl$ HAB	*ECHAMP*	No weight adjustment necessary PDE = 8 µg Tl/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D7 = 0.82 µg Tl > **FSD = D7**	
Thallium sulfuricum Tl_2SO_4 HAB	AESGP	No weight adjustment necessary. PDE = 8 µg Tl/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D7 = 0.82 µg Tl > **FSD = D7**	**Not agreed.** See answer to the second comment from AESGP under general comments.
Thallium sulfuricum Tl_2SO_4 HAB	BPI e.V.	No weight adjustment necessary PDE = 8 µg Tl/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D7 = 0.82 µg Tl > **FSD = D7**	
Thallium	*ECHAMP*	No weight adjustment necessary	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
sulfuricum Tl_2SO_4 HAB		PDE = 8 µg Tl/day (for all patient populations according to ICH guideline Q3D on elemental impurities) 10 g D7 = 0.82 µg Tl > **FSD = D7**	

Attached documents:

TWVO 2001: https://www.gesetze-im-internet.de/bundesrecht/trinkwv_2001/gesamt.pdf

WHO 2006: http://www.who.int/water_sanitation_health/dwq/gdwq0506.pdf

98/83/EC: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1998:330:0032:0054:EN:PDF (COUNCIL DIRECTIVE 98/83/EC of 3 November 1998 on the quality of water intended for human consumption)