April 2018
4th List of First Safe Dilutions (FSD)

Template for submission of comments on draft document

Written procedure decided by the HMPWG	**30 May 2013**
Adoption by written procedure	**15 September 2013**
Report of the outcome of the written procedure	**21 November 2013**

All instruction notes (in green) must be deleted before finalising the overview of comments.

Submission of comments on draft document

Table 1: Origin of comments

4th List of First Safe Dilutions (FSD) released for public consultation on 8 February 2018 until 15 May 2018

Organisation or individual	Contact details (e-mail address, telephone number, name of contact person)
ECHAMP EEIG. – European Coalition on Homeopathic and Anthroposophic Medicinal Products	Rue Washington 40 B-1050 Brussels 32 2 649 94 40 amandine.oset@echamp.eu

Interested parties are invited to send
comments together with a copy of the cited references.
This will facilitate the assessment of comments, suggestions and corresponding justifications.

When the reference consists of a book chapter, the copy must include
the page of the book showing the year of publication.

Comments without copies of the supporting literature will not be considered.

Comments should be sent electronically and in Word format (not pdf).

Comments and the identity of the sender will be made public
unless a justified objection is received at the time of the submission.

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Please submit comments on each document separately.

Table 2: Comments

GENERAL COMMENTS ON DRAFT DOCUMENT

Interested party	Comment and Rationale	Outcome
ECHAMP	According to ICH Guideline Q3D the PDE is calculated as follows: PDE = NO(A)EL x 50 kg / (F1xF2xF3xF4xF5) F1 = A factor to account for extrapolation between species. F1 takes into account the comparative surface area: body mass ratios for the species concerned and for man. Surface area (S) is calculated as: $S = kM^{0.67}$ in which M = body mass, and the constant k has been taken to be 10. F2 = A factor of 10 to account for variability between individuals F3 = A variable factor to account for toxicity studies of short-term exposure F4 = A factor that may be applied for severe toxicity F5 = A variable factor that may be applied if the no-effect level was not established For F1 (factor for extrapolation between species) a factor of 2-12 has to be used for the extrapolation from animal to human. Please notice that the comparative surface area: body mass ratios for the species concerned and for man are taken into account with this factor. For F2 (factor for variability between individuals) in general a factor of 10 is used. Please take into account that the average body weight in the equation for calculating the PDE was set to the relatively low value of 50 kg instead of the usual 60 or 70 kg, It is questionable if an additional weight adjustment is necessary. What is the background of the individual factors and how do they relate to each other? It should be carefully taken into account that: • F1 takes into account the comparative surface area: body mass ratios which is more precise than only the comparison of body weights • F1 can be lower than 10, the minimum is F1 = 2 for the extrapolation from dog to human • F2 is always 10 • The relatively low average body weight of 50 kg is used in the equation for	Leave blank (it will be completed by the Rapporteur).

Interested party	Comment and Rationale	Outcome
	calculating the PDE, which is a further additional safety factor. Divided by F2 = 10, a body weight of 5 kg results. This is near to the body weight of a newborn • If comparing the more precise body surface areas of adults (1.73 m^2) and newborns (0.25 m^2) to account for the variability between individuals, a factor of 7 results which is below the factor F2 = 10 It can therefore be assumed that with the factor F2 = 10 all differences between the individuals are already compensated and, together with the other numerous safety factors, an additional weight adjustment is not provided for in this approach. This is also reflected in the result of the calculation of a PDE, which is given with x mg/day, without the unit kg. This is in line with the statement in ICH Guideline Q3D that the PDEs established in this guideline are considered to be protective of public health for all patient populations. An additional weight adjustment is not necessary due to the numerous and kind of safety factors used for the calculation of a PDE and the PDE is appropriate to each age group.	
ECHAMP	The FSD of minerals containing the same element (e.g. Fe or P) should not be evaluated solely based on one single value from the food sector. Depending on the different minerals (elemental state or salts), they can have very different properties, which might affect e.g. oxidation states, solubility, bioavailability and toxicities. Assuming the evaluation method used for the minerals containing the same element would be transferred to the evaluation of phosphorus, the following would result: Adequate intakes (AI) of Phosphorus for infants aged 7 – 11 months are 160 mg/day (EFSA 2015). Converted to a new-born approximately 60 mg/day would result. It is clear that this result is not transferable to white phosphorus, as its properties are different from the phosphorus compounds concerned by the above mentioned calculation. Transferred to the determination of FSD this would mean that each substance (compounds or elements) should be evaluated in terms of its specific properties.	
Add rows as appropriate.		

SPECIFIC COMMENTS ON TEXT

Section number and heading	Interested party	Comment and Rationale	Outcome
Acidum phosporicum **H_3PO_4** HAB See Phosphoricum acidum	ECHAMP	Monograph HAB 2010 → Ph. Eur. for the raw material Phosphoric acid, dilute (0005): 9,5-10,5% H_3PO_4 The reference to Ph. Eur for raw material Phosphoric acid, dilute (0005) should be mentioned in column 1 as it is important to avoid the confusion with the stock **Phosphoricum acidum** which refers to Phosphoric acid, concentrated (0004).	Leave blank (it will be completed by the Rapporteur).
Borax **$Na_2B_4O_7 \cdot 10\ H_2O$** Ph. franç. See Natrium tetraboracicum	ECHAMP	The reference to Ph. Eur for raw material should be mentioned in column 1.	
Calcium fluoratum **CaF_2** **HAB**	ECHAMP	Firstly, Calciumfluorid is poorly soluble and the absorption compared with monovalent fluorid salts e.g. Natriumfluorid is less. Calcium is also used as antidote for oral fluoride intoxications for binding of fluoride and for reduction of the absorption of fluoride (*Dessler 2018*). Therefore Calciumfluorid is not comparable with e.g. the readily soluble Natriumfluorid. Secondly, 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. “Where the intakes are likely to approach, or be greater than 6 mg/day, it would be appropriate to consider setting a standard or local guideline at a concentration lower than 1.5 mg/litre.” *(WHO 1996*) This value corresponds with the “German Drinking Water Regulation” See Anlage 2 - Trinkwasserverordnung (TrinkwV): Fluoride: 1,5 mg/l	

Section number and heading	Interested party	Comment and Rationale	Outcome
		There is a further value special for water for preparation of baby food of 0.7 mg/l water. See: Mineral- und Tafelwasser-Verordnung) Anlage 6 (zu § 9 Abs. 3): „Geeignet für die Zubereitung von Säuglingsnahrung: Der Gehalt an Natrium darf 20 mg/l, an Nitrat 10 mg/l, an Nitrit 0,02 mg/l, an Sulfat 240 mg/l, an Fluorid 0,7 mg/l, an Mangan 0,05 mg/l, an Arsen 0,005 mg/l und an Uran 0,002 mg/l nicht überschreiten." Therefore the value for water for preparation of baby food should be used for the calculation: 0.7 mg/l multiplied with an intake of 0,8 l (*EFSA 2013*) results in an acceptable intake of 0,56 mg/l 10 g D4 contains = 521 µg F; therefore **FSD = D4**	
Calcarea iodata **$CaI_2 \cdot 4\ H_2O$** Ph. Eur. See Calcium iodatum	ECHAMP	Why is the value of 90 µg I/day from EFSA *(2013*) not used as acceptable amount (adequate to the value for calcium used for infants of the first half-year of life)? We do not agree with the acceptable amount of 30 µg I/day → we suggest to use 90 µg/day (value of *EFSA 2013*) 10 g D5 contain 88.09 µg I (< acceptable amount). → FSD = D5	
Calcium iodatum **$CaI_2 \cdot 4\ H_2O$** HAB See Calcarea iodata	ECHAMP	Why is the value of 90 µg I/day from EFSA (*2013*) not used as acceptable amount (adequate to the value for calcium used for infants of the first half-year of life)? We do not agree with the acceptable amount of 30 µg I/day → we suggest to use 90 µg/day (value of *EFSA 2013*) 10 g D5 contain 88.09 µg I (< acceptable amount). → FSD = D5	
China rubra Ph. franç. See Cinchona pubescens (HAB) See also Chininum arsenicosum (2nd list)	ECHAMP	The value of 9 mg quinine/day every 8 hours corresponding to 81 mg quinine for a 3 kg neonate cannot be retraced. The paediatric dosing in the mentioned text passage is given with 30 mg/kg/day, corresponding to a daily dosage of 90 mg/day for a 3 kg neonate. Applying the LHRD-approach, 0.9 mg quinine per day is the acceptable amount. 10 g D1 → 6.5 mg alkaloids 10 g D2 → 0.65 mg alkaloids (< LHRD)	

Section number and heading	Interested party	Comment and Rationale	Outcome
		→ FSD = D2	
Cinchona pubescens HAB See China rubra (Ph. franç.) See also Chininum arsenicosum (2nd list)	ECHAMP	The value of 9 mg quinine/day every 8 hours corresponding to 81 mg quinine for a 3 kg neonate cannot be retraced. The paediatric dosing in the mentioned text passage is given with 30 mg/kg/day, corresponding to a daily dosage of 90 mg/day for a 3 kg neonate. Applying the LHRD-approach, 0.9 mg quinine per day is the acceptable amount. Please add method of preparation 19f = 1.2.12 / 0.50-0.80% alkaloids (thereof 30-60% quinine) 10 g stock (D1) contains 48 mg quinine ➔ FSD = D3.	
Ferrum metallicum Fe HAB See Ferrum metallicum Ph. Eur.	ECHAMP	By HMPWG the FSD for iron is calculated based on the mean intakes per day adequate for the majority of infants of the first half-year of life. The EFSA Panel on Dietetic Products, Nutrition and Allergies used the observed mean iron intakes from breast milk of 0.3 mg per day (i.e. 0.35 mg/L x 0.8 L), as a basis to provide advice on intake levels of nutrient considered adequate for the majority of infants in the first half-year of life (*EFSA 2013*). The need of the infant is higher than the intake from breast milk. To meet the need well-filled iron stores at birth are necessary. The stored iron content in a healthy newborn is about 250 to 300 mg (*EFSA 2013*). The estimated iron requirement of a term infant is 1 mg/kg per day; in preterm infants the requirements are still higher (up to 4 mg/kg/day for infants weighing less than 1500 g at birth) (*AAP 1999*). The dose of iron received from human milk or infant formula is minute in comparison with the total body iron load (*AAP 1999*). The stored iron will cover the needs of the infant during the first four to six months of life. After this period, the recommended daily amount increases to 8 mg iron/day (*EFSA 2013*), therefore complementary food should be introduced. A longer duration of breastfeeding is associated with lower iron stores in children and a higher risk of anemia (*Maguire 2013*). The homeostatic regulation of absorption of iron ensures that infants with	

<table>
<tr><th>Section number and heading</th><th>Interested party</th><th>Comment and Rationale</th><th>Outcome</th></tr>
<tr><td></td><td></td><td>poorer iron status or in negative iron balance absorb a higher percentage of dietary iron (Schümann 2007). The absorption rate of iron in breast milk is greater than 50%, compared with typically less than 12% of iron absorption from cow milk-derived formula (AAP 1999).
That’s why the recommendation for infant formula is to fortify them with iron (AAP 1999, Moy 2000). In Europe, infant formula tends to contain 4 mg/L to 7 mg/L of iron. In the United States, iron concentrations of iron-fortified formulas range from 10 mg/L to 12 mg/L (AAP 1999, Moy 2000).

Examples of different infant formulas for use from birth on:

<table>
<tr><th></th><th>Iron in 100 ml</th><th>Daily dose (800 ml)</th></tr>
<tr><td>Similac pro-adavance</td><td>1.22 mg</td><td>9.76 mg</td></tr>
<tr><td>Similac advance</td><td>1.22 mg</td><td>9.76 mg</td></tr>
<tr><td>Similac Organic</td><td>1.22 mg</td><td>9.76 mg</td></tr>
<tr><td>Nestlé Beba Optipro 1</td><td>0.68 mg</td><td>5.44 mg</td></tr>
<tr><td>Nestlé Good Start 1 with DHA Ready-to-Feed Nurser Baby Formula</td><td>1 mg</td><td>8 mg</td></tr>
<tr><td>Nestlé Good Start Probiotic with PRO-Blend Stage 1 Baby Formula</td><td>1 mg</td><td>8 mg</td></tr>
<tr><td>Aptamil Pronutra Anfangsmilch Pre von Geburt an</td><td>0.53 mg</td><td>4.24 mg</td></tr>
<tr><td>Hipp Bio</td><td>0.70 mg</td><td>5.6 mg</td></tr>
<tr><td>Hipp Combiotik</td><td>0.5 mg</td><td>4 mg</td></tr>
<tr><td>Hipp HA Combiotik</td><td>0.7 mg</td><td>5.6 mg</td></tr>
<tr><td>Humana Anfangsmilch 1</td><td>0.6 mg</td><td>4.8 mg</td></tr>
<tr><td>Töpfer Lactana Bio 1 Anfangsmilch</td><td>0.56 mg</td><td>4.48 mg</td></tr>
<tr><td>Töpfer Lactana Bio Pre Anfangsmilch</td><td>0.53 mg</td><td>4.24 mg</td></tr>
</table>
</td><td></td></tr>
</table>

Section number and heading	Interested party	Comment and Rationale	Outcome
		There are no known medical contraindications to using iron-fortified formulas in formula-fed infants, especially no differences in prevalence to gastrointestinal complaints between iron-fortified formulas and low-iron formulas (*AAP 1999, Moy 2000*). Moreover, therapeutic iron up to 6 mg/kg per day given to infants is well tolerated (*AAP 1999, Moy 2000*). Several prospective studies of iron-fortified formulas containing 15 mg iron/L have found no excess of diarrhea or respiratory infections (*Moy 2000*). Because no data currently support the use of a low-iron formula as an alternative supplement for breast-fed infants and low-iron formula is associated with an unacceptably high risk of iron deficiency, the Committee on Nutrition recommends the use of iron-fortified cow milk or soy formula as a supplement for breastfed infants whose mothers choose not to exclusively breastfeed (*AAP 1999*). Therefore, the content of iron in breast milk is not the appropriate value for a safety assessment. An iron-fortified formula with 12 mg iron per liter is assessed as being safe for newborns. With a daily consumption of 800 ml milk, this corresponds to 9.6 mg iron for a 3 kg newborn child. 10 g Ferrum metallicum D1 contains 1060 mg Fe. 10 g D4 contains 1.06 mg Fe < 9.6 mg Fe. ➔ FSD = D4	
Ferrum metallicum Fe Ph. Eur.	ECHAMP	See comment for Ferrum metallicum HAB. 9.6 mg iron is assessed as being safe for a newborn child with 3 kg. 10 g Ferrum metallicum D1 contains 1010 mg Fe 10 g D4 contains 1.01 mg Fe < 9.6 mg Fe ➔ FSD = D4	
Ferrum phosphoricum	ECHAMP	See comment for Ferrum metallicum HAB.	

Section number and heading	Interested party	Comment and Rationale	Outcome
$FePO_4 \cdot x\ H_2O$ HAB		9.6 mg iron is assessed as being safe for a newborn child with 3 kg. 10 g Ferrum phosphoricum D1 contains 260 mg Fe 10 g D3 contains 2.6 mg Fe < 9.6 mg Fe ➔ FSD = D3	
Ferrum phosphoricum/ Ferri phosphas pour préparations homéopa-thiques Ph. franç.	ECHAMP	See comment for Ferrum metallicum HAB. 9.6 mg iron is assessed as being safe for a newborn child with 3 kg. 10 g Ferrum phosphoricum D1 contains 374 mg Fe. 10 g D3 contains 3.74 mg Fe < 9.6 mg Fe ➔ FSD = D3	
Ferrum phosphoricum/ Ferroso-Ferri phosphas pour préparations homéopa-thiques Ph. franç.	ECHAMP	See comment for Ferrum metallicum HAB. 9.6 mg iron is assessed as being safe for a newborn child with 3 kg. 10 g Ferrum phosphoricum D1 contains 362 mg Fe 10 g D3 contains 3.62 mg Fe < 9.6 mg Fe ➔ FSD = D3	
Ferrum sesquichlora-tum solutum $FeCl_3 \cdot 6\ H_2O$ HAB	ECHAMP	See comment for Ferrum metallicum HAB. 9.6 mg iron is assessed as being safe for a newborn child with 3 kg. 10 g Ferrum sesquichloratum solutum D1 contains 320 mg Fe 10 g D3 contains 3.2 mg Fe < 9.6 mg Fe ➔ FSD = D3	
Ferrum sulfuricum $FeSO_4$ HAB	ECHAMP	See comment for Ferrum metallicum HAB. 9.6 mg iron is assessed as being safe for a newborn child with 3 kg.	

Section number and heading	Interested party	Comment and Rationale	Outcome
		10 g Ferrum sulfuricum D1 contains 950 mg Fe 10 g D3 contains 9.5 mg Fe < 9.6 mg Fe ➔ FSD = D3	
Fucus vesiculosus HAB	ECHAMP	Why is the value of 90 µg I/day from EFSA (*2013*) not used as acceptable amount (adequate to the value for calcium used for infants of the first half-year of life)? We do not agree with the acceptable amount of 30 µg I/day → we suggest to use 90 µg/day (value of *EFSA 2013*) 10 g D3 = 10 µg I (< acceptable amount) ➔ FSD = D3	
Fucus vesiculosus Ph. franç.	ECHAMP	Why is the value of 90 µg I/day from EFSA (*2013*) not used as acceptable amount (adequate to the value for calcium used for infants of the first half-year of life)? We do not agree with the acceptable amount of 30 µg I/day → we suggest to use 90 µg/day (value of *EFSA 2013*) 10 g D1 = 20 µg I (< acceptable amount). ➔ FSD = D1	
Hyoscyamus niger HAB	ECHAMP	The reference to Ph. Eur. for the stock should be mentioned (column 1)	
Kalium iodatum KI Ph. franç.	ECHAMP	Why is the value of 90 µg I/day from EFSA (2013) not used as acceptable amount (adequate to the value for calcium used for infants of the first half-year of life)? We do not agree with the acceptable amount of 30 µg I/day → we suggest to use 90 µg/day (value of *EFSA 2013*) 10 g D5 = 76.83 µg I (< acceptable amount). ➔ FSD = D5	
Kalium iodatum KI HAB	ECHAMP	Why is the value of 90 µg I/day from EFSA (2013) not used as acceptable amount (adequate to the value for calcium used for infants of the first half-year of life)? We do not agree with the acceptable amount of 30 µg I/day →	

Section number and heading	Interested party	Comment and Rationale	Outcome
		we suggest to use 90 µg/day (value of EFSA 2013) 10 g D5 = 81 µg I (< acceptable amount). ➔ FSD = D5	
Magnesium carbonicum	ECHAMP	Magnesiumcarbonate is poorly soluble compared with monovalent carbonate salts and Magnesiumchloride (Magnesium chloratum) Hager: *Hager ROM 2014* „Aus dem Gastrointestinaltrakt können bis zu 10 % des Magnesiums aus basischem Magnesiumcarbonat resorbiert werden“ Due to reduced resorption, for calculation of FSD of Magnesium carbonicum the available amount of Magnesium in the daily dose (10 g) should be reduced by factor 10. → FSD= D2 (analogous Magnesium chloratum; readily soluble)	
Magnesium fluoratum	ECHAMP	Firstly, Magnesiumfluorid is poorly soluble and the absorption compared with monovalent fluorid salts e.g. Natriumfluorid is less. Therefore Magnesiumfluorid is not comparable with e.g. the readily soluble Natriumfluorid. Secondly, 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. “Where the intakes are likely to approach, or be greater than 6 mg/day, it would be appropriate to consider setting a standard or local guideline at a concentration lower than 1.5 mg/litre.” (*WHO 1996*) This value corresponds with the “German Drinking Water Regulation” See Anlage 2 - Trinkwasserverordnung (TrinkwV): Fluoride: 1,5 mg/l	

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		There is a further value special for water for preparation of baby food of 0.7 mg/l water See: Mineral- und Tafelwasser-Verordnung) Anlage 6 (zu § 9 Abs. 3): „Geeignet für die Zubereitung von Säuglingsnahrung: Der Gehalt an Natrium darf 20 mg/l, an Nitrat 10 mg/l, an Nitrit 0,02 mg/l, an Sulfat 240 mg/l, an Fluorid 0,7 mg/l, an Mangan 0,05 mg/l, an Arsen 0,005 mg/l und an Uran 0,002 mg/l nicht überschreiten.“ Therefore the value for water for preparation of baby food should be used for the calculation: 0.7 mg/l multiplied with an intake of 0,8 l (*EFSA 2013*) results in an acceptable intake of 0,56 mg/l 10 g D5 contains = 65 µg F; therefore **FSD = D5**	
Natrium carbonicum $Na_2CO_3 \cdot H_2O$ HAB See Natrum carbonicum	ECHAMP	The reference to Ph. Eur. for raw material should be mentioned (column 1).	
Natrium chloratum NaCl HAB See Natrum muriaticum	ECHAMP	The reference to Ph. Eur. for raw material should be mentioned (column 1).	
Natrium phosphoricum $Na_2HPO_4 \cdot 12 H_2O$ HAB See Natrum phosphoricum	ECHAMP	The reference to Ph. Eur. for raw material should be mentioned (column 1).	
Natrium sulfuricum Na_2SO_4 HAB See Natrum sulfuricum	ECHAMP	The reference to Ph. Eur. for raw material should be mentioned (column 1).	

Section number and heading	Interested party	Comment and Rationale	Outcome
Natrium tetraboracicum **$Na_2B_4O_7 \cdot 10\ H_2O$** HAB See Borax	ECHAMP	The reference to Ph. Eur. for raw material should be mentioned (column 1).	
Natrum carbonicum **$Na_2CO_3 \cdot H_2O$** Ph. franç. See Natrium carbonicum	ECHAMP	The reference to Ph. Eur. for raw material should be mentioned (column 1).	
Natrum muriaticum NaCl Ph. franç. See Natrium chloratum	ECHAMP	The reference to Ph. Eur. for raw material should be mentioned (column 1).	
Natrum phosphoricum **$Na_2HPO_4 \cdot 12\ H_2O$** Ph. franç. See Natrium phosphoricum	ECHAMP	The reference to Ph. Eur. for raw material should be mentioned (column 1).	
Natrum sulfuricum **Na_2SO_4** Ph. franç. See Natrium sulfuricum	ECHAMP	The reference to Ph. Eur. for raw material should be mentioned (column 1).	
Phosphoricum acidum **H_3PO_4** Ph. franç. See Acidum phosphoricum	ECHAMP	The reference to Ph. Eur. for raw material should be mentioned (column 1). Phosphoric acid, concentrated (0004) should be mentioned (column 1) / important to avoid the confusion with the stock Acidum phosphoricum which refers to phosphoric acid, dilute (0005).	
Phosphorus P HAB	ECHAMP	The acceptable daily amount defined by a FSD of D9 is stricter than the TTC-concept (0.15 µg/day). Following TTC calculation the maximum tolerable amount of $0.15x10^{-3}$ mg/day corresponds to a FSD of D8.	

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		However, according to the structure for toxicological assessment given in the Decision Tree in the “Points to consider on non-clinical safety of homeopathic medicinal products of botanical, mineral and chemical origin” of HMPWG from July 2007 the TTC-approach is not necessary in this case, since the substance white phosphorus is sufficiently chemically characterized and not genotoxic. Therefore, a calculation of a PDE is appropriate. Concerning PDE the following can be taken into account: We agree with the NOAEL of 0.015 mg/kg/day and the reference study but we do not agree with the calculation of the acceptable amount using the RfD-concept, as due to the PtC the PDE-concept is more suitable. Both concepts differ in the selection of safety/ uncertainty factors: According to “Reference Dose (RfD): Description and Use in Health Risk Assessments” (*US EPA 1993*) the factors used for calculation are defined as follows: Standard Uncertainty Factors (UFs): Use a 10-fold factor when extrapolating from valid experimental results in studies using prolonged exposure to average healthy humans. This factor is intended to account for the variation in sensitivity among the members of the human population and is referenced as "10H". Use an additional 10-fold factor when extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or are inadequate. This factor is intended to account for the uncertainty involved in extrapolating from animal data to humans and is referenced as "10A". Use an additional 10-fold factor when extrapolating from less than chronic results on experimental animals when there are no useful long-term human data. This factor is intended to account for the uncertainty involved in extrapolating from less than chronic NOAELs to chronic NOAELs and is	

Section number and heading	Interested party	Comment and Rationale	Outcome
		referenced as "10S". Use an additional 10-fold factor when deriving an RfD from a LOAEL, instead of a NOAEL. This factor is intended to account for the uncertainty involved in extrapolating from LOAELs to NOAELs and is referenced as "10L". Modifying Factor (MF): Use professional judgment to determine the MF, which is an additional uncertainty factor that is greater than zero and less than or equal to 10. The magnitude of the MF depends upon the professional assessment of scientific uncertainties of the study and data base not explicitly treated above; e.g., the completeness of the overall data base and the number of species tested. The default value for the MF is 1. According to ICH Q3D the factors used for a PDE-calculation are defined differently: PDE = NO(A)EL x Mass Adjustment/[F1 x F2 x F3 x F4 x F5] (A.1.1) The PDE is derived preferably from a NO(A)EL. If no NO(A)EL is obtained, the LO(A)EL may be used. Modifying factors proposed here, for relating the data to humans, are the same kind of "uncertainty factors" used in Environmental Health Criteria (Ref. 2), and "modifying factors" or "safety factors" in Pharmacopeial Forum. The modifying factors are as follows: F1 = A factor to account for extrapolation between species F1 = 1 for human data F1 = 5 for extrapolation from rats to humans F1 = 12 for extrapolation from mice to humans F1 = 2 for extrapolation from dogs to humans F1 = 2.5 for extrapolation from rabbits to humans F1 = 3 for extrapolation from monkeys to humans	

Section number and heading	Interested party	Comment and Rationale	Outcome
		F1 = 10 for extrapolation from other animals to humans F1 takes into account the comparative surface area: body mass ratios for the species concerned and for man. Surface area (S) is calculated as: S = kM0.67 (A.1.2) in which M = body mass, and the constant k has been taken to be 10. The body masses used in Equation A.1.2 are those shown below in Table A.1.1. F2 = A factor of 10 to account for variability between individuals A factor of 10 is generally given for all elemental impurities, and 10 is used consistently in this guideline F3 = A variable factor to account for toxicity studies of short-term exposure F3 = 1 for studies that last at least one half lifetime (1 year for rodents or rabbits; 7 years for cats, dogs and monkeys) F3 = 1 for reproductive studies in which the whole period of organogenesis is covered F3 = 2 for a 6-month study in rodents, or a 3.5-year study in non-rodents F3 = 5 for a 3-month study in rodents, or a 2-year study in non-rodents F3 = 10 for studies of a shorter duration In all cases, the higher factor has been used for study durations between the time points, e.g., a factor of 2 for a 9-month rodent study. F4 = A factor that may be applied in cases of severe toxicity, e.g., non-genotoxic carcinogenicity, neurotoxicity or teratogenicity. In studies of reproductive toxicity, the following factors are used: F4 = 1 for fetal toxicity associated with maternal toxicity F4 = 5 for fetal toxicity without maternal toxicity F4 = 5 for a teratogenic effect with maternal toxicity F4 = 10 for a teratogenic effect without maternal toxicity F5 = A variable factor that may be applied if the NOEL was not established F5 = 1 for a NOEL F5 = 1-5 for a NOAEL F5 = 5-10 for a LOEL F5 = 10 for a Lowest-Observed-Adverse-Effect Level (LOAEL)	

Section number and heading	Interested party	Comment and Rationale	Outcome
		The main differences between the RfD-approach and the PDE-approach are 1.) the factor to account for extrapolation between species (please refer also to the general comment regarding the PDE-approach) and 2.) the variable factor to account for toxicity studies of short-term exposure Comparison of the two approaches: In both cases, the reference study is the same: Condray, J.R. 1985. Elemental yellow phosphorus one-generation reproduction study in rats. IR-82-215; IRD No. 401-189. Monsanto Company, St. Louis, MO. Elemental yellow (white) phosphorus in corn oil was administered orally by gavage to groups of 15 males and 30 female Sprague-Dawley rats at doses of 0, 0.005, 0.015, or 0.075 mg/kg/day beginning at 80 days prior to mating and continuing through weaning of two complete reproductive cycles. **RfD-calculation** according to the Chemical Assessment Summary for white phosphorus is as follows *(US EPA 1993*): **I.A.3. Uncertainty and Modifying Factors (Oral RfD)** UF — This uncertainty factor includes a factor of 10 for interspecies diversity, 10 for intraspecies diversity, and 10 for incomplete reproductive/ developmental data and a less than adequate lifetime study. → 1000 MF — None → 1 RfD = 0.015 mg/kg/day / 1000 = 0.015 µg/kg/day **PDE-calculation**: A factor of 5 for interspecies diversity (taking into account the comparative surface area: body mass ratios for the species concerned, here for rat, and	

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		for man), 10 for intraspecies diversity, and 1 for reproductive studies in which the whole period of organogenesis is covered → 50 The differences lie in the more differentiated determination of the factor for interspecies diversity (RfD-concept uses always a factor of 10 while PDE-concept uses different factors taking into account the comparative surface area: body mass ratios for the species concerned and for man) and in the factor used for reproductive studies. The PDE-calculation is as follows: PDE = 0.015 mg/kg/day x 50 kg/[5 x 10 x 1 x 1 x 1] = 0.015 mg/day = 15 µg/day An additional weight adaption is not necessary, because: • F1 takes into account the comparative surface area: body mass ratios which is more precise than only the comparison of body weights • F1 can be lower than 10 • F2 is always 10 • The relatively low average body weight of 50 kg is used in the equation for calculating the PDE, which is a further additional safety factor. Divided by F2 = 10, a body weight of 5 kg results. This is near to the body weight of a newborn • If comparing the more precise body surface areas of adults (1.73 m^2) and newborns (0.25 m^2) to account for the variability between individuals, a factor of 7 results which is below the factor F2 = 10 It can therefore be assumed that with the factor F2 = 10 all differences between the individuals are already compensated and, together with the other numerous safety factors, an additional weight adjustment is not provided for in this approach. This is also reflected in the result of the calculation of a PDE, which is given with x mg/day, without the unit kg. Please refer also to the general comment about PDE.	

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		10 g D3 = 11 mg P ➔ 10 g D6 = 11 µg P (< acceptable amount of 15 µg P/day)	
Strychnos ignatii Ph. Eur. **(HAB 4a)**	ECHAMP	According to the points to consider the LHRD-approach is suitable: The lowest reported human therapeutic dose is 0.16 mg strychnine/kg (*CVMP 1999*). For neonates a dose of 0.48 mg strychnine results. Devided by 100 (following the LHRD-approach), 4.8 µg strychnine per day are safe. ➔ 10 g of Strychnos ignatii D5 are safe for neonates. Remark: the name of the stock in Ph. Eur. is Ignatia.	
Strychnos ignatii Ph. Eur. (Ph. franc.)	ECHAMP	According to the points to consider the LHRD-approach is suitable: The lowest reported human therapeutic dose is 0.16 mg strychnine/kg (*CVMP 1999*). For neonates a dose of 0.48 mg strychnine results. Devided by 100 (following the LHRD-approach), 4.8 µg strychnine per day are safe. ➔ 10 g of Strychnos ignatii D5 are safe for neonates. Remark: the name of the stock in Ph. Eur. is Ignatia.	
Add rows as appropriate.			

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