14 March of 2019
5th 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

5th List of First Safe Dilutions (FSD) as released for public consultation on 18th December 2018 until 19th March 2019.

Organisation or individual	Contact details (e-mail address, telephone number, name of contact person)
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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	**PDE and weight adjustment** Regarding the PDE calculation, the additional weight adjustment to 3 kg bodyweight is not appropriate. A detailed justification and statement is attached. For further details please refer to the pdf-file "general comment – PDE and weight adjustment".	
ECHAMP	**Effect of selection of literature reference on FSD in comparison with each other** In HMPWG practice, neonatal nutritional needs or the mean intakes from breast milk are sometimes used as literature references for toxicological evaluation. But nutritional needs or mean intakes of neonates are no toxicological data and therefore do not meet the requirements as an adequate reference for a toxicological assessment. The consequences become clear when comparing FSD. For Kreosotum for example the TDI of phenol (= toxicological data) is used for the assessment and an FSD of D4 results. The European GHS Classification for Kreosotum is Category 3 for oral acute toxicity. On the other hand, for Natrium nitricum the Reference Dose for Oral Exposure (RfD) was used as reference which also results in an FSD of D4. In terms of toxicity, Natrium nitricum is not classified as toxic according to the European GHS Classification. The consequences become even clearer looking at the evaluation of Ferrum metallicum from the 4th list of FSD is considered. The mean intakes of breast fed neonates are used as reference for the toxicological evaluation. An FSD of D5 results. In terms of toxicity, Ferrum metallicum is not classified as toxic according to the European GHS Classification. Moreover, in the case of oral intake of even higher doses of metallic iron, absorption is to be expected only to a small extent because the capacity of	

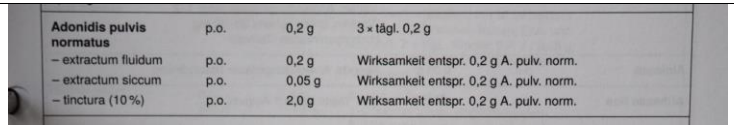
Interested party	Comment and Rationale	Outcome
	the gastric acid is limited with respect to the absolutely necessary ionization for the absorption (*GESTIS Substance database*). These examples illustrate that substances that are classified as non-toxic according to HMPWG result in being equally dangerous or even more dangerous in the assessment of FSD than substances that are officially classified as toxic. This is an imbalance that arises based on the selection of literature references. As a rule, toxicological relevant data should be used for the assessment of FSD to avoid this imbalance.	
ECHAMP	**Whole plant material** If there is no specification on the content of the toxicological relevant component in monographs, as a rule the whole plant material (100 %) is classified as the toxicologically relevant component. This is highly unrealistic. Secondary metabolites as e.g. naphthoquinones or alkaloids have no fundamental role in maintaining life processes of plants, but they are important for plants adaption to environment and defense processes. Therefore, content of plants secondary metabolites is often very low, with less than 1% of dry weight (1) (*Ramakrishnan & Ravishankar 2011, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3329344/pdf/psb-6-1720.pdf*). Thus, it reasonable to use a worst-case assumption of e.g. 10 % of these secondary metabolites in the plant for the calculation of the FSD, if no data is available. Furthermore, if literature data on the toxicologically relevant component is available, it should be accepted as a basis for calculation, possibly with an additional appropriate safety factor.	

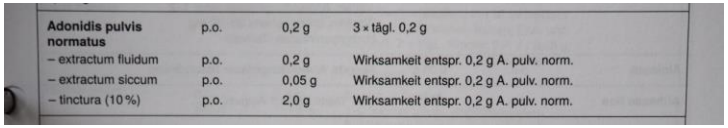
Interested party	Comment and Rationale	Outcome
	Both approaches are closer to reality than using the whole plant material for the calculations. **Conclusion** Literature data concerning secondary ingredients in general and for toxicologically relevant components in plants should be considered, where appropriate, with appropriate safety factors (e.g., 10%), even if there are no specifications for the toxicologically relevant components in the monograph. This has already been done, for example, for the evaluation of Phytolacca, by using the toxic component concentration of 30 % constituents of possible concern, which is published in the EMA-MRL document on Phytolacca (*EMEA/MRL/600/99-Final, 1999*). We appreciate this first approach a lot.	
ECHAMP	As commented below for Kreosotum, Convallaria (both HAB 2018) and Ranunculus (HAB 2017), there have been changes in some monographs in course of preparing the 5st list of First Safe Dilutions. In view of the long period used for data collection this can happen easily. Anyhow, since this can considerably alter the respective assessments and needs a lot of resources for commenting and correction afterwards, we plea to conduct a final check of status of underlying Pharmacopeia references before starting the consultation process.	
ECHAMP	Selection of data for calculation of FSD: Instead of generally using the lowest literature value for a toxicological effect we advocate to use the best data concerning quality and comparable application route. For a sound assessment the data should be as most reliable as possible. For example see the comment for Adonis vernalis below.	
ECHAMP	In column 4 there are used different units/names in case of calculation with LHRD. Mostly LHRD is used, but in single cases LHRD/100 is written. This	

Interested party	Comment and Rationale	Outcome
	is confusing and should be unified.	
ECHAMP	We propose for plant material containing cardiac glycosides e.g. Adonis vernalis, Convallaria majalis, Digitalis, Nerium oleander and Urginea maritima the exclusion from the TTC concept. The identified data of these relevant components showed neither genotoxic nor carcinogenic potential. Furthermore, these plant materials have a long history of use in herbal medicine therapy or as single components in allopathic medicinal products. For the assessment, and to establish a reasonable FSD, the application of e.g. the LHRD/100 concept (or likewise) seems sufficient and appropriate.	
Add rows as appropriate.		

SPECIFIC COMMENTS ON TEXT

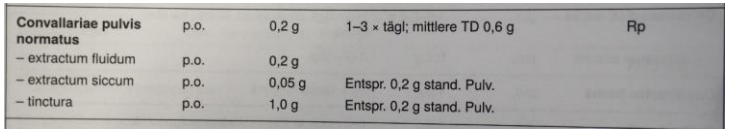
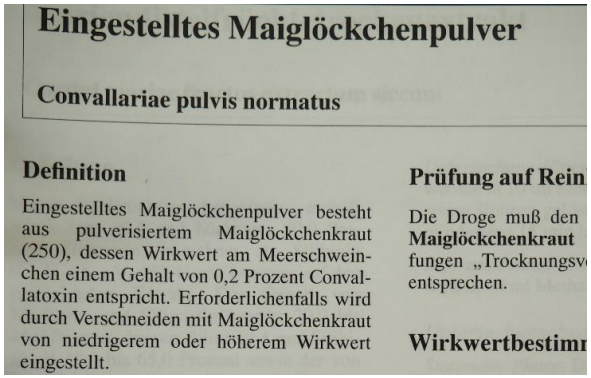
Section number and heading	Interested party	Comment and Rationale	Outcome
Adonis vernalis HAB	ECHAMP	We suggest to use the oral LHRD for calculation of FSD as the product is used for oral application. It is more scientific to calculate with the same application route. On the one hand, there is a recommended daily dosage “Normdosis” for Adonis vernalis of 0,6 g Adonis pulvis normatus with a standardized content of Cymarine (content of 0,2% Cymarin DAB 2012), which is equal to 0,0012 g Cymarin.	

Section number and heading	Interested party	Comment and Rationale	Outcome
		 Reference: Normdosen 2018/ DAB 2012 Calculation of FSD: LHRD: 1200 µg Cymarin LHRD/ 100: 12 µg Cymarin Calculation for neonate: 12 µg/60*3 = 0,6 µg Therefore the acceptable amount for neonates is 0,6 µg Cymarin 10 g Adonis vernalis D4 contain 0,1 µg Cymarin: No change of FSD = D4, but **change of toxic component concentration to 0.6 µg Cymarine per day** On the other hand, there is an oral LHRD = 7.5 mg/day cardenolides (60 kg) according to EMEA/MRL/1998 for Adonis, corresponding to LHRD/100 = 75 µg/day, corresponding to 75/60x3 = 3.75 µg/day (3 kg neonates) is suggested. Using 0.0050% cymarin in the stock and LHRD/100 = 3.75 µg/day: 10 g D3 contain 1 µg cymarin **FSD = D3**	
Adonis	ECHAMP	We suggest to use the oral LHRD for calculation of FSD as	

Section number and heading	Interested party	Comment and Rationale	Outcome
vernalis Ph.Franc.		the product is used for oral application. It is more scientific to calculate with the same application route. On the one hand, there is a recommended daily dosage “Normdosis” for Adonis vernalis of 0,6 g Adonis pulvis normatus with a standardized content of Cymarine (content of 0,2% Cymarin DAB 2012) which is equal to 0,0012 g Cymarin.  Reference: Normdosen 2018/ DAB 2012 Calculation of FSD: LHRD: 1200 µg Cymarin LHRD/ 100: 12 µg Cymarin Calculation for neonate: 12 µg/60*3 = 0,6 µg Therefore the acceptable amount for neonates is 0,6 µg Cymarin 10 g Adonis vernalis D4 contain 0,3 µg Cymarine Therefore change of FSD; **FSD =D4 instead of D5** On the other hand, there is an oral LHRD = 7.5 mg/day cardenolides (60 kg) according to EMEA/MRL/1998 for Adonis, corresponding to LHRD/100 = 75 µg/day,	

Adonidis pulvis normatus	p.o.	0,2 g	3 × tägl. 0,2 g
– extractum fluidum	p.o.	0,2 g	Wirksamkeit entspr. 0,2 g A. pulv. norm.
– extractum siccum	p.o.	0,05 g	Wirksamkeit entspr. 0,2 g A. pulv. norm.
– tinctura (10 %)	p.o.	2,0 g	Wirksamkeit entspr. 0,2 g A. pulv. norm.

Section number and heading	Interested party	Comment and Rationale	Outcome
		corresponding to 75/60x3 = 3.75 µg/day (3 kg neonates) is suggested. With 0.03 % max cardenolides in the stock: 10 g D3 contain 3 µg cardenolides **FSD = D3**	
Causticum Ph. Franç.	ECHAMP	It is not clear what is meant with “solution”. We understand it as the distillate, which is the stock. Please correct the mistake: The solution (= distillate) is not equal to the D1. The solution (= distillate) is the stock. **FSD = stock**	
Convallaria majalis HAB	ECHAMP	HMPWG used an old literature with another tincture (tincture 1:8) and refers to dried plant material while the mother tincture according to HAB (2018) is prepared with fresh aerial parts, containing 0.008 – 0.030 % (m/m) steroidal glycosides, calculated as convallatoxin. Since the toxic component concentration is mentioned in the HAB 2018 with max. 0.03 % steroid glycosides in the MT calculated as convallatoxin, the FSD-calculation based on the whole plant material is not comprehensible. It is more scientific to use the LHRD based on an exact amount of Convallatoxin for calculation of FSD. On the one hand, there is a recommended daily dosage “Normdosis” for Convallaria majalis of min. 0,2 g Convallariae pulvis normatus with a standardized content of Convallatoxin (content of 0,2% Convallatoxin DAB	

Section number and heading	Interested party	Comment and Rationale	Outcome
		2012), which is equal to 0,4 mg Convallatoxin. Reference Normdosen 2018/ DAB 2012  	
		Calculation of FSD: LHRD: 400 µg Convallatoxin LHRD/ 100: 4 µg Convallatoxin Calculation for neonate: 4 µg/60*3 = 0,2 µg Therefore the acceptable amount for neonates is 0,2 µg Convallatoxin Convallaria majalis MT (HAB 3a) contains max. 0,03 % (m/m) stereoglycosids calculated as Convallotoxin (HAB) 10 g MT contain 3 mg Convallatoxin 10 g D1 contain 0,9 mg Convallatoxin	

Section number and heading	Interested party	Comment and Rationale	Outcome
		10 g D5 contain 0,09 µg Convallatoxin Therefore change of FSD; **FSD =D5 instead of D6** On the other hand, with an assumed maximum amount of 1 % glycosides in dried plant material (Convallaria flos) [Hager 2018] the LHRD of 1.125 mg dried plant material equals 11.25 µg total glycosides. Therefore, the calculated threshold in terms of glycosides would be 187.5 ng/kg b.w. corresponding to 562.5 ng/3kg/day Therefore change of FSD; **FSD =D5 instead of D6** Furthermore, according to *EMEA/MRL/1998 for Convallaria majalis*, there is a LHRD = 7.2 mg/day cardenolides (60 kg), corresponding to LHRD/100 = 72 µg/day, corresponding to 72/60x3 = 3.6 µg/day (3 kg neonates). Using 0.030% cardenolides in the stock and LHRD = 3.6 µg/day: 10 g D4 contain 0.9 µg cardenolides **FSD = D4** Please notice: Convallaria 18c: is missing → please add in the 5th list of FSD Using 0.035% cardenolides in the stock and LHRD = 3.6	

Section number and heading	Interested party	Comment and Rationale	Outcome
		µg/day: 10 g D4 contain 1.05 µg cardenolides **FSD = D4**	
Convallaria majalis Ph.Franc.	ECHAMP	Regarding the toxic component concentration please refer to the general comment “Whole plant material”.	
Digitalis purpurea HAB	ECHAMP	It is suggested to use for LHRD reasoning, the maintenance dose of digitoxine for neonates from 0 to 1 month from the French Pharmacopoeia Posologie, which is 5 µg/kg/day (instead of 4 µg/kg/day), corresponding to LHRD/100 = 5x3/100 = 0.15 µg/day (for 3 kg neonates) Using 0.013% digitoxin in the stock and LHRD/100 = **0.15 µg/day**: 10 g D5 contain 0.026 µg digitoxin **FSD = D5** **No change in FSD, but in the acceptable amount**	
Digitalis purpurea Ph. Franç	ECHAMP	This entry should be deleted, because Digitalis 1.1.10 has no more monograph in the French Pharmacopoeia	
Kreosotum HAB	ECHAMP	The specification in the HAB monograph has been changed. According to HAB 2018 the content of Kreosotum D1 is 6.5-7.8% of total phenols. It does not change the resulting FSD, but the data and the calculation should be corrected. 10 g D1 contains 780 mg phenol	

Section number and heading	Interested party	Comment and Rationale	Outcome
		10 g D4 contains 0.78 mg phenol	
Nerium oleander HAB	ECHAMP	We suggest using an LHRD/100 for calculation of FSD instead PDE concept as LHRD is also used for other cardiac glycosides containing plants. There is an LHRD available based on “Teep“ (fresh plant trituration). One tablet contains 0.025 g fresh plant material. Dosage: 3 tablets per day (0.075 g fresh plant material) **Dosierung:** **Übliche Dosis:** 0,05 g Fol. Oleandri in Pillen (Leclerc); 15 Tropfen Folinerin-Tropflösung dreimal täglich (15 Tropfen enthalten 0,2 mg Folinerin = 240 FD. pro Dosis). Nach 8 Tagen verringert man die Dosis. 20 Zäpfchen Folinerin rektal in 8—14 Tagen (jedes Zäpfchen enthält 0,2 mg Glykosid) (Schwab). 1 Tablette der Frischpflanzenverreibung „Teep“ dreimal täglich. (Die „Teep“-Zubereitung ist auf 10% eingestellt, d. h. 1 Tablette enthält 0,025 g Pflanzensubstanz = etwa 100 FD. Zum Vergleich sei darauf hingewiesen, daß 0,1 g Folia Digitalis 200 FD. enthält.) Reference: Madaus, G. Lehrbuch der Biologischen Heilmittel Band III https://books.google.de/books?id=u8VFdY3kSiUC&pg=PA2015&lpg=PA2015&dq=Folinerin+Dosierung&source=bl&ots=sPEphzprtG&sig=ACfU3U2ghuxl9_X5Ou8gKnn_j-UCE0kfQA&hl=de&sa=X&ved=2ahUKEwiU5YeMlafgAhWN2qQKHRbjBuoQ6AEwAHoECAAQAQ#v=onepage&q=Folinerin%20Dosierung&f=false Calculation of FSD: LHRD = 75 mg fresh plant material	

Section number and heading	Interested party	Comment and Rationale	Outcome
		LHRD/100: 0,75 mg fresh plant Calculation for neonate: 0,75 mg /60*3 = 37,5 µg Therefore, the acceptable amount for neonates is 37,5 µg fresh plant 10 g Nerium oleander D1 contain 1666,67 mg fresh plant material 10 g Nerium oleander D6 contain 16,7 µg fresh plant Therefore, change of FSD; **FSD =D6 instead of D8** This additionally supported by the PDE calculation with Oleander extract used in a human study* = 415 ng Toxic component concentration: maximum of 2 % cardiac glycosides (calc. as cardenolide) in the dried leaves (Oleandri folium) [Hager 2018]. 10 g Nerium oleander D1 = 666.67 mg dried plant material corresponds to 13.33 mg glycosides. → 10 g Nerium oleander D6 =130 ng cardenolide corresponding to 43.3 ng/3 kg/day (=FSD D6) Therefore, change of FSD; **FSD =D6 instead of D8** * LOAEL 0.0083 mg/kg (F1 and F4 not applicable): (0.0083 x 50)/(10 x 10 x 10) = 415 ng "First-in-human study of pbi-05204, an oleander derived inhibitor of akt, fgf-2, nf-κB and p70s6k, in patients with advanced solid tumors" *Hong DS et al. 2014, Invest New Drugs (2014) 32;1204-1212*	

Section number and heading	Interested party	Comment and Rationale	Outcome
Nicotiana tabacum HAB See Tabacum	ECHAMP	We suggest to use a PDE for nicotine: There is an oral TD_{low} of nicotine for femal rats (*RTECS 2014*) of 59.4 mg/kg in 22 days. This results in a NOEL of 2.7 mg nicotine/kg/day. A PDE can be calculated: PDE = 2.7 mg/kg/day x 50 kg / (5 x 10 x 1 x 5 x 5) = 0.11 mg/day. 10 g Nicotina tabacum D4 contain 25 µg nicotine FSD = D4 We are of the opinion that the PDE calculation with a weight adjustment to 50 kg is sufficiently safe for all age groups, as described in the general comment “PDE and weight adjustment”. For the sake of completeness, however, a PDE-calculation with a weight adjustment to 3 kg is added. PDE = 2.7 mg/kg/day x 3 kg / (5 x 10 x 1 x 5 x 5) = 6.5 µg/day. 10 g Nicotina tabacum D5 contain 2.5 µg nicotine FSD = D5	
Tabacum Ph. Française	ECHAMP	We suggest to use a PDE for nicotine: There is an oral TD_{low} of nicotine for femal rats (*RTECS 2014*) of 59.4 mg/kg in 22 days. This results to a NOEL of 2.7 mg nicotine/kg/day. A PDE can be calculated:	

Section number and heading	Interested party	Comment and Rationale	Outcome
		PDE = 2.7 mg/kg/day x 50 kg / (5 x 10 x 1 x 5 x 5) = 0.11 mg/day. 10 g Nicotiana tabacum D4 contain 100 µg dried plant material FSD = D4 We are of the opinion that the PDE calculation with a weight adjustment to 50 kg is sufficiently safe for all age groups, as described in the general comment “PDE and weight adjustment”. For the sake of completeness, however, a PDE-calculation with a weight adjustment to 3 kg is added. PDE = 2.7 mg/kg/day x 3 kg / (5 x 10 x 1 x 5 x 5) = 6.5 µg/day. 10 g Nicotiana tabacum D6 contain 1 µg dried plant material FSD = D6 Regarding the toxic component concentration please refer to the general comment “Whole plant material”.	
Phytolacca americana HAB	ECHAMP	A general comment on the presentation: The information in column 9 is incomplete concerning status of plant material and should be supplemented. Calculation is based on LHRD of 60 mg/d of **dried** plant material → LHRD/100 = 0.6 mg/d (**dried!**) plant material,	

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		considering 30 % toxicologically relevant compounds as reported by EMEA/MRL/600/99-Final, 1999 → 180 µg/d constituents of possible concern → 180 ÷ 60 x 3 = 9 µg/d constituents of possible concern (neonate) Calculation is confusing because in the table the difference between dried and fresh plant is not made. We therefore propose to adopt the procedure as carried out by the calculation method used for Nerium oleander. Please adjust column 7 as follows: 10 g Phytolacca americana D1 = 1666.67 mg fresh/ 666.67 mg dried plant material = 200.0 mg of constituents of possible concern → 10 g Phytolacca americana D6 = 2.0 µg constituents of possible concern Other comments concerning the general method of calculation: - The cited EMA paper (*EMEA/MRL/600/99-Final, 1999*) supports our argument that in case of safety concerns a calculation with the whole plant material is neither necessary nor useful. Citing the calculation with the *indeed estimated value of 30%* of substances of possible concern shows that this is	

Section number and heading	Interested party	Comment and Rationale	Outcome
		a reasonable way of calculation for plants without content values in an official monograph. - In Germany, the lowest permitted potency of Phytolacca americana was D4 for a long time due to mitogen content of the plant and suspected toxicological effects. In 2004, the BfArM then informed that the evaluation of new studies has proven that homeopathic preparations for oral use in usual dosages are safe up from the mother tincture. Corresponding marketing authorizations and registrations were issued and are valid today. Therefore, we kindly ask that the newer evidence available to the public authorities is used for the assessment and not the guideline (*EMEA / MRL / 600/99-Final, 1999*) with its old data is used as reference.	
Ranunculus bulbosus HAB	ECHAMP	The rationale for using the TTC approach by HMPWG is genotoxicity suspicion for the protoanemonine constituent in conjunction with limited data set. Anyhow, the data basis for calculation of the HAB preparation of Ranunculus is no longer valid for the following reasons: 1) There has been an update of HAB monograph in 2017 with a newly introduced limit of 0.05 – 0.15% protoanemonin in mother tincture. Therefore, it is not	

Section number and heading	Interested party	Comment and Rationale	Outcome
		necessary to calculate with the whole plant material. 2) Additionally, in course of a deficiency letter procedure concerning Ranunculus with BfArM in 2010 it has been concluded that there is no need to calculate with a TTC value of 0.15µg/day for protoanemonin. It could be shown by using the Toxtree tool (https://ec.europa.eu/jrc/en/scientific-tool/toxtree-tool) that the chemical structure of protoanemonin do not rise a genotoxicicity suspicion. Therefore it was calculated with a value of 1.5µg/day. For detailed explanation please see the attached document: Ranunculus_argumentation.pdf This argumentation was later supported by a publication of Schrenk et al. (2013)* on protoanemonin in *Pulsatilla pratensis*, which concluded that “based on structural alerts protoanemonin is classified as a Cramer class III compound with the threshold of toxicological concern (TTC) of 180 µg/day . Neither computer aided toxicology methods (Toxtree and Derek Nexus®) nor a literature search revealed any evidence of genotoxic, carcinogenic or teratogenic potential of protoanemonin”. Schrenk et al. refers here to the updated concept of Munro et al. (published in 2008), resulted in a corrected Class III TTC value of 180 µg/person perday instead of 90 µg/person per day.	

Section number and heading	Interested party	Comment and Rationale	Outcome
		Following the above, FSD for Ranunculus (HAB) can be calculated as follows: Ph. Eur. 1.1.5 (HAB 3a): D1 = 3 MT + 7 ethanol Maximum protoanemonin content (0.15 %) in 10g MT: → 15 mg Maximum protoanemonin content in 10g D1: → 4.5 mg Maximum protoanemonin content in 10g D4: → 4.5 µg Maximum protoanemonin content in 10g D5: → 0.45 µg In case of calculation with the TTC value of 0,15 µg/day given by HMPWG, the FSD would be D6. In case of calculation with a Cramer class III-based value of 90 µg **FSD is D3**. The TTC concept including the Cramer classes and the associated maximum values are designed to apply per person and therefore no further weight adjustment is foreseen. For the sake of completeness, however, an additional calculation with a weight adjustment to 3 kg is added. In case of calculation with a Cramer class III-based value of 4.5 µg for a 3kg-newborn, **FSD is D4**. * Schrenk, D., et al. (2013). "Feasibility study of nonclinical safety assessments on homeopathic preparations using the example of protoanemonin in Pulsatilla pratensis L." Regul	

Section number and heading	Interested party	Comment and Rationale	Outcome
		Toxicol Pharmacol 66(1): 104-108.	
Ranunculus bulbosus Pharm. Franç.	ECHAMP	The rationale for using the TTC approach by HMPWG is genotoxicity suspicion for the protoanemonine constituent in conjunction with limited data set. The data basis for calculation of the preparation of Ranunculus is no longer valid for the following reason: In course of a deficiency letter procedure concerning Ranunculus with BfArM in 2010 it has been concluded that there is no need to calculate with a TTC value of 0.15µg/day for protoanemonin. It could be shown by using the Toxtree tool (https://ec.europa.eu/jrc/en/scientific-tool/toxtree-tool) that the chemical structure of protoanemonin do not rise a genotoxicicity suspicion. Therefore it was calculated with a value of 1.5µg/day. For detailed explanation please see the attached document: Ranunculus_argumentation.pdf This argumentation was later supported by a publication of Schrenk et al. (2013)* on protoanemonin in *Pulsatilla pratensis*, which concluded that “based on structural alerts protoanemonin is classified as a Cramer class III compound with the threshold of toxicological concern (TTC) of 180 µg/day. Neither computer aided toxicology methods (Toxtree and Derek Nexus®) nor a literature search	

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		revealed any evidence of genotoxic, carcinogenic or teratogenic potential of protoanemonin". Schrenk et al. refers here to the updated concept of Munro et al. (published in 2008), resulted in a corrected Class III TTC value of 180 µg/person per day instead of 90 µg/person per day. Following the above, FSD for Ranunculus bulbosus can be calculated as follows: Calculation with the whole plant material: Ph. Eur. 1.1.10 10 g MT: → 1 g fresh plant material 10 g D1: → 100 mg fresh plant material 10 g D6: → 1 µg fresh plant material In case of calculation with a Cramer class III-based value of 90 µg **FSD is D5**. The TTC concept including the Cramer classes and the associated maximum values are designed to apply per person and therefore no further weight adjustment is foreseen. For the sake of completeness, however, an additional calculation with a weight adjustment to 3 kg is added. In case of calculation with a Cramer class III-based value of 4.5 µg for a 3kg-newborn, **FSD is D6**.	

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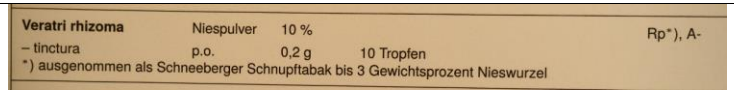
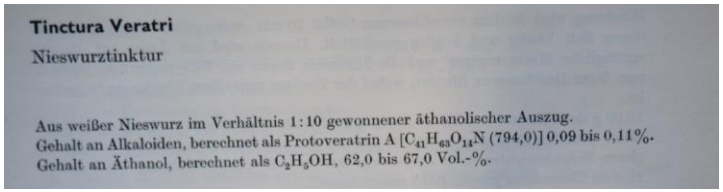
		* Schrenk, D., et al. (2013). "Feasibility study of nonclinical safety assessments on homeopathic preparations using the example of protoanemonin in Pulsatilla pratensis L." Regul Toxicol Pharmacol 66(1): 104-108.	
Urginea maritima HAB	ECHAMP	We kindly ask to submit the reference for the used LHRD (30 mg/day). The literature available to us gives at least a minimum dose of 60 mg/day or more. The mention of the scilliroside content is confusing because it does not matter for the actual calculation. This takes place exclusively based on the whole plant material.	
Veratrum album Ph. Franç.	ECHAMP	We do not agree with considering the whole plant material instead of alkaloids expressed in protoveratrin. Regarding the toxic component concentration please refer to the general comment “Whole plant material”. Since this is not clear, we suggest using an LHRD/100 for calculation of FSD instead PDE concept. There is a LHRD available for Veratri rhizome for tincture. Dosierung & Art der Anwendung Zur Einnahme als Pulver 0,02 bis 0,10 g pro Tag [118]. Innerlich: Tinktur 20 bis 60 Tr. pro Tag [118]. Äußerlich: 5 g Tinktur in einer Mischung aus 10 g Lanolin und 20 g Schmalz [118]. References: Hager Rom 2014/ Leclerc H (1976) Précis de Phytothérapie, Nachdruck 1983, Masson, Paris, S. 323–326 There is also a standard dose (Normdosis) for the tincture (AB DDR) available : 0,2 g	

Section number and heading	Interested party	Comment and Rationale	Outcome
		  Reference: Normdosen gebräuchlicher Arzneistoffe und Drogen 2018/ AB DDR 1975 Calculation LHRD based on 0,2 g Tinctura Veratri (1:10) which contain 0,02 g plant. LHRD/100: 0,2 mg Calculation for neonate: 0,2 mg /60*3 = 10 µg Therefore the acceptable amount for neonates is 10 µg whole plant material 10 g Veratrum album MT contain 1000 mg raw material 10 g Veratrum album D5 contain 10 µg raw material Therefore change of FSD; **FSD =D5 instead of D7**	

Appendices

General comment- PDE and weight adjustment

Ranunculus argumentation

Literature References

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