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<doc ref> Guidance on non-clinical documentation in applications for registration of homeopathic medicinal products for human use.

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**

Submission of comments on draft document

Table 1: Origin of comments

Guidance on non-clinical documentation in applications for registration of homeopathic medicinal products for human use

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	We appreciate adequate guidance for the assessment on the safety on Homeopathic Medicinal Products, and especially that evaluation is based on a *daily acceptable amount* and that there are cases where a full safety assessment is not expected. We also welcome that, *same non-clinical regulations and guidelines apply to homeopathic medicinal products (HMPs) as to all other medicinal products*. (Quotations from 1 Introduction, page 7) Nevertheless, we see that the latter principle is not followed in certain points without giving sound scientific reasons, as we explain in our specific comments hereunder. From a toxicological point of view there is no justification to use double standards in toxicological risk assessment. The dose makes the toxicity, not the registration category of a specific substance. Furthermore, we think that the document should be up-dated to the state of scientific knowledge. The literature reference given in the guideline are until year 2018, but further relevant toxicological knowledge has been published since then and should be taken into consideration. Please see our literature references in the specific comments. We would appreciate the opportunity for a personal exchange, e.g. in a dialogue meeting with HMPWG and other associations about this topic because it is of great importance for the homeopathic industry.	

SPECIFIC COMMENTS ON TEXT

Section number and heading	Interested party	Comment and Rationale	
Abbreviatons Pages 4-5	ECHAMP	Minor observations: -delete commas in p. 4 line 17, p. 4 line 20, p. 5 line 27, p. 5 line 31 -the abbreviation linked to Ph. Eur in p. 5 line 19 is not well placed.	
Introduction Page 7 line 11	ECHAMP	We appreciate very much that the focus of the non-clinical evaluation lies on a daily acceptable amount, and not on First Safe Dilution (FSD).	
4.1 page 9 lines 8-10	ECHAMP	Basing the evaluation on the whole raw material in case the causative toxic component is not known or a maximum content is not defined in the pharmacopoeial monograph, significantly overestimates the risk and is unrealistic. It should be accepted to calculate with 1) internal data on the content of the relevant toxicological compound including analytical methods and specifications with an upper limit in the respective inhouse monographs 2) literature data or analytic data from other pharmacopoeias for comparable preparations (e.g. using conversion factors (CF manufacturing method) see: https://www.hma.eu/uploads/media/PtC_HMP_non_biological_safety.pdf 3) a content of 10 % of toxic components (= secondary plant metabolites). Rationale: Toxic components of plants (such as naphthoquinones or pyrrolizidine alkaloids) are secondary metabolites, which have no fundamental role in maintaining life processes of plants, but are important for plants adaption to the environment or defense against predators. Content of secondary metabolites in thus often	

		very low, with less than 1 % of dry weight (Ramakrishnan A, Ravishankar GA. Influence of abiotic stress signals on secondary metabolites in plants. Plant Signal Behav 2011;6(11):1720-31). It is thus scientifically reasonable to use a worst case assumption of 10% of these secondary metabolites in a mother tincture. Without providing scientific data it would not be adequate to refuse this approach. An alternative approach could be the dry residue of the mother tincture, if no other data is available and no volatile constituents are suspected to be of toxicological concern. Even this would be a worst case far away from real content of toxicological relevant compounds.	
Section 4.1.1 Page 9, Line 24	ECHAMP	In case there is a HMP already registered according to simplified registration in the EU which does include a safety assessment for the stock, reference to this registration should be sufficient (also if from another applicant) without submitting an own safety assessment. This situation is already the case and will become more and more relevant for the future. Please include this possibility at first into the list in line 19. Among the about 150 stocks evaluated in the Consolidated list of first safe dilutions of the HMPWG, the highest FSD is D9 (for only 3 stocks, all other are <D9). This is in line with an overall worst-case calculations for all homeopathic manufacturing methods based on all possible individual worst case factors (please see our comment and calculation under TTC, page 17). The result is that a potency of C5/D9 is the overall safe potency for all stocks except those containing /compounds mentioned in page 17 line 21-34. For this reason, please add under 4.1.1 between line 23 and 25 the following condition: *"(A full non-clinical evaluation is not required…)* *if the stocks of the product do not contain compounds*	

		listed under page 17 line 21-34 "excluded compounds", and if the stocks are used at a calculated final dilution equal or higher to C5 or D9. In this case a justification of this matter of fact in the non-clinical expert report will suffice. I	
4.1.2 page 10 figure 1	ECHAMP	General comment: It is unclear why the decision tree of the HMPWG document PtC on non-clinical safety from 2007 (further called "PtC 2007") was changed. We think that it was more suitable than the present evaluation scheme. Please see also details in the following.	
4.1.2 page 10 figure	ECHAMP	The decision tree does not foresee the possibility that there is already a registered HMP according to Art. 14 in the EU including a suitable safety assessment for the stock. This is already the case and will become more and more relevant for the future. In this case, reference to that product (including from another applicant) should be sufficient without submitting an own safety assessment. Please add this possibility into the decision tree above the box "safety assessment required"	
4.1.2 page 10 figure 1	ECHAMP	Like in the PtC 2007, one of the first decisions to make should be if the raw material is allowed as food or food constituent, with the reasoning that "… substances that are also used in food, the assessment of the safety should consider the fact that they are allowed as food or as a constituent of food and should refer to the existing data of the food and food supplements area." (quotation from PtC 2007 page 2 under 3.1). Furthermore, human data are of higher relevance than data from animal studies. So, "the food box" should be placed over the box "safety assessment required" for those stocks which are used in food without restriction. Only if maximum limits in food exist, a safety assessment is needed.	
4.1.2 page 10 figure 1	ECHAMP	The decision tree should be completed by an arrow from the box "toxicological data available" guiding to the box "Is sufficient chemical or phytochemical characterization available" (see decision tree for FSD in PtC 2007). Otherwise the direct route to 4.3.5 TTC where sufficient	

		chemical or phytochemical characterization available is not given. See also our comments referring to section 4.3.5 TTC. Additionally “yes” should be added to the arrow between the box “toxicological data available” and “known genotoxic, carcinogenic or teratogenic potential?”	
4.1.2 page 10 figure 1	ECHAMP	The decision arrow “no” guiding from the box “Is there sufficient evidence for a threshold mechanism” to “Toxicity data result in toxicity limit value” should be replaced by a decision arrow guiding directly to “is sufficient chemical or phytochemical characterization available?”. With the current decision arrows it would finally be possible to calculate a PDE without evidence for a threshold related mechanism.	
4.1.2 page 10 figure 1	ECHAMP	The box 4.3.4 LHRD/100” should be replaced by a box “4.3.4 LHRD” in line with the title of this section	
4.1.5 Page 11 Line 28 - 37		Please take into account our below comments regarding sections 4.3.4.LHRD and 4.3.6 PDE, and adapt this section accordingly. Please up-date the reference guidance to the current version	
4.1.5 page 11 line 29	ECHAMP	“after chronic administration” can be deleted, as in line 28 it is already written “after repeated administration”; “on consecutive days” should be shifted to line 28, following “after repeated administration”.	
4.1.6 page 12 line 13-14	ECHAMP	It is not necessary or compatible with animal welfare to require in vivo studies in case of “structural alerts”. Please modify into “*in vitro studies*” Moreover, it is not necessary or compatible with animal welfare to conduct an in vivo study in case of a positive result in the in vitro Ames test. HMPWG suggests itself to follow the stepwise testing strategy set out for herbals in EMEA/HMP/107079/2007. Here, the first step is an Ames test. In case of a positive result, and only if “the genotoxic response cannot be attributed to any specific constituent” a	

		second in vitro test (such as mouse lymphoma or other mammalian cell assays) has to be conducted. If this test result is “unequivocally positive and considered relevant either in gene mutation or chromosomal damage”, it is advisable to conduct an in vivo test. To avoid unnecessary tests in animals, the same procedure must apply to the genotoxicity testing for HMPs. Please modify the wording in lines 13-16 (replace “*mainly in vivo*”) in order to be in line with EMEA/HMP/107079/2007	
4.1.6 page 12 line 13	ECHAMP	please add “*with raw material or stock*” after positive results	
4.2.2. page 13 line 25	ECHAMP	Please include the following references 1) Buchholzer M-L, Kirch M, Kirchner C, Knoess W. Toxicological assessment compilation of selected examples of raw materials for homeopathic medicinal products. Regulatory Toxicology and Pharmacology. 2019. 103 p.253-273 2) Buchholzer M-L, Werner C, Knoess W. Regul Toxicol Pharmacol 2014 Mar;68(2):193-200. Current concepts on integrative safety assessment of active substances of botanical, mineral or chemical origin in homeopathic medicinal products within the European regulatory framework 3) concering Food supplements: add BELFrit List https://ec.europa.eu/growth/tools-databases/tris/en/search/?trisaction=search.detail&year=2017&num=276 4) FDA EAFUS has been changed to “substances added to food” See https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus 5) in silico tools should be added, since in silico is mentioned in section 4.1.6: e.g. Tox tree http://toxtree.sourceforge.net/ 6) official lists for plants used in food, e.g. BELFRIT. Ministry of Health. The document reports.	

		Attachment 1 to the Ministerial Decree of 10 August 2018 on the use of vegetable, substances and preparations in food supplements as updated by Decree 9 January 2019; Ministero della Salute, Italy: 'Allegato 1 al DM 10 agosto 2018 sulla disciplina dell'impiego negli integratori alimentari di Sostanze e preparati vegetali comeaggiornato con Decreto 9 gennaio 2018; Et al.	
Section 4.3.2 Page 14 line 26		Will the HMPWG work on the FSD-lists continue? Is it planned to up-date the FSD-lists regularly?	
Section 4.3.2, line 11, page15	ECHAMP	Extrapolation to other administration routes should be possible using the FSD data. Please include reference to ICH Q3D (Reference No. 19) regarding modifying factors based on oral bioavailability, as well as reference to the conversion factors in the PtC 2007 Table 1, Page 4.	
4.3.3 page 15 line 32ff	ECHAMP	AI, EDI and RDA are not suitable starting points for a safety assessment, as they do not represent an upper safety limit for daily intake, but they do refer to a minimum quantity of a substance that must be taken up by a person in order to meet the daily requirements. A safety assessment must be based on a maximum quantity of a substance that can be taken up without adverse effects. Please delete AI, EDI and RDA.	
4.3.4 page 16 line 6	ECHAMP	Please add after the word “products” the following phrase: *“as well as dosage informations from other sources, e.g. pharmacopoeias in which herbals are included.”*Rationale: Not all herbal products used in phytotherapy are registered or authorized. HMPWG used and accepted in the past references from B.P.C. DAB, Normdosen and Hager See https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/HMPWG/2019_12_HMPWG_Overview_Comments_5th-List_FSD.pdf Compare with heart glycosides assessment.	
4.3.4	ECHAMP	Regarding F-Values:	

Page 16 Line 16, 22-23, 31		In accordance with Article 14 of the Directive, a safety factor of 100 should only be necessary in case the LHRD is derived from a prescription drug (as stated in line 24). The HMPWG requires this safety factor also for non - prescription substances. A number of modifying factors are used (F1-F5) for calculation of the PDE: F1 = extrapolation from animal to human F2 = 10 to account for differences between individual humans F3 = duration of study / short-term exposure F4 = severe toxicity F5 = 1 for NOEL, **F5 = 1 to 5 for NOAEL**, F5 = 5-10 for LOEL, F5 = 10 for LOAEL Since both, LHRD and FSD relate to humans F1 is equal to 1. [Q&A paper HMPWG –Questions and Answers on First safe Dilutions]. When a LHRD is used instead of a NOEL or LOEL, only factors F2 and F5 remain, the others are equal to 1. The values for F2 and F 5 should be scientifically well balanced: F 2) The Italian Authority for instance pointed out in relation to the Decision tree: It is not always necessary to state 100 as the value of for F2 x F5. So a Safety factor F2 = 1 can be admitted because the aspect of variability between individuals is covered with the dosage finding. This means that, if the LHRD is calculated based on a children dosage F2 is equal to 1. If the calculation is based on an adult dosage F2 equal to 10 can be appropriate. The evaluation should include the reasoning for the chosen values for F2 and F5 F 5) F5 is a variable factor that may be applied if the no-effect level was not established. The comparison with substances in approved allopathic remedies is not about LOAEL / NOAEL but about **LHRD / NOAEL**. Therefore a value of less than 10 is justified (LOAEL ≠ LHRD).	

		According to ICH guideline Q3C, “when only a LOEL is available, a factor of up to 10 could be used depending on the severity of the toxicity”. It is thus scientifically not justified to use F 5=10, as the LHRD is a dose where no toxic effects are to be expected. And this applies even more to non-prescription drugs.	
4.3.4. page 16 line 31	ECHAMP	There seems to be a typo: It says ‘interspecies’ but it should be the factor regarding variability between individuals, which is F2? “A number of modifying factors are used (F1-F5), but when a LHRD is used instead of a NOEL or LOEL, only factors F2 and F5 remain, where F2 = 10 to account for variability between individuals and F5 is a variable factor that may be applied if the no-effect level was not established… The other modifying factors are adjusted as follows: F1 is used for extrapolation between species, but since LHRD and FSD both relate to humans F1 = 1” [Q&A paper HMPWG – Questions and Answers on First safe Dilutions]	
4.3.5. page 16 lines 36-38, page17, line 1-34	ECHAMP	In section 4.3.5 only the genotoxicity part of the TTC concept is explained even though the TTC concept is not limited to risk assessment of genotoxic substances. This is in line with the decision tree that leads to section 4.3.5 TTC even in cases where no genotoxic potential is known. Therefore please correct information on TTC concept: In general, the TTC concept is not only used or has **not** been especially developed “to establish an acceptable daily amount for compounds with a **known genotoxic potential**” as said in the Draft guidance document. The TTC concept has been developed to develop generic approaches for safety assessment of large groups of chemicals or individual chemicals of **unknown toxicity in general**. Munro developed the first decision tree for toxic non-cancerogenic substances in 1996 in the area of consumer products e.g. food packaging and food additives. According to that concept the TTC of 1.5 µg /person/day protects against the toxicity of most unknown chemicals in consumer products with a risk of less than 1 excess cancer in 100,000, including those substances of	

		unknown toxicity **even <u>should they turn out to be carcinogens</u>** later on (Munro, 1996; p.835). The reasons that are given in the Draft for the use of a TTC of 0.15 µg instead of 1.5 µg/d in line 11-19 on page 17 are not clear. The TTC value of 1.5 µg/d should be of use also for risk assessment for HMPs because according to scientific literature a TTC of 1.5 µg/d protects against risks of compounds with unknown toxicity (e.g. impurities) from the consumption/use of consumer products (e.g. food packaging, food additives, cosmetics) (Munro, 1996) even without a given dosage regimen and **without a proven benefit** as discussed by HMPWG. Therefore, a lack of proven therapeutic benefit or a lower labelled dosage for special patient groups is not a reason for not considering the TTC 1.5 µg/d value. Moreover, the proper use of the TTC concept, as defined by Kroes et al. 2004 (0.15 µg/person/day with one excess cancer in 1,000,000) was considered to be over-conservative in the context of potentially mutagenic impurities in pharmaceuticals [EFSA-Q-2016-0080; Review of the Threshold of Toxicological Concern (TTC) approach and development of new TTC decision tree]. The TTC concept includes the Cramer structural classes and the use of QSAR analysis [EFSA-Q-2016-0080 and reference 13 on page 26 EMA/CHMP/ICH/83812/2013 – already cited in section 4.3.5]. In case of substances, where none of the evaluation principles are applicable (used as food, LHRD/100, PDE etc), or a QSAR (Quantitative structure–activity relationship) analysis raises suspicion of genotoxicity/cancerogenicity, the conservative TTC approach of 0.15 µg/person/day may be justified. However, a proper scientific method used in toxicological assessments, allows the subsumption of substances analysed with QSAR into Cramer classes (if structural data is provided). QSAR analysis is an accepted, scientific tool used in toxicological risk assessment. Considering that the homeopathic note for guidance is dedicated to all substances with unknown formula but not only to those with proven mutagenic or genotoxic	

		properties the general setting of TTC = 0.15 µg for all not investigated substances in the homeopathic field leads to a general risk tolerance level of 1 in 10 000 000. (mathematical derivation see Kroes 2004). That should be considered unproportionate. Proposal: The complete state-of-the-art TTC concept should be cited in the guidance including the Cramer scheme for non-cancer endpoints. By excluding Cramer classes a fundamental part of the TTC concept has not been considered by HMPWG for safety assessment of HMPs which means that different standards are applied tor HMP than to all other medicinal products (contradiction to statement in 1.Introduction).	
Section 4.3.5, page 17, line 11-12		There are homeopathic medicinal products according to simplified registration on the market with children's posology regime or restrictions for patient groups. This is to be taken into consideration for the safety assessment.	
Section 4.3.5, Page 17 line 20		Please refer to TTC decision tree from EFSA (EFSA 2016)	
Section 4.3.5, Page 17 line 28-29		Please delete the last part of the sentence: „*and mixtures of chemicals containing unknown chemical structures.*" Reasoning: It is not in line with state-of-the-art knowledge (EFSA 2019, Section 3.4) to include these mixtures into the list of compounds excluded from the TTC concept. Please include the following references into the document: EFSA 2016 Review of the Threshold of Toxicological Concern (TTC) approach and development of new TTC decision tree httpsefsa.onlinelibrary.wiley.comdoiepdf10.2903sp.efsa.2016.EN-1006 EFSA Journal 2019;17(6):57088. Guidance on the use of the Threshold of Toxicological Concern approach in food safety assessment. https://doi.org/10.2903/j.efsa.2019.5708	

Page 17 line 35	ECHAMP	Please add the following text: Applying the described TTC concept for homeopathic dilutions that do not contain the excluded compounds (line 21 – 34), and calculating the worst-case FSDs for all homeopathic manufacturing methods based on the most conservative theoretical assumption that the whole raw material genotoxic and on an intake of 10 g, the resulting safe potencies are between D7 and D9: Method 1.1.1 (HAB 1a): 10 g D8 contain 0,1 µg plant: < TTC 0,15 µg Method 1.1.3 (HAB 2a): 10 g D9 contain 0,0166 µg plant: < TTC 0,15 µg Method 1.1.4 (HAB 2b): 10 g D9 contain 0,0166 µg plant: < TTC 0,15 µg Method 1.1.5 (HAB 3a): 10 g D9 contain 0,0166 µg plant: < TTC 0,15 µg Method 1.1.6 (HAB 3b): 10 g D9 contain 0,0166 µg plant: < TTC 0,15 µg Method 1.1.7 (HAB 3c): 10 g D9 contain 0,0166 µg plant: < TTC 0,15 µg Method 1.1.8 (HAB 4a): 10 g D8 contain 0,1 µg plant: < TTC 0,15 µg Method 1.1.9 (HAB 4b): 10 g D8 contain 0,1 µg animal material: < TTC 0,15 µg Method 4.1.1 (HAB 6): 10 g D8 contain 0,1 µg raw material < TTC 0,15 µg Method 1.1.10 (Fr. Ph.): 10 g D7 contain 0,1 µg plant < TTC 0,15 µg Method 4.1.2 (Fr.Ph.): 10 g D8 contain 0,1 µg raw material < TTC 0,15 µg This means that no material risk occurs in dilutions ≥ D7, ≥ D8, ≥ D9, depending on the manufacturing method. (see also Habs, Koller, 2020) Therefore, for these stocks a final potency of D9 and higher can be considered as generally safe.	
4.3.6 Page 18 lines 1 – 3	ECHAMP	The ICH Q3D guidance states: "*"The PDEs established in this guideline are considered to be protective of public health for all patient populations."* *"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." Thus, to use a body weight of neonates of 3 kg for all patient groups is not compliant with this guideline. The PDE value is a scientific safety threshold for **daily lifelong exposure**. It includes the uncertainty factors F1-F5 to assure human safety in all age groups: Using F2 = 10 accounts for variability between individuals, means any patient group is covered including neonates. Therefore, please change the wording into*: "… a body weight of 50 kg is used for the calculation of a daily acceptable amount for all patient groups."* Please see further comments under 4.3.4 LHRD	
4.4 page 18 Line 33	ECHAMP	It depends on the evaluation principle used if a body weight adjustment is scientifically justified. Therefore, please add the end of the second sentence in the first indent: - … A body weight adjustment of the daily acceptable amount for all patient groups needs to be performed, *if applicable.*	
Section 4.4.1, page 19, line 10-13	ECHAMP	The statement on ADME questions the present draft guidance document and its aim *to provide a procedure for non-clinical evaluation that is more appropriate for HMP*s and goes far beyond to what was calculated by HMPWG for the first safe dilutions (HMPWG FSD lists). The safety factor arising in this text would mean in practice that even an extrapolation to 3 kg would not be accepted in most cases because in reality data on ADME in children do rarely exist.	

		As explained for Sections 4.3.4, 4.3.5, 4.3.6 a body weight adaption to 3 kg in most cases overestimates the risk by far already. It includes various safety factors in a multiple way anyway (e.g. 3kg, lifelong daily exposure of 10ml / 10g, TTC for genotoxic compounds of 0,15 µg/day), and is not in line with current scientific guidance because these approaches per se cover all population groups. Moreover, it is not necessary to know the ADME profile of a substance under evaluation, when a default value of F2 = 10 is used in the risk assessment. A factor of 10 results from the multiplication of default values of 3.16 each for uncertainties in toxicokinetic and toxicodynamic data, i.e. when no chemical specific data are available (see ICH Q3D). It thus already takes into account toxicokinetic and toxicodynamic differences between human individuals and is highly protective of various subpopulations, including infants and children. Possible pharmacokinetic differences in ADME are already included into the calculation. Again, we point out that even extrapolating from an adult to a 3 kg child is already an additional step in the safety evaluation which is neither common nor necessary from a toxicological point of view. The reference (18) (EMA/189724/2018) describes extrapolation for paediatric population in the development of new medicines. This reflection paper has to be read in context with the Paediatrics Regulation which explicitly excludes homeopathic and herbal medicinal products from its scope, and is therefore not applicable. Please delete lines 10-13 without replacement.	
Section 4.4.1, page19	ECHAMP	Given the definition for adults of 70 kg in the excipients guideline, we have to use 3 different weight adjustments for adults in the assessments. This is not only confusing but also inconsistent. Please also refer on our comments regarding PDE, LDHR. We want to emphasize that there are established scientific concepts suitable as such also for the safety assessment	

		of HMP registered according to Art. 14 without including the same safety factor multiple times.	
Section 4.5.3, page 21, line 20-21	ECHAMP	Although the benefit-risk assessment is not applicable to the non-clinical evaluation of HMPs in the simplified registration procedure, this does not mean that HMP registered according to Art. 14 /simplified registration do not have any benefit. HMPs are medicinal products. According to Art. 1 of Directive 2001/83/EC medicinal products per se have a benefit.	
Sections 4.5.4 and 4.5.5	ECHAMP	Please include reference to Tables 1 and 2 of the PtC 2007 regarding conversion factors for different pharmaceutical forms and manufacturing methods.	
Section 4.5.7, page 22, line7	ECHAMP	According to GHP / HAB general chapter H 5.3. excipients are defined and well known. Therefore, for these, safety evaluation is not necessary.	
Section 5 Non-clinical Documentation		In general we appreciate guidance on how to adequately structure the safety assessment for homeopathic medicinal products. Nevertheless, since our member companies have worked out and established already many Modules 2.4 for registration procedures in the EU, it should be made clear that other structures in accordance with ICH M4 CTD CPMP/ICH/2887/99 are always accepted.	
Section 7 Literature References Page 26-27	ECHAMP	Please add the literature reference given at the end of this document into this section.	
Annex I, example 2, page 32	*ECHAMP*	Example Chimaphila umbellata D6, pillules The whole plant of Chimaphila umbellata is allowed as food without restriction (lists BELFRITand Ministero della Salute Italy, see references) This means that in the table under evaluation principle the answer on – “Food or food constituent” is “YES”. This shows very clear that the presented calculation based on unrealistic 100% raw material being genotoxic is by far unproportionate.	

Literature References:

EFSA Journal 2016; 13(3):1006E. Review of the Threshold of Toxicological Concern (TTC) approach and development of new TTC decision tree
https://efsa.onlinelibrary.wiley.com/doi/abs/10.2903/sp.efsa.2016.EN-1006

EFSA Journal 2017;15(5):4849. Guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age
https://efsa.onlinelibrary.wiley.com/doi/abs/10.2903/j.efsa.2017.4849

EFSA Journal 2019;17(6):5708. Guidance on the use of the Threshold of Toxicological Concern approach in food safety assessment.
https://doi.org/10.2903/j.efsa.2019.5708

Habs M, Koller M. Material Risks of Homeopathic Medicinal Products: Regulatory Frameworks, Results of Preclinical Toxicology, and Clinical Meta-Analyses and Their Implications. Complementary Medicine Research (2020): 1-21. DOI: 10.1159/000507952.
https://www.karger.com/Article/Pdf/507952

Ramakrishnan A, Ravishankar GA. Influence of abiotic stress signals on secondary metabolites in plants. Plant Signal Behav 2011;6(11):1720-31