Question and Answer document: Issue 1-5
Public consultation period on HMA website until 20 June 2014

Overview of comments received on draft document

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<td>Working out of structure and content of a Question and Answers document 1-6 by the FSD-subgroup</td>
<td>7 March 2013</td>
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<tr>
<td>Discussion and adoption of the draft version Question 1-5 by the FSD-subgroup</td>
<td>11 October 2013</td>
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### Overview of comments received

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

Q&A 1-5 as released for public consultation until 20.06.2014

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<tr>
<td><strong>ECHAMP E.E.I.G.</strong>&lt;br&gt;<strong>ECHAMP E.E.I.G.</strong>&lt;br&gt;Rue Gray, 100&lt;br&gt;B-1040 Brussels&lt;br&gt;Contact person:&lt;br&gt;Amandine Oset&lt;br&gt;Tel.: +32 2 649 94 40&lt;br&gt;e-mail: <a href="mailto:amandine.oset@echamp.eu">amandine.oset@echamp.eu</a></td>
<td><strong>ECH Dr Hélène RENOUX – General Secretary</strong>&lt;br&gt;Email: <a href="mailto:generalsecretary@homeopathyeurope.org">generalsecretary@homeopathyeurope.org</a>&lt;br&gt;ECH Secretariat:&lt;br&gt;Noorwegenstraat&lt;br&gt;49 9940 Evergem (Ghent)&lt;br&gt;BELGIUM</td>
<td><strong>Laboratoires Lehning</strong>&lt;br&gt;Marie-Aude HERMAN&lt;br&gt;<a href="mailto:marie-aude.herman@lehning.fr">marie-aude.herman@lehning.fr</a>&lt;br&gt;+ 33 3 87 76 72 24</td>
<td><strong>AESGP - Association of the European Self-Medication Industry</strong>&lt;br&gt;Christelle Anquez-Traxler, Pharm D&lt;br&gt;Regulatory and Scientific Affairs Manager&lt;br&gt;7 avenue de Tervuren, B-1040 Brussels</td>
<td>Tel:+3227355130</td>
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<tr>
<td>Interested party</td>
<td>Comment and Rationale</td>
<td>Outcome</td>
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<tr>
<td>ECH</td>
<td>The European Committee for Homeopathy is always happy to participate in the open discussion of the HMPWG documentation. Besides the following comments related to the consultations on “Questions and Answers on First Safe Dilutions” We look forward to further fruitful discussions and cooperation.</td>
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<tr>
<td>Laboratoires Lehning</td>
<td>Can you please specify where the list of first safe dilution has been published?</td>
<td>Not endorsed: It hasn’t been published. Aim of the present process is to create a List of first safe dilutions.</td>
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<tr>
<td>Laboratoires Lehning</td>
<td>Can you please further describe how the HMPWG applies the method of calculation of the FSD as described in the Points to Consider on non-clinical safety of homeopathic medicinal products of botanical, mineral and chemical origin? Indeed, in the previously published draft of different FSD, the calculation ( n = -\log ) (concentration of PDE, LHRD/100 or TTC) has not been used.</td>
<td>Not endorsed: Germany used a different calculation as it is more convenient in our point of view. Both approaches lead to the same result.</td>
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<td>Laboratoires Lehning</td>
<td>Can you please provide a template of Module 4 dedicated to homeopathic combination medicinal products?</td>
<td>Not endorsed: There is no specific template for combination medicinal products necessary. The assessment has to be provided for each single substance. Some reflection on possible additive and or synergistic effects of the different active substances should be added.</td>
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<tr>
<td>Section number and heading</td>
<td>Interested party</td>
<td>Comment and Rationale</td>
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<tr>
<td>Question 1</td>
<td>ECHAMP</td>
<td>No comments</td>
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<tr>
<td>Answer on question 1</td>
<td>ECH</td>
<td>No comment</td>
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<td>Question 2</td>
<td>ECH</td>
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<td>Answer on question 2</td>
<td>ECH</td>
<td>No comment</td>
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<td>Question 3</td>
<td>ECH</td>
<td>No comment</td>
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<td>Answer on question 3</td>
<td>ECH</td>
<td>In its answer on the question whether contraindications, especially allergies should be taken into account, the HMPWG states that only one FSD is applicable per stock. However, this statement seems contradictory to some of the FSDs that have been published so far, e.g. in case of Silybum marianum or Atropa belladonna. ECHAMP and its member companies highly welcome this approach. It would be appreciated if it will be maintained, as it should be distinguished between toxicological and immunological safety as well as the application to children and adults.</td>
<td>Not endorsed: It was common agreement within the group that a First Safe Dilution can only be a single one.</td>
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<td>Q&amp;A 3</td>
<td>ECH</td>
<td>No comment</td>
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<td>Question 3</td>
<td>AESGP</td>
<td>We agree to the fact that “the FSD is the dilution of stock that is safe in all patient groups and so generally contraindications are not relevant”. However, there seems to be a contradiction between this sentence and the second paragraph of the answer, which requests the addition of contraindications on the product labelling in case of risk of allergy. We would therefore like to suggest that this second paragraph be deleted.</td>
<td>Not endorsed: To delete the second paragraph would mean in consequence to implement a first safe dilution for all substances with an allergic property at least D7, in particular cases even higher.</td>
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<td>Question 4</td>
<td>How is the concept of First Safe Dilutions to be applied to homeopathic medicinal products which are combination products?</td>
<td>No comments</td>
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<td>Answer on question 4</td>
<td>ECHAMP</td>
<td>Theoretically we agree, that we should include possible additive and/or synergistic effects of the different active substances, but for homoeopathy/ phyotherapy it is in practice quite impossible to find literature on such data.</td>
<td>Not endorsed: It should be added “if available”, otherwise it should be indicated that no literature on such data is available.</td>
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<tr>
<td>Q&amp;A 4</td>
<td>ECH</td>
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<tr>
<td>Answer to question 4</td>
<td>Laboratoires Lehning</td>
<td>&quot;Module 4 should include consequences for calculation of product-specific safe dilutions&quot;. Can you please specify what safety margin should be considered by the applicant for each active substances in combination preparations?</td>
<td>For the assessment of active substances in combination preparations the same criteria as for single medicinal products are valid. Some reflection on possible additive and or synergistic effects of the different active substances should be added.</td>
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<td>Question 5</td>
<td>What is the background to use the value of TTC 0.15 µg/d</td>
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<td>Answer on question 5: Background to use the value of TTC 0.15 µg/d</td>
<td>ECHAMP</td>
<td>The first part of the answer given by HMPWG is the quoting of a section of the HMPWG “Points to consider on non-clinical safety of Homeopathic Medicinal Products of Botanical, Mineral and Chemical Origin” (in the following: HMPWG PTC) which states a TTC value of 0.15 µg/d. As a reference Kroes et al. (2004) is cited where a TTC value of 0.15 µg/d is recommended for substances with genotoxic potential.</td>
<td>Not endorsed: The reasons of HMPWG for choosing a TTC value of 0.15 µg/d for genotoxic substances instead of 1.5 µg/d mg/d are explained in question 5 (cited (1)-(3)) for the rest the HMPWG followed the &quot;GUIDELINE ON THE ASSESSMENT OF GENOTOXICITY OF HERBAL SUBSTANCES/PREPARATIONS&quot; chiefly. Availability of data and particulars of different treatment concept have to be taken into account. Moreover there are a lot of very specific ways (anthroposophical, biochemical, etc.) of using homeopathic remedies. They are used by therapist as well as in self-medication. Therefore a</td>
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adopted this opinion in its "Guideline on the assessment of genotoxicity of herbal substances/preparations" (EMEA/HMPC/107079/2007), stating that the "same approach might be considered for genotoxic constituents in herbal substances/preparations". This means that 1.5 µg/day is accepted for all identifiable genotoxic compounds and the risk level is less strict (1:10^5) than in the approach from Kroes et al. Moreover, the CHMP emphasizes that "it should be recognized in this context that the methods on which the TTC value is based, are generally considered very conservative since they involved a simple linear extrapolation from the dose giving a 50% tumour incidence (TD50) to a 1 in 10^6 incidence, using TD50 data for the most sensitive species and most sensitive site (several "worst case" assumptions)."

We therefore request that a TTC of 1.5 µg/day is likewise accepted for genotoxic homeopathic medicinal products.

Moreover, there is a gap in Annex I of the HMPWG PTC paper for the evaluation of homeopathic substances without genotoxic potential. In this Annex a TTC value of 0.15 µg/d is required even for substances without genotoxic potential for which toxicity data for the derivation of a PDE are not available. Contrarily, Kroes et al. recommends a TTC limit of at least 1.5 µg/d for substances without genotoxic potential. It is unclear why HMPWG in its PTC on the one hand cites Kroes et al. but on the other hand does not reflect the conclusions made by Kroes et al. for substances without genotoxic potential. For those substances a TTC limit of 1.5 µg/d already implies a safety factor of 1:10^6 (excess cancer risk of <1 in 1,000,000 over a lifetime).

Besides, PDE values in general are much higher than a TTC of 1.5 µg/d. This means that also from this perspective, a TTC of 1.5 µg/d is very conservative.

Even EFSA (2012) accepts TTC limits from 18 to 1800 µg/d for substances without toxicological alert depending on their chemical structure.

We therefore request that a TTC of at least 1.5 µg/day is accepted for homeopathic substances without genotoxic potential for which a PDE cannot be derived.

dosage of 10ml isn’t necessarily a theoretically one. And an intake over a longer period or even lifetime isn’t unthinkable. Taking into account this specific background the HMPWG decided to determine the TTC value of 0.15 µg/d for genotoxic substances. Disclaiming for a body weight adjustment is balancing this difference in our point of view.

It is possible to apply for a lower dilution. In this case further information is required as e.g. an AMES test and an assessment of the outcome in CTD Module 4.

It is not correct, that in Annex I of the HMPWG PTC paper for the evaluation of homeopathic substances a TTC value of 0.15 µg/d is required for substances without genotoxic potential. It is required for substances with unknown genotoxic potential.

In our point of view there is no inconsistence in terms of a higher PDE than TTC value. You only use the TTC concept if there is no or very little information available about the substance. To determine a PDE is merely possible on the basis of valid studies.

Suitable packaging information in terms of dosage are not required for article 14 medicinal product. For these medicinal products 10 ml must be safe.
We also refer to the TTC comparison table at the end of this comment.

In the second part of the HMPWG Answer on Question 5 it is stated:
“Taking into account the fact that
- In the “allopathic field”, children will usually get lower quantities of the medicinal product which is not systematically the case in homeopathy (1)
- A benefit risk assessment is not applicable in the context of the simplified procedure and as such safety always prevails (2)
- The FSD is considered the most conservative approach which must apply to all patients groups and all treatment durations, (3)

it has been decided to set the TTC value at of 0.15 µg/d as recommended in the “Points to consider on non-clinical safety of homeopathic medicinal products of botanical, mineral and chemical origin” (July 2007)”

ECHAMP’s assessments on these arguments are:
- **(ad 1)** According to the HMPWG PTC the calculation of the FSD is to be made with a (purely theoretical) posology of 10g/10ml oral intake and not with a usual posology. Therefore, it is not acceptable to again include the factor 10 in the already conservative TTC limit value of 1.5 µg/d.

Besides, there are some member states which allow a posology or amounts of daily intake for different age groups for homeopathic medicinal products registered according to Art. 14.

- **(ad 2)** We completely agree that safety always prevails. But this does not mean that we accept a multiplication of the same safety factors at various levels of the safety calculation. The safety for the consumer is best protected by suitable packaging information.

Following the argumentation of the HMPWG for simplified procedure, the FSDs calculated with a TTC value of 0.15 µg/d for the simplified registration procedure do not represent a valid starting point for the calculation of first safe dilutions of homeopathic medicinal products with indication and posology.
foreseen for marketing authorization according to Art. 16.2 because the arguments given by HMPWG do not apply for this regulatory group of homeopathic products. So, it should be explicitly stated in a separate publication by HMPWG that for homeopathic medicinal products authorised according to Art. 16.2 this given TTC limit is not applicable.

- (ad 3) ECHAMP accepts the FSD as conservative approach. However, ECHAMP does not accept the multiplication of safety factors without practical relevance. The TTC concept per se refers to an intake over lifetime. Homeopathic medicinal products are not foreseen for intake over a lifetime. Again, the argumentation to include an additional safety factor of at least 10 in order to cover all treatment durations of homeopathic medicinal products means a multiple inclusion of safety factors for the same issue. The derivation of the TTC of 1.5 µg/d is based on data for the most sensitive species and already includes several worst case assumptions. Thus, again, it represents already the most conservative approach of a lifelong treatment duration.

If the FSD calculations result in unreasonably high FSD levels because of inappropriate safety factors, the original aim of the FSD list to avoid the elaboration of individual Module 4 will not be reached. On the basis of the TTC value proposed by HMPWG together with the other safety factors described in the HMPWG PTC it is not probable that the FSD list will be of any practical use for the industry or the agencies because individual Module 4 will be needed for most homeopathic preparations.

We would highly welcome if the HMWG takes the opportunity of this Q&A paper to clarify that based on recent publications on the acceptance of the TTC concept a TTC value of at least 1.5 µg/d is accepted for homeopathic substances without genotoxic potential for which PDE deviation is not possible as well as for homeopathic substances with genotoxic potential.

ECHAMP misses transparency respectively explanation or feedback why industry’s argumentation is ignored although repeatedly expressed in responses on consultations and hearings. We highly would appreciate a constructive and truly bilateral dialogue on this matter.
Therefore ECHAMP would welcome a personal exchange and discussion on this topic between its toxicological specialists with the specialists of the HMPWG FSD sub-working group.

| Q&A 5 | ECH | This topic has been already discussed many times. We disagree with the TTC value of 0.15 µg/day, since it is too strict and simply not adapted to homeopathy. **We propose a conservative pragmatic default threshold value of 1.5 µg/day in the safety assessment of complex homeopathic mother tinctures.**

**Rationale**

The Q&A paper gives the following reason for setting the TTC value to 0.15 instead of 1.5 µg/day: "A benefit risk assessment is not applicable in the context of the simplified procedure and as such safety always prevails". This notion does not justify the use of the TTC concept, and also not the conservative approach setting the TTC value 10 times lower. There is no reason to also transfer these recommendations to applications according to article 16.2 (2001/83) national marketing authorizations.

In the "GUIDELINE ON THE ASSESSMENT OF GENOTOXICITY OF HERBAL SUBSTANCES/PREPARATIONS" it is stated: "In the absence of data usually needed for the application of one of the established risk assessment methods, implementation of a generally applicable approach as defined by the TTC is proposed. A TTC value of 1.5 µg/day intake of a genotoxic impurity is considered to be associated with an acceptable risk (excess cancer risk of <1 in 100,000 over a lifetime) for most pharmaceuticals." This approach is also valid for homeopathic and anthroposophic medicinal products.

Please consider point 3.4. in this context ("Calculation of the first safe dilution") of the "Points to consider on non-clinical safety of botanical, mineral and chemical origin", additionally:

"… the worst case scenario should be adopted. This implies that the proposed dose of stock is present in 10 ml of oral solution or in 10 g of trituration"

Nobody intakes 10 ml of dilution or 10 g of trituration every day! These are exceptions, for instance in cases of accidental overdoses.

Not endorsed: The TTC value of 0.15 µg/day is determined according to the PTC on Non-clinical Safety of Homeopathic Medicinal Products of Botanical, Mineral and Chemical Origin (2007) for substances with unknown genotoxic potential.

National marketing authorisation are within the responsibility of each country.

The "GUIDELINE ON THE ASSESSMENT OF GENOTOXICITY OF HERBAL SUBSTANCES/PREPARATIONS" is followed chiefly. Availability of data and particulars of different treatment concept have to be taken into account.

Moreover there are a lot of very specific ways (anthroposophical, biochemical, etc) of using homeopathic remedies. They are used by therapist as well as in self-medication. Therefore for example the dosage of 10ml isn’t necessarily a theoretically one. And an intake over a longer period or even lifetime isn’t unthinkable. Taking into account this specific background the HMPWG decided to determine the TTC value of 0.15 µg/d for genotoxic substances, see also comment to ECHAMP).

As there is no further body weight assessment needed this conservative approach is balanced.

The applicant is free to submit a complete dossier and apply for a lower dilution.

Using the TTC concept is a pragmatically toxicological approach to assess substances for which neither analytical (chemical or phytochemical) nor toxicological data are available. If there is knowledge available about the substance other approaches are used, e.g. PDE or the TTC-value can be applied on the relevant toxicological principle of a mixture if the content of it has been determined using a validated method.
Therefore the TTC value of 1.5 μg/day like most of the other pharmaceuticals should be accepted.

Kroes et al. (2004) uses a decision tree. The threshold value of 0.15 \( \times 10^{-3} \) mg/day has been derived for certain chemical structures (so-called alerts) which are notorious for their genotoxicity in various test systems, not for homeopathic MT.

The TTC concept is aimed at providing a tool for the risk assessment of defined chemical structures (such genotoxic impurities). It is a wrong scientific basis to apply it for ill-defined homeopathic preparations.

The 'GUIDELINE OF THE LIMITS OF GENOTOXIC IMPURITIES' is aimed at assessing and limiting the risk of impurities in medicinal. This issue is completely unrelated to the occurrence of natural compounds/plant constituents in a homeopathic mother tincture.

EFSA does not consider the use of the TTC concept for ill-defined mixtures, as HMA does.

**Other comments:**

- "With respect to the use of the TTC for the determination of an FSD it is considered that there is no need for further adjustment for body weight". This goes against the common scientific practice in toxicology. It is scientifically not comprehensible to use one threshold without body weight adjustment. Contrary, in some List Entries (for example Rheum officinale), the TTC was calculated for 3 kg babies.

- The notion that "in the allopathic field, children will usually get lower quantities of the medicinal product which is not systematically the case in homeopathy" is not correct. E.g. the German Com D foresees the dosage to be proportional to the age groups. "After consulting the physician, babies under 12 months are not administered more than a third of the adult’s dose. Children aged 1-6 are not administered more than half of the adult’s dose, children aged 6-12 are not administered more than two thirds of adult’s dose.”

- The wording ‘genotoxic homeopathic medicinal product’ as used in the answer, is scientifically unacceptable. In particular that any homeopathic preparation substantially consists of constituents like water and ethanol which are acknowledged to be non-genotoxic.

Commission D is a national committee and has no validity in the EU.

We agree to use the wording "homeopathic medicinal product including a substance with genotoxic potential" instead of 'genotoxic homeopathic medicinal product'
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<th>AESGP</th>
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<tr>
<td>1. Background information on TTC principle (“3.2”)</td>
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The answer explains that “... the recommendations formulated in the Guideline of the Limits of Genotoxic Impurities (CPMP/SWP/5199/02) are chiefly followed. However, the recommendations by Kroes et al (2004) with respect to the level of the Threshold of Toxicological Concern (TTC) are applied.”

According to Kroes [1], the numerical limit value of $0.15 \cdot 10^{-3}$ mg/day shall only apply if structural alerts are apparent: “The analysis of the expanded database of 730 compounds focused on identifying the structural alerts that would give the highest calculated risks if present at very low concentrations in the diet. The differences between the different structural alerts was most apparent in the data for the fraction of compounds within each group giving an estimated upper bound risk of cancer of greater than one in one million, when present in the diet at a concentration of 0.15 mg per person per day (0.0025 mg/kg bw/day). It should be emphasised that any group of compounds containing alerts for carcinogenicity should be of concern in the safety review of substances entering the food supply. However, some structural groups were identified to be of such high concern that a TTC-based assessment is not acceptable, and making an individual evaluation unavoidable (Cohort of Concern, CoC).

Kroes [1] uses a decision tree. The decision tree has been developed in order of decreasing concern, beginning to eliminate those compounds from the decision tree at an early stage which belong to the Cohort of Concern (CoC) and therefore a TTC determination is considered inappropriate. In the next step a distinction is made between substances raising structural alerts but without belonging to the CoC and others, i.e. substances without any structural alert. This is followed by a series of questions designed to identify structural characteristics indicative of decreasing potency and with increasing TTC values. The decision tree considers in the first steps the potential for genotoxicity and removes from further consideration chemicals with the structural alerts found in the most potent genotoxic carcinogens (CoC).

The decision tree only leads to $0.15 \cdot 10^{-3}$ mg/day if the question “Are there alerts that raise concern for potential genotoxicity” is to be not endorsed: According to Annex 1 of the "PIC on Non-clinical Safety of Homeopathic Medicinal Products of botanical, mineral and chemical origin", TTC should only be applied if there is a sufficient phytochemical or chemical characterization provided for a starting material, otherwise the FSD will be CH12.
answered with YES. Otherwise $1.5 \times 10^{-7}$ mg/day applies. Later in the decision tree, adverse effects that would show a threshold in the dose response curve are addressed lead to higher numerical values.

Concerning chemicals or herbals for which no or only few data is available, but which do not have structural alerts, the HMA’s approach leads to an unjustified discrimination. This is shown by a tabulated comparison of the different standards and regulations in Table 1 Regulatory framework, see below.

In a recent Expert statement, Prof. Schrenk (2014) [5, Encl. 1] has stated the following:

"It is absolutely clear from the publication by Kroes et al. (2004) that the TTC concept is aimed at providing a tool for the risk assessment of defined chemical structures, which occur as minor components in e.g. consumer products. The typical field of application of this concept is the occurrence of minor contaminants or residues in food, cosmetics, food additives etc. Recently, the concept has also been applied to the issue of impurities in medicinal drugs (Müller et al., 2006).

The use of the same concept to evaluate the risk related to the consumption/intake of an ill-defined mixture of many, even hundreds of components, is unscientific. It means a misuse of the concept and contradicts the major ideas and aims of TTC. The use of TTC requires an analysis of the features of a given chemical structure, i.e., a structure-based in silico approach in order to provide a more solid basis for risk assessment of chemicals. Likewise, computational based analysis methods like Toxtree or the OECD Toolbox could be used as appropriate in silico methods.

A major property of this approach is the similarity between chemical structures, which is thought to provide some information of the range of risk associated with that structure. It is evident from these considerations that the use of the TTC concept for the assessment of a chemically ill-defined mixture of many different structures is completely senseless and is in marked contrast to the rules of rational toxicology. Therefore, if the TTC threshold is applied, it should be used as in the safety assessment of contaminants in food or in the field of genotoxic impurities in pharmaceuticals. The TTC threshold should be applied to single components within the homeopathic mother tincture and not to complete mixture of many different structures."
Furthermore, the notion is made that the approach follows recommendations formulated in the ‘Guideline of the Limits of Genotoxic Impurities’.

According to the Expert Statement [5], the Guideline is aimed at assessing and limiting the risk of impurities in medicinal (mostly synthetic drugs where an assessment of chemically defined and identified (or plausible) impurity structures is warranted. This issue is unrelated to the occurrence of natural compounds/plant constituents in a homeopathic mother tincture.

The Q&A Document comes to the conclusion that “… therefore a TTC of $0.15 \times 10^{-3}$ mg/day is defined”.

The Expert statement [5] explains the following:

“The threshold value of $0.15 \times 10^{-3}$ mg/day has been derived by Kroes et al. (2004) for certain chemical structures (so-called alerts) which are notorious for their genotoxicity in various test systems. Furthermore, a carcinogenic action (mostly in rodents) of chemicals bearing these structures has been established. It is completely misleading to extend this concept to an ill-defined mixture of a large number of constituents since the lack of knowledge of the chemical structures does, of course, not allow, to perform any structure-based comparison with the ‘alert structures’. Therefore, the use of this threshold for genotoxic impurities for an ill-defined mixture of a large number of constituents is unscientific and represents a violation of the principles of rational toxicology.”

2. Comparison with allopathic medicines

The notion is made that “in the allopathic field, children will usually get lower quantities of the medicinal product which is not systematically the case in homeopathy.”
From our point of view this is not correct. E.g. in Germany the Advisory Board for Homeopathy (Commission D)* issues a dosage for each homeopathic medicine stipulating that the dosage is to be proportional to the age groups. Therefore the dosage is adapted to the age and reduced in younger patient.

*) In Germany the Advisory Board for Homeopathy (Commission D) of the Federal Institute for Drugs and Medical Devices was appointed as a governmental regulatory body in 1978 to assess the available data on safety and efficacy of homeopathic preparations. This review resulted in the publication of monographs known as the Commission D monographs.

3. Considerations on the simplified procedure

The text states that “a benefit risk assessment is not applicable in the context of the simplified procedure and as such safety always prevails”.

We understand that the FSD principle is to allow marketing of a product without producing particular evidence and discussion on the safety of the individual ingredients of the medicinal products as long as each ingredient is present in amount below the FSD. This very conservative approach setting the TTC value 10 times lower than for pharmaceuticals in general seems to be justified by this lack of evidence. However, according to this Q&A, this approach does not apply to marketing authorisation of homeopathic products according to Art. 16 of the European Directive.

4. FSD as most conservative approach

The Q&A document states that “… the FSD is considered the most conservative approach which must apply to all patients groups and all treatment durations”.

and not binding in the EU.

4. FSD as most conservative approach

Partly agreed: instead of the wording “genotoxic homeopathic medicinal product” “homeopathic medicinal product including a substance with genotoxic potential” is appropriate.

In case of a valid description of the genotoxic
We would like to refer to the Expert statement of Prof. Schrenk (2014) [5] explaining the following:

"Even under the simplistic consideration of an extreme precautionary principle and despite the wrong scientific basis of the above mentioned approach, it is a matter of fact that any homeopathic preparation substantially consists of constituents like water and ethanol which are acknowledged to be non-genotoxic. Since these are well known to represent the major part of the mother tincture (a D2 homeopathic preparation consists, e.g. of at maximum 0.01 g substance, and at least 0.99 g water/ethanol mixture) in most preparations, it appears severely over-conservative to assume that water, ethanol etc. should be considered as genotoxic carcinogens. Furthermore, there is no practical need for such an approach since the contents of innocuous solvents in the mother tincture are well known. The wording 'genotoxic homeopathic medicinal product' as used in the answer is scientifically unacceptable.

With respect to treatment duration, the TTC concept has been established for lifetime exposure, which is not feasible for most types of medication including use of homeopathic medication. Alternatives using less-than-lifetime corrections as published by Müller et al. (2006) for drug impurities are discussed in the literature."

5. Application of the TTC threshold by EFSA

The Q&A states that "This TTC threshold is also applied by EFSA, however expressed here on a μg/day basis".

According to the Expert statement [Encl. 1] the following should be taken into account:

"The statement suggests that EFSA considers the use of the TTC concept for ill-defined mixtures as HMA does. This notion is incorrect. The ‘Scientific Opinion on exploring options for providing advice about possible human health risks based on the concept of Threshold of Toxicological Concern (TTC)’ states under 4.4.3.3. ‘Mixtures’: 'It is

5. Application of the TTC threshold by EFSA

Partially agreed: According to Annex 1 of the "PtC on Non-clinical Safety of Homeopathic Medicinal Products of botanical, mineral and chemical origin", TTC should only be applied if there is a sufficient phytochemical or chemical characterization provided for a starting material, otherwise the FSD will be CH12.
possible to apply the TTC approach to mixtures containing only substances with closely related chemical structures, but then dose addition should be assumed and the exposures should be summed. However, there has been little evaluation of the applicability of the TTC approach to mixtures containing substances of unknown structure. Accordingly, such mixtures should be excluded from the TTC approach (EFSA, 2012). Therefore, if the TTC threshold is applied, it should be used as in the safety assessment of contaminants in food or in the field of genotoxic impurities in pharmaceuticals. The TTC threshold should be applied to single components within the homeopathic mother tincture and not to complete mixture of many different structures.

6. Adjustment of body weight

The last sentence states: “With respect to the use of the TTC for the determination of an FSD it is considered that there is no need for further adjustment for body weight taking into account both the conservatism in the TTC approach (0.15 μg/day instead of 1.5 μg/day as recommended in the Guideline on the Limits of Genotoxic Impurities CPMP/SWP/5199/02 and ICH M7) and the anticipated benefit of the medicinal product.”

We do appreciate that the benefit of the homeopathic medicinal products is positively highlighted in this context. Nevertheless we do not agree to the assumption that due to a lower TTC no body weight adjustment is necessary, for the following reasons:

1) The TTC concept is based on the daily exposure in an adult of 60 kg.
2) The body weight adjustment of a safety threshold is common scientific practice in toxicology. It is scientifically not comprehensible to use one threshold without body weight adjustment.
3) The dosage of many homeopathic medicinal products is recommended according to the age group and body weight, implying a lower exposure in smaller patient.
4) Due to the specific manufacturing preparation of homeopathic remedies supplementary dilution factors are already included.

As a consequence the TTC approach including a supplementary safety factor of 10 and being more conservative for homeopathic

6. Adjustment of body weight

Not endorsed. AESGP recommends TTC value of 1.5μg/day with body weight adjustment. As the FSD has to be valid for all patient groups, it has to be calculated for a new-born infant (1.5 μg ÷ 60 kg x 3 kg = 0.075 μg/day). This calculation would lead to a more conservative value as using TTC 0.15 μg without body weight adjustment.

There are no dosage recommendations foreseen for registered homeopathic medicinal products.
medicinal products as compared to other medicinal products is not necessary and not justified.

7. Conclusion

Complex mixtures of substances can be found in homeopathic mother tinctures and thus in homeopathic medicinal products. A reasonable and pragmatic scientific approach for the risk assessment of a potential genotoxicity would be is to consider a default threshold value and not the TTC concept.

- The direct application of the “TTC for genotoxic substances with known genotoxic alerts” of i.e. 0.15 µg/day to the complete complex mixture is scientifically not justified. This assumption is, also in a “worst case scenario”, not justified.
- If the TTC is applied, it should be used as in the safety assessment of contaminants in food or in the field of genotoxic impurities in pharmaceuticals.
- The TTC should only be applied to single components within the homeopathic mother tincture and not to a complete mixture of many different structures including water and ethanol.
- The dosage for children is adapted to age and body weight in many homeopathic products. In case the TTC concept is applied, this aspect reinforces the idea that no supplementary safety factor of 10 has to be applied and the TTC of 1.5 µg/day is valid.
- Homeopathic medicinal products are not taken daily over the whole life. This aspect has to be taken into consideration when applying safety thresholds (staged TTC approach).
- The homeopathic mother tincture or the homeopathic medicinal product cannot be equated to a “genotoxic homeopathic medicinal product”.

For the reasons discussed above, we propose to use a **conservative pragmatic default threshold value of 1.5 µg/day** in the safety assessment of complex homeopathic mother tinctures.

The following Table (Table 2) shows which limits have been set within
the regulatory framework based on the consideration of an accepted risk, see below.

8. References


http://www.hma.eu/uploads/media/PtC_HMP_non_biological_safety.pdf


