EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

# Overview of comments received on European Union herbal monographs on *Foeniculum vulgare* Miller subsp. *vulgare* var. *vulgare*, fructus and *Foeniculum vulgare* Miller subsp. *vulgare* var. *dulce* (Mill.) Batt. & Trab., fructus

Table 1: Organisations and/or individuals that commented on the draft European Union herbal monographs and European Union list entries on *Foeniculum vulgare* Miller subsp. *vulgare* var. *vulgare*, fructus and *Foeniculum vulgare* Miller subsp. *vulgare* var. *dulce* (Mill.) Batt. & Trab., fructus as released for public consultation on 15 December 2022 until 15 March 2023.

| | Organisations and/or individuals |
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| 1 | AESGP - Association of the European Self-Medication Industry |
| 2 | Kooperation Phytopharmaka GbR (Koop Phyto) |

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Table 2: Discussion of comments

## Specific comments on text

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| 2. Qualitative and quantitative composition | AESGP | Section 2 lists only the "herbal substance" (fresh or dry fruit) but no "herbal preparations". Typically, HMPC herbal monographs list the comminuted herbal substance under "herbal preparations" for use as a herbal tea infusions if the comminuted herbal substance is covered by the monograph as well. As fennel fruit has to be comminuted for use in tea bags. the comminuted herbal substance should be listed under "herbal preparations" as well, in order to make clear that the monograph also covers the use of tea bags with the respective posology. | Not endorsed.<br><br>Data from literature (Raffo et al. 2011) showed that fennel teas prepared using freshly comminuted fruit (just before the preparation of the infusion) contains higher amount of estragole compared to teas prepared using intact seeds. This has been also confirmed by the results of lab scale experiments provided by AESGP to determinate the extraction rates of estragole from fruits to infusions, which have shown that the extraction rates of estragole were lower when teas were prepared using uncrushed fruits instead of freshly comminuted fruits, resulting in a lower intake of estragole. Moreover, in the same experiment, the extraction rate of estragole from whole fennel fruits to the infusion was also lower than the one observed for fine-cut fennel (see Annex 1). This is in line with data from Van den Bergh *et al.* (2014) who showed that infusions prepared from whole fennel fruits contained about 3-fold less estragole compared to infusions prepared from fine-cut fennel material.<br><br>Therefore, the revised monographs will include only whole fruits for the preparation of fennel infusions to |

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| | | | minimize the estragole intake. |
| 4.2. Posology and method of administration | AESGP | According to both draft revised monographs, the daily dose for adults and adolescents is 4.5 g of the herbal substances (bitter or sweet fennel fruit), and the daily dose for children between 4 and 12 years of age is 3.0 g of the herbal substances.<br>Results of experimental determination of transition rates show a transition rate of average 5% from freshly crushed whole fennel or fine cut fennel in filter bags into a herbal tea preparation. Given a maximum amount of 0.05 mg estragole per day and an estragole content of 1.25 mg/g Fennel fruit, this would result in a maximum daily intake of only 0.82 g fennel fruit per day, which is, however, not at all in line with the dosage recommendation of the monograph. The calculation is shown in Annex 1. Only in case of uncrushed fennel fruit the daily intake of estragole seems a bit lower, although using uncrushed fennel is not *lege artis*.<br>In the revised monograph the daily posology is reduced to the lowest dosage of the usual traditional dosage range of **1.5** to 2.5 g three times daily for adults and of **1.0** to 1.66 g three times daily (3-5 g per day) for children between 4 and 12 years of age as set out in the previous monograph. This dosage limitation achieves a reduction in the uptake of estragole, although this is not sufficient to comply with the advised guidance value.<br>Based on the data of the laboratory test (Annex 1), the daily dose of 4.5 g fennel fruit for adults or 3 g for children would result in a maximum intake of 0.28 mg estragole per day for | Not endorsed.<br><br>Data on the content of estragole in comminuted and whole fennel fruits from German tea manufacturers, over the last four years, have been used to estimate the daily intakes of estragole, assuming an extraction rate of 5.0% as determined from previous laboratory trials. Calculated estragole intakes ranged from 0.25 mg to 0.49 mg per day for adults and from 0.17 mg to 0.32 mg per day for children between 4 and 12 years of age.<br><br>The proposal to mention these values as accepted "tolerance values" is not endorsed for the following reasons:<br>• it is not clear if the data provided by the German tea manufacturers refer to sweet or bitter fennel fruits;<br>• calculated extraction rates of 5.0% should be confirmed by further experiments, taking into account that a high variability has been reported in literature.<br><br>Finally, it should be kept in mind that the draft revised monographs do not impose any mandatory regulatory limit for estragole in line with the HMPC "Public statement on the use of herbal medicinal products |

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| | | adults and 0.19 mg estragole for children between 4 and 12 years of age.<br>More extensive data from tea manufacturers on fennel batches over the last four years (Annex 2) show that the estragole content is on average 1.55 mg/g herbal drug (comminuted fruits), i.e. slightly higher than the average value of 1.25 mg/g in the laboratory trial from 2019 reported in the annex 1. For whole fruits, the estragole content is on average 2.2 mg per g of drug, i.e. noticeably higher than in the 2019 laboratory trial with 1.34 mg/g.<br>Depending on the total oil content, estragole contents range from 1.11-2.16 mg/g (comminuted fruits). Based on the daily dosage for fennel tea of 4.5 g for adults and 3 g for children, an estragole intake from 0.25 mg-0.49 mg per day for adults and 0.17 mg-0.32 mg per day for children between 4 and 12 years of age results.<br>The findings presented in Annex 2 demonstrate that estragole is present in the essential oil at an average of 2.6%, with little variation over all batches. Data from different manufacturers and different origins of the herbal drugs have been used. It becomes evident that apparently no fennel batches which meet the minimum quality requirements according to Ph.Eur. with a relevantly lower estragole content are available. For fennel tea with bitter fennel, the minimum essential oil content of 4% according to Ph.Eur. must be met until the end of the shelf-life. As the essential oil is subject to a decrease trend, a slightly higher content must usually be specified for the release of a batch. This requirement makes it impossible to select batches | containing estragole". This implies that higher daily intakes of estragole than the guidance value defined in the above mentioned PS can be justified within a risk assessment based on adequate safety data to be assessed within a marketing authorisation application. This is applicable for adults, adolescents and children. |

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| | | with a specifically lower oil content and correspondingly lower estragole content.<br>In summary, with the available fennel batches (data from the last four years) and existing pharmacopoeia quality requirements for the minimum oil content, there is at the present time no practical way to minimize the estragole content to meet the Guidance Value.<br>The HMPC has implemented a noticeable reduction in daily estragole intake by lowering the daily dosage of the drug to the lower traditional dose limit. However, further lowering of estragole to meet the Guidance Value of 0.05 mg per day (adults) is currently not possible. According to the Public Statement on estragole, estragole intake should be lowered as far as is practically achievable. In the case of fennel tea, this means that currently the daily intake can be realized at max. 0.5 mg per day for adults and max. 0.3 mg per day for children between 4 and 12 years of age.<br>We propose that these values are be mentioned as accepted **Tolerance Values** in the monograph, for the following reasons:<br>The acceptance is justifiable by the following facts:<br>• the intake duration is limited to a few weeks per year<br>• medicinal tea from fennel has only a minimal share of estragole exposure from foods<br>• the Guidance Value of 0.05 mg per day was set with a maximum safety requirement and represents a target and not a limit value | |

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| 4.2. Posology and method of administration | Koop Phyto | According to both draft revised monographs, the daily dose for adults and adolescents is 4.5 g of the herbal substances (bitter or sweet fennel fruit), and the daily dose for children between 4 and 12 years of age is 3.0 g of the herbal substances.<br>From our point of view, the proposed posology reflects a practically feasible approach. | |
| 4.2 Posology and method of administration (Duration of use) | AESGP | The draft revised monographs state for adults and adolescents that fennel fruit are not to be taken for more than 2 weeks and for children between 4 and 12 years of age less than one week. As the duration of use is limited to two weeks or even one week, respectively, and the Guidance Value is related to the daily intake, establishing a Tolerance Value as mentioned above is justified from our point of view. This is supported by ICH M7 which permits higher intakes adjusted to a less-than-lifetime exposure. Thus, the limitation of the duration of use is an essential factor for justification of higher daily estragole intakes within a product-specific "as- low-as-practically-achievable" assessment. | The proposal to include "tolerance values" in the monograph is not endorsed (see above); however, it is acknowledged that the short duration of use can justify, within a risk assessment, the use of a less-than-lifetime exposure approach according to ICH M7 guideline when determining the daily intake of estragole for an herbal medicinal product containing fennel fruits. |
| 4.2 Posology and method of administration (Duration of use) | Koop Phyto | The draft revised monographs state for adults and adolescents that fennel fruit are not to be taken for more than 2 weeks and for children between 4 and 12 years of age less than one week. In section 3.3. Recommendations of its Public Statement on estragole-containing herbal medicinal products the HMPC explicates:<br><br>*"Taking into consideration the argumentation above, the short-term duration of treatment by an herbal medicinal product and an increase in an acceptable daily dose may be determined by* | The HMPC agrees that a short duration of use could support higher daily estragole intakes within a product-specific "as- low-as-practically-achievable" assessment to be justified within a marketing authorization application. |

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| | | *calculating the less-than-lifetime exposure according to the ICH M7 scheme. However, the calculation has to be based on the accepted posology of the specific herbal medicinal product taking also into consideration the non-avoidable intake by food."*<br><br>Hereby, the HMPC refers to two fundamental principles established in the ICH M7 Guideline, i.e., the principle of cumulative dose in the pathogenesis of cancer and its consideration with the optional adjustment of toxicologically derived (lifetime) ADIs by taking into account the cumulated exposure resulting from one or more successive treatment episodes reasonably expected for a specific product (less-than-lifetime principle).<br>The duration of treatment with fennel tea is restricted to two or even less than one week (children from 4-12y) for all indications and age groups. Typically, a longer treatment will not be necessary anyway because of the mostly self-limiting nature of the underlying pathologies.<br>The repeated pronunciation in the mentioned HMPC public statement regarding the applicability of the ICH M7 principles (see also **Section 3.3 Recommendations**: "*However, the consideration of the guidance value, which can be calculated according to the guideline M7, should be regarded as a helpful tool for statements e.g. on sensitive patient groups, acceptance of estragole containing excipients or also on the duration of use or acceptable daily doses*") implies that these principles are applicable to both, products for adults/adolescents and for | |

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| | | children, well in accordance with the ICH M7 Guideline which does not differentiate between products for different age groups. The guidance value has been derived by application of the utmost conservative algorithm provided by the ICH M7 Guideline which by definition of this guideline serves for derivation of an ADI, i.e., lifetime daily exposure level. It is from this point (an ADI or, by analogy, the HMPC guidance value) that an adjustment for less-than-lifetime exposure scenarios departs (**see ICH M7, 7.3. Acceptable in-takes in relation to less-than-lifetime (LTL) exposure**).<br><br>**We feel it important to clarify that the limitation of the duration of use is not an implicit factor within the derivation of the guidance value but – quite to the contrary – is an essential factor allowing for higher daily estragole intakes within a product-specific "as- low-as-practically-achievable" assessment.** | |
| Section 4.4. Special warnings and precautions for use | AESGP | According to both draft revised monographs, the use in children between 4 and 12 years of age is not recommended if the daily intake of estragole exceeds the guidance value of 1.0 µg/kg b.w., unless justified by a risk assessment based on adequate safety data, and the use is not recommended in children under 4 years of age without the advice of a paediatrician.<br>From our point of view, for children between 4 and 12 years of age a daily intake of 0.3 mg estragole should be accepted as a Tolerance Value (see comments on Chapter 4.2. Posology and method of administration). | Not endorsed (see above). |

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| Section 5.3. Preclinical sfety data | AESGP | The HMPC Assessment Report states: *"Aqueous extracts of fennel did not show any mutagenic activity in the Ames test using Salmonella typhimurium strains TA 98 and TA 100, with or without S9-metabolic activation. Also fennel powdered seeds at 10, 20 and 40 µg/ml did not show to be genoxotic in Comet assay after 4 h of treatment in HepG2 cells. Results from studies carried out in the laboratory animals showed a weak mutagenic potential of anethole. Trans-anethole is reported as "generally recognised as safe" at the intake of 54 µg/kg b.w./day) and the ADI is about 0-2 mg/kg b.w. (JEFCA, 1999). Zeller & Rychlik (2006) have experimentally determined an extraction rate of 16% for trans-anethole from bitter fennel fruits to teas. Taking into account the content of essential oil reported in literature for bitter and sweet fennel fruits (Raal et al. 2012, Mihats et al. 2016, Telci et al. 2019), it is not expected that the daily intake of trans-anethole would be above the ADI set by JEFCA when comminuted sweet and bitter fennel fruits are taken as they are or as herbal teas according to the posologies reported in the monograph."*<br>With regard to carcinogenicity the Assessment Report refers to the assessment of estragole only: *"Though there is no evidence of carcinogenicity for fennel herbal substance or preparations, studies have shown the carcinogenic effects of estragole and 1'-hydroxyestragole in mice and rats (liver tumors). These evidences are considered relevant also for humans"* and refers to the 'Public statement on the use of herbal medicinal products containing estragole' (EMA/HMPC/137212/2005 Rev 1) and its conclusion that the intake of estragole from (T)HMPs | There is no evidence of genotoxicity for bitter and sweet fennel fruits and their preparations; however, the available data are too poor to draw any conclusion due to several methodology deficiencies of the studies. In addition, adequate carcinogenicity data are lacking. Estragole metabolic activation pathway and DNA adduct formation are amply demonstrated in animals and the same pathway is operative in human *in vitro* systems. In addition, it is probable that toxicokinetic processes in humans are similar to those in rodents in which carcinogenicity has been observed, thus extrapolation can be regarded as plausible. Therefore, any further study on genotoxicity/carcinogenicity of fennel preparations is welcomed and will be taken into consideration during the scientific evaluation supporting future revision process of the monograph. |

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| | | in the general population should be as low as possible.<br>The statement on carcinogenicity refers to estragole only under specific experimental conditions. There is neither *in vitro* nor *in vivo* evidence for a carcinogenic effect of fennel fruit in the literature. For this reason, it is not justified to conclude that the mentioned *in vivo* data on individual substances are also relevant for humans. Thus, as also mentioned by the HMPC in the a.m. statement, data on estragole are different from those on fennel fruit. **Thus, these findings cannot be transferred to fennel preparations which therefore have to be assessed in a different manner than pure estragole.**<br>In this context we would like to mention a research project at the Technical University of Kaiserslautern (Professor Dr. Jörg Fahrer, January 2022 until December 2024) which addresses the questions if and to which extent genotoxic effects occur using primary or primary-like human liver cells and if the dose-response curves are indicative to assume the existence of a 'virtually no effect' point of departure of the genotoxic mode of action of estragole. This project will also investigate if differences in genotoxicity or cytotoxicity can be observed using a bitter fennel infusion or a mixture of characteristic substances thereof as compared to pure estragole. | |

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| Section 5.3. Preclinical sfety data | Koop Phyto | **1. Assessment of fennel fruit vs. pure estragole**<br><br>The HMPC Assessment Report on Fennel states: "*Aqueous extracts of fennel did not show any mutagenic activity in the Ames test using Salmonella typhimurium strains TA 98 and TA 100, with or without S9-metabolic activation. Also fennel powdered seeds at 10, 20 and 40 µg/ml did not show to be genotoxic in Comet assay after 4 h of treatment in HepG2 cells. Results from studies carried out in the laboratory animals showed a weak mutagenic potential of anethole. Trans-anethole is reported as "generally recognised as safe" at the intake of 54 µg/kg b.w./day) and the ADI is about 0-2 mg/kg b.w. (JEFCA, 1999). Zeller & Rychlik (2006) have experimentally determined an extraction rate of 16% for trans-anethole from bitter fennel fruits to teas. Taking into account the content of essential oil reported in literature for bitter and sweet fennel fruits (Raal et al. 2012, Mihats et al. 2016, Telci et al. 2019), it is not expected that the daily intake of trans-anethole would be above the ADI set by JEFCA when comminuted sweet and bitter fennel fruits are taken as they are or as herbal teas according to the posologies reported in the monograph.*"<br><br>With regard to carcinogenicity the draft revised Assessment Report refers to the assessment of pure estragole and its metabolite, 1´-OH-estragole only: "*<u>Though there is no evidence of carcinogenicity for fennel herbal substance or preparations, studies have shown the carcinogenic effects of</u>* | Partially endorsed.<br><br><u>Point 1. Assessment of fennel fruit vs. pure estragole:</u><br>There is no evidence of genotoxicity for bitter and sweet fennel fruits and their preparations; however, the available data are too poor to draw any conclusion due to several methodology deficiencies of the studies. In addition, adequate carcinogenicity data are lacking.<br>Estragole metabolic activation pathway and DNA adduct formation are amply demonstrated in animals and the same pathway is operative in human *in vitro* systems. In addition, it is probable that toxicokinetic processes in humans are sufficiently similar to those in rodents in which carcinogenicity has been observed, thus extrapolation can be regarded as possible.<br>Therefore, the exposure to estragole in the general population should be as low as possible until new relevant data showing absence of carcinogenicity of fennel fruits is available.<br>In the assessment report, under section 3.4 "Overall conclusions on non-clinical data", the sentence "*Though there is no evidence of carcinogenicity for fennel herbal substance or preparations, studies have shown the carcinogenic effects of estragole and 1'-hydroxyestragole in mice and rats (liver tumors). These evidences are considered relevant also for humans. Therefore, the EMEA/HMPC assessment in* |

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| | | *estragole and 1'-hydroxyestragole in mice and rats (liver tumors). These evidences are considered relevant also for humans*" and refers to the 'Public statement on the use of herbal medicinal products containing estragole' (EMA/HMPC/137212/2005 Rev 1) and its conclusion that the intake of estragole from (T)HMPs in the general population should be as low as possible.<br><br>In our opinion, the quoted sentence links two completely different entities and statements in an inadmissible manner. Reason: First of all, 1´-hydroxyestragole is not a natural constituent of fennel fruit but an estragole metabolite in mammals. Therefore, it is not appropriate to put this substance in direct context with fennel fruit, even more so since the extent of metabolic activation of estragole to 1´-OH-estragole in humans is an important but still unresolved question. Estragole and fennel fruit are two different entities. Estragole is a chemically defined single substance, whereas fennel fruit is a multi-substance mixture with very different individual constituents where estragole is only one – and a minor one - of them. Further, it is undisputed that estragole in its chemically pure form can cause carcinogenic effects in mice and rats at high doses. This statement is only valid for the pure substance estragole under very specific experimental conditions. It is not valid for fennel fruit. It is rather true that there is no evidence for a carcinogenic effect of fennel fruit so far, either *in vitro* or *in vivo*. Furthermore, from our point of view, it is not possible to prove a previously unproven carcinogenicity of fennel fruit | *the 'Public statement on the use of herbal medicinal products containing estragole' (EMA/HMPC/137212/2005 Rev 1) concluded that the intake of estragole from HMPs in the general population should be as low as possible, which includes a short-time duration of use (maximum 14 days) and a discussion about the single / daily doses necessary according to the risk assessment.*" has been rephrased as follows: "*There is no evidence of genotoxicity for bitter and sweet fennel fruits and their preparations; however, the available data are too poor to draw any conclusion due to the methodology deficiencies of the studies or to the lack of sufficient information. In addition, adequate carcinogenicity data are missing. On the other hand, studies have shown the carcinogenic effects of estragole and 1'-hydroxyestragole in mice and rats (liver tumors). Although toxicokinetics and metabolism of estragole have not been thoroughly studied in humans, there is evidence that under in vivo administration of estragole to humans, the liver is exposed to the compound and the first step in metabolic activation, the formation of 1'-hydroxyestragole, is possible. Thus, it is probable that toxicokinetic processes in humans are similar to those in rodents in which carcinogenicity has been observed, that extrapolation can be regarded as possible. Therefore, the EMEA/HMPC assessment in the 'Public* |

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| | | by referring to the experimental carcinogenicity of the isolated pure substance estragole as was done in the sentence cited above.<br><br>**For this reason, it is not justified to draw a conclusion that the mentioned *in vivo* data on individual substances are also relevant for humans. Thus, as also mentioned by the HMPC, data on estragole are different from those on fennel fruit, and from our point of view cannot be transferred without further scientific assessment.**<br><br>**2. Research Project "Dose-response studies on the genotoxic potential of estragole in human liver cells"**<br><br>As stated by the HMPC the safety assessment of estragole in regard of its potential genotoxic and/or carcinogenic effects of relevance for humans is currently subject to great uncertainties. These include the question of whether the carcinogenic effects observed in animals follow a linear dose-response relation or whether they are subject to a threshold mechanism. A research project at the Technical University of Kaiserslautern (Professor Dr. Jörg Fahrer, January 2022 until December 2024) addresses the questions if and to which extent genotoxic effects occur using primary or primary-like human liver cells and if the dose-response curves are indicative to assume the existence of a 'virtually no effect' point of departure of the genotoxic mode of action of estragole. The | *statement on the use of herbal medicinal products containing estragole' (EMA/HMPC/137212/2005 Rev 1) concluded that the intake of estragole from HMPs in the general population should be as low as possible, which includes a short-time duration of use (maximum 14 days) and a discussion about the single / daily doses necessary according to the risk assessment relevant for the concerned HMP."*<br><br><u>Point 2. Research Project "Dose-response studies on the genotoxic potential of estragole in human liver cells":</u><br>It is pointed out that any further study on genotoxicity/carcinogenicity of fennel preparations is welcomed and the results, once available, will be taken into consideration during the scientific evaluation supporting future revision process of the monograph.<br><br><u>Point 3. Discussion of the HMPC Guidance value:</u><br>It is reiterated that the «guidance value» of 0.05 mg is not a limit (e.g. higher intakes of estragole could be determined on the basis of ICH M7 less-than-lifetime exposure approach). In addition, higher dosages of bitter and sweet fennel fruits for infusion or in other herbal preparations than those reported in the revised monographs could be used if supported by the evidence of traditional use and justified by an |

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| | | genotoxicity test battery includes DNA adduct measurements, γ-H2AX analysis, Comet assay and Micronucleus assay. Cytotoxicity is studied in HepG2-CYP1A2, HepaFH3 cells and primary hepatocytes to exclude the impact/interference of potential cytotoxic effects on genotoxicity endpoints. In addition, it will be analyzed how DNA repair may affect the genotoxicity of estragole using time course experiments. Finally, it will be investigated if differences in genotoxicity or cytotoxicity can be observed using a bitter fennel infusion or a mixture of characteristic substances thereof as compared to pure estragole.<br><br>**3. Discussion of the HMPC Guidance value**<br><br>The HMPC, in the absence of sufficient data for establishing an ADI by lege artis methodology derived a "guidance value" by applying a maximally and probably overtly conservative approach, departing from an - estimated – dose level. While there may be good reason for doing so in seeking the utmost protective solution the feasibility of the $TD_{50}$ approach as such has recently been scrutinised by various authors particularly when departing from very high dose levels and from studies with less than at least three dose levels. In a recent expert report on Current approaches in the toxicological risk assessment of estragole Schrenk elaborates on whether the available data would allow for a different approach in the case of estragole. The expert identifies the study per-formed under the National Toxicology Programme (NTP) as a source of such | adequate risk assessment within a MAA based on adequate safety data. |

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| | | data. Despite not meeting the requirements of a full long term carcinogenicity study because of its limited duration (3 months), this study provides very valuable data when considering that preneoplastic lesions like those observed in the NTP study have been suggested as surrogate markers for carcinogenesis by various authors in the recent literature.<br><br>The expert points out that in general<br>• Hepatic preneoplastic foci show an early onset after starting carcinogen treatment with virtually no lag phase and are thus useful as a quantitative surrogate marker at early timepoints<br>• Carcinogen dose levels causing significant increases in hepatic preneoplasia are in the range of tenfold lower than those inducing tumours at the same time after start of treatment<br>• The authors of the NTP study applied five different dose groups, thus the data set allows for a robust BMDL10 modelling for the surrogate parameter preneoplastic foci in the liver, which is considered the major target organ of estragole. Based on the analysis of these data the expert found that the dose-response characteristics for estragole-related hepatic DNA adduct formation *in vitro* and for a significant increase in preneoplasia *in vivo* in rats are both strongly hypolinear suggesting no (measurable) effects at relevant (human) dose levels<br>• The data indicate a BMDL10 of 40.6/57.2 mg/kg b.w./d for female and male rats, respectively. Application of an MoE of 1,000 would result in a level of 40µg/kg b.w./d for adults. | |

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| | | The expert Schrenk arrives at the conclusion that a daily exposure of **2-3 mg estragole would be of low concern** for an adult. Considering a b.w. of 50 kg for adults, as established by convention for the assessment of medicinal products, the acceptable daily exposure would be at the lower end of this range, i.e., 40 µg/kg b.w./d x 50 kg b.w. = 2 mg. This amount is by a factor of 40 higher than the amount resulting by application of the HMPC guidance value.<br><br>(Note: The Belgian Advisory Committee on Plant Preparations has very recently published a statement on the acceptable daily intake of estragole by food supplements containing *Ocimum basilicum* essential oil [2]. The committee recommends a maximum daily dose of 3 mg for the sum of estragole and methyleugenol.)<br><br>When applying an ADI of 40 µg/kg b.w./d as proposed by Schrenk [1] to the example of bitter fennel fruit infusion an adaptation of the monograph dosage would not be required:<br><br>Max. daily dose Fennel fruit (HMPC 2007, adults): 7.5g<br><br>Min. content Fennel Oil in Fennel fruit (Ph.Eur.) 40 mL/kg<br>Typical content Fennel Oil in Fennel fruit[1] 60 mL/kg<br>Max. content of estragole in Fennel fruit (Ph.Eur.) 5%<br>Average content estragole in Fennel Fruit 2.6% | |

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| | | Default transfer rate of estragole from fruit to infusion 5%<br><br>Model calculation:<br>7,500 mg/d x 6% x 2.6% x 5% = 0.585 mg/d (585 µg/d)<br><br>This would still be 3.4 times lower than the (lower) maximum level calculated by Schrenk and still without consideration of the ICH M7 rules for less-than-lifetime (LTL) exposure. In that case, the ADI would be even much higher, i.e., ca. 4.000 µg/d (for LTL variables see example below).<br><br>In a complementary scenario, starting from the HMPC guidance value, application of the ICH M7 LTL principles to fennel tea considering the qualitative parameters would result in an LTL-adapted ADI as follows. In this scenario the cumulative duration of exposure is a result of all treatment episodes in which patients may probably be exposed to the agents throughout their lifetime.<br><br>A simplified scenario for adults can be based on the assumption that a patient would apply the maximum daily dose of fennel tea (7.5 g, HMPC 2007) 5 times every year throughout his entire lifetime with an average single treatment episode duration of 10 days. Clearly, this is a worst-case assumption:<br>(10d x 5/y x 70y)/365 = 9.58 years<br><br>This cumulative exposure duration falls within the category of 1-10 years according to Section 7.3 of the ICH M7. | |

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| | | Accordingly, a factor of 7 (6.66) may be applied for adjustment of the ADI. Thus, an ADI of 7 instead of 1 µg/kg b.w./day would be acceptable, resulting in an acceptable daily dose of 350 µg for an adult (50 kg). In consideration of the unfavorable assumptions included in both the algorithm underlying the HMPC guidance value and the cumulative exposure scenario outlined above this is well comparable with the 585 µg/day derived by application of the proposal of Schrenk.<br><br>Either way it is clearly obvious that the guidance value of 1 µg/kg b.w./d as such is not a suitable measure for directly assessing a given product.<br><br>[1]Note: The values given for the typical content of Fennel oil in Fennel fruit, for the maximum content of estragole in Fennel fruit, for the average content estragole in Fennel fruit and for the default transfer rate of estragole from fruit to infusion are based on the findings of experimental results given in the Comments of AESGP on the on the Draft Revisions of European Union herbal monograph on Bitter fennel fruit and Sweet fennel fruit submitted in November 2022. | |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
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| 6. Pharmaceutical particulars | AESGP | According to both draft revised monographs, the amount of estragole has to be specified in herbal preparation for oral use. The HMPC further states that because of the generally accepted evidence of genotoxic carcinogenicity, exposure to estragole should be kept as low as practically achievable. Under Item 6 Pharmaceutical particulars, specific information is only available for pregnant and breast-feeding women (*"the daily intake of estragole has to be below 0.05 mg/person per day")* and in children below 12 years of age *("the daily intake of estragole has to be below 1.0 µg/kg bw")*. For all other patient groups including the use in adults, no reference is made to a maximum daily intake.<br>From our point of view, the general statement *"exposure to estragole should be kept as low as practically achievable"* leaves space for interpretation. In this context, the following issues have to be taken into consideration:<br>• The European Pharmacopoeia monographs "Fennel, bitter" and "Fennel, sweet" specify a minimum content of 4% or 2% essential oil, respectively, which contains minimum 60.0% anethole and minimum 15.0% fenchone or minimum 80.0% anethole, respectively.<br>• The issue arises whether the essential oil content and/or the estragole content can be reduced by breeding experiments. (as suggested by HMPC in the Assessment Report: *"However, each action from selection of cultivars and cultivation of the plant to the* | The Committee is aware of the technical hurdles to select low estragole content cultivars to ensure a daily intake of estragole close to the guidance value of 0.05 mg/person, due to the strong positive correlation between low content of estragole (< 5.0%) and trans-anethole. This is one of the reasons why this guidance value should not be interpreted as a strict regulatory limit for use of fennel in adults and adolescents. However, to minimise the exposure to estragole, only the lowest dose of fennel fruits available from traditional use has been included in the monograph. This approach does not impede Companies to use higher posologies of fennel fruits supported by evidence of traditional use within a Marketing Authorisation Application, provided that the daily intake of estragole is adequately justified by a risk assessment based on adequate safety data. |

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| | | *manufacture of herbal medicinal product containing fennel fruits, which could minimise the exposure of humans to estragole, should be recommended."*<br><br>With regard to the goal of reducing the estragole intake via herbal medicinal products to an amount "as low as practically achievable", the HMPC recommends, inter alia, that "…low Estragole plant varieties" should be used. Indeed, breeding/selection of special cultivars is an approach frequently applied for the reduction of unwanted constituents in cultivated plants (e.g., cucurbitacins in various vegetables or erucic acid in rapeseed). As regards the estragole content of Bitter fennel fruit, targeted research has been conducted already in the 1990ies. Together with results of their own extensive screening studies, Pank and coauthors have published the state of knowledge on this issue in 2003 [Pank 2003]. They arrived at the conclusion that it is extremely difficult to reduce the estragole content (of Bitter fennel fruit essential oil) considerably below ca. 2.2% while maintaining the anethole content of ≥ 60% as required by the Ph.Eur.. The authors report that within their own study only in 1 of 8,390 samples they found an estragole content below 1% with a concurrent anethole content meeting the pharmacopoeia requirement.<br>A large screening and breeding programme was performed between 2010 and 2021 by PHARMAPLANT GmbH, Artern (Germany) with the goal of identifying Bitter fennel lines with an estragole content << 2.2% while compliant with all other Ph.Eur. requirements. The results of this extensive work clearly | |

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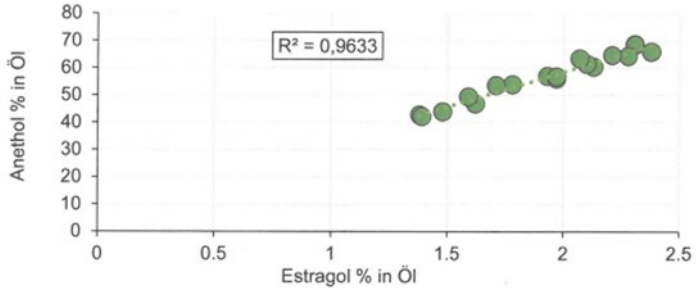
| | | confirms the findings of the studies reported by Pank and coauthors as demonstrated by the strong correlation between estragole and anethole content (see Figure 1).<br>  <br><br>**Figura 1: Correlation between Anethole and Estragole concentration; exemplary data from 20 Foeniculum vulgare Miller ssp. vulgare var. vulgare clones (Internal Report Pharmaplant 2021)[2]**<br><br>Of note, for a given *Fennel* cultivar there is as well a year-to year variability of the essential oil content and composition. Apart from these compositional aspects the agricultural feasibility must be provided as well, e.g., hardyness, drought resistance (increasingly important) and pest resistance (*Mycosphaerella*).<br>**Taken together the available data show that reducing the Estragole content of a herbal medicinal product by sourcing low estragole content cultivars is no viable option.**<br>With regard to the above-mentioned interpretation of the | |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
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| | | general statement *"exposure to estragole should be kept as low as practically achievable",* the daily dosage recommendation of 4.5 g fennel fruit for adults and the requirement to keep the exposure to estragole as low as practically achievable, confirm such a wide interpretation, keeping in mind that 0.05 mg estragole per day is no fixed limit, permitting also daily intake above 0.05 mg estragole. This is also in line with the HMPC consideration from the March 2022 Meeting: "There was an agreement that the concerns are most prominent with the fennel oil given its high content of estragole and that, for herbal teas, the extraction process reduces the amount of estragole. HMPC had agreed to recommend 'guidance values' in the public statement (PS) rather than 'limits'. Some members pointed to the expectation that, when revising the monographs, HMPC would respect the set 'guidance values' in the posology adopted for the herbal preparations. Other members were concerned that the posology would no longer reflect the TU data/evidence that support the recommended uses; they pointed to the known variability of estragole concentration depending on the variety and geographical origin as well as to the long history of safe use of fennel in Europe. In relation to the 'guidance values', the HMPC PS states that '*the consideration of* ***a guidance value****, which has been calculated according to the ICH guideline M7,* ***is*** *regarded as* ***a helpful tool for*** *statements e.g. on sensitive patient groups, acceptance of estragole containing excipients or also on the duration of use or* ***acceptable daily doses***'." [Committee on Herbal Medicinal Products (HMPC). Minutes for | |

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| | | the meeting on 28-30 March 2022 (EMA/HMPC/218711/2022) of 8 May 2022.]<br>In order to reach or come as close as possible to the guidance value of 0.05 mg/person per day, the HMPC states in the Assessment Report that *"the lowest dose should be consistently selected if ranges of single and daily doses are available from traditional use. … This implies that in case of adults and adolescents, despite of evidence of long-standing use for doses of 1.5 g and 2.5 g of (freshly) bitter and sweet fennel fruits with 0.25 l of boiling water three times daily as a herbal tea, only the lower dose will be included in the monograph. This corresponds to a daily dose of 4.5 g (1.5 g x 3 times daily). Similarly, for children between 4 and 12 years of age, only the lower dose of 3.0 g daily to be taken in three divided doses has been included in the monograph; this corresponds to 1.0 g of (freshly) bitter and sweet fennel fruits in 100 ml boiling water as a herbal infusion, three times daily."*<br>We therefore understand that the HMPC would on the one hand allow to maintain both fennel fruit monographs with a suitable dosage recommendation and on the other hand ensure a safe use by taking a guidance value into account. This is also an argument that the dosage recommendations in the revised monographs on Fennel fruit offer a certain degree of flexibility and room for interpretation.<br>As mentioned above, we therefore propose to interprete the Guidance Value of 0.05 mg/day not as a limit value and to accept a daily intake of 0.5 mg estragole for adults and 0.3 mg estragole for children between 4 and 12 years of age as a | |

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| | | **Tolerance Value**, taking into consideration that the duration of use is limited to a few weeks per year and ICH M7 permits higher intakes adjusted to a less-than-lifetime exposure. Moreover, the Guidance Value of 0.05 mg per day was set with a maximum safety requirement and does not represent a limit value.<br>As a practical consequence instead of reducing the daily dosage of fennel tea to an amount which is no longer effective, from our point of view a safety assessment should be carried out by the applicant by determining the amount of estragole in the finished medicinal product and, depending on the result, by discussing whether measures should be taken that may lead to a reduction in the amount of estragole. *This seems to be a current regulatory practice by a health authority.* E.g., in such cases a risk assessment could be performed which includes determination of the estragole amount in the final product and a discussion on whether depending on the value further measures should be undertaken which – according to the HMPC public statement – lead to a reduction of the estragole amount. All in all, the long and safe use of Fennel tea as a medicinal as well as a food product should be taken into consideration.<br><br>**Conclusion**<br><br>**Batch data obtained with fennel fruit demonstrate that there is at present no practical way to minimize the estragole content in order to meet the Guidance Value, taking into consideration the existing pharmacopoeia** | |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
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| | | **requirements for the minimum oil content. Data from breeding experiments show that reducing the estragole content by sourcing low estragole content cultivars is no viable option. As further lowering of estragole to meet the Guidance Value of 0.05 mg per day (adults) is currently not possible and according to the HMPC the estragole intake should be lowered as far as practically achievable, we propose that the given values (per day max. 0.5 mg for adults and max. 0.3 mg for children between 4 and 12 years of age) are mentioned as accepted Tolerance Values in the monograph. This proposal takes into account the limited duration of use, the ICH M7 option of higher intakes adjusted to a less-than-lifetime exposure and the fact that the Guidance Value was set as a target with a maximum safety requirement and represents a target and not a limit value.** | |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
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| 6. Pharmaceutical particulars | Koop Phyto | According to both draft revised monographs, the amount of estragole has to be specified in herbal preparations for oral use. The HMPC further states that because of the generally accepted evidence of genotoxic carcinogenicity, exposure to estragole should be kept as low as practically achievable.<br>Under Item 6. Pharmaceutical particulars, specific information is only provided for pregnant and breast-feeding women ("*the daily intake of estragole has to be below 0.05 mg/person per day*") and in chil-dren below 12 years of age ("*the daily intake of estragole has to be below 1.0 µg/kg bw*"). For all other patient groups including the use in adults, no reference is made to a maximum daily intake.<br><br>Instead, "*exposure to estragole should be kept as low as practically achievable*". **Thus, 0.05 mg estragole per day is a guidance value for calculations in rough orders of magnitude which does not need to be kept in every case. This is also in line with the HMPC's considerations from the March 2022 Meeting:**<br>"There was an agreement that the concerns are most prominent with the fennel oil given its high content of estragole and that, for herbal teas, the extraction process reduces the amount of estragole. HMPC had agreed to recommend 'guidance values' in the public statement (PS) rather than 'limits'. Some members pointed to the expectation that, when revising the monographs, HMPC would respect the set 'guidance values' in the posology adopted for the herbal preparations. Other members were concerned that the | See above comments. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
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| | | posology would no longer reflect the TU data/evidence that support the recommended uses; they pointed to the known variability of estragole concentration depending on the variety and geographical origin as well as to the long history of safe use of fennel in Europe. In relation to the 'guidance values', the HMPC PS states that '*the consideration of **a guidance value**, which has been calculated according to the ICH guideline M7, is regarded as **a helpful tool** for statements e.g. on sensitive patient groups, acceptance of estragole containing excipients or also on the duration of use or **acceptable daily doses'***." [Committee on Herbal Medicinal Products (HMPC). Minutes for the meeting on 28-30 March 2022 (EMA/HMPC/218711/2022) of 8 May 2022.]<br><br>**The minutes of the HMPC March 2022 meeting clearly underline the principal intention of using a guidance value of 0.05 mg estragole per day for calculations which can be adapted case-by-case in consideration of both ICH M7 principles and practicability aspects.**<br><br>In order to reach or come as close as possible to the guidance value of 0.05 mg/person per day, the HMPC states in the Assessment Report that "*the lowest dose should be consistently selected if ranges of single and daily doses are available from traditional use. … This implies that in case of adults and adolescents, despite of evidence of long-standing use for doses of 1.5 g and 2.5 g of (freshly) bitter and sweet fennel fruits with 0.25 l of boiling water three times daily as a* | |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | *herbal tea, only the lower dose will be included in the monograph. This corresponds to a daily dose of 4.5 g (1.5 g x 3 times daily). Similarly, for children between 4 and 12 years of age, only the lower dose of 3.0 g daily to be taken in three di-vided doses has been included in the monograph; this corresponds to 1.0 g of (freshly) bitter and sweet fennel fruits in 100 ml boiling water as a herbal infusion, three times daily."*<br><br>**However, taking the above-mentioned rationale from the expert report of Schrenk and/or LTL calculations based on ICH M7 into account, considerably higher daily exposures would be acceptable for fennel tea which would not necessarily require a general dose reduction in the monograph. This should be a matter of further considerations with regard to the Guidance Value.**<br><br>**Conclusion**<br>**For good reasons – in particular, because of the absence of sufficient scientific data - the HMPC has not established a precise limit for the acceptable daily intake of Estragole with herbal medicinal products. Instead, choosing a maximally conservative approach, the HMPC has derived a "guidance value". However, for target groups assumed to be particularly sensitive, i.e., children from 4-11 years as well as pregnant or breastfeeding women the HMPC chose to apply the guidance value as a virtual ADI.** | |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
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| | | **In reducing the dosage for fennel tea to the lower range of traditionally justified doses the Committee sees one approach of keeping Estragole exposure for adolescents (12-18y) and adults "as low as practically achievable" in accordance with the Public Statement. In this context, we would like to emphasise that the guidance value indicates a rough dimension for calculations that need to be adapted case-by-case. In this context, the limitation of the duration of use is an essential factor that allows for higher daily estragole intakes by application of ICH M7 principles and a product-specific "as-low-as-practically-achievable" assessment. In addition, the expert report of Schrenk shows that a different, well-founded approach to the assessment of available data is possible in accordance with the scientific literature that would allow a considerably higher daily intake and, as a consequence, maintain the established posology of fennel fruit. This should be a matter of further considerations with regard to the interpretation and application of Guidance Value both in the revised Fennel fruit Monographs and regulatory handling of individual HMPs containing Fennel preparations.** | |

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## *Annex 1: Calculation of the maximum daily amount of Fennel derived from a daily intake of 0.05 estragole*

| Transition Rate (Lab-Test 2019 & Company Data) | | | | | | | |
|---|---|---|---|---|---|---|---|
| Medicinal Tea (100% Fennel) | Estragole (drug) mg per g | Essential Oil % | Estragole per bag | Estragole per cup mg | Estragole transition | | max. g Fennel / day -> 0,05 mg Estragole |
| Whole Fennel 2,2 g, freshly crushed (Lab-test 2019) | 1,34 | 5,2% | 2,948 | 0,209 | 7,1% | | 0,53 |
| Fine-cut Fennel 2,0 g filterbag (batch 1 Lab-test 2019) | 1,26 | 4,5% | 2,520 | 0,123 | 4,9% | | 0,81 |
| Fine-cut Fennel 2,2 g filterbag (batch 2 lab-test 2019) | 1,27 | 5,1% | 2,794 | 0,105 | 3,8% | | 0,95 |
| Fine-cut Fennel 2,2 g filterbag (batch 3 lab-test 2019) | 1,21 | 4,9% | 2,662 | 0,119 | 4,5% | | 0,84 |
| Fine-cut Fennel 2,2 g filterbag (company A data) | 1,15 | 4,6% | 2,520 | 0,116 | 4,9% | | 0,95 |
| **mean-value** | **1,25** | 4,9% | **2,689** | **0,134** | **5,0%** | | **0,82** |
| | | | | | | | |
| **Non compliant Medicinal Tea (100% Fennel)** | | | | | | | |
| Whole Fennel 2,2 g, uncrushed (Lab-test 2019)* | 1,34 | 5,2% | 2,948 | 0,041 | 1,4% | | 2,72 |
| Fine-cut Fennel 2,2 g filterbag (company B data batch 1)** | 0,49 | 2,5% | 1,080 | 0,074 | 6,9% | | 1,49 |
| Fine-cut Fennel 2,2 g filterbag (company B data batch 2)** | 0,64 | 2,7% | 1,408 | 0,052 | 3,7% | | 2,11 |
| Fine-cut Fennel 2,2 g filterbag (company B data batch 3)** | 0,83 | 3,7% | 1,826 | 0,076 | 4,2% | | 1,45 |
| | | | | | | | |
| * Non-compliant preparation | | | | | | | |
| ** Essential Oil below Ph.Eur. | | | | | | | |

***Annex 2: Data from batch analyses on whole and comminuted fennel fruit obtained by German manufacturers between 2018 and 2022***

| Batch data (German Medicinal Tea Manufacturers): whole fruits | | | |
|---|---|---|---|
| Spalte1 | Estragole (drug) mg per g | Essential Oil % | Estragole in Oil % |
| B2018-1 | 2,32 | 9,29 | 2,5 |
| B2018-2 | 2,33 | 9,36 | 2,5 |
| B2019-1 | 2,55 | 9,09 | 2,8 |
| B2019-2 | 1,98 | 7,08 | 2,8 |
| B2019-3 | 2,12 | 7,85 | 2,7 |
| B2019-4 | 2,41 | 8,93 | 2,7 |
| B2020-1 | 2,19 | 8,44 | 2,6 |
| B2021-1 | 2,09 | 7,74 | 2,7 |
| B2021-2 | 2,03 | 7,51 | 2,7 |
| **mean-value** | **2,22** | **8,37** | **2,67** |

| Batch data (German Medicinal Tea Manufacturers): comminuted fruits | | | |
|---|---|---|---|
| Spalte1 | Estragole (drug) mg per g | Essential Oil % | Estragole in Oil % |
| A2018 (1) | 1,15 | 4,56 | 2,53 |
| A2018 (2) | 1,26 | 5,01 | 2,52 |
| A2018 (3) | 1,56 | 6,47 | 2,41 |
| A2018 (4) | 1,51 | 6,03 | 2,50 |
| A2019 (1) | 1,75 | 6,12 | 2,86 |
| A2019 (2) | 1,95 | 6,55 | 2,98 |
| A2019 (3) | 1,19 | 4,63 | 2,57 |
| A2019 (4) | 1,11 | 4,30 | 2,58 |
| A2020 (1) | 1,55 | 5,77 | 2,69 |
| A2020 (2) | 1,77 | 6,55 | 2,70 |
| A2020 (3) | 1,45 | 4,90 | 2,95 |
| A2020 (4) | 1,45 | 4,94 | 2,94 |
| A2021 (1) | 1,13 | 4,70 | 2,40 |
| A2021 (2) | 1,41 | 5,65 | 2,49 |
| A2021 (3) | 1,63 | 6,38 | 2,56 |
| A2021 (4) | 1,69 | 6,32 | 2,67 |
| B2018 (1) | 1,23 | 4,55 | 2,7 |
| B2018 (2) | 1,73 | 6,39 | 2,7 |
| B2019 (1) | 1,93 | 7,42 | 2,6 |
| B2019 (2) | 1,92 | 7,40 | 2,6 |
| B2022 (1) | 1,44 | 5,34 | 2,7 |
| B2022 (2) | 1,68 | 6,47 | 2,6 |
| B2022 (3) | 1,46 | 5,60 | 2,6 |
| C2018 (1) | 1,39 | 5,60 | 2,5 |
| C2018 (2) | 1,24 | 4,89 | 2,5 |
| C2018 (3) | 1,56 | 5,45 | 2,9 |
| C2019 (1) | 1,74 | 6,78 | 2,6 |
| C2019 (2) | 1,63 | 6,07 | 2,7 |
| C2019 (3) | 2,16 | 8,60 | 2,5 |
| C2019 (4) | 1,57 | 6,18 | 2,5 |
| C2020 (1) | 1,91 | 7,42 | 2,6 |
| C2021 (1) | 1,44 | 5,41 | 2,7 |
| C2021 (2) | 1,60 | 6,02 | 2,7 |
| C2022 (1) | 1,42 | 5,36 | 2,7 |
| **mean-value** | **1,55** | **5,88** | **2,63** |