29 May 2024
EMA/HMPC/324881/2023
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on public statement on *Foeniculum vulgare* Miller subsp. *vulgare* var. *vulgare*, aetheroleum (EMA/HMPC/522456/2021)

Table 1: Organisations and/or individuals that commented on the draft public statement on *Foeniculum vulgare* Miller subsp. *vulgare* var. *vulgare*, aetheroleum as released for public consultation on 31 August 2022 until 30 November 2022.

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

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Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
AESGP	The withdrawal of the monograph on Foeniculum vulgare Miller subsp. vulgare var. vulgare, aetheroleum is not justified, for the following reasons: **1. Assessment of fennel oil vs. pure estragole** The HMPC Assessment Report already mentions with reference to the HMPC Public Statement on the use of herbal medicinal products containing estragole (EMA/HMPC/137212/2005 Rev 1): *"The genotoxic mechanisms of estragole contained in the fennel oil might be counteracted by detoxification mechanisms (see above Monien et al., 2019) and antimutagenic abilities of other fennel oil components (see above Tripathi et al., 2013), but further evidence is needed to confirm these findings."* The HMPC Assessment Report on Bitter fennel oil states that *"Fennel oil was found to be mutagenic in vitro in only one test although more recently it showed antimutagenic activity in mouse models of experimentally cyclophosphamide (CP)-induced genotoxicity and it did not show to be genotoxic in Comet assay after 4 h of treatment in HepG2 cells at 0.5, 1.0 and 2.0 µl/ml."* With regard to carcinogenicity the Assessment Report refers to the assessment of estragole only: *"Though there is no evidence of carcinogenicity for fennel oil, studies have shown the carcinogenic effects of estragole and 1'-hydroxyestragole in mice and rats (liver tumours). 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.	Not endorsed. Point 1: Assessment of fennel oil vs. pure estragole The evidence available so far, is not sufficient to draw any conclusion on the potential genotoxicity of fennel oil and further *in vitro* and *in vivo* studies according to the current non-clinical guidelines are needed. In addition, 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. Thus, it is possible that similar mechanisms to the toxicokinetic processes in rodents in which carcinogenicity has been observed could take place in humans. Therefore, there is some risk with daily intakes of estragole when bitter fennel oil is taken as an expectorant in cough associated with cold according to the posologies supported by evidence of traditional use. Taking into account the availability of safer therapeutic options, the benefit-risk balance on *Foeniculum vulgare* Miller subsp. *vulgare* var. *vulgare*, aetheroleum is considered unfavourable with respect to a European Union herbal monograph. In the assessment report, under section 3.4 "Overall conclusions on non-clinical data", the sentence

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	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 oil 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 oil. **Thus, these findings cannot be transferred to fennel oil which therefore has to be assessed in a different manner than pure estragole.** **2. Essential oils with low estragole content** The European Pharmacopoeia monograph "Bitter fennel fruit oil" (1826) specifies a content of maximum 6.0 % estragole. As the Assessment Report states that *"taking into account the maximum amount 6% of estragole permitted in the bitter fennel oil according to the relevant Ph. Eur. monograph, these intakes may raises safety concerns due to risks of genotoxicity and carcinogenicity in humans"*, an option of producing essential oils with low estragole content could consist in the selection of special fennel cultivars, as discussed in the following. 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	"*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 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: "*The evidence available so far, is not sufficient to rule out genotoxicity of fennel oil and further in vitro and in vivo studies according to the current relevant guidelines are needed. In addition, carcinogenicity studies with fennel oil were not available. On the other hand, studies have shown the carcinogenic effects of estragole and 1'-hydroxyestragole in mice and rats (liver tumours). 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 possible that*

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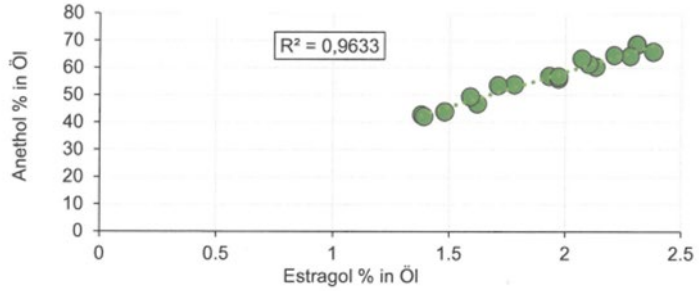
	in 1 of 8,390 samples they found an estragole content below 1% with a concurrent anethole content meeting the pharmacopoeia requirement. A large screening and breeding programme was performed between 2010 and 2021 by PHARMAPLANT GmbH, Artern (Germany) with the goal of identifying Bitter fennel lines with an estragole content << 2.2% while compliant with all other Ph.Eur. requirements. The results of this extensive work clearly 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).  Figure 1: Correlation between Anethole and Estragole concentration; exemplary data from 20 Foeniculum vulgare Miller ssp. vulgare var. vulgare clones (Internal Report Pharmaplant 2021)[1] 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,	*similar mechanisms to the toxicokinetic processes in rodents in which carcinogenicity has been observed could take place in humans. Therefore, the EMEA/HMPC assessment in 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."* <u>Point 2: Essential oils with low estragole content</u> 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. The amount of estragole in a medicinal product should be based on safety evaluation of that particular medicinal product. <u>Point 3: Ongoing research project on genotoxic effects of estragole</u>

[1] Entwicklung einer Sorte des bitteren Fenchels *Foeniculum vulgare* Mill. ssp. *vulgare* mit niedrigem Estragolgehalt. Pharmaplant GmbH, Artern 2022. Note: Additional data can be made available to the HMPC upon request.

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	drought resistance (increasingly important) and pest resistance (*Mycosphaerella*). **Taken together the available data show that reducing the Estragole content of fennel by sourcing low estragole content cultivars is no viable option.** In case essential oils with low estragole content are produced despite the mentioned difficulties, there is a need for regulatory acceptance of efficacy/traditional use of fennel oils with low estragole content, i.e. efficacy or traditional use should not be questioned. We would therefore welcome clarification about such regulatory acceptance of the efficacy/traditional use of fennel oils with low estragole content. **3. Ongoing research project on genotoxic effects of estragole** A current 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. **We strongly recommend taking the results of this research project into consideration before any regulatory action i.e., withdrawal of the monograph, is undertaken.** **Conclusion** **From our point of view, the requirements laid down in Article 16a(1)(e) of Directive 2001/83/EC are fulfilled, i.e. that the data on the traditional use of the medicinal product are sufficient; in particular the product proves not to be harmful in the specified conditions of use. For this reason, withdrawal of the monograph on *Foeniculum vulgare***	It is pointed out that any further study on genotoxicity/carcinogenicity of bitter fennel oil is welcomed and the results, once available, will be taken into consideration to eventually reconsider the the benefit-risk balance on *Foeniculum vulgare* Miller subsp. *vulgare* var. *vulgare*, aetheroleum with respect to a European Union herbal monograph, which remains negative to date.

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	Miller subsp. *vulgare* var. *vulgare*, aetheroleum is not justified, particularly taking into consideration the currently generated new safety data which, after final assessment of the research results, may allow maintaining the EU herbal monograph on Fennel oil.	
Koop Phyto	From our point of view, withdrawal of the monograph on *Foeniculum vulgare* Miller subsp. *vulgare* var. *vulgare*, aetheroleum is not justified, for the reasons reported below under "Specific comments on text".	

Specific comments on text

Section number and heading	Interested party	Comment and Rationale	Outcome
Problem statement	Koop Phyto	**1. Limitations of use for Bitter fennel oil** In a recent expert report on Current approaches in the toxicological risk assessment of estragole Schrenk [2022] elaborates on whether the available data would allow for a different approach in the case of estragole. The expert identifies the study performed under the National Toxicology Programme (NTP) as a source of such data. This study, although not meeting the requirements of a carcinogenicity study because of its limited duration (3 months) provides very valuable data when considering preneoplastic lesions which	<u>Point 1: Limitations of use for Bitter fennel oil</u> The toxicological assessment in the context of a marketing authorisation application should be referred to the bitter fennel oil. Until clear data showing the absence of genotoxicity/carcinogenicity of bitter fennel oil become available, exposure to estragole is considered as the key marker to estimate the benefit/risk assessment from this safety standpoint. With regard to the establishment of the monograph for bitter fennel oil, exposure to estragole in adults,

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		have been suggested as surrogate markers by various authors in the recent literature. The expert points out that in general • Hepatic preneoplastic foci show an early onset after starting carcinogen treatment with virtually no lag phase and are thus useful as quantitative surrogate markers at early timepoints • 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 • The authors of the NTP study used five different dose groups, thus the data set allows for a robust BMDL 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 The expert Schrenk arrives at the conclusion that a daily exposure of 2-3 mg estragole would be of low concern for an adult.	based on the posology reported by Keller 1992 which is mentioned in the previously adopted monograph for bitter fennel oil, is expected to be well above 2-3 mg per day. There is no further posology for bitter fennel oil in adults and adolescents supported by evidence of traditional use. <u>Point 2: Research Project "Dose-response studies on the genotoxic potential of estragole in human liver cells"</u> It is pointed out that any further study on genotoxicity/carcinogenicity of bitter fennel oil is welcomed and the results, once available, will be taken into consideration to eventually reconsider the the benefit-risk balance on *Foeniculum vulgare* Miller subsp. *vulgare* var. *vulgare*, aetheroleum with respect to the establishment of a European Union herbal monograph, which remains negative to date. <u>Point 3: Fennel oil to be assessed in a different manner than pure estragole: Data and justification?</u> The evidence available is not sufficient to draw any conclusion on the potential genotoxicity of fennel oil and further in vitro and in vivo studies according to the current non-clinical guidelines are needed. Carcinogenicity data for fennel oil are lacking. Estragole metabolic activation pathway and DNA adduct formation are amply demonstrated in animals

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		2. Research Project "Dose-response studies on the genotoxic potential of estragole in human liver cells" 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 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.	and the same pathway is operative in human in vitro systems. Thus, it is possible that similar mechanisms to the toxicokinetic processes in rodents in which carcinogenicity has been observed could take place in humans. Therefore, there is some risk to expose patients to high daily intakes of estragole when bitter fennel oil is taken as an expectorant in cough associated with cold according to the posologies supported by evidence of traditional use. Taking into account the availability of safer therapeutic options, the benefit-risk balance on *Foeniculum vulgare* Miller subsp. *vulgare* var. *vulgare*, aetheroleum is considered unfavourable with respect to the establishment of a European Union herbal monograph. 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 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*

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		Against this background we strongly recommend taking the results of this ongoing research project into consideration before any regulatory action i.e., withdrawal of the monograph, is undertaken. This is fully in line with the text of the draft Public Statement on Fennel Oil which expressively states that the HMPC would "welcome the provision of the safety data to allow maintaining an EU herbal monograph". **3. Fennel oil to be assessed in a different manner than pure estragole: Data and justification?** The draft revised HMPC Assessment Report already mentions with reference to the HMPC Public Statement on the use of herbal medicinal products containing estragole (EMA/HMPC/137212/2005 Rev 1): *"The genotoxic mechanisms of estragole contained in the fennel oil might be counteracted by detoxification mechanisms (see above Monien et al., 2019) and antimutagenic abilities of other fennel oil components (see above Tripathi et al., 2013), but further evidence is needed to confirm these findings."* The draft revised HMPC Assessment Report on Bitter fennel oil states that *"Fennel oil was found to be mutagenic in vitro in only one test although more recently it showed antimutagenic activity in mouse models of experimentally cyclophosphamide (CP)-induced genotoxicity and it did not show to be genotoxic in Comet assay after 4 h of treatment in HepG2 cells at 0.5, 1.0 and 2.0 µl/ml."* With regard to carcinogenicity the Assessment Report refers to the assessment of estragole only:	*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: "*The evidence available is not sufficient to rule out genotoxicity of fennel oil and further in vitro and in vivo studies according to the current relevant guidelines are needed. In addition, carcinogenicity studies with fennel oil were not available. On the other hand, studies have shown the carcinogenic effects of estragole and 1'-hydroxyestragole in mice and rats (liver tumours). 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 possible that similar mechanisms to the toxicokinetic processes in rodents in which carcinogenicity has been observed could take place in humans. Therefore, the EMEA/HMPC assessment in 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*

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		"Though there is no evidence of carcinogenicity for fennel oil, studies have shown the carcinogenic effects of estragole and 1'-hydroxyestragole in mice and rats (liver tumours). 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. 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 oil but an estragole metabolite in mammals. Therefore, it is not appropriate to put this substance in direct context with fennel oil, 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 oil are two different entities. Estragole is a chemically defined single substance, whereas fennel oil is a mixture of individual constituents where estragole is only 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 oil. It is rather true that there is no evidence for a carcinogenic effect of fennel oil so far, either *in vitro* or *in vivo*. Furthermore,	*days) and a discussion about the single/daily doses necessary according to the risk assessment."* Point 4: Essential oils with low estragole content The Committee is aware of the technical hurdles to obtain bitter fennel oil with a content of estragole close to zero while keeping all the other main constituents (i.e. *trans*-anethole, fenchone) still compliant with the Pharmacopoeial requirements. Indeed, daily intakes of estragole higher than a proposed guidance value 0.05 mg /person/day from medicinal products containing the fennel oil could be still accepted when supported by the evidence of traditional use and justified by risk assessment based on adequate safety data within a Marketing Application. With respect to the possibility to maintain a European Union herbal monograph the benefit-risk balance on *Foeniculum vulgare* Miller subsp. *vulgare* var. *vulgare*, aetheroleum has been considered unfavourable. Indeed, based on the posologies supported by the evidence of traditional use as an expectorant in cough associated with cold, the daily intake of estragole with bitter fennel oil would expose patients to risks which are not balanced by the beneficial effects in this therapeutic indication, taking

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		from our point of view, it is not possible to prove a previously unproven carcinogenicity of fennel oil by referring to the experimental carcinogenicity of the isolated pure substance estragole as was done in the sentence cited above. **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 oil, and from our point of view cannot be transferred without further scientific assessment.** **4. Essential oils with low estragole content** The European Pharmacopoeia monograph "Bitter fennel fruit oil" (1826) specifies a content of maximum 6.0 % estragole. The recent draft Assessment Report states: "*taking into account the maximum amount 6% of estragole permitted in the bitter fennel oil according to the relevant Ph. Eur. monograph, these intakes may raise safety concerns due to risks of genotoxicity and carcinogenicity in humans"*. For Bitter Fennel Fruit the HMPC proposes to reduce the daily dose to the lowest level still justified by traditional use in order to reduce the intake of Estragole via fennel tea to "as low as practically achievable". By analogy, such approach should be discussed for fennel oil as well. Of note, the Ph.Eur. specifies a **maximum** content (6%) of estragole in Bitter Fennel oil. Thus, the question	into account the availability of other safer therapeutic options.

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		arises what would be the **minimum** estragole content achievable in Fennel oil. The pharmacopoeial maximum value is based on the classical production by means of steam distillation. However, additional processing steps such as a second rectification step are technically established to reduce the estragole content, while the typical GC fingerprint pattern is maintained. Such technical solutions are marketed under the description "Fenchel Öl – estragolarm" (corresponding to "Fennel oil – estragole-reduced"). Maximally rectified Bitter Fennel oil has an upper limit as low as 0.05% estragole. It has to be noted that the reduction of estragole goes along with the reduction of the bitter tasting component fenchone to max. 3%. This oil type does not comply with the current Ph.Eur. specification for fenchone in Bitter Fennel oil (12.0% to 25.0%) while all other components remain compliant with the GC fingerprint according to Ph.Eur. or individual requirements, particularly trans-anethole with min. 60% (Ph.Eur. 55.0% to 75.0%). This oil type has been developed specifically for flavouring purposes. It is well conceivable that oil qualities could be accessible by controlled rectification with a markedly reduced estragole content, e.g., 0.25%, but an only moderately reduced fenchone content and a high trans-anethole content. In this exemplary case the daily dose of 200 mg Fennel oil would correspond to a daily intake of 500 µg estragole, which compares quite well with the acceptable intake level calculated by application of the less-than-lifetime algorithm of the ICH M7 Guideline (chapter 7.3), starting from the HMPC guidance value (detailed description see Comments	

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		of Kooperation Phytopharmaka on the draft revised monographs for Bitter/Sweet Fennel fruit). In consideration of the information outlined above a withdrawal of the HMPC monograph for Bitter Fennel oil would not be justified. **Conclusion** **From our point of view, withdrawal of the monograph on *Foeniculum vulgare* Miller subsp. *vulgare* var. *vulgare*, aetheroleum is not justified, particularly taking into consideration new safety data which allow maintaining the EU herbal monograph on Fennel oil, e.g. those which are currently generated in the ongoing research project at the University of Kaiserslautern. With regard to the toxicological assessment on which the HMPC draft public statement is based, it is not justified from our point of view to conclude that *in vivo* data on pure estragole are also relevant for humans. Such data cannot be transferred to without further scientific assessment. Regarding the daily exposure to estragole, the expert report of Schrenk concludes that 2-3 mg estragole would be of low concern for an adult. This should be a matter of further considerations with regard to limitations of use for fennel oil. Modern rectification techniques provide possibilities for a substantial reduction of the estragole content of Fennel**	

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		oil to levels which limit the daily intake within the boundaries derived from the ICH M7 Guideline.	

References

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Schrenk D. Current approaches in the toxicological risk assessment of estragole. Expert Report, October 2022