European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON 'COMMUNITY HERBAL MONOGRAPH ON *FOENICULUM VULGARE* MILLER SUBSP. *VULGARE* VAR. *VULGARE*, FRUCTUS ' EMEA/HMPC/137428/2006,

COMMUNITY LIST ENTRY ON *FOENICULUM VULGARE* MILLER SUBSP. *VULGARE* VAR. *VULGARE*, FRUCTUS ' EMEA/HMPC/428817/06,

'COMMUNITY HERBAL MONOGRAPH ON *FOENICULUM VULGARE* MILLER SUBSP. *DULCE* (MILLER) THELLUNG, FRUCTUS ' EMEA/HMPC/263293/2006,

and 'COMMUNITY LIST ENTRY ON *FOENICULUM VULGARE* MILLER SUBSP. *DULCE* (MILLER) THELLUNG, FRUCTUS ' EMEA/HMPC/428963/06

Table 1: Organisations that commented on the documents as released for consultation on 25 October 2006 until 28 February 2007

	Organisation
1.	Association of the European Self-Medication Industry (AESGP)
2.	European Forum for Complementary and Alternative Medicine (EFCAM)
3.	European Federation of Associations of Health Product Manufacturers (EHPM)
4.	European Scientific Cooperative on Phytotherapy (ESCOP)
5.	Irish Medicines Board
6.	Kooperation Phytopharmaka, Germany
7.	National Agency for Medicines, Finland
8.	Medicines and Healthcare products Regulatory Agency, United Kingdom

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Table 2: Discussion of comments

General comments	Comment and rationale	Rapporteur's comments
Comments on draft Entries to the Community List	1. Fennel is used in China for more than 1300 years. Fennel is documented in China for medicinal use since 659. It first appears in the Chinese herbal classic "Tang Materia Medica" published in 659 AD[1]. It is widely cultivated throughout China[10], and it is official in every edition of the Chinese Pharmacopoeia since 1953[2-9]. 2. Fennel produced in China is not only used in China but also in Europe. At one time, large quantities of fennel in Europe were imported from India, China and Egypt as documented in Trease and Evans' Pharmacognosy[11]. 3. The indications of fennel in traditional Chinese medicine are similar to those listed in the draft monograph. 4. No safety concern has been raised over the use of fennel in traditional Chinese medicine. **Based on the above documented evidence on the traditional use of fennel in China, it is recommended that the type of tradition for fennel also include "Chinese" in addition to "European".** 1-10: List of References supporting the comments provided	We agree that fennel is used in Traditional Chinese Medicine with similar indications. This is discussed in the assessment report.
	Common name in all EU official language NL (Nederlands): Venkel	Dutch common name has been introduced.

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3. Pharmaceutical form	As described under Posology in section 4.2, the most common dosage forms of fennel fruit are herbal teas and aqueous infusions. The pharmaceutical form should therefore read: Herbal substance or herbal preparation in solid or liquid dosage forms for oral use.	Partially endorsed. Aqueous infusions are prepared extemporaneously. The pharmaceutical form on the market is the herbal substance or the herbal preparation consisting in the comminuted herbal substance as described in section 2. Qualitative and quantitative composition. According to the documentation available, solid dosage forms or herbal teas are on the market.
4.1 Therapeutic indications	From our point of view, the following indications are suitable for a well-established medicinal use: ▪ Dyspeptic complaints such as mild spasmodic gastro-intestinal ailments, bloating, flatulence. ▪ Catarrh of the upper respiratory tract. These indications are justified by the following references: CZYGAN 2002, BRAND 1993, WEISS 2002. Clinical experience and expert opinions are available as well as supportive pharmacological data which thus meet the requirements for the well-established medicinal use.	Published clinical data are insufficient to support the well established use. References mentioned reinforce rather the plausibility of the traditional use.
4.1 Therapeutic indications	The term "menstruation period" should be replaced by "menstrual period"	Endorsed.
4.2. Posology and method of administration	We welcome the dosage recommendation for the different age groups of children, which seems to be reasonable and scientifically supported. We question why the dosage recommendation for fennel powder is included only in the draft monograph on sweet fennel fruit and not in the one on bitter fennel fruit nor in either of the draft entries to the Community list	The recommended posology has been set according to the posology of the products on the European market, which substantiate the traditional use. The presence on the European market of the fennel powder is documented only for sweet fennel. The dosage recommendation for the draft entry into the Community list of sweet fennel fruit has been amended accordingly.

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4.2. Posology and method of administration	For the **well-established medicinal use** we propose the same posologies as the ones currently listed under "traditional use" for respectively adults and children. These recommendations are justified by the references mentioned under "indications" as well as ESCOP. We welcome the dosage recommendation for the different age groups of children. **As adolescent are technically children, we would propose not to differentiate adolescent as a stand alone group but to add this subcategory under '*children*'.** However, with reference to ESCOP, the use in children is also true for indication c). Therefore, this should be added. **Duration of administration:** We would propose to replace the current statement by **"no restriction".** A limitation of use to two weeks cannot be deduced from preclinical data (see 5.3.).	Not agreed. The well established use is not supported by sufficient scientific data. The growth and maturation of organs and the metabolic changes occurring during the different ages produce substantial differences in children and adolescents. These differences should require specific studies on safety and efficacy. Due to the lack of these studies, we believe that it is necessary to keep differences in posology for the paediatric population. The recommended posology has been set according to the posology of the products on the European market. No documentation to substantiate the traditional use in children has been found for the indication c). Because of the lack of available safety data on long-term use of fennel preparations, and due to the presence of compounds such as trans-anethole and estragole, a limit of two weeks is consistent with a self-medication indication, which is the case of a traditional herbal medicinal product. If symptoms persist or worsen after two weeks it is necessary to consult a doctor.

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4.2. Posology and method of administration	For time being, the indication for paediatric population (under 12 years of age) can not be accepted because of the following reasons: - The risk is mainly focused on estragole, a component found in fennel and known to be mutagenic/carcinogenic according to non-clinical data. - There is also exposure to estragole in 'every day life' from natural sources. Thus, a thorough risk evaluation has to be done in order to understand the risk related particularly to use of this product in early childhood. Considering the nature of the potential risk, the long-standing use in some European countries does not exclude the risk related to these products. - Even the short time of use may potentiate allergenic reactions in small children.	According to this comment, the rapporteur does not recommend the use in young children due to the lack of adequate data for a safety assessment and because of the presence of estragole. The HMPC does not consider relevant the genotoxic risk related to estragole due to the small amount present in herbal infusions prepared from fennel. Mutagenic activity has been considered unimportant on the basis of the studies carried out in vitro and on the laboratory animals. We agree that, taking into account the nature of the mutagenic/carcinogenic risk of estragole, the long-standing use in some European countries does not exclude the risk related to these products. This kind of risk can only be assessed through long-term studies involving large samples of consumers. The use in children under 4 year of age requires advice from a paediatrician. In children between 4 and 12 years of age, with the aim to minimise the exposure to estragole, a short-term use (less than one week) of fennel tea in mild transitory symptoms may be considered acceptable. The potential facilitation of allergenic reaction could be likely to happen even for short-term in small children per se, because the youngest age. However, the long standing use in some European countries does not provide data reporting an increase of allergenic reactions in children.

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4.2. Posology and method of administration	The Interested Party does not agree with the proposed use of fennel in the paediatric age group for the following reasons. 1 We do not agree with the recommendation that Fennel "may be considered in case of acute symptoms" as children with acute abdominal symptoms should have an immediate medical review. 2.The following recommendation is proposed "Administration for more than 1 week is not recommended because of the lack of safety data on long- term use" However there is no safety data in short or long term use in children to support its use. 3. A paediatric indication for the 3 month to 1 year age group contradicts the advice given in Section 4.6 on lactation which states: "In absence of sufficient data the use during pregnancy and lactation is not recommended" 4. According to the HMPC's Public safety statement on the use of herbal medicinal products containing estragole. "the exposure of estragole to sensitive groups such young children, pregnant and breastfeeding women should be minimised." Therefore recommending the use of fennel in children contradicts this previous HMPC advice.	Full rapporteur's agreement. The indication for prescribing the use of fennel tea in infants and children under 4 years of age is restricted to the entire paediatrician (see III.3). For children between 4 and 12 years of age a short-term use (less than one week) of fennel tea in mild transitory symptoms has been considered acceptable by HMPC. Agreed Agreed

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4.2. Posology and method of administration	1. The proposed use of the above herbal drugs as traditional herbal medicinal products for symptomatic treatment of acute symptoms of mild, spasmodic gastro-intestinal complaints including bloating, and flatulence in children under 12 years is not supported by appropriate data for safe use.	
	2. Evidence of traditional use for the proposed indications in children is considered lacking.	Evidence of traditional use for the proposed indications in children is not homogenous in all the European Countries but it is not completely lacking.
	3. There are concerns about misinterpretation of the proposal for treatment of 'acute symptoms' as this could be due to a serious underlying condition.	Agreed. For children between 4 and 12 years of age a short-term use (less than one week) of fennel tea in mild transitory symptoms has been considered acceptable by HMPC.
	4. There are safety concerns about the use of herbal infusions of potentially variable concentration in children, especially babies.	Agreed. The indication for prescribing the use of fennel tea in infants and children under 4 years is restricted to the entire paediatrician (see III.3).
	5. The use of relatively large volumes of herbal infusions in babies is considered unacceptable without supporting safety data. Volumes of conventional medicines administered to babies are usually kept to a minimum to ensure that feeding regimens are not disrupted. Volumes of fluids other than milk are usually below 20mls.	
	6. The proposal to use fennel preparations in children conflicts with the HMPC Public safety statement on the use of herbal medicinal products containing estragole which advises that *"the exposure of estragole to sensitive groups such young children, pregnant and breastfeeding women should be minimised."*	Agreed. The proposed revised use of fennel tea restricted to paediatrician advice for children under 4 years and for short-term use (less than one week) in mild transitory symptoms is considered by HMPC as a minimisation of the exposure to the estragole taking into account the posology and the amount of essential oil passing into fennel tea.

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4.4 Special Warnings and Precautions and 4.5 Interactions Monographs and list entries	The IPs question whether it is appropriate, in proportion to the perceived possible danger, to mention the cross-reactivity risk to Asteraceae. In absence of any documented evidence, the IPs propose to delete the statement in section 4.4.	Endorsed.
4.6. Pregnancy and lactation	The 1st paragraph states: *"**There are no data from the use of fennel fruit in pregnant patients**"*. We recommend replacing this sentence by the following: *"Although clinical data on the safety of using fennel fruit in pregnancy is missing, fennel may be used during pregnancy and lactation at the recommended dosage"* and to delete the 3rd sentence. We refer to our comments under section 5.3. Furthermore, thoughts should be given to the alternatives pregnant women do have to treat bloating and related intestinal symptoms which often occur during pregnancy. In case notable side effects of fennel fruit preparations had occurred in pregnant women this would have been indubitably reported in the literature or in pharmacovigilance systems given the careful medical monitoring women benefit during their pregnancy.	Not endorsed. The sentences reported in the monograph are in agreement with the statements in annexes I and III of the 'Guideline on SPCs' and the template for a Community herbal monograph (EMEA/HMPC/107436/05) Rev. 2 See comments in section 5.3

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4.6. Pregnancy and lactation	Although no formal data exist on the use of fennel fruit in pregnancy, it should be take into consideration that fennel fruit has been used for generations, ideed since antiquity, in pregnancy and as a galactogogue during lactation, with no history of adverse events. In a 1992 review of *Foeniculum vulgare*, Keller concluded that "…fennel (especially infusion of fennel) does not seem to represent any special risk in pregnancy and lactation" [Keller 1992]. Two major reviews published in 1999 on the safety evaluation of *trans*-anethole, by the JEFCA [Joint FAO/WHO 1999] and the USA Flavour extract Manufacturers Association [Newborn 1999, were reassuring with respect to the reproductive toxicity of *trans*-anethole, based on studies on rats. In contrast, the 1995 study by Dhar (not mentioned in the 1999 review) reported anti-infertility, anti-implantation and early abortifacient effects of trans-anethole in rats [Dhar 1995]. The results of Dahr may well be questioned, but they cannot be ignored withouth further animal studies and we accepted that caution is required in the amount of anethole ingested in the form of fennel fruit preparation during pregnancy. However, the amount of fennel oil (and hence anethole) passing from comminuted or crushed fennel fruit into teas and aqueous infusions,- the time-honoured way of taking fennel fruit – is relatively low. It has been shown that only about 10% of the oil passes into a fennel tea infusion [Fehr 1982]. Taking this into account, the use of fennel fruit during pregnancy and lactation *as teas/aqueous infusions only* at the recommended dosage should be acceptable [ESCOP, Bradley 2006]	Not agreed Despite the European Scientific Cooperative on Phytotherapy reports that the drug and preparations of fennel at the recommended dosage may be used during pregnancy and lactation (ESCOP, 2003), no data are available in relation to the use of fennel during pregnancy and lactation at the recommended dosages. According to the recommendations of the HMPC Public statement on the use of herbal medicinal products containing estragole, "the exposure of estragole to sensitive groups such young children, pregnant and breastfeeding women should be minimised." (EMEA/HMPC/137212/2005) See also previous comments for the same section 4.6.
4.7. Effects on ability to drive and use machines	We propose to say: "No data available."	Not endorsed. The sentence is in compliance with the template for a Community herbal monograph EMEA/HMPC/107436/05 Rev. 2
4.8. Undesirable effects	We suggest to delete "and gastro-intestinal system" because there are no reports available.	Endorsed.

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5.3. Preclinical safety data	The 2nd paragraph states: *"For trans-anethole anti-implantation, early abortifacient and antifertility activity has been reported in rats"*. We would like to comment on this statement as follows: **a) Studies on reproduction/developmental studies** In the study of DHAR (1995), 50, 70 or 80 mg/kg trans-anethole (not defined) were given on day 1-10 of pregnancy (n=6/treatment), a reduction of the number of the implantations sites by 33, 66 or 100 % respectively, was described. In further experiments anethole was administered on day 1-2 or on day 3-5 of pregnancy. An antifertility effect was observed only by treatment on day 3-5; application on day 1 and 2 was ineffective. Malformations were not observed. These findings are in clear contrast to those cited in NEWBERNE et al, 1999. The FEMA GRAS Assessment of trans-anethole does not show any hints on adverse effects of the substance on fertility or reproduction, although trans-anethole was studied in three experimental sets. Doses of 0, 25, 175 or 350 mg/kg b.w. were given by gavage to rats (n=10/treatment) starting on day 7 prior to mating up to day 4 of lactation. Only in the highest dose group a slight increase of gestation time, increases in pup mortility and stillbirths and reductions of body weight of the pups were noted. No gross physical abnormalities were associated with anethole treatment. In a four generations study in rats (n=40), anethole was added at a concentration of 1% to the diet (corresponding to 700 mg/kg b.w.). The only effect observed was a reduced body weight and a reduction of the body weight increase in the pups. In a further experiment, this delay in the growth of the pups could be explained by the reduced palatability of trans-anethole. The authors concluded that trans-anethole did not produce any reproductive toxicity at doses that are still palatable.(LE BOURHIS 1973, cited in JECFA 1999).	The sentence referring to the dose dependent antimplantation, early abortifacient and antinfertility activity reported at high doses of trans-anethole in rats has been deleted from the monograph. Experimental data on trans-anethole cited by the IPs are included in the assessment report. Despite the lack of human data, they do not exclude potential toxicity of trans-anethole and fennel fruit at higher doses and for prolonged use, especially for sensitive population groups such as children, pregnant and breastfeeding women. On the contrary, experimental conditions showed a) reduction in the number of the implantation sites causing antifertility effect, b) increasing of gestation time, pup mortality and stillbirths, reduction of body weight of the pups. Although some of these effects were noted at highest doses, they do not support fennel safety in pregnancy.

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	The findings of the publication of DHAR seem to be of questionable relevance. They are in clear contrast to those cited in NEWBERNE et al, 1999. which described three independent investigations (ARGUS (1992, cited in JECFA 1999, JECFA 1999, LE BOURHIS 1973, cited in NEWBERNE et al. 1999). These investigations have been performed in a sufficient number of animals and in a very elaborated and accurate way, and therefore should be regarded to be reliable. The very weak effects seen in these well-conducted and documented experiments even by excessive doses of anethole up to 1400 mg/kg b.w./day clearly put a question mark behind the results of DHAR (1995). He reported a 100% inhibition of implantation at a dose of 80 mg/kg b.w./day administered p.o., i.e., 50% of the NOEL which had been determined with 175mg/kg b.w./day (ARGUS RESEARCH LABORATORIES 1992, cited in NEWBERNE et al. 1999 and JECFA 1999). The author does not adequately describe the quality and source of neither the anethole used in the study nor any other material. Figures in the paper do not indicate standard deviations. The reported increase of implantation inhibition from 33% at 50 mg/kg b.w. to 66% at 70 mg/kg and to 100% at 80 mg/kg appears rather drastic for a biological effect. Furthermore, the number of animals per group (n=5) was rather small. Thus two extensive, well-documented studies (ARGUS 1992 and LE BOURHIS 1973, both cited in JECFA 1999) suggest that anethole, the major constituent of aniseed oil, is safe during pregnancy and lactation for both the mother and the offspring. The study of DHAR (1995) suggests a strong anti-implantation effect of anethole but is very poorly documented. Teratogenic effects were not observed in any of the studies. **b) Estrogenicity of anethole** For trans-anethole an estrogenic activity has been discussed on the basis of in vitro findings and animal experiments.	Estrogenic activity is mentioned only in the monograph of bitter fennel oil.

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	The assumption of an estrogenic activity is mainly based on older reports, starting with a study of ZONDEK and BERGMANN (1938) who describe anise oil to be estrogenic in the Allen-Doisy-test (200µl/day for seven days, s.c.). In 1980, ALBERT-PULEO described studies with anise oil and compounds isolated after exposing the oil excessively to oxygen and UV light. The authors considered desmethyl-anethole and polymerisation products of anethole to be responsible for the observed activity. In an attempt to verify the hypothesis that stilbene-like dimerisation products of anethole presents estrogen-like effects, KRAUS and HAMMERSCHMIDT (1980) subjected fennel oil (>80% anethole) to extreme storage conditions in terms of light, oxygen and temperature. They did not detect any anethole dimers in the so-treated oil. MIETHING et al (1990), however, found 0.39ppm of 4,4´-dimethylstilbene in aniseed oil exposed to daylight for 6 months. The authors concluded that the dimer was a reaction product of anethole and anisaldehyde. The fact that isolated anethole is practically free of anisaldehyde likely explains the contradictory results. From these findings it can be concluded that an estrogenic activity observed in older experiments may be due to compounds which result from inappropriate storage. Thus storage has to be performed under appropriate conditions in accordance with the European Pharmacopoeia. **Receptor-binding studies** In two papers, results on the estrogenic activity of trans-anethole in yeast cells were published: TABANACA et al (2004) observed an estrogenic activity with an IC_{50} value of 625 µg/ml, as compared to 17 β-estradiol the effectivity was 8.6 x 10^{-8}. HOWES et al (2002) observed an estrogenic activity of trans-anethole only at a concentration of 10 mM, i.e. at a concentration of 1.48 mg/ml (corresponding to 1.48 g/l). All lower concentrations studied were ineffective. In order to obtain an IC_{50} value according to TABANACA et al (625 mg/l), an intake of at least 2.5 g would be necessary and, according to HOWES et al, the intake would even need to be higher (6 g per volunteer).	Experiments of **Tabanca** et al., report an IC_{50} value of 625 µg/ml. They refer to Pimpinella anisum fruit oils, not to fennel. (Tabanca et al 2004 Estrogenic activity of isolated compounds and essential oils of Pimpinella species from Turkey, evaluated using a recombinant yeast screen Planta Med. 2004; 70:728-35). The study of Howes (2002) confirming that high concentrations of trans-anethole have the potential to interact with estrogen receptors in rodents, leads to suggest caution with the use of fennel in human sensitive population groups.

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	In vitro findings The metabolism and the metabolites which were formed at different concentrations of trans-anethole, were investigated in isolated rat hepatocytes by NAGAKAWA and SUZUKI (2003). At a weakly toxic concentration (0.5 mM) trans-anethole was mainly metabolized to 4-methoxycinnamic acid (4MCA), 4-hydroxy-1-propenylbenzene (4OHPB) and to the monosulfate conjugate of 4OHPB. Free unconjugated 4OHPB reached less than 0.5 µM, whereas at the toxic concentration of 1 mM unconjugated, free 4OHPB reached 10 µM. It seems to be of special interest that the rate of formation of free unconjugated 4OHPB, a minor metabolite, is only relevant at high toxic concentrations. The authors showed that only the free unconjugated metabolite 4OHPB formed from anethole by *O*-demethylation is responsible for the estrogenic effects of anethole, i.e., for receptor binding as well as for stimulation of the growth of MCF-7 cells (estrogen receptor positive mammary carcinoma cells). Receptor binding was observed with IC_{50} values of 5×10^{-5} M for 4OHPB, whereas neither anethole nor its metabolite 4MCA showed interference with 17β-estradiol receptor binding up to a concentration of, respectively, 10^{-3} or 10^{-4} M. 4OHPB stimulated cell proliferation of MCF-7 cells in a range of 10^{-6} to 10^{-8} M, whereas neither anethole nor its metabolite 4MCA showed any effect. The authors concluded that 4OHPB is responsible for the estrogenicity of anethole. The metabolism of trans-anethole in human volunteers has been studied (NEWBERNE et al 1999, CALDWELL 1987). In contrast to rodents there was no clear dose-related dependency on the rate and the route of elimination (doses of 1, 50 or 250 mg anethole were applied). Elimination was much faster in humans than in rodents. 8 hours after application in men the bulk of the dose was eliminated in expired air and urine, whereas in rats or mice it took 48-73 hours in high doses. 13-17 % of the metabolites in urine of the volunteers were *O*-demethylation products.	Conclusions of the **Nakagawa** and Suzuki's experiments, based on studies on rodents, are the following: "These results suggest that the biotransformation of anethole induces a cytotoxic effect at higher concentrations in rat hepatocytes and an estrogenic effect at lower concentrations in MCF-7 cells based on the concentrations of the hydroxylated intermediate, 4OHPB". To date very little is known about the metabolism of trans-anethole by humans. Caldwell's research group published two articles on metabolism of trans-anethole in humans, both including essentially the same experiments (Sangster, Caldwell et al., 1987; Caldwell and Sutton, 1988). The fundamental conclusion of the authors is only that "the pattern of urinary metabolites of trans-anethole is unaffected by dose size". Any consideration on risk influence is lacking. These Caldwell's experiments show essentially the difference in anethole metabolism between rodents and humans.

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	Thus it obvious that neither in mice nor in rats a satisfying testing of anethole toxicity is possible. Especially at higher doses, the marked differences in metabolism may result in an overestimation of the possible risk (CALDWELL 1987). **In vivo studies** In one study a significant increase in uterus weight of juvenile rats was seen following application of 80 mg/kg b.w. for three days (DHAR, 1995). The relevance of this finding is questionable since the findings on a possible anti-fertility activity of the author were not confirmed by other, more reliable studies (NEWBERNE et al, 1999). **For these reasons a restriction of use of fennel preparations in pregnant and breastfeeding women appears to be inappropriate.** **Furthermore we suggest adding a comment at the end of 5.3 stating that the content of estragole is limited by the European Pharmacopoeia.**	The work of Dhar is a scientific article reporting original experiments. The Newberne's article, discussed in the assessment report, is an assessment of studies on anethole not reporting new original experiments. As discussed in the assessment report, the body of scientific data indicates that reproductive system is a target for the action of fennel extracts and its principal constituent trans-anethole. Changes in male and female organs and tissues involved directly or indirectly in the reproductive mechanisms have been described in laboratory animals. Consequences of these changes are not easily predictable or detectable and they cannot definitely be excluded in humans. Therefore the use of a self-prescription THMP such as fennel fruit in sensitive population groups such as pregnant and breastfeeding women cannot be recommended, also according to the European current 'Guideline on SPCs'. The remark on the estragole content is covered by the footnote 1: The material complies with the Ph. Eur. monograph.