Centrum für Therapiesicherheit in der Chinesischen Arzneitherapie

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C T C A L e t t e r - O c t 2 0 2 5

This Newsletter addresses the following topics

- Risk assessment of estragole in Foeniculi Fructus **(***xiao hui xiang***)**
- Statement on the carcinogenic potential of Talcum **(***hua shi***)**
- Alleged hepatotoxicity associated with *Curcuma* preparations

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Risk Assessment of Estragole in Foeniculi Fructus (*xiao hui xiang*)

Background

The potential carcinogenicity of estragole, a natural constituent of several herbal medicinal products and foodstuffs, has been the subject of scientific and regulatory debate for approximately 25 years. The fact that the safety of fennel has recently been increasingly questioned has caused considerable concern among naturopaths. In 2001, the Scientific Committee on Food of the European Union classified estragole as genotoxic and carcinogenic [1]. This assessment was subsequently endorsed by the Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA).

The most recent *Public Statement on the Use of Herbal Medicinal Products Containing Estragole*, updated on 9 June 2023 [2], indicates that the metabolic activation of estragole, which underlies its carcinogenic potential, is not linearly dose-dependent and has limited relevance at low exposure levels. Consequently, short-term administration of herbal medicinal products at recommended dosages does not pose a significant carcinogenic risk for adults. Nonetheless, risk minimization is strongly advised for vulnerable populations, including young children, pregnant women, and breastfeeding mothers. Existing evidence remain insufficient to establish precise safe threshold values.

Regulatory Framework

The HMPC withdrew its monographs on bitter and sweet fennel in 2024. With regard to estragole intake from herbal medicinal products, it recommends a maximum daily dose of 0.05 mg for adults, including pregnant and breastfeeding women, and 1.0 µg/kg body weight per day for children up to 11 years [2].

How was the recommended intake value for estragole determined?

The European Food Safety Authority (EFSA) established a provisional guideline value using the *Margin of Exposure (MOE)* approach. For risk calculation in humans, it relied on the estragole dose in female mice which, after 12 months of continued oral exposure, increased the incidence of hepatocellular carcinoma by 10% (*BMDL10*). This dose was then divided by a safety factor of 10,000 [3].
The composite safety factor accounts for the body surface area correction between species, the uncertainty associated with extrapolating toxicological data from mice to humans, and the potential interindividual variability within the human population.

What implications does this have for Chinese Herbal Medicine?

The use of Foeniculi Fructus (*xiao hui xiang*) in Chinese herbal medicine does not occupy the same prominent role as it does in Western phytotherapy or as in food. Nevertheless, this herb is included in several classical formulations, such as *Nuangan jian* (Warm the Liver Decoction), *Tiantai wuyao san* (Top-Quality Lindera Powder), *Shaofu zhuyu tang* (Drive out Blood Stasis in the Lower Abdomen Decoction), and *An zhong san* (Calm the Middle Powder). Standard dosages range from 3 to 6 g, with specific prescriptions listing amounts from 1.5 to 9 g.

The European Pharmacopoeia specifies a minimum essential oil content of 2% for sweet fennel and 4% for bitter fennel in the dried fruit, whereas the Chinese Pharmacopoeia sets a minimum of 1.5% for *Foeniculum vulgare* without distinguishing between sweet and bitter fennel, making both subspecies acceptable.

Estragole typically comprises 2–5% of the oil in bitter fennel and 3–10% in sweet fennel [4], though values as high as 47.5% have been reported [5]. Raal et al. analyzed fennel oils from various countries and found estragole levels ranging from 2.4 to 17.0%. In the dried herbal drug, Afifi et al. reported lower concentrations: 4.5 µg/g and 0.63 µg/g in sweet fennel from Italy and Austria, respectively, and 0.08 µg/g in bitter fennel from Austria [6]. Thus, estragole concentrations in fennel seeds are highly variable.

While assessing the risk of aqueous extracts such as decoctions, the relevant parameter is not the estragole content of the raw material but rather the proportion transferred into the extract. Mihats et al. investigated 42 fennel tea products and 3 instant teas available on the Austrian market. Average estragole concentrations were 565 µg/L in infusions from tea bags and 639 µg/L from whole fennel fruits, with maxima of 2,477 µg/L and 4,644 µg/L, respectively. Grounded fennel seeds yielded 4.4–5.9 times higher concentrations compared to intact fruits. For instant teas marketed specifically for infants, estragole levels were below the detection limit [3]. The extraction efficiency for estragole, as cited in various studies by the HMPC, was determined to be 12.5% in one case, while other investigations report values of less than 2% or between <0.1% and 2.5% [2].

Calculated estragole exposures based on Mihats et al. ranged from **0.25–5.04 µg/kg for children, 0.32–6.42 µg/kg for women, and 0.15–2.93 µg/kg for men**. **For infants** with an assumed body weight of 5 kg, consuming one cup of fennel tea results in an estimated estragole exposure of **0.5–20.78 µg/kg**. These values should be evaluated against the EMA recommendation of **≤1 µg/kg** for children. The results apply to average consumption levels; with higher intake, any exceedances would correspondingly increase [3].

These results were obtained from tea preparations using one tea bag or the manufacturer-specified dose of fennel seeds (2.0–7.6 g), and for instant teas 2–5 g of powder or granules, steeped for 6–10 minutes in boiling water [3]. It is uncertain to what extent the results can be extrapolated to typically prepared TCM decoctions. While extended decoction times may volatilize part of the essential oil (estragole boiling point 216°C), it may also increase the relatively small amount of estragole which is transferred into the tea. It can be assumed that the values determined for teas are roughly comparable to those expected for decoctions.

Another factor affecting extrapolation of data is that the carcinogenicity studies used pure estragole, not fennel fruits. Administration within an (*mein Programm sagt hier "an"*) herbal matrix or as part of a formula may modify the results (the so-called matrix effect). The HMPC has also considered this issue, noting that the very limited available data provide only weak indications of either a possible overestimation or underestimation of the carcinogenicity risk. [2]. In any case, an assumption of risk reduction cannot be made.

In the risk assessment, it must be taken into account that the EFSA derived limits were established assuming lifelong exposure (12 months in mice). In the case of only occasional consumption of fennel tea or comparable preparations, the risk is expected to be substantially lower.

► Practical Implications

The carcinogenicity risk of fennel fruits within the framework of typical Traditional Chinese Medicine (TCM) therapy is based on relatively limited data and can be considered relatively low. Nevertheless, it cannot be entirely dismissed. Relying strictly on the HMPC guidelines with reference values for estragole dose is of limited practical use. We recommend generally avoiding long-term intake of fennel fruits, minimizing use during pregnancy and lactation as much as possible, and limiting administration to young children to few medically indicated episodes.

Talcum: „Probably Carcinogenic to Humans"

Talc (*hua shi*) is a naturally occurring mineral that can sometimes be contaminated with asbestos. Both substances are chemically related silicate compounds that differ in their crystal structure: talc is a non-fibrous sheet silicate mineral with the chemical formula $Mg_3Si_4O_{10}(OH)_2$, whereas asbestos is a fibrous silicate mineral. Talc forms platy, sheet-like structures, while asbestos forms long, fibrous crystals.
Talc has widespread applications, including in cosmetics and food products. The International Agency for Research on Cancer (IARC) previously classified asbestos-contaminated talc as "carcinogenic to humans" (Group 1) [7], whereas talc free of asbestos was considered "not classifiable as to its carcinogenicity to humans" (Group 3). More recently, the IARC has re-evaluated asbestos-free talc and upgraded its classification to "probably carcinogenic to humans" (Group 2A) [8].

What is the basis for this classification?

A large body of cohort and case-control studies has examined human exposure to talc, including occupational exposure. These studies have been scrutinised in detail by the International Agency for Research on Cancer (IARC). The vast majority of investigations focused on exposure via inhalation. However, these studies do not allow a definitive conclusion regarding the carcinogenicity of talc, due to several confounding factors: potential contamination with asbestos, co-exposure to other potentially carcinogenic substances, misclassification or recall bias, and/or small sample sizes. A relatively clear association has been observed between inhaled talc exposure and ovarian cancer, but even in this case, it remains uncertain whether asbestos contamination can be reliably excluded.

One study detected asbestos fibers in 8 out of 10 ovarian tumor samples and talc in all samples [9]. The IARC postulates that perineal or intravaginal application of talc may allow the particles to reach the abdominal cavity via the uterus and fallopian tubes, subsequently reaching the ovaries.

In addition, a study from Taiwan (1997–2013) reported an increased incidence of gastric cancer following oral talc consumption as part of Traditional Chinese medicine [10] (adjusted hazard ratio = 2.13, 95% confidence interval 1.54–2.94, $p < 0.001$). Regarding potential asbestos contamination, the IARC notes that the talc used in this study may have been contaminated, as strict monitoring for asbestos in pharmaceutical-grade talc in Taiwan was only implemented starting in 2005. Therefore, the results cannot be confidently attributed to asbestos-free talc.

Due to the generally uncertain asbestos contamination in human studies, the IARC considered experimental animal studies, which can exclude this confounding factor. Most inhalation studies reported no significant increases in tumor incidence. However, a methodologically high-quality study in rats exposed to verified asbestos-free talc demonstrated a significant trend toward increased benign and malignant pheochromocytomas, as well as bronchoalveolar adenomas and carcinomas [11].

A few carcinogenicity studies with oral administration considered methodologically insufficient for risk assessment showed no elevated tumor incidence. Studies employing parenteral administration (e.g., intraperitoneal, intrapleural, intratracheal, or even intrabursal injections into the ovary) also revealed no significant increases in tumor rates, though these studies exhibited substantial methodological limitations.

The IARC's assessment was primarily based on the pharmacological effects of talc that may support its carcinogenic potential. Talc has been shown to cause chronic inflammation and influence cell proliferation, cell death, and nutrient supply in human primary cells., all of which are mechanisms potentially relevant to carcinogenesis.

Our Assessment

In our view, the IARC classification rests on somewhat tenuous grounds, as it primarily bases the assessment of carcinogenicity on mechanistic considerations, while the actual effects observed in humans and animals do not provide conclusive evidence of talc's carcinogenicity. Talc only partially fulfils the key mechanistic properties associated with carcinogenesis: evidence is lacking for electrophilicity, genotoxicity, impairment of DNA repair, epigenetic alterations, and modulation of receptor-mediated effects.

Implications for Traditional Chinese Medicine

For Traditional Chinese Medicine, the primary concern is the risk associated with oral intake of talc. In animal studies, orally administered talc is largely excreted rapidly. In humans, the only study addressing oral exposure is that of Chang CJ et al., which reported an increased incidence of gastric cancer. The IARC notes: *"In this study, the talc was assumed to be of pharmaceutical purity and free of asbestos contamination; however, asbestos contamination of this talc could not be excluded before 2005. In addition, the study captured a short exposure period, had short follow-up, and there was some concern about confounding by indication."*

An oral administration study in rats using both talc and an asbestos-containing drug reported in each group a gastric leiomyosarcoma in one out of 32 animals [12]. This finding may support the observation by Chang et al., but it cannot be reliably distinguished from a incidental finding.

Talc Not Reliably Tested for Asbestos

In our view, the carcinogenic risk of pure talc when taken orally within the context of Traditional Chinese Medicine (TCM) is not conclusively established, but it also cannot be excluded. However, talc used in TCM does not appear to be systematically tested for asbestos contamination.

The Chinese Pharmacopoeia [13] includes Talcum (*hua shi*) but does not mandate testing for asbestos contamination. In the volume addressing excipients, it is stated regarding talc: *“Asbestos should not be detected”*, and relevant test methods are provided. The European Pharmacopoeia [14] contains a monograph on talc, presumably considering it only as an excipient, since talc is not recognised as a medicinal product in modern medicine. Regarding asbestos, the monograph states: *“The manufacturer is responsible for demonstrating by the test for amphiboles and serpentines that the product is free from asbestos.”*

As far as we can determine, Chinese producers generally follow the Chinese Pharmacopoeia, which does not require testing in the medicinal product section. One study found asbestos contamination in 9 out of 54 Chinese pharmaceutical talc samples, ranging from 0.3% to 0.8% [15] .There are no internationally agreed limits for asbestos or asbestos-contaminated talc regarding oral intake. In Europe, the European Pharmacopoeia is authoritative, and some local suppliers can demonstrate that their talc is asbestos-free, while for others this is presumably not guaranteed.

► Conclusion

Suppliers should be required to test Talcum for asbestos contamination. In all cases, we recommend limiting both the dose and duration of use, and avoiding topical application, particularly in the female genital area. Use during pregnancy, lactation, and in children should be avoided. Talcum should be decocted in a bag, and inhalation should be strictly avoided during processing of the material.

No evidence of hepatotoxicity associated with *Curcuma* preparations used within the framework of TCM

A recent review addressed the hepatotoxicity of herbs used in Ayurvedic medicine [16], some of which are also integral to Traditional Chinese Medicine (TCM). Among these is *Curcuma*. The plant classically used as a spice refers to the species *Curcuma longa* (Curcumae longae Rhizoma, *jiang huang*). Other *Curcuma* preparations used in Chinese medicine include Curcumae Rhizoma (*e zhu*, derived from the species *Curcuma phaeocaulis*, *Curcuma kwangsiensis*, *Curcuma wenyujin*) and Curcumae Radix (*yu jin*, derived from all the aforementioned *Curcuma* species).

The review concluded that turmeric – alongside a few other herbs – carries a high risk of hepatotoxicity. This property is attributed to the constituent curcumin. While curcumin is generally considered hepatoprotective at low doses, high doses have been shown to be hepatotoxic in animal studies.

Regarding hepatotoxicity associated with turmeric or curcumin products, numerous case reports and adverse event notifications exist [17], primarily from the USA (38 cases), but also from Italy (17 cases with probable causality), France (10 cases with probable causality), Australia (18 cases), Canada (9 cases) [18], and Germany (2 cases). The French cases were analyzed in detail: 2 cases showed a very probable causal relationship, 7 cases showed a probable causal relationship (including one life-threatening case, grade 3+), and 3 additional cases that were classified as grade 3.

Regulatory warnings

This situation has led to statements and warnings from various authorities. The Italian NutraIngredients warned against use in individuals with pre-existing liver or gallbladder conditions and during pregnancy [19]. The European Food Safety Authority (EFSA) established an **acceptable daily intake (ADI)** of 180 mg of curcumin for a 60 kg individual, which was reduced to 85% of this value for dietary supplements. The French ANSES supported this recommendation, emphasizing that formulations with enhanced bioavailability of curcumin require special considerations. By comparison, ANSES estimated exposure from high consumption of curcumin-containing foods at 27 mg [20].

The Australian Therapeutic Goods Administration (TGA) recorded 18 adverse event reports, including one fatal case, and issued a warning regarding hepatotoxicity, noting that this risk applies not only to *Curcuma longa* but also to other *Curcuma* species [18].

Product Analysis, Outcome

When all cases for which sufficient information is available are examined, the products involved are exclusively those containing alcoholic extracts of turmeric, curcumin as a pure substance in high doses, or formulations with enhanced bioavailability of curcumin. Almost all of these products are dietary supplements; among the few affected medicinal products, alcoholic extracts are present, and one also contains *Chelidonium majus*, which is considered to be potentially hepatotoxic, too.

Bioavailibility

The rhizome of *Curcuma longa* typically contains 0.3–5.4% curcuminoids (curcumin and chemical analogs), with a maximum of 10%. Curcumin and its analogs are lipophilic and therefore very poorly water-soluble (solubility 10–20 µg/mL), but they are soluble in alcohols and organic solvents of medium polarity, particularly acetone [17]. After 15- or 20-minute cooking, the loss of curcumin is 27% to 32%. Curcumin is relatively unstable in aqueous solution but is more stable in human blood, with an elimination rate of 20% per hour [17].

Curcumin is poorly absorbed. Synthetic curcumin demonstrated a bioavailability of less than 1% in rats. A human study using single oral doses of curcumin (500 to 12,000 mg) showed that at doses of 500 to 8,000 mg, curcumin was undetectable in serum. At doses above 8,000 mg, curcumin was detected in only 2 of 24 participants [17].

Modern Methods to enhance bioavailability

To increase the biologically available amount of curcumin, piperine was initially added. Piperine can enhance curcumin absorption by up to 20-fold. Even more effective are a range of newer techniques, such as nanotechnology, liposomal encapsulation, phytosomal complex formation, and others. These methods can increase curcumin bioavailability 4- to 185-fold. Pharmacological effects of curcumin have generally been observed only in products of high bioavailability [17].

Within the framework of Traditional Chinese Medicine (TCM), the compound curcumin likely plays a minor role. The Chinese Pharmacopoeia [13] specifies a minimum content of 1% curcumin and 7% essential oil for Curcumae longae Rhizoma. For Curcumae Rhizoma, only 1% essential oil is required, and for Curcumae Radix, no minimum content is specified. Considering the low water solubility of curcumin, and assuming a daily dose of 10 g of Curcumae longae Rhizoma decocted in 400 mL of water, the maximum curcumin content would be approximately 8 mg. This is far below the EFSA-set ADI of 180 mg.

► Conclusion

For the use of Chinese *Curcuma* preparations in the form of decoctions or granules, no hepatotoxic risk is apparent. Liver injuries attributable to these preparations within the context of Traditional Chinese Medicine are not known. However, when taken as powdered raw material, substantially higher doses of curcumin are consumed, in which case a potential risk cannot be excluded.

Important Notice:

Please report suspected adverse reactions associated with Chinese Herbal Medicine (CHM) directly to the CTCA at www.ctca.center.

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