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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Ilex paraguariensis* St. Hilaire, folium

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC as amended (traditional use)

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	Whole or cut dried leaves of *Ilex paraguariensis* St. Hilaire. To avoid fermentation the leaves are toasted briefly as soon as they are picked
Herbal preparation(s)	Comminuted herbal substance for herbal tea
Pharmaceutical forms	Herbal tea The pharmaceutical form should be described by the European Pharmacopoeia full standard term
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1. Introduction

1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance(s)

Maté folium is

- the whole or cut dried, non-roasted leaves of *Ilex paraguariensis* St.Hilaire, *Aquifoliaceae* [DAC 2004 M-066; Pharmacopée française, 1994 – Mate vert]

- the whole or cut dried and roasted leaves of *Ilex paraguariensis* St. H., *Aquifoliaceae* [DAC 2004 M-065]. Due to its polycyclic aromatic hydrocarbons (PAH) content, this substance is excluded from the HMPC monograph. See below and section 3.3.

Ilex paraguariensis (Aquifoliaceae) is a species of holly native to subtropical South America in Argentina, Eastern Paraguay, Western Uruguay and South Brazil.

The plant is a shrub or small tree growing up to 15 - 20 meters. The leaves are evergreen, 6-20 cm [Blaschek *et al.* 2007] long and 3-9 cm [Blaschek *et al.* 2007, Frohne 1999] wide, with a serrated margin. Plants are flowering from September to December. Small white unisex flowers with 4-5 petals and sepals. Plants produce red stone fruits with 4-8 seeds.

Soon after harvesting the leaves are briefly toasted at 300°C for about 1 min to avoid fermentation (inactivation of phenoloxydase) [Knöss 2005]. This procedure is called "sapeco". So called "Green Maté" is yielded after drying at 80 -100°C/about 24 h, powdering and removing twigs. Sometimes, a further roasting produces "roasted Maté", in Brazil known as "chá mate". The conditions vary from one processing plant to another. Quality of the product will depend on variations in each of the steps.

Compounds of Maté depend on the origin, harvest time (light condition), age and mass of leaves, drying method and on the adulterations with other Ilex species [Athayde *et al.* 2000, Scherer *et al.* 2002, Ohem 1990, Ohem and Hölz 1988, Ohem 1996, Heck and de Mejia 2007, Bastos *et al.* 2006a, 2006b, 2007].

Adulterants are *Ilex dumosa*, *I. theezans*, *I. brevicuspis*, *I. conocarpa*, *I. microdonta*, *I. argentina* and *I. pseudobuxus*. They contain little or none of the compounds of *I. paraguariensis*. Adulterations are problematic for quality due to their different concentration of xanthins and saponins [Heck and de Mejia 2007].

The drug contains purines like caffeine (0.5 -2.5% [Haaf 2004]), theobromine (0.12-0.7% [Scherer *et al.* 2002, Filip *et al.* 1998, Vasquez and Moyna 1986, Reginatto *et al.* 1999]) and none [Haaf 2004] or small amounts of theophylline (0.1-0.4% [Ohem 1996, Mazzafera 1994]). Other investigations yielded higher amounts of caffeine 0.1 to 2.7% and higher or smaller amounts of theobromine 0.6-2.17% [Haaf 2004, Scherer *et al.* 2002, Schneider *et al.* 2006]. According the DAC 2004, the unroasted leaves contain a minimum of 0.6% caffeine and the roasted leaves contain a minimum of 0.4% caffeine.

Further constituents are phenolic compounds like chlorogenic acid (2.8%), caffeic acid (0.023%), mono- and dicaffeoyl quinic acid (10-20 %) [Haaf 2004, Ohem 1996] and three isomeric dicaffeoylquinic acids: 3,5-dicaffeoylquinic acids (3.04%), 4,5-dicaffeolquinic acid (2.89%) and 3.4-dicaffeoylquinic acid (0.855%) and flavonoids like quercetin (0.003%), rutine (0.06%), and kaempferol (0.0012%) [Blaschek *et al.* 2007].

The content of saponins varies from 5 to 10 %. All are desmosides of ursolic acid and oleanolic acid [Schneider *et al.* 2006, Schenkel and Montanha 1996, Gosmann and Schenkel 1989, Gosmann *et al.* 1995].

The amount of volatile compounds depends on the drying procedure (about 0.01 -0.78% [Blaschek *et al.* 2007]). Predominant aroma components of Maté tea include among others geraniol, linalool, eugenol and geranial. Aroma components are produced by degradation reactions occurring during manufacture of the dried leaves [Lozano *et al.* 2007, Kawakami and Kobayashi 1991].

Other compounds are carotine (0.004-0.023 mg/g), ascorbic acid (0.2 -2.0 mg/g) [Knöss *et al.* 1998] and mineral salts, like manganese, sodium, potassium, magnesium, iron, zinc and copper [Filip *et al.* 2000, 2001, Blaschek *et al.* 2007, Dickel *et al.* 2007, Garcia *et al.* 1997]. The presence of Mg, Al, Si, P, S, Cl, K, Ca, Ti, Mn, Fe, Cu, Zn, and Rb at different concentrations was reported, which accounts for about 3.4% of the total mass. Preparing the infusion yields a loss of about 90% of K and Cl, 50% of Mg and P, and 20% of Mn, Fe, Cu, Zn, and Rb in the leaves. Water temperature favours the extraction of K and Cl, while the concentration of other elements remains practically constant [Giulian *et al.* 2007].

After drying process two compounds are formed: caffeoylshikimic acid and dicaffeoylshikimic acid. In relation to the moisture of the leaves, the caffeine and the 5-caffeoylquinic acid content varied. Caffeic acid was present in 45% of the infusion from dried leaves whereas quercetin, myricetin and kaempferol were not detected in the extract [Bastos *et al.* 2007, 2006a].

Additionally, PAH were detected in prepared Maté. A total content of 0.6 to 2.3 µg/L, with naphthalene, acenaphthene and phenanthrene having the highest concentration, were found by Zuin *et al.* 2005. Other authors reported smaller amount [Rojo de Camargo et al, 2002, Kamangar *et al.* 2008]. It is highly propable that PAH develop during the roasting process over wood fire. Because of that, the roasted leaves according the DAC monograph M-065 are excluded from the HMPC monograph.

- Herbal preparation(s)

Comminuted herbal substance [according DAC Mate viride, 2004, M-066]

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

DE:
There are combination medicinal products with anise, fennel, rosemary, coriander, senna leaf and fruit, motherwort herba and hawthorn on the German market. Indications are laxative and traditional use as a support in case of cardio-vascular disorder caused by strain on the nerves. During the 80s and 90s products containing Maté have been used medically.

SE:
There is one combination medicinal product with *Salix alba*, *Valeriana officinalis, Cola nitida* and *Juniperus communis*. There is a lack of information about indication and posology.

For combination products there are no information about the amount/content of the partners. Therefore a recommendation of a plausible dosage is not possible and so the combinations are not addressed.

1.2. Information about products on the market in the Member States

Regulatory status overview

Member State	Regulatory Status				Comments (not mandatory field)
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	food supp.
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	food supp.
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	2 medicinal products on the market
Germany	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	as combination and as food, traditional use of medicinal products in the past
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	as combination
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	food supp.
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Herb itself is not classified as a medicinal product
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	food supp.
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Herbal tea as food supp.
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	1 combination product and 1 natural remedy

Member State	Regulatory Status				Comments (not mandatory field)
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known

MA: Marketing Authorisation
TRAD: Traditional Use Registration
Other TRAD: Other national Traditional systems of registration
Other: If known, it should be specified or otherwise add 'Not Known'
This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

1.3. Search and assessment methodology

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

Maté and its herbal preparations have been well known as stimulants in Europe for decades.
Literature data support the traditional use of Maté as a medicinal product for traditional use. Several monographs have described Maté as a medicinal product for the treatment of mental and physical tiredness (e.g. Commission E monograph) and as a diuretic agent.

The requested status overview showed that only a few marketing authorisations for Maté containing products exist in Europe. But many products containing Maté are marketed as combination or as food supplement.
The following herbal preparation is on the European market since a period of 30 years and is included in the HMPC monograph on traditional use.

- comminuted herbal substance (2 medicinal products on the French market; as food supplement since 1973 in Spain; and the German Commission E monograph from 05.05.1988)

2.2. Information on traditional/current indications and specified substances/preparations

Documentation of tradition in the European context:

Maté folium has an old tradition as a caffeine containing beverage. Due to caffeine, theobromine, flavonoids and saponins a stimulating and a diuretic effect are plausible. Maté tea is also marketed as a food supplement without any standardized regulations for classification.
Some monographs in European Pharmacopoeias or other accepted documents are established.

DE:
Monograph of the Commission E for herbal medicinal products (Federal Institute for drugs and medical devices) from 5.5.1988: indication: mental and physical tiredness, posology: 3 g drug/day, effects: analeptic, diuretic, positive inotropic, positive chronotropic, glycogenolytic, lipolytic.

Monographs of the Deutscher Arzneimittel Codex (DAC) 2004 "Mate folium toasted" and "Mate folium viride"; indication: mental and physical tiredness; posology: 3 g drug/day,

Diepenbrock (1960): Maté –Gold-tea; indication: support of metabolism

List und Hörhammer (1976): Maté tea, indication: stimulant and stimulant on the bowel's function, posology: single dose 1.0 g

UK:
British Herbal Pharmacopeia (1996): indications: physical and mental fatigue, headache, weight loss, nervous depression, rheumatic pain; posology: 2-4 g/day

FR:
In France maté leaves preparations are permitted for the treatment of asthenia, as a supportive adjunctive treatment in weight loss programs orally and topically, and to increase the renal excretion of water [Cahier de l'Agence No 3 1998]. Posology according Pharmacopée française 1989: 2.5-5 g/day.

Assessor's comment:

Based on the plausible effects and the described traditional use, from the above mentioned indications only the following indications are appropriate for a traditional use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment:
Oral use:
- Traditionally used for symptoms of fatigue and sensation of weakness.
- Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.

In summary, the literature data mentioned an oral use in the following indications:

- mental and physical fatigue
- weight loss
- diuretic actions
- antioxidant actions
- antidiabetic actions
- bile stimulant
- cardioprotective actions
- anti-inflammatory/rheumatic pain
- stimulant of bowel function

None of these indications are supported by sufficient pharmacological and clinical data (see sections 3 and 4). Thus a well-established use cannot be supported.

Documentation of the tradition in other countries:

Maté was used as a beverage by ancient Indians in Brazil and Paraguay some hundred years ago, however *Ilex paraguariensis* was first cultivated by the Jesuit missionaries in the 17th century. As early as the 18th century Maté was brought to Portugal. Even then, its therapeutic effects as a stimulant were known.

At present consumption of Maté is common in parts of Brazil, Uruguay, Paraguay and Argentina. In those areas, the beverage largely has replaced coffee and tea. Due to its coffeine and theobromine content, it has traditionally used as a stimulant and diuretic. Due to its properties, in the last decades, the consumption of Maté has spread to many areas including the Middle East, Germany, and the United States. Michl and Haberler 1954 had already investigated the purine content of Maté in order to explain its effects. Already in 1883, Peckolt described the use of Maté. In the survey by Mendes and Carlini 2007 from 24 Brazilian books published between 1930 and 2003, *Ilex paraguariensis* is described as a

popular plant for treatment of weakness, muscular and mental fatigue, providing vitality, resistance and dynamics.

2.3. Specified strength / posology / route of administration / duration of use for relevant preparations and indications

Posology and indications of the traditional herbal preparations of Maté folium

Comminuted herbal substance for herbal tea preparation

ES: as food supplement
Posology: 2-4 g/day

FR: Indication: treatment of asthenia, as a supportive adjunctive treatment in weight loss programs orally and topically, and to increase the renal excretion of water [Cahier de l'Agence No 3 1998].
Posology: 2.5-5 g/day [Pharmacopée française 1989 "Tisanes"]

DE (Com E): Indication: mental and physical tiredness
Posology: 3 g /day

Assessor's comment:

Range of posology: 2-5 g herbal substance
From discussion of the MLWP reflecting the available data on indication and posology, the most common posology of 3 times daily a herbal tea prepared with 1 g herbal substance for the following indication on the stimulating activity was recommended: Traditional herbal medicinal product for symptoms of fatigue and sensation of weakness.
A second indication was derived addressing the traditional use as a diuretic: 1-2 times daily a herbal tea infusion prepared with 2.5 g herbal substance for the following indication: Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.

3. Non-Clinical Data

3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

Diuretic, anti-fatigue and stimulating effect:

[Alikaridis 1987]: A literature survey on chemical constituents of Ilex species is given. General and medicinal uses of the plant are also described. Due to its high methylxanthine content a stimulating and diuretic effect of Maté is postulated and plausible.
Ohem reported a diuretic effect of Maté due to its content of flavonoids, saponins, theobromine and caffeine in combination with chlorogenic acid [Ohem 1990, 1996]. There are no studies reported, which investigated the diuretic effect of *Ilex paraguariensis* preparations.

***In vivo* studies (caffeine):**

[Lieberman *et al.* 2002]: This study examined whether moderate doses of caffeine would reduce adverse effects of sleep deprivation and exposure to severe environmental and operational stress on cognitive performance. 68 volunteers receive either 100, 200, or 300 mg caffeine or placebo in capsule form after 72 h of sleep deprivation and continuous exposure to other stressors. Caffeine, in a dose-

dependent manner, mitigated many adverse effects of exposure to multiple stressors. Caffeine (200 and 300 mg) significantly improved visual vigilance, choice reaction time, repeated acquisition, self-reported fatigue and sleepiness with the greatest effects on tests of vigilance, reaction time, and alertness. The greatest effects of caffeine were present 1 h post-administration, but significant effects persisted for 8 h.

Antioxidant effects:

In order to characterize the antioxidant properties of *Ilex paraguariensis* infusions were analyzed by using different experimental models. The antioxidant capacity was *in vitro* evaluated by measuring the inhibition of luminal-induced chemiluminescence assay and the inhibition of 2,2'-thiobarbituric-reactive substances formation in liposomes [Actis-Goretta *et al.* 2002, Filip *et al.* 2000]. Others examined the peroxidase-like activity [Anesini *et al.* 2006] or used the ferric thiocyanate method [Bastos *et al.* 2006b] or the TROLOX® (registered trade-mark of Hoffman-LaRoche, 6-hydroxy-2,5,7,8-tetramethychroman-2-carboxylic acid) equivalent antioxidant capacity (TEAC)[Ivanova *et al.* 2005]. Beside water extracts, organic extracts were investigated [Bastos *et al.* 2007, Gugliucci and Stahl 1995, Sari *et al.* 2007, Schubert *et al.* 2007, Turkmen *et al.* 2006]. Polyphenolic content of Mate extracts were analyzed by several authors [Bastos *et al.* 2007, Bravo *et al.* 2007, Bracesco *et al.* 2003, Carini *et al.* 1998, Chandra and Gonzalez De Mejia 2004, Filip *et al.* 2001, 2007, Ivanova *et al.* 2005, Rivelli *et al.* 2007]. Comparative studies were performed with red and white wine, green tea and black tea [Bixby *et al.* 2005, Turkmen *et al.* 2006].

Lunceford *et al.* 2005 showed that polyphenol rich Mate extracts possess significant *in vitro* antiglycation activities (glycation means a nonenzymatic adduct formation between sugar dicarbonyls and proteins, that is one key molecular basis of diabetic complications due to hyperglycemia). Ramirez-Mares *et al.* 2004 evaluated the chemopreventive activity of Ardisia tea and Maté tea. Schinella *et al.* 2000 showed that an aqueous extract (5 g/100 ml) of Maté inhibited the H_2O_2-induced peroxidation of red blood cell membranes.

One *in vivo* study was performed by Colpo *et al.* 2007. Using two behavioral models, i.e., haloperidol-induced orofacial dyskinesia (evaluated measuring vacuous chewing movements, VCMs) and memory dysfunction, evaluated in a water-maze task, were examined. Rats treated with Maté (50 g/l, ad libitum, 60 days) did not exhibit the increase in VCMs observed in control rats treated with haloperidol ($p < 0.001$). In the water maze task, haloperidol treated animals displayed an impairment in memory acquisition ($p < 0.05$) compared to rats treated with vehicle. Maté prevented the effects of haloperidol in this behavioural paradigm. The results indicate that *Ilex paraguariensis* exhibits an antioxidant role probably related to the presence of polyphenols.

Cardioprotective actions:

Menini *et al.* 2007 demonstrated that Mate extracts (5 g /50-100 ml, 0.5 l/day) may prevent the loss of cardioprotective function of high-density-lipoprotein affored by paraoxonase 1.

Schinella *et al.* 2005 demonstrated that Maté (10 g/250 ml) extract attenuates the myocardial dysfunction provoked by ischemia and reperfusion and that this cardioprotection involves a diminution of oxidative damage through a nitric oxide-dependent mechanism.

Baisch *et al.* 1998 studied the effect of aqueous Mate extract (30 g/130 ml) on precontracted mesenteric arterial bed. The injection of extract (300-1050 µg) significantly inhibited, in a concentration-dependent manner, the maximal contractile response induced by NG-nitro-L-arginine methyl ester.

Several *in vivo* studies were performed. Felippi *et al.* 2006 showed that consumption of Maté extract elevated cholesterol and low-density lipoprotein (LDL) in hypercholesterolmic mice and improved *ex vivo* endothelial function of atherosclerotic mice aorta.

Görgen *et al.* 2005 showed that chronic ingestion of Mate extract significantly decreased ATP, ADP and AMP hydrolysis in blood serum. They concluded that due to the changes in balance of purine, Maté can be a drug target for the treatment of cardiovascular diseases.

Mosimann *et al.* 2002 studied whether Maté could reduce the progression of arteriosclerosis in cholesterol-fed-rabbits. After 2 months of treatment, serum total cholesterol and triacylglycerol of cholesterol-fed rabbits were approximate 20-fold higher. However, Maté extract did not affect the serum lipid profile of control and cholesterol-fed rabbits ($p>0.05$). Similarly, hepatic cholesterol content was approximately 3-fold higher in hypercholesterolemic rabbits and these levels were not different between the two groups. Average aortic cholesterol content of Maté group was 3-fold lower than that of cholesterol-fed rabbits (0.62 vs. 2.02 mg/g of tissue, $p<0.05$).

Mosimann *et al.* 2006 showed that *Ilex paraguariensis* extract can inhibit the progression of atherosclerosis in cholesterol-fed rabbits, although it did not decrease the serum cholesterol and antioxidant enzymes.

Stein *et al.* 2005 showed that the chronic oral administration of *I. paraguariensis* extract (110 g/l) in rats fed hypercholesterolemic resulted in a significant reduction in serum levels of cholesterol and triglycerides.

Anti-obesity and weight loss actions:

Some reviews about the most popular plants, including *Ilex paraguariensis*, used for weight loss were published [Dickel *et al.* 2007, Pittler and Ernst 2004, Pittler *et al.* 2005]. All authors concluded that the evidence for the most dietary supplements as aids in reducing body weight is not convincing.

One *in vivo* study was performed by Pang *et al.* 2008. The anti-obesity effect of *Ilex paraguariensis* extract and its molecular mechanism in rats rendered obese by a high-fat diet (HFD) were investigated. *I. paraguariensis* extract (dry extract (5:1), ethanol 15%) supplementation significantly lowered body weight, visceral fat-pad weights, blood and hepatic lipid, glucose, insulin, and leptin levels of rats administered HFD. The results showed that *I. paraguariensis* extract can have a protective effect against a HFD-induced obesity in rats, but supplementation of HFD with *Ilex paraguariensis* extract did not affect the food efficiency ratio (FER= Body weight gain for the experimental period/Food intake for the experimental period).

Chemopreventic and anticancerous actions:

[Arbiser *et al.* 2005]: Natural product extracts were screened using ras-transformed endothelial cells (SVR cells) as a bioassay, and found that extracts of Maté tea (*Ilex paraguayensis*) inhibit the growth of endothelial cells. The extract was fractionated and found to have novel cinnamate esters that inhibit proteasome activity. Based upon the structures of the compounds isolated from Maté tea, synthetic analogs of these compounds for proteasome activity were examined. Cinnamic acid amides had no inhibitory activity against proteasomes, whereas cinnamate esters displayed the activity.

[Gonzalez de Mejia and Ramirez 2004]: The objective was to evaluate the cytotoxicity of tea aqueous extracts and selected polyphenols on HepG2 cancer cells, and ornithin decarboxylase (ODC) and topoisomerase activities. Tested were epigallocatechin gallate, quercetin, gallic acid, green tea, Ardisia and Maté. Maté tea was the most active with 50% cell growth inhibition of 57 mg/ml, total growth inhibition of 74 mg/ml and 50% net cell killing of 83 mg/ml. The authors concluded that Ardisia and Maté teas may have public health potential as chemopreventive agents.

[Gonzalez de Mejia *et al.* 2005]: The objectives of this study were to determine the phenolic content of yerba mate tea products (MT) (*Ilex paraguariensis*) and evaluate their capacity to inhibit topoisomerase I (Topo I) and II (Topo II) activities and oral carcinoma cell proliferation. Total polyphenols of aqueous extracts of dried MT leaves were measured by the Folin-Ciocalteu assay, using chlorogenic (CH) and gallic (GA) acids as standards. Topoisomerase inhibition was determined by a clone-forming assay, which uses yeast (*Saccharomyces cerevisiae*) strains as a model. Controls included dimethyl sulfoxide (1.66%); camptothecin (50 µg/mL), a Topo I inhibitor; and amsacrine (100 µg/mL), a Topo II inhibitor. Cytotoxicity studies were conducted using a nontumorigenic human keratinocyte cell line HaCaT and two human squamous cancer cell lines (SCC-61 and OSCC-3). MT was found to be a rich source of phenolic compounds. Total polyphenol content of various commercially available traditional MT products ranged from 236 to 490 mg equiv of CH/g of dry leaves. Such levels were significantly different among products depending on their origin ($P < 0.001$). Higher anti-topoisomerase II activity was observed against JN394t2-4 strain for Nobleza Gaucha MT (IC_{50} = 0.43 µg equiv of CH) in comparison to GA (IC_{50} = 112 mM) and CH (IC_{50} > 1500 mM). MT showed catalytic anti-topoisomerase activity against Topo II but not against Topo I. In addititon, MT exhibited dose-dependent cytotoxicity against all squamous cell lines tested. In comparison to premalignant cell line HaCaT [28 µg equiv of (+)-catechin mL-1], the cell line SCC-61 [21 µg equiv of (+)-catechin mL-1] was the most sensitive to MT, resulting in 50% inhibition of net cell growth. It was concluded that MT is rich in phenolic constituents and can inhibit oral cancer proliferation. The effect on cancer cell proliferation may be mediated via inhibition of topoisomerase II. The lack of correlation between polyphenol content and the inhibition of topoisomerases suggested that the effect of MT on topoisomerase inhibition may be due to other still unidentified biologically active phytochemicals constituents.

[Ramirez-Mares 2004]: The aim of this study was to evaluate the chemopreventive activity of tea aqueous extracts (2.7 g/250 ml water) in comparison to selected polyphenols using a battery of in vitro marker systems relevant for the prevention of cancer. The effects of (-) epigallocatechin gallate (EGCG), quercetin (Q), gallic acid (GA), green tea (GT, *Camellia sinensis*), ardisia tea (AT, *Ardisia compressa*) and Maté tea (MT, *Ilex paraguariensis*) extracts were tested. Cytotoxicity, TPA-induced ODC and quinone reductase activities were evaluated *in vitro* using HepG2 cells. The topoisomerase inhibitory activity was also tested, using the *Saccharomyces cerevisiae* yeast system. Results suggest that MT, AT and GT are cytotoxic to the HepG2 cells, with MT demonstrating dominant cytotoxicity. Topoisomerase II, but not topoisomerase I, was the cellular target of MT, AT, EGCG, Q and GA, which acted mainly as true catalytic inhibitors. The cytotoxic activity and the inhibition of topoisomerase II may contribute to the overall chemopreventive activity of AT and MT extracts. The authors concluded that Ardisia and Maté teas may thus share a public health potential as chemopreventive agents.

Other effects:

Additionally investigations were conducted:

- the iron-binding capacity of fractions Mate extracts [Anghileri and Thouvenot 2000],

- the inhibition of the passive diffusion of cholic acid through dialysis membranes due to a Mate saponins [Ferreira *et al.* 1997],

- the antiparkinsonian activity of the hydroalcohol extract of *Ilex paraguariensis* [Milioli *et al.* 2007],

- the anti-inflammatory action of Maté ingestion [Matsunaga *et al.* 2000, Lanzetti *et al.* 2008],

- the potential effects on diabetic complication [Gugliucci and Menini 2002, Wada *et al.* 1996, Hin-Pang *et al.* 2007],

- the bile stimulant actions of Maté [Gorzalczany *et al.* 2001] .

Assessor's overall conclusions on pharmacology

Maté has a long tradition as a popular beverage with medicinal benefits: particularly, it has been used as a stimulant or a diuretic agent. However, *in vivo* studies with Maté were not performed to support these effects of Mate preparations. The traditional use of Maté for physical and mental tiredness can be explained by its content of a purine alkaloid: caffeine. The caffeine content of Maté is 0.5 – 2.5% of dried leaves. This is equal to 15-75 mg caffeine in 3 g Maté / daily dose according to the monograph Maté of the Commission E [Blumenthal *et al.* 1998]. Other reports have given an amount of 50-100 mg caffeine in a 6 oz (177 ml) Mate infusion. Ohem 1996 reported a diuretic effect due to its content of flavonoids, saponins, theobromine and caffeine in combination with chlorogenic acid.

The pharmacological properties of caffeine are multiple: first of all it is known as a stimulant, including central nervous system stimulation, relaxation of smooth muscle and vasoconstriction. Its effect on cognitive function was supported by Lieberman *et al.* 2002. They examined the effects of 100- 300 mg caffeine.

Antioxidant effects
Numerous *in vitro* studies and one *in vivo* study have been performed in order to examine the antioxidant capacity of Maté. It has been found that the consumption of Maté contributes to the antioxidant intake. It has been shown that the antioxidant activity positively correlates with the concentration of total polyphenols in particular caffeoylquinic derivatives. Its antioxidant effects may have potential health benefits such as lowering of human LDL, arthritis, inflammation, liver diseases and reduction of heart disease and cancer. Maté possesses a much higher antioxidant capacity than green tea and a slightly lower capacity than red wine. [Newell *et al.* 2007, Dralyuk *et al.* 2006].

Cardioprotective actions
Only a few *in vitro* and *in vivo* studies showed a possible effect on cardiovascular diseases. It has been demonstrated that Maté is capable of vasorelaxation of arterial beds in rats. It is also able to reduce ATP, ADP and AMP hydrolysis, which can help to balance the circulatory system. It has the ability to inhibit atherosclerosis and reduce serum concentrations of cholesterol and triglycerides, thus suggesting that Maté may be able to lower the risk for heart disease [Heck and de Mejia 2007].

Antiobesity and weight loss actions
Obesity and overweight are associated with diabetes, hypertension and other diseases that cause morbidity, mortality and high health-care expenditure. *Ilex paraguariensis* preparations may have applications in modulating physiological processes which influence gut motility, food intake and energy balance. These effects could be related to its stimulant and lipolytic activities of the caffeine content and the saponine content since saponines are reported to interfere with cholesterol metabolism [Dickel *et al.* 2007]. The reviewed studies provide some encouraging data but no evidence beyond a reasonable doubt that any specific dietary supplement is effective for reducing body weight. To confirm an effect, only a few clinical studies were performed. See chapter 4.2.2.

Hypergylcemia may be a cause for diabetic complications due to dicarbonyls involved in advanced glycation end product formation. Oxidation has been linked to glycation and Maté extracts show a dose-dependent inhibition of dicarbonyl action [Heck and de Mejia 2007].

Maté is also traditionally used in gastrointestinal disorders as eupeptic and choleretic agent. This effect may be attributed to a Maté induced increase in bile flow [Gorzalczany *et al.* 2001].

In the last decades, Maté has become very popular. Thus many areas of scientific interest on the metabolic effects of Maté are covered, but a complete assessment on clinical relevance is not possible, due to a lack of clinical investigations. In summary, the pharmacological data support the traditional indication as a stimulant and diuretic agent for more than 30 years.

Therefore, the following wording for the indications is suitable:

Oral use:

Traditional herbal medicinal product for symptoms of fatigue and sensation of weakness.

Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.

3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

No relevant data on the pharmacokinetics of Maté or *Ilex paraguariensis* preparations are available.

Ohem and Hölz 1990 cited that *in vitro* tests (resorption test according Koch) showed an increased transfer of caffeine in artificial blood, due to the presence of chlorogenic acids in Maté. Pharmacological studies showed that the lethal dose of caffeine was increased by n-chlorogenic acid, after intravenous administration. No details for the tests were given.

Interactions with other medicinal products

An August 11, 2005, United States patent application (documents #20050176777, #20030185908, and #20020054926) cites yerba mate extract as a monoamine oxidase (MAO) inhibitor; the maximum inhibition observed *in vitro* was 40–50%. In addition, it has been noted by the U.S. Army Center for Health Promotion and Preventive Medicine that yerba mate can cause high blood pressure when used in conjunction with other MAO inhibitors (such as phenelzine and tranylcypromine). See also 5.5.2

Assessor's overall conclusions on pharmacokinetics

For the herbal substance or the herbal preparation no sufficient data are available. Therefore, no conclusion can be drawn.

3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

- single dose toxicity:

  no data for herbal or herbal substance or herbal preparation were available
- repeat dose toxicity:

  no data for herbal or herbal substance or herbal preparation were available
- reproductive toxicity

  no data for herbal or herbal substance or herbal preparation were available

Caffeine data:

[Christian and Brent 2001]: This document provides an extensive and critical literature review of the effects of caffeine on reproduction, pregnancy and development of the offspring of caffeine-exposed pregnancies in multiple animal species. The sum of evidence indicates that caffeine is not a reproductive toxicant, even at high dosages that produce pharmacological and mild toxic effects in the parental animals. The NOEL for reproductive effects of caffeine is in the range of 80-100 mg/kg/day dosage.

Assessor's comment:

This review of the animal studies on reproductive toxicity of caffeine consumption concluded that a moderate consumption of caffeine (<5-6 mg/kg/day) via caffeinated beverages does not cause an increase in any reproductive risks.

[Momoi *et al.* 2008]: Caffeine consumption during pregnancy is reported to increase the risk of in utero growth restriction and spontaneous abortion. In the study, the hypothesis that modest maternal caffeine exposure affects in utero developing embryonic cardiovascular (CV) function and growth without altering maternal hemodynamics was tested. Caffeine (10 mg/kg/day subcutaneous) was administered daily to pregnant CD-1 mice from embryonic days (EDs) 9.5 to 18.5 of a 21-day gestation. Maternal and embryonic CV functions were assessed at baseline and at peak maternal serum caffeine concentration using high-resolution echocardiography on EDs 9.5, 11.5, 13.5, and 18.5. Maternal caffeine exposure did not influence maternal body weight gain, maternal CV function, or embryo resorption. However, crown-rump length and body weight were reduced in maternal caffeine treated embryos by ED 18.5 ($P < 0.05$). The authors concluded that the results suggested that modest maternal caffeine exposure has adverse effects on developing embryonic CV function and growth.

- carcinogenicity and genotoxicity

Maté data:

Leitao and Braga 1994 analyzed the mutagenic and genotoxic effects of mate aqueous solutions (prepared from instant Maté powder 200 mg/l) in bacterial cells. Maté solutions showed mutagenic effects in the Ames test (TA 97, TA 98, TA100 and TA 102 strains) at concentrations of 20 to 50 mg/plate (mutagenic factor 3.5 to 5.6) and genotoxic activity in the induce test (phage induction in a lysogenic strain of *Escherichia coli*; WP2s(λ)strain) with a maximal phage induction at concentrations of 10 to 20 mg/plate. Above these concentrations the mate solutions were cytotoxic. Addition of catalase (5U/ml), S9 rat liver microsomal fraction (20 µl/ml), thiourea (100 µM) or dipyridyl (10 µM) completely inhibited the lysogenic induction produced by Maté. The authors concluded that oxygen reactive species present in Maté play an essential role in its genotoxicity.

Assessor's comment:

The described tests were performed according the OECD Guideline for testing of chemicals. The test utilizes prokaryotic cells, which differ from mammalian cells in factors like uptake, metabolism, chromosome structure and DNA repair processes. The test therefore does not/could not provide direct information on the mutagenic and carcinogenic potency of a substance in mammals [OECD Guideline, 1997].

In vitro metabolic activation systems cannot entirely mimic the mammalian in vivo conditions. Therefore the bacteria strains were exposed to S9 rat liver microsomal fraction, thiourea and dipyridyl. S9 rat liver microsomal fraction abolished the genotoxic activity of Maté, thiourea suppressed the genotoxic effect.

Indeed epidemiological studies have shown that in regions where the consumption of Maté is high, the incidence of esophageal tumors is higher. But experiments using human cell lines are lacking. Sewram *et al.* 2003 and Castellsague *et al.* 2000 showed that the high temperature of the infusion may be responsible for this finding. Their findings are supported by Islami *et al.* 2009.

Further studies were described by Fonseca *et al.* 2000. See this chapter *in vivo* studies.

These findings are reasonable because a liver metabolism of Maté cannot already be performed in the oesophageal region. A higher incidence of bladder and kidney cancer cannot be explained by the results yielded after treatment with S9 rat liver microsomal fraction. Therefore, further studies with mammalian cell lines are necessary.

[Vargas-Alves 2008a]: The present study evaluates the clastogenic and/or aneugenic potential of maté (*Ilex paraguariensis*) – previously tested for the presence of 48 organophosphorous pesticides – in the culture of human lymphocytes in the absence of exogenous metabolic activation. Peripheral blood was obtained once from three healthy female donors for lymphocyte cell cultures. The cultures were treated with maté infusion (filtered in sterilized sartorius filter with a 0.22 mm pore membrane), distilled water (negative control), and 6 µg/ml bleomycin (positive control). For each experimental person, 3000 binucleated cells (BN) from two independent cultures (1000 cells from replicate cultures) were scored for the presence of micronuclei (MN). No statistical differences between maté infusion concentrations were observed: 1400 µg/ml (0.001 ± 0.002), 700 µg/ml (0.0006 ± 0.0015), 350 µg/ml (0.002 ± 0.002), 175 µg/ml (0.002 ± 0.003) and negative control (0.001 ± 0.001). The authors concluded that there is no clastogenic or/and aneugenic basis underlying maté action in the cytokinesis block micronucleus assay.

Furthermore, the same authors focused on the reasons of discrepancies between their data and the mutagenic response previously reported. First of all, Leitao and Braga (1994) used a form of instant Mate beverage, Fonseca *et al.* (2000), as reported below, tested lyophilized aqueous extracts of maté, on the contrary their group used a maté infusion, which is similar to the way it is used in human consumption. Secondly, the data from the three investigations are related to different maté commercial suppliers.

***In vivo*:**

[Miranda *et al.* 2008]: Yerba mate (*Ilex paraguariensis*) is rich in several bioactive compounds that can act as free radical scavengers. Since oxidative DNA damage is involved in various pathological states such as cancer, the aim of this study was to evaluate the antioxidant activity of mate tea as well as the ability to influence DNA repair in male Swiss mice. Forty animals were randomly assigned to four groups. The animals received three different doses of mate tea aqueous extract (350 mg/g phenolic compounds; prepared by dissolving instant mate tea), 0.5, 1.0 or 2.0 g/kg, for 60 days. After

intervention, the liver, kidney and bladder cells were isolated and the DNA damage induced by H_2O_2 was investigated by the COMET assay. The DNA repair process was also investigated for its potential to protect the cells from damage by the same methodology. The data showed that mate tea is not genotoxic in liver, kidney and bladder cells. The regular ingestion of mate tea increased the resistance of DNA to H_2O_2-induced DNA strand breaks and improved the DNA repair after H_2O_2 challenge in liver cells, irrespective of the dose ingested. Due to these results the authors suggested that mate tea could protect against DNA damage and enhance the DNA repair activity. Protection may be afforded by the antioxidant activity of the mate tea's bioactive compounds.

Assessor's comment:

According to the authors, the data presented showed that Maté tea is not genotoxic in liver, kidney and bladder cells. The COMET assay has not been validated and consequently it is not known how specifically and reliably it could differentiate between genotoxicants and non-genotoxicants. It is also sensitive to artefacts and false positives.

[Vargas-Alves *et al.* 2008b]: The aim of the study was to evaluate the pathological alterations as well as the immunohistochemical expression in samples from the tongues of "Maté drinking" rats. In the study, 75 adult Wistar, aged 5 months (weighing over 300 g each) that had ingested Maté on a daily basis for 9 weeks were analyzed. Following sacrifice, the tongue was removed for anatomical-pathological and immunohistochemical evaluation. Results: In the anatomical-pathological and immunohistochemical examination, no alterations compatible with neoplasic processes were observed in the 75 pieces analyzed. The authors concluded that associations were not found in the samples of tongue from "Maté drinking" rats in the anatomical-pathological and immunohistochemical examinations.

[Fonseca *et al.* 2000]: Aqueous extracts of *Ilex paraguarariensis* (Mate-chimarrão; 200 g/l)) were analyzed for the presence of genotoxic, mutagenic, and clastogenic activities through bacterial trials based on the induction of the SOS functions (functions for repairing damaged microbial DNA.), as well as in human lymphocytes in vitro and in mammalian cells *in vivo*. The extracts of Maté-chimarrão were genotoxic, as assessed by lysogenic induction in *E. coli*, and they also induced mutagenesis in *Salmonella typhimurium*. The addition of S9 microsomal fraction, catalase, thiourea, or dipyridyl counteracted the genotoxic activity of Maté-chimarrão, suggesting that oxygen reactive species play an essential role in the genotoxicity of Maté-chimarrão extracts. The extracts were not clastogenic *in vivo* (bone marrow cells of rats) in the performed experimental conditions, but the authors observed an increased frequency of chromosomal aberrations in Maté-chimarrão-treated human peripheral lymphocytes. The results supported that a high consumption of Maté-chimarrão can potentiate carcinogenesis in the human oropharynx and esophagus.

[Pereira-Jotz *et al.* 2006]: To make a histological comparison between the aerodigestive tracts of a group of rats submitted to the consumption of erva-Maté *Ilex paraguariensis*, with a control group. Seventy-five adult Wistar rats were tested, 60 rats drinking Maté at room temperature and 15 rats drinking water (control group), during a period of 5 months. The histology of the aerodigestive tracts of these animals was analyzed. Results: There was a significant difference ($p=0.02$) between those that were given Maté and the control group. The authors concluded that there is evidence to suggest that the consumption of Maté affects the upper aerodigestive tract in the animals studied, but not inducing cancer.

PAH-content:

[Kamangar *et al.* 2008]: This study was conducted to determine whether drinking Maté could lead to substantial exposure to PAH, including known carcinogens, such as benzo[a]pyrene. Methods: The

concentrations of 21 individual PAHs were measured in dry leaves of eight commercial brands of yerba Maté from Barzil (roasted) and in infusions made with hot (80°C) or cold (5°C) water. Measurements were done using gas chromatography/mass spectrometry, with deuterated PAHs as the surrogates. Infusions were made by adding water to the leaves (5 g/30ml water; 80 °C or 5 °C, 5 minutes), removing the resulting infusion after 5 min, and then adding more water to the remaining leaves. This process was repeated 12 times for each infusion temperature. Results: The total concentrations of the 21 PAHs in different brands of yerba Maté ranged from 536 to 2,906 ng/g dry leaves. Benzo[a]pyrene concentrations ranged from 8.03 to 53.3 ng/g dry leaves. For the Maté infusions prepared using hot water and brand 1, 37% (1,092 of 2,906 ng) of the total measured PAHs and 50% (25.1ng of 50 ng) of the benzo[a]pyrene content were released into the 12 infusions. Similar results were obtained for other hot and cold infusions. Conclusion: Very high concentrations of carcinogenic PAHs were found in yerba Maté leaves and in hot and cold Maté infusions. Results support the hypothesis that the carcinogenicity of Maté may be related to its PAH content.

[Rojo de Camargo and Toledo 2002]: In order to estimate the contribution of Maté tea (chá mate; roasted mate) and regular coffee as a source of PAHs in the diet of the population of Campinas, SP, Brazil, different batches and brands of these products, totaling 18 samples, were analysed for PAH. The consumption data were obtained from a dietary survey (frequency recall), which took place in Campinas in 1993. PAH levels in the products were determined by high performance liquid chromatography with fluorescence detection (HPLC-FLD). Different PAHs were detected in all samples of coffee, at levels varying with the brands and the beverage preparation technique. The mean total PAH content in coffee was 10.12 µg/kg, while Maté tea showed a relatively lower level of contamination (S=0.70 µg/kg). Considering the per capita average daily consumption estimates of 69.79 g of Maté tea and 86.77 g of coffee, one can assume that Maté tea and coffee contribute with approximately 0.05 µg and 0.88 µg of total PAHs, respectively, to the dietary intake of these contaminants by the studied population (n=600).

[Zuin *et al.* 2005]: A simple procedure based on stir bar sorptive extraction (SBSE) and HPLC-FLD is presented for the determination of 15 PAHs in herbal tea prepared with Maté leaves (*Ilex paraguariensis* St. Hil.; 1 g/100 ml water). The results of the commercial Maté tea samples found by the SBSE approach were compared with those obtained by liquid-liquid extraction, showing good agreement. Mean values of 15 PAH were given. Total PAH content ranged from 0.64 – 1.23 µg/l.

Assessor's overall conclusions on toxicology

Maté extracts (lyophilizied and resolved) showed mutagenic effects in the Ames test (TA 97, TA 98, TA100 and TA 102 strains) at concentrations of 20 to 50 mg/plate (mutagenic factor 3.5 to 5.6) and genotoxic activity in the induce test (phage induction in a lysogenic strain of *E. coli*; WP2s(λ)strain) [Leitao and Braga 1994]. The same extracts were not clastogenic *in vivo* (bone marrow cells of rats) but the authors observed an increased frequency of chromosomal aberrations in mate-chimarrão-treated human peripheral lymphocytes [Fonseca *et al.* 2000]. A hot-water extract of Maté (without lyophilization) showed no clastogenic or/and aneugenic basis underlying maté action in human lymphocytes in the cytokinesis-block in the micronucleus assay [Vargas-Alves *et al.* 2008a]. So it can be presumed that a hot-water infusion is not comparable to the tested lyophilized extracts.

Several *in vitro* and *in vivo* studies have been conducted on the anticancer properties of Maté. These may be attributed to its antioxidant effects and to the proteasome inhibition induced by Maté. Compounds that may be responsible are 3,5 dicaffeoylquinic acid, rutin and quercetin. On the other hand there are several epidemiological studies that suggested an association between Maté consumption and an increased risk of developing esophageal, lung and bladder cancer. Compounds that may contribute to the development of cancer are PAH. It is highly probable that PAH develop

during the processing of Maté, as Maté is commonly dried over a smoky wood fire [Heck and de Mejia 2007]. The amount that is extracted by preparation of the infusion is 0.22 – 1.88 % of the analyzed PAH content, thus a limitation is not necessary [Kamangar *et al.* 2008, Blaschek *et al.*2007].

In comparison, total PAH content in coffee is higher than in Maté, but the benzo[a]pyrene content is higher [Blaschek *et al.* 2007]. Coffee is a worldwide consumed beverage and it is not classified as a carcinogenic to humans due to its PAH.

The international Agency of research on cancer (IARC) listed in 1991 Maté in group 3 and Hot Maté in group 2A. That means Maté is not classifiable as to its carcinogenicity to humans and Hot Maté drinking is probably carcinogenic to humans. These classifications were concluded on basis of the known experimental data in the year 1991.

Roasted Maté leaves propably contain more PAH than dried leaves. Because of that, roasted leaves are not included in the HMPC monograph.

4. Clinical Data

For the most studies cited, a detailed description of the used herbal substance(s)/herbal preparation(s) was not available.

4.1. Clinical Pharmacology

4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

Antioxidant effects:

[Gugliucci 1996]: First the oxidability of LDL in whole plasma from 3 healthy fasted human subjects before and after intake of *Ilex paraguariensis* were examined. Intake of water extracts of *Ilex paraguariensis* inhibit copper-induced autoxidation of LDL in whole plasma as shown by the end-term production of thiobarbituric acid reactive substances (TBARS), and as a consequence are able to impair the appearance of Schiff base induced fluorescence, higher electrophoretic mobility and fragmentation of apoB. When LDL was isolated from plasma prior to oxidation no significant differences in lag-time, slope or maximum rate of oxidation could be detected. The authors then concluded that antioxidants in *Ilex paraguariensis* are absorbed and reach sufficient high levels in plasma to inhibit copper-induced LDL autoxidation by increasing aqueous-phase antioxidant capacity.

Assessor's comment:

The number of volunteers was only 3 and there is a lack of information on the concentration of the preparation of water extract.

[Pasqualotto *et al.* 2006]: The objective of this study was to evaluate and compare the seminal antioxidant enzymatic activity (SOD and catalase levels) among fertile and infertile men who consumed Maté. Maté intake was correlated with SOD levels (r=0.268; P=0.04) and catalase levels (r=0.311; P=0.01). Patients who drank more than 300 ml of Maté per day had higher SOD and catalase compared to men who did not drank Maté.

Anti-obesity and weight loss:

[Andersen and Fogh 2001]: To determine the effect of a herbal preparation `YGD' containing Yerbe Mate, Guarana (seeds of *Paullinia cupana*) and Damiana (leaves of *Turnera diffusa* var. *aphrodisiaca*) on gastric emptying and to determine the effect of the same preparation on weight loss over 10 days

and 45 days and weight maintenance over 12 months, the following tests were performed. Methods: Gastric emptying was observed using ultrasound scanning in seven healthy volunteers following YGD and placebo capsules taken with 420 ml apple juice. Body weight was observed before and after 10 days of treatment with three YGD capsules or three placebo capsules before each meal for 10 days in 44 healthy overweight patients attending a primary health care centre. Forty-seven healthy overweight patients entered a double-blind placebo-controlled parallel trial of three capsules of YGD capsules before each main meal for 45 days compared with three placebo capsules on body weight. Body weight was monitored in 22 patients who continued active (YGD capsules) treatment for 12 months. Results: The herbal preparation YGD was followed by a prolonged gastric emptying time of 58 ±15 min compared to 38±7.6 min after placebo (P = 0.025). Body weight reductions were 0.8 ± 0.05 kg after YGD capsules compared to 0.3 ± 0.03 kg after placebo capsules over 10 days, and 5.1 ± 0.5 kg after YGD capsules compared to 0.3 ± 0.08 kg after placebo over 45 days. Active treatment with YGD capsules resulted in weight maintenance of the group (73 kg at the beginning and 72.5 kg at the end of 12 months). The herbal preparation, YGD capsules, significantly delayed gastric emptying, reduced the time to perceived gastric fullness and induced significant weight loss over 45 days in overweight patients treated in a primary health care context. Maintenance treatment given in an uncontrolled context resulted in no further weight loss, nor weight regain in the group as a whole. The herbal preparation is thus shown to be one that significantly modulates gastric emptying.

Assessor's comment:

The study was performed with a preparation that contained not only Maté, but also Guarana and Damiana. Therefore the effects cannot only be attributed to Maté consumption.

[Martinet *et al.* 1999]: In this study the effects of oral administration of 12 plant preparations with anti-obesity action, in non-obese women and men were investigated. Six subjects took the Maté dry extract: 5 caps with 0.3 g lyophilised hot water extract (21.4%) from herb of Maté totalizing 1.5 g dry extract. Six subjects took solid placebo caps in double- blind-study. No significant increase in energy expenditure has been noted after treatment with any of these preparations. No change in respiratory quotient (RQ) was shown, except after treatment with maté (*Ilex paraguariensis*) extract, where a drop in RQ was observed, indicating a rise in the proportion of fat oxidized. The results suggested the poor potential of these plant preparations in the treatment of obesity, except possibly for the maté extract.

[De Pasquale 1991]: A controlled double-blind clinical trial of Maté for subjects on a low-calorie diet was performed to confirm the weight loss properties of Maté. 30 subjects with a body mass index BMI >20 received, beside Maté-tablets or Maté instant tea, a low calorie diet and an exercising therapy (physical activity) for 45 days. The averages of weight loss between the two groups were not significantly different. Positive effects like less hungry feeling, diuresis, psycho- and muscle tonus were better in Maté group. Cholesterol and triacylglycerides level decreased more in Maté group. Heart rate and arterial blood pressure showed a higher tendency to normal values in Maté group.

Assessor's overall conclusions on pharmacodynamics

Clinical studies on antioxidative effects are rare. Only one study has been shown that Maté inhibits the LDL oxidation by inhibiting lipid peroxidation [Gugliucci *et al*. 1996]. It has been shown that this mechanism is possible, but it is speculation whether this is possible *in vivo*. The described study involved only 3 volunteers and there is no information about the used Maté preparation (e.g. concentration and amount).

Only a few clinical studies were performed to confirm an effect of Maté on weight-loss. Obese men and women consuming Maté have shown a decrease in respiratory quotient, indicating an increase in fat

oxidation [Martinet *et al.* 1999]. A decrease in weight, after Maté consumption, has only been shown for combinations of Maté with Damiana and Guarana or Maté with Green tea, Asparagus, Black tea Guarana and Kidney beans [Andersen and Fogh 2001, Opala *et al.* 2006]. Further studies are necessary.

Clinical data on pharmacodynamics are rare, thus a well-established use of Maté cannot be demonstrated.

Long-standing use of Maté preparations establish the traditional use of *Ilex paraguariensis* leaves for symptoms of fatigue and sensation of weakness and as a diuretic agent.

4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

No data for the herbal substance or herbal preparations are available.

Caffeine data:

[Deutscher Arzneimittel Codex: German Commission B monograph caffeine 1989, 2004]: Caffeine is a xanthine derivate that exerts its physiological effects in large part through antagonism of central adenosine receptors. Caffeine shows an absorption half-life of 2-13 min and is readily absorbed after oral or parenteral administration. Absorption of methylxanthines relates more to lipophilicity than to water solubility. After administration of 5 mg/kg a lag time of 5-9 min, maximum plasma concentration C_{max} within 30-40 min and 9-10 µg/ml was measured. Protein binding is low (30-40%) and the volume of distribution amounts to 0.52-1.06 l/kg. Caffeine rapidly distributed to all body compartments, also in breast milk, crosses the placenta and blood-brain barrier. In adults, about 70% of the dose is metabolized to paraxanthine, about 6-10% to theobromine and about 3-4% to theophylline. These compounds are further demethylated to monoethylxanthines and than to methyl uric acids. Plasma half-life lies between 4.1 and 5.7 h, but it varied widely among individuals. Caffeine and its metabolites have a renal elimination. 48-h urine contained 86% of the administered dose. In neonates, the half-life of caffeine yielded values of 65-130 h. Decreases to adult values by 4 to 9 months post-term and is inversely proportional to gestational/post-conceptual age.

[Bchir *et al*. 2006]: The present study investigated pharmacokinetic and electroencephalographic responses to caffeine (140 mg) in 2 groups of healthy volunteers reporting, or not, caffeine-related sleep disturbances. Significant differences in caffeine consumption and smoking habits were observed between the 2 groups. Plasma samples were taken from each subject before (T0) and after caffeine intake at 0.5, 1, 2, 4, 6 and 24 h. Three pharmacokinetic parameters: half-life ($t_{1/2}$), maximum time (T_{max}) and C_{max} were calculated from caffeine plasma concentration measurements, determined by reversed phase HPLC analysis. Caffeine-sensitive subjects showed significantly greater half-life values when calculated on 24 h after the administration than tolerant subjects ($p<0.05$). Since the elimination kinetics were similar on the first 6 h after caffeine administration, the increased caffeine clearance observed overnight, when smoking was resumed in the control group, may indicate a short delay for the induction of hepatic cytochrome, reported here for the first time. Electrophysiological responses to caffeine, including vigilance and cortical activity, were assessed by ambulatory electroencephalographic (EEG) recorded during a period of 6 h before and after caffeine consumption. Following caffeine intake, the caffeine-intolerant subjects presented an increase in vigilance levels with faster peak alpha, beta frequency and lower delta and theta power when compared to tolerant subjects. Pharmacokinetic parameters and EEG data showed significant differences between sleep-sensitive and control subjects. These variations may be explained by cigarette smoking and the higher caffeine intake observed in the subjects of the control groups while caffeine sleep-sensitive subjects have a significantly lower caffeine intake, as already reported in previous studies on patients with sleep disturbances.

[Lelo *et al.* 1986]: The pharmacokinetics of caffeine (CA), paraxanthine (PX), theobromine (TB) and theophylline (TP) were studied in 6 healthy male volunteers after oral administration of each compound on separate occasions. The total plasma clearances of CA and PX were similar in value (2.07 and 2.20 ml min-1 kg-1, respectively) as were those for TP and TB (0.93 and 1.20 ml min-1 kg-1, respectively). The unbound plasma clearances of CA and PX were also similar in magnitude (3.11 and 4.14 ml min-1 kg-1, respectively) as were those of TP and TB (1.61 and 1.39 ml min-1 kg-1, respectively). The half-lives of TP and TB (6.2 and 7.2 h, respectively) were significantly longer than those of CA and PX (4.1 and 3.1 h, respectively). The volume of distribution at steady state of TP (0.44 l kg-1) was lower than that of the other methylxanthines (0.63-0.72 l kg-1). The unbound volume of distribution of TP (0.77 l kg-1) was however the same as that of TB (0.79 l kg-1) whereas the unbound volume of distribution of PX (1.18 l kg-1) was similar to that of CA (1.06 l kg-1).

Assessor's overall conclusions on pharmacokinetics

Due to lack of data for Maté preparations, no conclusions can be drawn.

4.2. Clinical Efficacy

4.2.1. Dose response studies

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

[Matzkies 1989]: 79 Persons received 1,200 kcal reduction diet for 28 days. Side-effects were measured daily. 100 g tea containing Maté leaves (20 g / 7 cups per day) were given per week in 39 persons. Thus the symptom of tiredness was reduced from 33% to 10% during the trial. In the beginning of this trial 24% of the persons felt hungry, in the end only 6% did (p=0.07). In comparison to the controlled group remarkable reductions of following symptoms were noticed: headache, depression, pain, thirst and lack of concentration.

Assessor's comment:

A reduction of tiredness and other side-effects of calorie reduction diets was observed, but a weight loss due to the consumption of Maté could not be detected. The information on the Maté posology is unsatisfactory.

There are a few studies that investigated the effect on weight loss of preparations that containing Maté beside other drugs like Guarana and Damiana or Asparagus, Green tea, Black tea and Kidney beans [Opala *et al.* 2006, Ruxton 2004]. Due to the lack of information about the amount and contribution of Maté, the effect of Maté cannot be assessed.

4.2.3. Clinical studies in special populations (e.g. elderly and children)

Not reported.

4.3. Overall conclusions on clinical pharmacology and efficacy

Although Maté has been used for symptoms of fatigue and sensation of weakness, clinical trials supporting this use are lacking. Only one study, performed by Matzkies 1989 in order to detect a reduction of side-effects while being on a calorie-reduced diet, supported a reduction of tiredness. Also

for the described diuretic, anti-inflammatory, bile stimulant cardio protective and chemoprotective effects, no clinical data are available.

All reported studies in order to detect the efficacy of Maté in reducing weight were performed with administration of a combination product. Because of that, the clinical relevance of Maté in weight management cannot be assessed.

5. Clinical Safety/Pharmacovigilance

5.1. Overview of toxicological/safety data from clinical trials in humans

5.2. Patient exposure

[Goldenberg 2002]: Maté consumption has been associated with an increased rate of oral, oropharyngeal, esophageal, and laryngeal cancers. The purpose of this study was to review the literature and discuss the role of Maté consumption in the development of oral and oropharyngeal cancer and the potential carcinogenic mechanisms. A review of the relevant literature linking Maté consumption with oral and oropharyngeal cancer and the carcinogenicity of Maté was performed. The search was performed using Medline, library catalogues, OCLC first search and ISI web of science databases. Case control studies on Maté drinking populations and, *in vivo* and *in vitro* studies on the carcinogenicity of Maté were reviewed. The populations reviewed in many of these studies also used alcohol and tobacco products confounding the influence of Maté as an independent risk factor. There is evidence in the literature that Maté consumption is itself carcinogenic and plays a role in the development of cancers of the oral cavity and oropharynx. The author concluded that although the exact mechanism of carcinogenesis is still unknown, available information suggests that Maté drinking should be considered one of the risk factors for oral and oropharyngeal cancer.

[Goldenberg *et al.* 2003]: The purpose of this study was to review the literature and discuss the role of Maté consumption as a risk factor for head and neck cancers. The review was performed of the relevant literature linking maté consumption with head and neck cancer and the proposed carcinogenicity of maté. Case control studies on maté-drinking populations and *in vivo* and *in vitro* studies on the carcinogenicity of maté were reviewed. The populations included in many of these studies also used alcohol and tobacco products, confounding the influence of maté as an independent risk factor. Evidence in the literature suggests that maté consumption is carcinogenic and plays a role in the development of cancers of the oral cavity, pharynx, larynx, and esophagus. Both chemical and thermal carcinogenesis mechanisms have been suggested. Available information suggests that maté drinking is a risk factor for upper aerodigestive tract cancer.

[Abnet 2007]: In this review, hot Maté is listed according the IARC as an agent with a moderate level to influence the risk of developing cancer. It is concluded that further research will be required to disentangle the effect of Maté and the temperature at which it is consumed. Alternatively the author supposed that a contamination with PAH, which are introduced during preparation of the leaves, may be the carcinogenic agent.

5.3. Adverse events and serious adverse events and deaths

[Bates *et al.* 2007]: This bladder cancer case-control study involved 114 Argentinean case-control pairs. Maté consumption was recorded for time of interview, and 20 and 40 years previously. Maté con bombilla consumed 20 years ago was associated with bladder cancer in ever-smokers (odds ratio (OR)=3.77, 95% confidence interval (CI): 1.17–12.1), but not in never-smokers. Maté cocido was not associated with bladder cancer. These results are consistent with a previous study in Uruguay.

[Castellsague *et al.* 2000]: To estimate the effects of consuming hot beverages, including Maté (an infusion of the herb *Ilex paraguayensis*), tea, coffee and coffee with milk, and other food items on esophageal cancer risk, data from 830 cases and 1,779 controls participating in a series of 5 hospital-based case-control studies of squamous-cell carcinoma of the esophagus conducted in high-risk areas of South America were analyzed. After adjusting for the strong effects of tobacco and alcohol consumption, both heavy Maté drinking (> 1 l/day) and self-reported very hot Maté drinking were significantly associated with esophageal cancer risk in men and women. The magnitude and strength of the association for Maté amount and, to a lesser extent, Maté temperature, were higher for women than men. The joint effects of Maté amount and Maté temperature were more than multiplicative, following a statistically significant synergistic interaction (p = 0.02) which was particularly evident among heavy drinkers (> 1.50 l/day) of very hot Maté (OR = 4.14, 95% CI: 2.24-7.67) compared to light drinkers (<0.50 l/day) of cold, warm/hot Maté. Consumption of other very hot beverages, such as tea and coffee with milk but not coffee alone, was also significantly associated with an increased risk, in the 2- to 4-fold range. Statistically significant protective associations were identified for high consumption of vegetables, fruits, cereals and tea. In contrast, frequent consumption of meat, animal fats and salt was associated with a moderately increased risk. This pooled analysis added evidence for a carcinogenic effect of chronic thermal injury in the esophagus induced by the consumption of very hot drinks, including Maté.

[De Stefani *et al.* 1988]: A case-control study of oral and pharyngeal cancer involving interviews with 108 cases and 286 controls was carried out in the University Hospital of Montevideo, Uruguay. The study was restricted to males and cases afflicted with lip, salivary gland and nasopharyngeal cancer were excluded. Point estimates of relative risk (RR) associated with smoking variables, alcohol variables, nutritional items and ingestion of hot infusions of the herb *Ilex paraguariensis* ('Maté') were obtained by logistic regression analysis. Dark tobacco smokers showed a RR 3.4 times higher than light tobacco users and heavy drinkers of wine displayed an OR of 17.2. Maté exposure showed a significant dose-response, after adjustment for age, tobacco and alcohol intake, with a 5-fold increase in risk for heavy consumers. Joint exposure to black tobacco and wine displayed very high risks and no significant interactions were observed. The results suggested that the high rates of oropharyngeal cancer could be explained by the multiplicative effect of black tobacco smoking, wine drinking and Maté ingestion.

[De Stefani *et al.* 1991]: A case-control study of bladder cancer involving interviews with 111 incident cases and 222 controls was carried out in Montevideo, Uruguay. The analysis was conducted separately for each sex. Point estimates of RR associated with smoking variables, ingestion of infusions of the herb *Ilex paraguariensis* (maté), and selected dietary items were obtained by stratified and logistic regression analysis. Among men, smokers of black tobacco showed a RR 2.7 higher than blond tobacco smokers and maté exposure showed a significant dose-response, after adjustment for age, residence, social class, hospital, type of tobacco, smoking intensity, smoking duration, and vegetable consumption, with a seven-fold increase in risk for heavy consumers. Joint exposure to type of tobacco and maté consumption showed a multiplicative effect. Women showed a similar increase in risk with maté consumption. The results suggested that the high mortality rates of bladder cancer observed in Uruguay could be explained by the combined effect of black tobacco smoking and maté ingestion.

[De Stefani *et al.* 1996]: During the period from January 1988 to December 1994, a case-control study that included 497 cases of lung cancer and 497 controls was carried out at the Instituto de Oncologia, Montevideo, Uruguay, to evaluate the relationship between the drinking of Maté and the risk of lung cancer in men. Maté drinking has been associated with risk of most upper-aerodigestive tract cancers. After adjusting for major covariates, including pack-years of cigarette smoking, the amount of Maté was associated with a 1.6-fold increase in risk for heavy drinkers, compared with light drinkers, with a significant dose-response pattern. When the analysis was performed by cell type, small cell lung cancer

showed a significant increase in relative risk for Maté amount (OR, 2.9; 95% CI, 1.3-6.2) and Maté duration (OR, 3.6; 95% CI, 1.3-9.9). On the other hand, pulmonary adenocarcinoma was not associated with Maté drinking.

[De Stefani *et al.* 1998]: In the period January 1988-December 1995, a case-control study of diet and renal cell carcinoma (RCC) risk involving 121 cases and 243 hospitalized controls was carried out in Montevideo, Uruguay. After adjusting for major covariates, red meat intake was associated with a 3.4 increase in risk for the highest category of intake, with a significant dose-response pattern. Also, barbecued meat, protein and heterocyclic amine intakes were associated with significant increases in risk of RCC. The consumption of the beverage known as 'Maté' was associated with an increased risk of 3.0 for heavy drinkers.

[De Stefani *et al.* 1987]: One hundred seven patients afflicted with incident laryngeal cancer and 290 controls with diseases considered not related to tobacco and alcohol exposure were interviewed in the University Hospital of Montevideo, Uruguay. The study followed a case-referent design, and epidemiologic analysis was carried out at the Louisiana State University, New Orleans. Dark tobacco smoking was the strongest risk factor, with an RR 2.5 times higher than that showed by light (flue-cured) tobacco smokers and 35 times that of non-smokers. Alcohol exposure displayed lesser effects but its interaction with tobacco smoking resulted in very high risks (more than 100 times higher). Among particular types of alcoholic beverages, red wine showed RRs similar to those displayed by hard liquor consumption. Maté was associated with a threefold increase in risk, after controlling for the effects of age and tobacco and alcohol consumption.

[De Stefani *et al.* 2007]. An additional case-control study in order to further explore the role of nonalcoholic beverages in bladder carcinogenesis. Methods: In the time period 1996–2000, 255 incident cases with transitional cell carcinoma of the bladder and 501 patients treated in the same hospitals and in the same time period were frequency matched on age, sex, and residence. Both cases and controls were face-to-face interviewed on occupation, tobacco smoking, alcohol drinking and intake of maté, coffee, tea, and soft drinks. Statistical analysis was carried out by unconditional multiple logistic regression. Results: Ever maté drinking was positively associated with bladder cancer (OR 2.2, 95% CI 1.2–3.9) and the risk increased for increasing duration and amount of maté drinking. Both coffee and tea were strongly associated with bladder cancer risk (OR for coffee drinking 1.6, 95% CI 1.2–2.3; OR for tea drinking 2.3, 95% CI 1.5–3.4). These results were confirmed in a separate analysis of never-smokers. The authors suggested that drinking of maté, coffee and tea may be risk factors for bladder carcinoma in Uruguay.

[Fagundes *et al.* 2006]: The highest rates of esophageal squamous cell carcinoma (ESCC) in Brazil occur in Rio Grande do Sul, the most Southern state, which has incidence rates of 20.4/100,000/year for men and 6.5/100,000/year for women. Exposure to carcinogenic PAHs through tobacco smoke and other sources may increase the risk of ESCC. The aims of the study were to investigate the degree and sources of PAH exposure of the inhabitants of this region of Southern Brazil. Methods: Two hundred healthy adults (half smokers, half non smokers, half male and half female) were recruited, given a standardized questionnaire, and asked to provide a urine sample for measurement of 1-hydroxypyrene glucuronide (1-OHPG), a PAH metabolite). Urine 1-OHPG concentrations were measured using immunoaffinity chromatography and synchronous fluorescence spectroscopy and urine cotinine was measured using a dipstick test. The authors examined factors associated with 1-OHPG concentration using Wilcoxon tests and multiple linear regression. Results: Urine 1-hydroxypyrene glucuronide (1-OHPG) was successfully measured on 199 subjects. The median (interquartile range) of urine 1-OHPG in the 199 participants was 2.09 pmol/ml (0.51, 5.84). Tobacco smoke exposure and maté drinking were statistically significantly associated with higher urine 1-OHPG concentrations in the multivariate linear regression model. Conclusion: Tobacco smoke and maté both contribute to high levels of benzo[a]pyrene exposure in the people of Southern Brazil. This high PAH exposure may contribute to

the high rates of ESCC observed in this population. The increased urine 1-OHPG concentrations associated with maté suggested that contaminants, not just thermal injury, may help explain the increased risk of ESCC previously reported for maté consumption.

[Munoz *et al.* 1987]: Thermal injury resulting from drinking very hot beverages has been incriminated as a risk factor for oesophageal cancer, although no information is available on the lesions caused by this injury in human or experimental animals. The drinking of hot maté tea is very common in areas of moderately high incidence of oesophageal cancer in south-eastern areas of South America. This study investigated the prevalence of precancerous lesions of the oesophagus in 60 unskilled male workers, of whom half were daily maté drinkers and the remainder were non-maté drinkers. These 2 groups were matched for age, smoking and alcohol intake. Maté drinkers were 2.2 times more likely ($p = 0.046$) to develop histologically confirmed esophagitis than non-maté drinkers.

[Munoz *et al.* 1998]: The relationship between social class indicators, body mass index (BMI), selected life-style habits (alcohol, coffee, maté and tea drinking) and colorectal cancer was investigated in a case-control study conducted between 1993 and 1997 in Cordoba, Argentina, a relatively high mortality area for colorectal cancer. Cases were 190 patients below 80 years of age with incident, histologically confirmed colorectal adenocarcinomas, and controls were 393 patients admitted to hospital for a wide spectrum of acute, non-neoplastic disorders. The consumption of coffee, maté and tea was not significantly related to colorectal cancer, but the ORs were below unity (0.9 (0.7-1.3) for coffee, 0.9 (0.6-1.5) for maté and 0.8 (0.6-1.2) for tea drinkers).

[Pintos *et al.* 1994]: Maté drinkers have high risks of upper aerodigestive tract cancers, but it is conceivable that this high risk may be attributable to confounding by smoking alcohol, and other exposures. To test this hypothesis, the data from a case-control study of upper aerodigestive tract cancers conducted in Southern Brazil were analyzed. The authors matched noncancer controls (N = 756) to cases (N = 378) on the basis of age, sex, and period of admission. They estimated the effect of maté consumption by conditional logistic regression with adjustment for smoking, alcohol, sociodemographics, and several dietary items, considered as confounders. The unadjusted RR for all upper aerodigestive tract cancers was 2.1 [95% CI = 1.6-2.7]. Some excess risk persisted after adjustment for potential confounders (RR = 1.6; 95% CI = 1.2-2.2). Most of the excess risk for maté drinkers was for oral (RR = 1.9; 95% CI = 1.1-3.3) and laryngeal (RR = 2.2; 95% CI = 1.1-4.5) cancers. There was no evidence of associations with coffee and tea drinking. The authors concluded that the association of maté consumption with upper aerodigestive tract cancer risk is unlikely to result from insufficient control of confounding by critical exposures. Owing to its high prevalence in Southern South America, maté drinking may be linked to as many as 20% of all cases occurring in this region.

[Pütz *et al.* 2002]: In an attempt to correlate the TP53 mutation pattern of squamous cell carcinomas of the esophagus (ESCC) and life style factors of patients from the high risk area Rio Grande do Sul, Brazil, 135 ESCC were analyzed, after prescreening by p53 immunohistochemistry, by SSCP and DNA sequencing of TP53, exon 5-9. Forty-nine somatic TP53 mutations (and 1 case with p53 polymorphism) were identified as missense (n = 39), frameshift (n = 6), silent (n = 1), amber (n = 1) or intron border mutations (n = 2) that cause splicing aberrations. They were preferentially found in exon 5 (36.7%) and exon 8 (32.7%). Several mutations were located in the mutation hot spot codons 248, 273 and 282, mainly at CpG sites. Transition mutations were observed in 53.1% (among them 50% G > A), transversion mutations in 34.7% (among them 47.1% G > T) and frameshifts in 12.2%, the latter 2 mainly in smokers and alcohol drinkers. Transitions were more prevalent in females than in males ($p < 0.05$). TP53 mutations, mainly transversions, were more frequently found in heavy smokers ($p = 0.03$), with the same tendency after chronic alcohol consumption. Comparison with the worldwide IARC database disclosed differences in the TP53 mutation pattern of the Brazilian tumors, with a higher accumulation of TP53 mutations in exon 8 and a higher prevalence of transition mutations. Mutations at the reported hot spot codon 176 were missing. Although difficult because of the documented

coexposure to various life style risk factors in most patients of this series, the hypothesis is proposed that besides smoking and alcohol drinking the commonly consumed hot Maté tea in this high risk area for ESCC is responsible for this different pattern of TP53 mutations because of chronic hyperthermic irritation and inflammation in the esophagus with an endogenous formation of radicals or carcinogenic factors that lead to a higher prevalence of transition mutations.

[Rolon *et al.* 1995]: A hospital-based case-control study, including 131 cases of esophageal cancer and 381 controls, was carried out in Paraguay to investigate the role of hot and cold Maté drinking in esophageal cancer risk. Detailed information on Maté drinking and on tobacco smoking, alcohol consumption, and dietary habits was obtained by interview. Amount and duration of cold or hot Maté drinking were not associated with esophageal cancer risk. However, temperature at which Maté was drunk was significantly associated with risk. As compared to drinkers of warm or hot Maté, drinkers of very hot Maté had an increased risk for esophageal cancer even after adjusting for the strong effects of alcohol and tobacco consumption (adjusted OR = 2.4; 95% CI = 1.3-4.3). This effect seemed to be mainly due to the temperature at which Maté cocido (one of the two ways in which hot Maté is prepared) was drunk (OR = 6.5; 95% CI = 3.2-12.2). As expected, very strong dose-response associations were found for alcohol consumption and cigarette smoking. After correcting for these and the consumption of other food groups, diets rich in fats and red meats, especially beef, were associated with esophageal cancer risk. The authors concluded that cold Maté drinking does not increase the risk of esophageal cancer. This study identified the very hot temperature at which Maté is drunk, and not the amount or the duration, as an important risk factor for esophageal cancer in this population.

[Sewram *et al.* 2003]: A retrospective hospital-based case-control study was carried out at the Oncology Institute of Montevideo, Uruguay, to investigate the role of maté consumption in esophageal cancer risk. The study included 344 cases with squamous cell carcinoma of the esophagus and 469 controls recruited between January 1988 and August 2000. Maté consumption was significantly associated with an increased risk of developing esophageal cancer and showed a clear dose response, with a RR of 2.84 [95% CI, 1.41–5.73] for those drinking more than 1 l/day of maté as compared with nondrinkers. Subjects who self-reported drinking maté at a very hot temperature had an almost 2-fold increase in risk [OR, 1.87; 95% CI, 1.17–3.00] compared with those drinking warm to hot maté, after adjusting for cumulative consumption of maté. Maté amount and temperature were observed to have independent effects and, although no departure from multiplicativity was observed between the two covariates, those drinking more than 1 l/day of maté at a very hot temperature had a 3-fold increase in risk (OR, 2.95; 95% CI, 1.30–6.74) compared with those drinking less than 0.5 l/day of maté at a warm to hot temperature. Subjects with high cumulative exposure to maté in the presence of low alcohol and tobacco exposures presented a lower-risk estimate (OR, 1.52; 95% CI, 0.88–2.62), whereas those with high cumulative exposures to maté, alcohol and tobacco presented a 7-fold increase in esophageal cancer risk (OR, 7.10; 95% CI, 3.75–13.46). The population-attributable fraction as a result of maté consumption was calculated to be 53%, of which the sole effect of amount and temperature was 14.8 and 12.6% respectively, and 14.9% was attributable to high maté consumption at high temperature.

[Vassallo *et al.* 1985]: Esophageal cancer has constituted a major public health problem in Uruguay, with age-adjusted death rates of 14.5/100,000 for males and of 3.8/100,000 for females. A case-control study was undertaken to ascertain the possible association of the drinking Maté with cancer of the esophagus, after controlling for well-known risk factors, such as alcohol and tobacco consumption. Two hundred twenty-six patients with esophageal cancer and 469 controls (control:case = 2.1) were interviewed at the time of admission or consultation at the Oncology Institute of Montevideo from 1979 through 1984. Males showed elevated risks of esophageal cancer associated with heavy tobacco (RR = 10.8) and alcohol (RR = 10.3) exposures. Among females, the independent effects of tobacco and

alcohol were non significant. Maté consumption (0.5 -1 l/day) had an independent effect in both males and females, with OR of 6.5 and 34.6, respectively, for heavy users. Moreover, a well-defined dose response was evident in both sexes.

[Victoria *et al.* 1987]: There is a cluster of high-incidence areas of oesophageal cancer in south-eastern South America, including Southern Brazil, Uruguay and parts of Argentina. This case-control study investigated the hypothesis that this may be due to the drinking of maté, a traditional beverage drunk at a very high temperature, and also studied the role of other known risk factors such as alcohol and tobacco. Cases (171) and age- and sex-matched controls (342) were recruited from hospitals in the State of Rio Grande do Sul in Southern Brazil. The crude OR for daily maté drinkers was 1.92 relative to those drinking less frequently than daily ($p = 0.006$). Other risk factors included the drinking of cachaça (a sugar cane spirit), smoking, rural residence, low fruit consumption and high intake of meats. After adjustment for these variables through conditional logistic regression, the OR associated with daily maté drinking was reduced to 1.47 (90% CI = 0.87-2.50). Although the study failed to provide evidence of a strong association between maté and esophageal cancer, the cluster of high rates could be explained by relative risks of the magnitude observed. This is due to the fact that approximately 70% of adult males and 50% of females are daily drinkers. In addition, this study revealed that alcohol, tobacco smoking and rural residence are the main risk factors for oesophageal cancer in this population

[Spinella *et al.* 2001]: Anecdotal, uncontrolled observations suggest that herbal stimulants containing ephedrine (ephedra or ma huang) and caffeine (cocoa, coffee, tea, maté, guarana, cola or kola) can exacerbate seizures in people with epilepsy, especially when taken in combination.

Assessor's comment:

Data on Maté are insufficient. Therefore an effect of Maté on people suffering from epilepsy cannot be assessed. For a detailed comment on the risk of cancer/cancerogenic potential, see 5.6.

5.3.1. Serious adverse events and deaths

[McGee *et al.* 1976]: Veno-occlusive disease of the liver with clinical and pathological features similar to those of the condition occurring in the Caribbean is described in a young woman resident in Britain. The diagnosis was made from liver biopsies and hepatic venography and was confirmed at necropsy. Small amounts of pyrrolizidine alkaloids were recovered from a sample of Maté (Paraguay) tea, owned by the patient, to which she was addicted. It seems probable that the consumption of large amounts of this tea was the cause of the hepatic disease.

Assessor's comment:

Only one case of veno-occlusive disease of the liver associated with Maté tea consumption was described. The small amounts of pyrrolizidine alkaloids were only recovered in the patient's sample of Maté tea. Thus it could be assumed that the presence of pyrrolizidine alkaloids was caused by adulterations [McGee *et al.* 1976].

[Hsu *et al.* 1995]: An outbreak of cholinergic poisoning occurred in New York City during a 3-day period. Seven individuals from three families of South American origin were affected. Signs and symptoms of illness included dry skin, hyperthermia, tachycardia, dilated pupils, agitation, and hallucinations. Onset of illness in all cases was temporally associated with consumption of a tea that was labelled "Paraguay Tea" and was purchased from a grocery store specializing in South American foods. Paraguay tea, made from the leaves of the holly, *Ilex paraguariensis*, contains caffeine and theophylline and is a popular beverage in South America. Samples of the tea analyzed with gas

chromatography contained belladonna alkaloids but neither caffeine nor theophylline. An investigation by the New York City Department of Health personnel determined that the tea was from a single lot, imported by one distributor, and sold at one grocery store. Unsold inventories of the tea were quarantined, and no further cases of anticholinergic poisoning were reported.

[Meggs *et al.* 1995]: Inadvertent anticholinergic poisoning can result from consumption of foods contaminated with plants that contain belladonna alkaloids. During March 1994, the New York City Department of Health investigated seven cases of anticholinergic poisoning in members of three families; three of the seven ill persons required emergency treatment for characteristic manifestations. For all cases, manifestations occurred within 2 hours after drinking tea made from leaves purchased commercially and labelled as Paraguay tea, an herbal tea derived from the plant *Ilex paraguariensis*, which is native to South America. The report summarized the investigation of these cases.

Assessor's comment:

In all cases, the authors attributed the disease to an adulteration of the herbal tea. Adverse events due to the content of caffeine can be sleeplessness, uneasiness, tachycardia and gastro-intestinal complaints. The following contraindications result from these known adverse events including a benefit-risk assessment: gastric and duodenal ulcers, cardiovascular disorders such as hypertension and arrhythmia, hyperthyroidism.

5.4. Laboratory findings

No data for the herbal substance or herbal preparations are available.

5.5. Safety in special populations and situations

5.5.1. Intrinsic (including elderly and children) /extrinsic factors

No data for the herbal substance or herbal preparations are available.

Assessor's comment:

Use in children and adolescents under 18 years of age is not recommended because data are not sufficient. In general, an appearance of tiredness in children and adolescents should be investigated by a physician. A treatment with Maté containing preparations, without clarifying the causes, does not seem to be adequate.

5.5.2. Drug interactions

No clinical data for the herbal substance or herbal preparations are available.

An August 11, 2005, United States patent application (documents #20050176777, #20030185908, and #20020054926) cites yerba mate extract as a MAO inhibitor; the maximal inhibition observed *in vitro* was 40–50%. In addition, it has been noted by the U.S. Army Center for Health Promotion and Preventive Medicine that yerba mate can cause high blood pressure when used in conjunction with other MAO inhibitors (such as Nardil® and Parnate®).

> [U.S. patent 20030185908]: "The MAO inhibitors of the present invention are useful for a variety of therapeutic applications, such as the treatment of depression, disorders of attention and focus, mood and emotional disorders, Parkinson's disease, extrapyramidal disorders, hypertension, substance abuse, smoking substitution, anti-depression therapy, eating disorders, withdrawal syndromes, and the cessation of smoking."

Caffeine interactions:

[Thomson Microdex 2007]: Drug interactions and/or related problems of caffeine intake: Monoamine oxidase (MAO) inhibitors, including furazolidone, procarbazine and selegiline (large amounts of caffeine may produce dangerous cardiac arrhythmias or serve hypertension because of the sympathomimetic side effects of caffeine; concurrent use with small amounts of caffeine may produce tachycardia and mild increase in blood pressure).

Assessor's comment:

On the basis of the data available concerning drug interactions for Maté and caffeine, the following is recommended as regards 'interactions with other medicinal products and other forms of interactions' for inclusion in the HMPC monograph: "Persons taking MAO-inhibitor drugs should use Maté with caution" and "Caffeine containing preparations reduce sedative action and increase side effects caused by sympathomimetic drugs".

5.5.3. Use in pregnancy and lactation

[Martin *et al.* 2007]: The premature newborn of a mother who reported drinking Maté during pregnancy presented with increased jitteriness and irritability, high-pitched cry, hypertonia in the limbs, and brisk tendon reflexes consistent with neonatal withdrawal syndrome. High concentrations of caffeine and theobromine were detected in various maternal and neonatal biological matrices (placenta, cord serum, neonatal urine, maternal and neonatal hair, meconium, and breast milk), demonstrating both acute and chronic prenatal and postnatal exposure to these methylxanthines, contained in high amounts in homemade Maté. Symptoms progressively disappeared at 84 hours of age, although intermittent irritability was still present when the infant was discharged at 24 days of age. Fluctuating caffeine (and theobromine) content in different breast milk feeds likely generated the baby's irritability, due to either the physiological stimulatory effects of the methylxanthines or postnatal withdrawal syndrome as the substances cleared from the body. The mother was strongly advised to initiate a considerable, progressive, constant reduction of Maté consumption to a maximum of 2 cups a day for the duration of breastfeeding.

[Santos *et al.* 2005]: To assess the effect of Maté drinking during pregnancy on preterm and small for gestational age (SGA) birth, a cross-sectional study was done. From 1 January to 31 December 1993, in the first 24 h after delivery, all 5,304 mothers giving birth at the hospitals in Pelotas, Southern Brazil, were interviewed and several of their characteristics were gathered. Birthweight was recorded and gestational age at birth assessed using the Dubowitz score. All 5,189 single births were analyzed. The prevalence of SGA and preterm birth was 8 and 9.1%, respectively. Maté intake at least once a week during the entire pregnancy period was reported by 68% of the mothers. Crude analyses showed a 30% increase in the risk of SGA among daily Maté drinkers compared with non-consumers (prevalence ratio = 1.3; 95% CI 1.1–1.6), whereas no statistical association was detected with preterm births. After controlling for confounders, the significance of the association with SGA birth no longer held and the lack of association with prematurity remained unchanged. Prevalence of daily Maté drinking was high among pregnant women and, contrary to the hypothesis, no harmful effect on intrauterine growth or duration of pregnancy was detected.

Assessor's comment:

The level of exposure to Maté drinking during pregnancy was obtained retrospectively. Only weekly frequency but not the amount of Maté consumed was investigated. Non-Maté drinkers (references) may have consumed caffeine from other sources.

[Matijasevich *et al.* 2006]: The objective of this study was to examine the association between caffeine intake during pregnancy and fetal mortality in Montevideo, the capital city of Uruguay, taking into account several potential confounding factors. A population-based case-control study was conducted between 1 August 2002 and 31 December 2003. A total of 382 cases and 792 controls were recruited. Cases consisted of women hospitalised with a medically confirmed diagnosis of spontaneous antepartum fetal death, in all maternity hospitals during the study period. Antepartum fetal death was defined as a fetal death in which the attending doctor certified that the death occurred prior to the onset of labour. Fetal deaths were included if they were of at least 20 weeks' gestational age or weighed >350 g. Controls were women who had a live, vigorous and term adequate-for-gestational-age newborn. Multiple gestations and fetuses/newborns with evident congenital malformations were excluded. Only a small proportion of the mothers (8.1% of the cases and 9.5% of the controls) did not consume caffeine during pregnancy. Among consumers, Maté drinking was the most frequent source of caffeine in both cases and controls. After controlling for mother's and her partner's education, history of abortions and/or fetal deaths, vomiting/nausea during the first trimester of gestation and attendance for prenatal care, the category of mean caffeine intake of > or = 300 mg/day showed a significantly increased risk of fetal death (OR 2.33 [1.23; 4.41]) compared with no caffeine consumption during pregnancy. The study also found that less-educated women, mothers who did not attend for prenatal care and women with a history of abortions and fetal death were at an increased risk of fetal death. As Maté drinking is highly consumed among pregnant women in Uruguay, the association found with fetal death makes it a preventable risk factor.

Assessor's comment:

The aim of the study was to examine the association between caffeine intake and fetal mortality. The caffeine amount of Maté was assumed at 0.17 mg/ml. The differences between the caffeine sources (coffee or Maté) were not examined.

Caffeine consumption during pregnancy:

[Infante-Rivard *et al.* 1993]: To determine if caffeine intake before and during pregnancy was associated with an increased risk for fetal loss, an incidence-density case-control study was performed. A total of 331 women with fetal loss and 993 controls with a normal pregnancy at the same period of pregnancy were investigated. Crude and adjusted ORs for fetal loss were estimated using conditional logistic regression. A trend test for increasing caffeine intake was also used. Caffeine intake was divided into quartiles; the baseline for comparison was less than 48 mg per day. The adjusted ORs for fetal loss associated with caffeine intake before pregnancy were 1.29 (95% CI, 0.85 to 1.95) for 48 to 162 mg; 1.37 (95% CI, 0.92 to 2.04) for 163 to 321 mg; and 1.85 (95% CI, 1.18 to 2.89) for more than 321 mg. The same comparisons were made for caffeine intake during pregnancy, and the respective adjusted ORs were 1.15 (95% CI, 0.82 to 1.63), 1.95 (95% CI, 1.29 to 2.93), and 2.62 (95% CI, 1.38 to 5.01). After controlling for confounding factors, there was a strong association of caffeine intake during pregnancy and fetal loss, compatible with a linear trend on the logistic scale in which ORs increased by a factor of 1.22 (1.10 to 1.34) for each 100 mg of caffeine ingested daily during pregnancy.

[Ford *et al.* 1998]: To examine the association between maternal caffeine consumption during pregnancy and the risk of sudden infant death syndrome (SIDS). Methods: A nationwide case-control study surveying parents of 393 SIDS victims and parents of 1,592 control infants. Caffeine consumption in each of the first and third trimesters was estimated by questionnaire. Heavy caffeine intake was defined as 400 mg/day or more (equivalent to 4 or more cups of coffee per day). Results: Infants whose mothers had heavy caffeine consumption throughout their pregnancy had a significantly increased risk for SIDS (OR 1.65; 95% CI 1.15 to 2.35) after adjusting for likely confounding factors.

Conclusion: Caffeine intake has been associated with fetal harm and SIDS. Reducing heavy caffeine intake during pregnancy could be another way to lessen the risk of SIDS. The authors remarked that this needs confirmation by others.

[Bracken *et al.* 2003]: Whether caffeine consumption during pregnancy represents a fetal hazard remains uncertain. The authors report on a large prospective study designed to examine this question. In 1996–2000, 2,291 mothers with singleton live births in Connecticut and Massachusetts were evaluated after their first prenatal visit and were questioned about caffeine consumption and important confounding factors. Urine samples were provided to analyze urinary caffeine, cotinine, and creatinine levels. Mothers were followed throughout pregnancy to monitor changes in consumption. Pregnancy outcomes were obtained from medical records. Self-reports of caffeine consumption in the first and third trimesters were not associated with intrauterine growth retardation, low birth weight, or preterm delivery. For every 1 mg/g creatinine increase in urinary caffeine, risk of intrauterine growth retardation was essentially unchanged (OR = 0.96, 95% CI: 0.85, 1.08). In contrast, a 0.005 mg/g creatinine increase in urinary cotinine significantly increased risk (OR = 1.003, 95% CI: 1.001, 1.005). Mean birth weight was reduced by reported caffeine consumption (−28 g per 100 mg of caffeine consumed daily, 95% CI: −0.10, −0.46, p = 0.001) but not mean gestational age. Decaffeinated coffee did not increase risk for any perinatal outcome. This small decrease in birth weight, observed for maternal caffeine consumption, is unlikely to be clinically important except for women consuming 600 mg of caffeine daily (approximately six 10-ounce (1 ounce = 28.3 g) cups of coffee).

Assessor's comment:

Caffeine crosses the placenta and achieves blood and tissue concentrations in the fetus that are similar to maternal concentrations. One case of a mother who reported drinking Maté during pregnancy was described. The premature newborn presented with increased jitter and irritability, high-pitched cry, hypertonia in the limbs, and brisk tendon reflexes consistent with neonatal withdrawal syndrome. Studies have shown that heavy caffeine consumption may increase the risk of spontaneous abort and reduced birth weight.

The Food Standards Agency has recommended that pregnant women should limit their caffeine intake to less than 300 mg of caffeine a day. A higher intake may be associated with fetal loss.

Caffeine is distributed into breast milk. Although the concentration of caffeine in breast milk is 1% of the mother's plasma concentration, caffeine can accumulate in the infant, due to its increased half-life. The infants may show signs of caffeine stimulation such as hyperactivity and wakefulness when breast-feeding mother drank caffeine-containing beverages.

The study of Santos *et al.* 2005 showed no harmful effect, but they did not investigate the amount of Maté consumed. Additionally, the level of exposure to Maté drinking during pregnancy was obtained retrospectively and the non-Maté drinkers (taken as references) may have consumed caffeine from other sources.

There is insufficient information on the excretion of Maté/metabolites in the milk. A risk to the suckling child cannot be excluded. Medicinal products containing Maté should not be used during breast-feeding.

Due to the caffeine content of Maté and the effects reported by Santos *et al.* 1998, 2005 and Martin *et al.* 2007, the following wording, from the appendix 3 of the EMA 'Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling' (EMEA/CHMP/203927/2005), is recommended for inclusion in the HMPC monograph: "*There are no or limited data from use during pregnancy and lactation. The use should be avoided during pregnancy and lactation.*"

5.5.4. Overdose

No data for Maté preparations are available.

Caffeine data: single dose toxicity

[Hunnius *et al.* 2009]: lethal dose is about 10 g.

Caffeine data: repeat dose toxicity

[James and Crosbie 1987]: Conflicting results have been reported as to whether habitual caffeine use is associated with symptoms of poorer health. The aim of the study was to further examine the association between caffeine use and somatic and psychological symptomatology while controlling for potentially confounding influences such as concurrent substance use. Information was obtained on the somatic and psychological health, substance use, and biographic background of 96 individuals divided into 3 equal-sized groups matched on age and sex. One group consisted of subjects who were chosen specifically because of their habitually high caffeine intake. The other 2 groups consisted of comparison subjects of psychiatric patients and university students who represented widely varying levels of somatic and psychological health. The results indicated that, at high intake levels, caffeine may have detrimental effects on somatic and psychological health.

[Blaschek *et al.* 2007]: Caffeine may cause side effects like insomnia, anxiety, tremulousness, raised blood pressure, increase of stomach acid and gastroesophageal reflux.

5.5.5. Drug abuse

No data for Maté preparations are available.

Caffeine tolerance development

[Evans and Griffith 1992]: Thirty-two healthy subjects with histories of moderate caffeine consumption abstained from dietary caffeine throughout the study. Subjects were stratified into 2 groups based on several factors including caffeine preference, which was assessed using a caffeine versus placebo choice procedure. Subsequently, subjects received either caffeine (300 mg t.i.d.) or placebo (placebo t.i.d.) for 18 consecutive days, and thereafter were exposed again to a caffeine versus placebo choice procedure. The study documented tolerance development to the subjective effects of caffeine: after chronic dosing, administration of caffeine produced significant subjective effects in the chronic placebo group but not in the chronic caffeine group. The study also provided indirect evidence for tolerance development: during chronic dosing, the chronic caffeine and placebo groups did not differ meaningfully on ratings of mood and subjective effect. When subjects were categorized into caffeine choosers or non-choosers, caffeine choosers tended to report positive subjective effects of caffeine and negative subjective effects of placebo. Non-choosers, in contrast, tended to report negative subjective effects of caffeine. Chronic caffeine did not alter the reinforcing effects of caffeine as assessed by caffeine versus placebo choice, possibly because the relatively short duration of caffeine abstinence in the placebo condition was not sufficient to result in maximal withdrawal effects after termination of the relatively high caffeine dose. This study provided the clearest evidence to that date of complete tolerance development to a CNS effect of caffeine in humans.

5.5.6. Withdrawal and rebound

No data for Maté preparations are available.

It is well known that a caffeine withdrawal causes symptoms like headache.

5.5.7. Effects on ability to drive or operate machinery or impairment of mental ability

No studies on the effect of Maté on the ability to drive and use machines have been performed.

Caffeine:

[Deutscher Arzneimittel Codex: Caffeine-monograph Commission B 2004]: The intended use of caffeine does not affect the ability to drive or operate machinery. Caffeine did not compensate at all the alcoholic involved ability to drive or to operate machines. In particular cases, an increased resorption of alcohol may occur.

5.6. Assessor's overall conclusions on clinical safety

There are numerous publications indicating both a chemoprotective potential of Maté tea (high content of antioxidants) and an increased risk for cancer of the mouth and pharynx, esophagus, bladder and kidney (see chapter 5.3). However, it has to be considered that an increased risk for oral and pharyngeal cancer is postulated in case of frequent intake of very hot liquids, as for example Maté tea (Ghadirian 1987, Islami *et al.* 2009). The performed case control studies are insufficient concerning the quality of the case report forms, the inclusion/exclusion criteria and diagnoses documented. Thus, valid epidemiological and mechanistic studies are missing to establish a causal relationship of Maté consumption and cancer of the bladder and kidney.

In conclusion at present, there is no evidence that Maté tea contains more potent genotoxic ingredients than other roasted, fried or smoked food. As compared to Maté tea, coffee and smoked food contain similar or even higher amounts of PAH. In consumers of coffee and smoked products of cheese, meat and fish, the formation of corresponding PAH metabolites is expected which is documented for the consumption of meat from the barbecue. Valid studies investigating how far the consumption of barbecued meat, smoked or roasted food could mean an additional cancer risk are not available. Based on the present scientific data, it can be assumed that considering the background exposure of an average food consumer, there is no relevant additional genotoxic or carcinogenic risk when consuming moderate amounts of Maté tea. For the risk assessment, also the postulated, possible chemoprotective effects due to the high rate of antioxidants have to be considered. Valid data, however, are not available at present.

On the basis of the above-mentioned data and a possible summation of caffeine from foodstuff, the following conditions of useare recommended:

Contraindications

- "Gastric and duodenal ulcers, cardiovascular disorders such as hypertension and arrhythmia, hyperthyroidism."

Warnings

- "The use in children and adolescents under 18 years of age is not recommended due to lack of adequate data."

- "Not recommended before bedtime as it may cause sleep disturbances."

Interactions

- "Persons taking MAO-inhibitor drugs should use Maté with caution. Caffeine containing preparations reduce sedatives action and increase side effects caused by sympathomimetic drugs."

Pregnancy and lactation

- "There are no or limited data from use during pregnancy and lactation. The use should be avoided during pregnancy and lactation."

As regards the indication as an adjuvant in minor urinary complaints, the following warning is recommended:-"If complaints or symptoms such as fever, dysuria, spasms or blood in urine occur during the use of the medicinal product, a doctor or qualified health care practitioner should be consulted."

The contraindications ('Hypersensitivity to the active substance(s)' and 'Conditions where a reduced fluid intake is recommended, e.g. obstruction of the urinary tract' are also recommended.

Due to a possible caffeine tolerance development [Evans and Griffiths 1992], it is recommended to limit the duration of use to 1 week for the first indication (symptoms of fatigue and sensation of weakness) and to 2 weeks for the second indication (adjuvant in minor urinary complaints).

The Community herbal monograph also should indicate that adequate tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

6. Overall conclusions

Maté tea is well known and used as a traditional herbal medicinal product for centuries in South America and for decades in European countries. Sufficient data are available to develop a Community monograph on the traditional use of *Ilex paraguariensis* St. Hilaire, folium *(Maté leaves*), provided the indications are suitable for self-medication. The indications were established, considering the Commission E monograph and the Cahier de l'Agence No 3 and reflecting also the requirements for traditional herbal medicinal products. The following indications are agreed:

"Traditional herbal medicinal product for symptoms of fatigue and sensation of weakness.

Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints."

Based on the present scientific data, it can be assumed that there is no relevant genotoxic or carcinogenic risk when consuming moderate amounts of Maté tea. Although several studies on the carcinogenicity of Maté were examined, due to a positive AMES-test and to the high incidence of oesophageal and renal cancer in Brazil, Argentina, Paraguay and Uruguay, at present it can be concluded that there is no evidence that Maté tea contains more potent genotoxic ingredients than other roasted, fried or smoked food. For the estimation of a potential risk, it has to be taken into account that, in the above-mentioned countries, large quantities of Maté are consumed (average: 7 kg/inhabitant/year) and that it is usually consumed at very high temperature.

For the risk assessment also the postulated, possible chemoprotective effects due to the high rate of antioxidants have to be considered. Valid data, however, are not available at present.

Annex

List of references