22 May 2012
EMA/HMPC/85696/2012 Rev.1[1]
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on the draft Public statement on the use of herbal medicinal products containing thujone (EMA/HMPC/732886/2010)

Table 1: Organisations and/or individuals that commented on the draft Public statement on the use of herbal medicinal products containing thujone as released for public consultation on 15 February 2011 until 15 May 2011.

	Organisations and/or individuals
1	AESGP (The Association of the European Self-Medication Industry)
2	Chemisches und Veterinäruntersuchungsamt (CVUA) Karlsruhe, Germany

[1] Comments received from an Interested Party (CVUA) have been added and discussed.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7051
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
CVUA	The CVUA Karlsruhe is a governmental institution involved in food control and also the official medicines control laboratory (OMCL) for the German Federal State Baden-Württemberg. We have conducted regulatory control of thujone in consumer products for several years and the EMA public statement mentions three of our research studies (Kröner et al. 2005, Lachenmeier et al. 2006, Lachenmeier & Uebelacker 2010). In general, we want to comment that it would be advantageous if there might be some adjustment between the regulatory bodies for foods and medicines in the case of herbal products that may be legally sold as either food or medicine, e.g. as in the case of sage tea (see details in Lachenmeier & Uebelacker 2010).	This matter has been and will be discussed at HMPC and also in more general surroundings.

SPECIFIC COMMENTS ON TEXT

Section number and heading	Interested party	Comment and Rationale	Outcome
Introduction	AESGP	Comment: The maximum dose of thujone is quoted in the public statement for *Artemisia absinthium* as 3.5 mg/day, whereas the final monograph for Artemisia (234463/2008) mentions 3.0 mg/day. Proposed change (if any): To avoid confusion, the value must be corrected (in the monograph or in the public statement, where applicable).	Corrected in the public statement.

Section number and heading	Interested party	Comment and Rationale	Outcome
2.1 Regulatory status of thujone or thujone-containing products	AESGP	Comment: Reference should be made to the more recent version of the Council of Europe “Natural sources of flavouring – Report N.2” (August 2007). The values are unchanged compared to the 1999 version, but it is worth noting that the values mentioned in 1999 have been confirmed in 2007 (after the date of entry into force of the directive). Proposed change (if any): Include the reference: Council of Europe “Natural sources of flavouring – report N.2” – August 2007.	A sentence added in page 3 (The Council has confirmed these values in its later report (The Council of Europe 2007)). The reference added into the list of references.
Page 3, Introduction, Line 4	CVUA	Comment: The statement "Thujone has been regarded as a severe neurotoxicant since 1800's" is exaggerated and conjectural, especially without a reference to substantiate this claim. It should be noted that it became only common knowledge that thujone is a constituent of wormwood oil at the beginning of the 20th century. The structure was discovered by Semmler in 1900 [Semmler F. W.: Ueber Tanaceton und seine Derivate. Berichte der deutschen chemischen Gesellschaft 33, 275-277 (1900)]. The modern supposition that the proposed neurotoxic properties of absinthe were caused by thujone can probably be traced back to a 1975 Nature paper [del Castillo J, Anderson M, Rubottom GM: Marijuana, absinthe and the central nervous system. *Nature* 1975, 253:365-366]. Proposed change (if any): Delete sentence or clarify, e.g. by changing "thujone" to "wormwood oil associated with absinthe consumption".	Partially endorsed: ‘since 1800s’ is deleted. It has to be remembered, that the original reason for the public statement was the generally held belief that thujone is neurotoxic.
Page 3, Section	CVUA	Comment: The table (cited from SCF 2002) presents rather old	The table has been deleted.

Section number and heading	Interested party	Comment and Rationale	Outcome
1.2, Table with occurrence data		data, probably derived including unspecific assays (prior to GC analysis) Proposed change (if any): Update or delete.	
Page 4, section 2.1, line 3-4	CVUA	Comment: It must be noted that the SCF did NOT confirm this assessment. The SCF commented: "The Committee considered the available data inadequate to establish a TDI/ADI but noted that some of the deficiencies in the database were being addressed in ongoing NTP studies and recommended that the results of these should be reviewed when available." Proposed change (if any): Change statement.	Endorsed. 'Confirmation is replaced by the following sentence: The Scientific Committee on Food (SCF 2002) "considered the available data inadequate to establish a TDI/ADI, but noted that some of the deficiencies in the database were being addressed in ongoing NTP studies and recommended that the results of these studies should be reviewed when available."
Page 4, section 2.1, line 4-7	CVUA	Comment: The exposure assessment considering the consumption of 1 L of alcoholic beverage appears to be a "worst case scenario" being irrelevant in the context of herbal medicines. Proposed change (if any): Delete	A sentence is deleted. However, it is worth pointing out that the SFC did this statement. It never dealt with herbal medicines and it was only there to illustrate the amounts which are possible even for "food", but another example has been given later (see a later response).
Page 4, section 2.1, line 8	CVUA	Comment: Directive 88/388/EEC was amended by Regulation (EC) No 1334/2008 Proposed change (if any): Update food regulations	A section is modified: According to the Directive 88/388/EEC 1988 as amended by Regulation (EC) No 1334/2008 a maximum thujone level of 10 mg/kg in alcoholic beverages, except those produced from Artemisia species, and of 35 mg/kg in alcoholic beverages produced from Artemisia species are allowed.
Page 4, section 2.1, line 10-13	CVUA	Comment: The model calculation of thujone exposure by alcoholic beverage consumption appears to be lacking in validity. The thujone concentrations in the beverages seldomly reach the limits (see Lachenmeier et al. 2006). A daily	The calculation is just an example to illustrate potential intake. A modified sentence replaces the old one: As a worst-case calculation, an intake of 4-8 cl (40-80 ml) of absinthe corresponds to approximately 1.2-2.4 mg

Section number and heading	Interested party	Comment and Rationale	Outcome
		consumption of 80 ml of absinthe with 60-70% vol (which approximates about 4 drinks) should be treated as worst-case scenario. Proposed change (if any): Delete	thujone per person. This is without any restriction in duration of use.
Page 4, section 2.1, line 14	CVUA	Comment: It could be added that the use of thujone as such as flavouring is also not authorized in Europe [Regulation (EC) No 1334/2008, Annex III Part A]. Proposed change (if any): Add.	Endorsed. A new section: The use of thujone as such as a flavouring substance is not authorized in Europe (Regulation (EC) No 1334/2008). Also, thujone is not authorised for such a use in the USA.
Page 4, section 2.1, line 15-16	CVUA	Comment: It must be noted that the SCF states that: "Both estimates were based on the maximum limits proposed by the CoE". As the maximum limits are seldomly exceeded, this is a worst-case scenario. A valid Europe-wide exposure estimate based on mean intakes and analytical data appears to be lacking. Proposed change (if any): State that this is a worst-case scenario based on maximum limits.	A sentence added: This is a worst-case scenario based on maximum limits.
Page 4, section 2.2., last line	CVUA	Comment: The porphyrinogenic effect was only proven *in vitro* but not *in vivo*. Proposed change (if any): clarify	Clarified: In primary cultures of chick embryo liver cells, thujone induces 5-aminolevulinic acid synthase leading to the accumulation of copro- and protoporphyrins (Bonkovsky et al. 1992). This suggests that thujone may be porphyrinogenic.
Page 4, section 2.5., line 1-2	CVUA	Comment: Some studies on wormwood preparation are available in the literature. However, the thujone content was inadequately characterized. A wormwood preparation was tested for acute (24 h), sub-	Usefulness for the purposes of this document of these papers is doubtful: Thujone content in the preparations used was inadequately characterized and at least the one preparation contained other herbal substances.

Section number and heading	Interested party	Comment and Rationale	Outcome
		acute (4 weeks) and chronic (6 months) toxicity (Omer et al., 2007). Five doses ranging from 0.575 to 5.812 g/kg were administered (thujone content less than 5 mg/kg). In the 6-month toxicity studies, body weight, organ weights and haematological findings did not indicate any toxicity. Teratogenic studies on rats after 6 months feeding also did not show any effects (Omer et al., 2007). A human study also did not report any side effects during a six-week study period where 250 mg wormwood in capsules was administered three times a day (Krebs et al., 2009). Omer, B., Krebs, S., Omer, H., Noor, T.O., 2007. Steroid-sparing effect of wormwood (Artemisia absinthium) in Crohn's disease: a double-blind placebo-controlled study. Phytomedicine 14, 87-95. Krebs, S., Omer, T.N., Omer, B., 2010. Wormwood (Artemisia absinthium) suppresses tumour necrosis factor alpha and accelerates healing in patients with Crohn's disease - A controlled clinical trial. Phytomedicine 17, 305-309. Proposed change (if any): Revise.	Animal toxicity studies (acute, subacute, chronic) mentioned in the two papers cited refer to unpublished work from LiTaka laboratories (India) and suffer from the same deficiency, i.e. thujone doses are not known.
Page 6, Section 2.7., lines 2-3	CVUA	Comment: The claim "Convulsions resembling epilepsy have been reported after the ingestion of isolated thujone (Cobb 1922)" is incorrect in relation to toxicity to humans. Thujone is mentioned only on page 1419 of the Cobb (1922) paper. It states: "For example, in our laboratory we have been using wormwood oil (the essential oil of absinthe) and thujone to produce convulsions in rabbits. We find that an intact animal will have a severe convulsion after intravenous injection of 1 C.c. of a 1 per cent. solution of thujone, whereas decerebrate	Reference to Cobb is deleted.

Section number and heading	Interested party	Comment and Rationale	Outcome
		and spinal animals will need two or three times the dose. But sufficiently large doses will produce similar convulsions." As this refers only to experimental animals, we fail to see the relevancy in this paragraph discussing toxicity to humans. The human case report in Cobb (1922) is not related to thujone intoxication. Proposed change (if any): Delete sentence or move to discussion of animal toxicity.	
Page 6, Section 2.7., lines 6-7	CVUA	Comment: The SCF (2002) is correctly cited, but according to our own literature review there is no evidence to make a quantitative comparison regarding the sensitivity between experimental animals and humans. It is correct that the anecdotal evidence from the mentioned intoxication cases points to seizures being a health endpoint in humans, but no dose-response information for quantitative comparison was available in any of the studies. The statement that "humans are at least as sensitive to thujone neurotoxicity as experimental animals" appears not to be based in science. Proposed change (if any): Revise.	Actually the sentence starts with a reservation about the difficulty to determine exposing doses (in human toxicity cases), so the statement of SCF is preserved.
Page 6, Section 2.7., lines 13-14	CVUA	Comment: The study was not a "clinical" study but rather a drinking trial. The results of the study are questionable because it was not placebo controlled, not double blinded, included limited non-homogenous collective (n=25), and no physiological parameters were determined. The confounding of alcohol appears so large that no judgement about thujone can be derived from this study. See also our detailed criticism in Lachenmeier & Uebelacker (2010).	“Clinical study” has been replaced by “drinking trial”. A reservation has been added to the end of the section: Because of the confounding by alcohol it is difficult to estimate the contribution of thujone as such to the effects.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Proposed change (if any): Add some judgment about the relevancy of the study or delete	
Page 7, section 3, lines 1-4	CVUA	Comment: See our criticism about the transferability from animals to humans above. The human data are based only on two case reports (Centini et al. 1987, Milett et al. 1981), where confounding cannot be excluded. The Cobb (1922) study provides no insight into the effect of thujone on humans. The data about human intoxications with thujone-containing preparations appear to be inadequate to make any conclusion about thujone effects in humans. While we basically agree with the first sentence that the findings in animals may be of relevance for humans, we clearly disagree with the second sentence, and especially the doses stated. A daily dose of 15 mg (about 0.2 mg/kg bodyweight) is still in the range of an acceptable intake (see Lachenmeier & Uebelacker) and at least 50 times below the NOEL in the long-term NTP study. We currently fail to see the proof how this dose can "clearly affect CNS measures". Proposed change (if any): Revise paragraph. Delete second sentence or explain in further detail how these values have been calculated	On the basis of the paucity of human studies, the section is amended in the following way: Few available studies suggest that low doses (of the order of 1.5 to 3.85 mg) have no effects attributable to thujone. Higher doses (15 mg) have been suggested to cause some subtle effects on attention and mood, but clearly further investigations are urgently needed.
Page 7, section 3, 5th paragraph	CVUA	Comment: We would base the assessment on the long-term NTP study rather than on the 14-week study. Proposed change (if any): Revise.	Currently, HMPC has recommended this specific study in its assessment of Artemisia absinthium (EMA/HMPC/234463/2008). The statement for Artemisia was done before the long term studies were published. A new paragraph is added taking the NTP long-term

Section number and heading	Interested party	Comment and Rationale	Outcome
			study as a basis: In the NTP 2-year study, there was no NOEL for rats, because it seems that even a low dosage induced seizures. Thus no safety factors can be applied. In mice the NOEL is given as 12 mg/kg and by using a safety of 100, a human equivalent dose is about 0.1 mg/kg meaning an ADI of 7 mg/day. However, it should be kept in mind that the rat seems to be more sensitive and normally the more sensitive species constitutes a a basis for safety factor calculations.
Page 7, section 3, 6th paragraph	CVUA	Comment: 1. It must be pointed out again that the assumed food intakes are worst case scenarios based on maximum limits and not on market surveys. 2. Where does the postulated TDI of 0.7 mg/person come from? This is not mentioned anywhere else in the document. 3. The thujone-impact by food (and medicines) certainly needs further consideration. We suggest that Europe-wide surveys for both product groups should be conducted to derive a better exposure estimate. The following risk assessment should consider both forms of intake. Proposed change (if any): Revise.	1. this is already added to 2.1. 2. this figure is an average of a range given by SCF (2002) on dietary exposures. 3. Agree, but nothing added to the statement.
Page 7, last paragraph	CVUA	Comment: We cannot see how the study of Dettling et al. (2004) provides insight into a "significant pharmacological effect" in relation to the ingestion of herbal medicines. The study is unsuitable for regulatory uses (see criticism above) and we also do not see how this can be overcome by the use of a "safety margin".	HMPC discussed the Dettling study in the assessment of Artemisia and found it useful in spite of its weaknesses. In any case, the sentence has been amended to reflect these uncertainties: .. gives some evidence of an effect of "borderline relevance",...

Section number and heading	Interested party	Comment and Rationale	Outcome
		Proposed change (if any): Revise.	
Page 8, line 1	CVUA	Comment: The consideration of a "therapeutic margin of thujone" has no validity. The scientific literature fails to identify any beneficial effect of isolated thujone. It remains open if the therapeutic effects of thujone-containing herbs derive from thujone or other ingredients. Proposed change (if any): Change to "Therapeutic margin of thujone-containing herbs", clarify the wording in general.	Strictly speaking this is true, but herbal medicinal products are a special case: thujone in preparations can be regarded as a “biomarker” or “representative” for the therapeutic effects of thujone-containing herbal medicinal preparations. In any case, the change suggested has been introduced.
Page 8, lines 2-9	CVUA	Comment: We agree with the assessment. It is notable that ADI levels set for foods may be exceeded in certain occasions without implying a health risk for the consumer (see, e.g. the risk assessment of the German federal institute for risk assessment regarding the exceedance of the thujone limit in certain absinthes: http://www.bfr.bund.de/cd/2199). Therefore, the specification of a range that does not pose special concerns appears to be justified. Until further data are available, the food intake could be considered by adding a warning notice to the product information stating that no sage- or wormwood-containing foods shall be co-ingested while using thujone-containing medicines. Proposed change (if any): Revise.	No comments.
Page 9, line 6	CVUA	Comment: Update reference Lachenmeier & Uebelacker 2010 Proposed change (if any): 58: 437–443	Updated.