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**COMMITTEE ON HERBAL MEDICINAL PRODUCTS
(HMPC)**

FINAL

**PUBLIC STATEMENT ON THE USE OF HERBAL MEDICINAL
PRODUCTS CONTAINING PULEGONE AND MENTHOFURAN**

DISCUSSION IN THE HMPC	January 2005 March 2005
RELEASE FOR CONSULTATION	April 2005
DEADLINE FOR COMMENTS	June 2005
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ADOPTION BY HMPC	November 2005

The Committee on Herbal Medicinal Products endorses without any changes the 'Position Paper on the use of herbal medicinal products containing pulegone and menthofuran' adopted by the Herbal Medicinal Products Working Party (HMPWP) in May 2004.

Public Statement on the use of herbal medicinal products containing pulegone and menthofuran

BACKGROUND

Following the publication of the opinion of the Scientific Committee on Food (SCF) on pulegone and menthofuran the CPMP Herbal Medicinal Products Working Party has prepared this position paper reviewing the SCF opinion and recommending future action in relation to herbal medicinal products containing peppermint oil (*Mentha piperita* L.), mint oil (*M. canadensis* L., syn. *M. arvensis* var *piperascens* Malinv. Ex Holmes) and pennyroyal oil (*M. Pulegium* L. or *Hedeoma pulegoides* (L.) Pers).

INTRODUCTION

Peppermint oil (Ph Eur) contains maximum 4.0 % pulegone and between 1.0 and 9.0 % menthofuran. Mint oil, partly dementholised (Ph Eur) contains maximum 2.0 % pulegone, but no limit is given for menthofuran.

There is no Ph Eur monograph on pennyroyal or pennyroyal oil. It is known from the literature that pennyroyal herb contains 1-2% essential oil of which pulegone is the principal component (60-90%) (Barnes et al., 2002).

Current regulatory status

Maximum levels for pulegone in foodstuff and beverages to which flavourings or other food ingredients with flavouring properties have been added: 25 mg/kg in foodstuff, 100 mg/kg in beverages, with the exception of 250 mg/kg in peppermint or mint flavoured beverages and 350 mg/kg in mint confectionery (Annex II of Directive 88/388/EEC). Pulegone may not be added as such to foodstuff.

Committee of Experts on Flavouring Substances (CEFS) of the Council of Europe (1997): Menthofuran is the proximate hepatotoxin of pulegone. Tolerated daily intake (TDI) of menthofuran and pulegone was set to 0.1 mg/kg bw, based on a no effect level (NOEL) of 20 mg/kg bw/d in the 28 days oral toxicity study in rats (Thorup et al. 1983 a,b) with a safety factor of 200.

Menthofuran is listed in the register of chemically defined flavouring substances laid down in Commission Decision (1999/217/EC, 2002/113/EC).

USA: Pulegone and menthofuran have FEMA GRAS status and are listed among the authorised synthetic flavouring substances.

JECFA (Joint FAO/WHO Expert Committee on Food Additives, 2000): "No safety concern" was applied to (R)-(+)-pulegone and structurally related flavouring agents including (R)-(+)-menthofuran.

SCF'S CONCLUSION

Pulegone is mainly metabolised through pathways involving menthofuran and these two substances show similar toxicity. Evaluation of their toxicity should be made together. The Committee noted that only a limited database was available on pulegone and menthofuran and considered that these data were inadequate for the derivation of an ADI (acceptable daily intake). To establish a NOEL for pulegone and menthofuran, at least a further 90-day study is required together with studies on genotoxicity at the gene and chromosome level, and probably also reproductive and developmental toxicity studies.

HMPWP'S COMMENTS

The interest in toxicity of pulegone, menthofuran and peppermint oil appears to have been provoked by three reports in the literature. It was reported that pulegone, when given to rats for 28 days, caused histopathological changes in the liver (vacuolisation) and the brain ("cystlike spaces") (Thorup et al. 1983a,b; Olsen and Thorup, 1984). The histopathological changes were seen in rats receiving 80 and 160 mg/kg/day of pulegone. However, all hematological and clinical chemical parameters were found to be within the normal range in all groups. There were neither obvious signs of clinical symptoms due

to encephalopathy. Based on these studies the NOEL (no effect level) of pulegone was considered to be 20 mg/kg bw/day.

Later “confirmatory” studies by the same group, however, reported that there were no significant histopathological changes in the liver nor the brain. The “cyst-like spaces” reported in the brain in the earlier studies were thus not confirmed and may have arisen from inadequate tissue fixation procedures (Molck et al. 1998). In this study the clinical biochemical examinations revealed increased plasma glucose, alkaline phosphatase and ALAT and a decreased creatinine in the dosed group.

In later studies the liver toxicity of pulegone has been confirmed and a mechanism of action has been proposed based on its metabolism to menthofuran and other reactive metabolites, which are the ultimate hepatotoxins (see SCF report).

Pharmacovigilance information

A literature review of cases of human intoxication with pennyroyal oil (pulegone content 62-97%) indicate that ingestion of 10 ml (corresponding to ca 5.4-9 g pulegone, ca 90-150 mg/kg bw for a 60 kg person; calculated with a relative density of 0.9 as for peppermint oil) resulted in moderate to severe toxicity and ingestion of greater than 15 ml (corresponding to ca 8-13 g pulegone, ca 130-215 mg/kg bw for a 60 kg person) resulted in death. The clinical pathology was characterised by massive centrilobular necrosis of the liver, pulmonary edema and internal haemorrhage (SCF, 2002).

A non-urgent information request was sent out to the member states concerning use and association of licensed herbal medicinal products containing pennyroyal oil, peppermint oil and mint oil with reports of liver damage.

The highest recommended daily dose in EU is 1.2 ml peppermint oil i.e. 1080 mg peppermint oil, which contains maximum 140 mg pulegone + menthofuran (Ph Eur). For a 60 kg person this would correspond to a daily intake of 2.3 mg/kg bw. Clearly, this recommended daily dose of peppermint oil in herbal medicinal products results in an intake of pulegone/menthofuran that exceeds the TDI (0.1 mg/kg) set for food by CEFS.

No certain cases of liver damage caused by peppermint oil or mint oil were reported.

HMPWP’s conclusions concerning herbal medicinal products containing peppermint, mint oil and pennyroyal oil:

1. The first reports on brain toxicity of pulegone appear to have been erroneous.
2. Serious/lethal cases of intoxication from pennyroyal oil with a high content of pulegone indicate that pulegone is a hepatotoxin. A plausible mechanism for liver toxicity of pulegone and menthofuran has been proposed, which is supported by experimental data.
3. No approval of medicinal products containing pennyroyal oil appears to have been granted in EU and its use in unlicensed products should be discouraged.
4. The reported NOEL of pulegone and menthofuran (20 mg/kg bw/d) has not been determined with required accuracy, and remains uncertain. Despite that a TDI for pulegone and menthofuran has been set for food (0.1 mg/kg bw).
5. Doses up to ca 2.3 mg/kg bw/day of pulegone (exceeding the TDI for food) are commonly encountered in herbal medicinal products in Europe. Pharmacovigilance has hitherto revealed no certain cases of liver toxicity in humans caused by peppermint oil or mint oil. Pharmacovigilance does not indicate that the use of herbal medicinal products in these doses is associated with liver disorders.
6. The therapeutic indications for peppermint oil and mint oil are mainly related to common cold and gastrointestinal disturbances and presumably the vast majority of these products are used in self-medication. An underreporting of side effects may be suspected.

Proposal for regulatory actions:

- No immediate actions are proposed, but alerted pharmacovigilance of peppermint oil and mint oil containing products is recommended.
- An increased awareness in the medical community concerning high intake of peppermint oil and mint oil containing products as a potential cause of otherwise unexplained liver reactions would be desirable.
- A limit for menthofuran should be included in the monograph for mint oil of the European Pharmacopoeia.
- The use of penny royal oil should be discouraged.
- Similar considerations should be given to other herbal products containing significant amounts of pulegone and menthofuran.

References

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