WORKING PARTY ON HERBAL MEDICINAL PRODUCTS

FINAL POSITION PAPER ON THE USE OF HERBAL MEDICINAL PRODUCTS CONTAINING ASARONE

<table>
<thead>
<tr>
<th>DISCUSSION IN THE HMPWP</th>
<th>November 2002, February 2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>RELEASE FOR CONSULTATION</td>
<td>July 2003</td>
</tr>
<tr>
<td>DEADLINE FOR COMMENTS</td>
<td>October 2003</td>
</tr>
<tr>
<td>RE-DISCUSSION IN THE HMPWP</td>
<td>November 2003</td>
</tr>
<tr>
<td>PUBLICATION OF FINAL POSITION PAPER</td>
<td>December 2003</td>
</tr>
</tbody>
</table>

The views presented in this document are those of the HMPWP, which has been created as a forum for exchange of experience in the field of herbal medicinal products. This document is released for the purposes of transparency and has no legal force with respect to Directive 2001/83/EC.
I. **ASARONE**

Registry Number: 494-40-6

Formula : C\textsubscript{12}H\textsubscript{16}O\textsubscript{3}

Mw : 208,255

Synonyms : 1(2,4,5-trimethoxyphenyl)-1-propene ; asarone ; asarum camphor

*α*-asarone  = 1,2,4-trimethoxy-5-(1-propenyl)benzene, 9CI (E) form

Registry Number : [2883-98-9]

Synonyms :  • trans-α asarone
             • isoasarone

*β*-asarone  = 1,2,4-trimethoxy-5-(1-propenyl-benzene, 9CI (Z) form

Registry Number : [5273-86-9]

CA Index name : Benzene, 1,2,4-trimethoxy-5(12)-1-propenyl-(9CI)

Synonyms :  • β asarone (6CI) ;
             • Benzene, 1,2,4-trimethoxy-5-[1-propenyl]-(Z)- ;
             • Benzene, 1,2,4-trimethoxy-5-propenyl-(Z)-(8CI) ;
             • (Z) asarone ;
             • cis-β-asarone ;
             • cis-asarone ;
             • cis-isoasarone

*γ*-asarone  = 1,2,4-trimethoxy-5-(2-propenyl)benzene

Registry Number : [5353-15-1]

Synonyms :  • Euasaron
             • Isoasaron
             • Sekishon
II. β-asarone is a natural constituent of some aromatic plants and their essential oil fractions, especially of species of the genus *ACORUS* (Araceae).

EO = Essential Oil, MEOC = Major Essential Oil Component

<table>
<thead>
<tr>
<th>Botanical name</th>
<th>Plant part</th>
<th>Content of β-asarone</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Acorus calamus</em> var. <em>americanus</em> (Raf.) Wulff. (= <em>Acorus americanus</em> Raf.) (Diploid.)</td>
<td>Leaf (EO)</td>
<td>not detected</td>
</tr>
<tr>
<td></td>
<td>Rhizome (EO)</td>
<td>not detected</td>
</tr>
<tr>
<td><em>Acorus calamus</em> L. var. <em>calamus</em> (=<em>Acorus calamus</em> L.var. vulgaris L.)(Triploïd)</td>
<td>Leaf (EO)</td>
<td>50-65 % (MEOC)</td>
</tr>
<tr>
<td></td>
<td>Rhizome (EO)</td>
<td>9-19 % (MEOC)</td>
</tr>
<tr>
<td></td>
<td>Dried rhizome</td>
<td>0.3%</td>
</tr>
<tr>
<td><em>Acorus calamus</em> L. var. <em>angustatus</em> Bess (= <em>Acorus triqueter</em> Turcz.) (Tetraploïd)</td>
<td>Leaf (EO)</td>
<td>MEOC</td>
</tr>
<tr>
<td></td>
<td>Rhizome (EO)</td>
<td>85 - 95 %</td>
</tr>
<tr>
<td></td>
<td>Dried rhizome</td>
<td>4.4 – 8.3%</td>
</tr>
<tr>
<td><em>Orthodon asaroniferum</em> Fujita</td>
<td>Not identified in literature (EO)</td>
<td>25%</td>
</tr>
<tr>
<td><em>Orthodon isomyristicineferum</em> Fujita</td>
<td>Not identified in literature (EO)</td>
<td>25%</td>
</tr>
<tr>
<td><em>Piper lolot</em> DC.</td>
<td>Rhizome and Root exts</td>
<td>38% in n-hexan extracts</td>
</tr>
</tbody>
</table>

Asarone (α and β or α or β) has also been reported to occur in the following plants, but its content has not been mentioned:

*Acorus gramineus* Ait. (asarone*); *Asarum europaeum* L. (α asarone); *Asarum arifolium* Michx (α asarone); *Daucus carota* L. (α asarone); *Helichrysum arenarium* (L.) Moench. (β asarone); *Magnolia salicifolia* Maxim.(α asarone); *Piper angustifolium* R. & P. (asarone*); *Piper sumatranum* DC. var. *andamanica* (asarone*); *Sassafras albidum* (Nutt.) Nees (asarone*) - * unspecified
III. Medicinal uses

The rhizomes of *A. calamus* are used extensively in traditional medicine worldwide. Reported uses include: stomach cramps; dysentery; asthma; anthelmintic; insecticide; tonic; stimulant.

IV. Toxicity

Mammalian toxicity and carcinogenicity of asarones (α and β) has been demonstrated. The alkenylbenzenes, α and β asarone, are genotoxic and hepatocarcinogens in rodents.

V. Pharmacology

α and β asarone demonstrated:
- a mobility inhibition (α and β)
- a nematocidal activity (α and β)
- anticoagulant effect in the mouse and the rat (β)
- sedative and hypothermic effects in rats (β)
- insecticidal activity (LC$_{100}$ = 16 µg/ml) using the *Aedes aegypti* larvicidal assay (β)
- feeding-deterrent activity against some stored Coleoptera (α)

α and β asarone exhibit neuroprotective action against the NMDA - or Glutamic acid - induced excitotoxicity through the blockade of NMDA receptor function.

Conclusion

In view of the toxicity of α and β asarone, their concentration in herbal medicinal products should be reduced to minimum and diploid varieties should always be preferred.

In analogy with the food regulation (limitation of the intake of β-asarone from food and alcoholic beverages), a limit of exposure from herbal medicinal products of approximately 115 µg/day, i.e. about 2 µg/kg bw/day could be accepted temporarily until a full benefit/risk assessment has been carried out.
References

Abel C.
Chromosome-damaging effect of beta-asarone on human lymphocytes.

Charobot, E.; Dupon, T.J.; Pillet, L.
Les huiles essentielles et leurs principaux constituants
(1899), 606-607.

Cho, Jungsook; Kim, Young Ho; Kong, Jae-Yang; Yang, Chae Ha; Park, Chang Gook.
Protection of cultured rat cortical neurons from excitotoxicity by asarone a major essential
oil component in the rhizomes of Acorus gramineus.

Ciccia, G.; Coussio, J.; Mongelli, E.
Insecticidal activity against Aedes aegypti larvae of some medicinal South American plants.

Do, Dinh Rang; Doan, Thanh Tuong; Vu, Thi Luu.
 Constituents of the leaf oil and leaf extract of Piper lolot.

Gildemeister, E.
Die Atherischen Öle
Tome I, (1910), 505-507.

Gildemeister, E.
Die Atherischen Öle
Tome I, (1910), 86-87.

Hasheminejad, G.; Caldwell, J.
Genotoxicity of the alkenylbenzenes alpha and beta-asarone, myristicin and elimicin as
determined by the UDS assay in cultured rat hepatocytes.

Hegnauer R.
Chemotaxonomie der Pflanzen
Birkhäuser Verlag Basel und Stuttgart; Band 3 (1964), 188-189.

Hegnauer R.
Chemotaxonomie der Pflanzen
Birkhäuser Verlag Basel und Stuttgart; Band 4 (1966), 308-309.
Hegnauer R.
Chemotaxonomie der Pflanzen
Birkhäuser Verlag Basel und Stuttgart ; Band 5 (1969), 313-319

Hegnauer R.
Chemotaxonomie der Pflanzen

Hegnauer R.
Chemotaxonomie der Pflanzen
Birkhäuser Verlag Basel und Stuttgart ; Band 8 (1989), 44-45 ; 48-49 ; 76-77 ; 84-85 ; 314-315 ; 638-639.

Kevekordes, S. ; Spielberger, J. ; Burghaus, C.M. ; Birkenkamp, P. ; Zietz, B. ; Paufler, P. ; Diez, M. ; Bolten, C. ; Dunkelberg, H.
Micronucleus formation in human lymphocytes and in the metabolically competent human hepatoma cell line Hep-G2 : results with 15 naturally occurring substances.
Anticancer Res. (2001), 21 (1A), 461-469.

Kim, S.G. ; Liem, A. ; Stewart B.C. ; Miller J.A.
New studies on trans-anethole oxide and trans-asarone oxide.
Carcinogenesis (1999), 20(7), 1303-1307.

Lemberkovics, Eva ; Czinner, Erika ; Balazs, Andrea ; Bihatsi-Karsai, Eva ; Vitanyi, Gyorgy ; Lelik, Laszlo ; Bernath, Jeno ; Szoke, Eva.
New data on composition of essential oil from inflorescence of everlasting (Helichrysum arenarium (L.) Moench.).

Malhotra S. et al.
Piper sumatranum var. andamanica lieferte Asarinin, Asaron, Asarylaldehyd.
Phytochemistry (1990), 29, 2733

Isolation of β asarone, an antibacterial and anthelmintic compound, from Acorus calamus in South Africa.

Pierce, S. ; Schmidt, G.H.
Effect of etheric Acorus calamus oil and beta-asarone on the larger corn borer Prostephanus truncatus (Horn) (Col., Bostrichidae).
Poplawski, J. ; Lozowicka, B. ; Bubis, A. ; Lachowska, B. ; Winiecki, Z. ; Nawrot, J.
Feeding-deterrent activity of alpha-asarone isomers against some stored Coleoptera.

Rubio-Poo, C. ; Lemini, C. ; Garcia-Mondragon, J. ; Zavala, E. ; Silva, G. ; Mendoza-Patino,
N. ; Mandoki, J.J.
The anticoagulant effect of beta-asarone in the mouse and the rat.

Singh, C. ; Jamwal, Urmila ; Singh, P.
_Acorus calamus_ (sweet flag) : an overview of oil composition, biological activity and usage.

Sinha A.K.; Joshi,B.P.; Dogra, R.
One step conversion of toxic β-asaron from _Acorus calamus_ into 1-(2,4,5-
trimethoxyphenyl)-1,2-dihydroxypropane and asaronaldehyde occuring in _Piper clusii_.

Mobility inhibition and nematocidal activity of asaron and related phenylpropanoids on
second-stage larvae of _Toxocara canis_.

Tsai, R.S. ; Carrupt, P.A. ; Testa, B. ; Caldwell, J.
Structure-genotoxicity relationships of allylbenzenes and propenylbenzenes : a quantum
chemical study.

Zanoli, P. ; Avallone, R. ; Baraldi, M.
Sedative and hypothermic effects induced by beta-asarone, a main component of _Acorus
calamus_