

OPINION ON GLYCYRRHIZIN

(shortened version)

Following the publication of an earlier opinion on glycyrrhizin in liquorice products (1990) the SKLM has reconsidered the safety to health of glycyrrhizin. The german version of the opinion was adopted on 20 February 2004, the english version was agreed on 31 August 2004. Deletions in the original text are labelled by "[...]" For more information, please refer to the original document.

Glycyrrhizin (synonym: glycyrrhizinic acid) is a substance which has fifty times the sweetening power of sucrose as well as a distinct liquorice taste. Glycyrrhizin occurs (up to 14%) as the potassium and the calcium salt in the roots of the liquorice plants *Glycyrrhiza glabra*, *G. glandulifera* and *G. typica* which are being cultivated in Europe and the Near East. It is the 2 β -glucuronido- α -glucuronide of glycyrrhetic acid (Römpp, 2003). The glycyrrhizin-containing liquorice juice extracted from plants serves as the raw material for the production of liquorice products.
[...]

In the SKLM consideration of 1990 it was not possible to arrive at a final position on the acceptable limit for glycyrrhizin in the light of the then existing state of knowledge. It was, however, recommended, that on average a consumer should not ingest more than 100 mg glycyrrhizin per day on a regular basis. The provision of corresponding advice on the packaging labels could have addressed this recommendation. It was also considered essential to inform the risk groups, sufferers from heart and

circulatory disease as well as those affected by high blood pressure, that it would be disadvantageous for them to consume more than small amounts of liquorice products (SKLM,1990).

Accordingly, the Federal Health Department (BGA) proposed recommendations for consumption which, for liquorice containing 0.2%-0.4% of glycyrrhizin, advised a maximum consumption of 25 g/day for intake over a lifetime and, for liquorice with a glycyrrhizin content of 0.4%-1%, a maximum consumption of 10 g/day for intake over a lifetime (BGA,1991). These recommendations served as the basis of a voluntary agreement with the German manufacturers. As no corresponding regulations existed in other European countries this agreement was abandoned by the manufacturers after some time for reasons of competitiveness.

In the meantime a placebo-controlled, randomised, double-blind study in humans was carried out and published in the Netherlands. In this study groups of 9-11 healthy female trial participants ingested orally 0, 1, 2 or 4 mg glycyrrhizinic acid/kg body weight per day over a period of 8 weeks. At the highest dose 9 of 11 participants showed signs of pseudohyperaldosteronism such as water retention and a reduction of potassium levels, of rennin activity and of aldosterone concentration in the blood plasma. Systolic and diastolic blood pressure were slightly but significantly raised as compared to the control group yet remained within normal limits. The dose without effect was 2 mg/kg body weight per day (van Gelderen et al.,2000).

In recent years a number of case reports have also been published which demonstrated that even doses at or just below the recommended maximum consumption level of 100 mg/day could cause signs of pseudohyperaldosteronism in particularly sensitive reacting individuals (Russo et al., 2000; Rosseel and Schoors, 1993).

Genetically-determined variation in the activity of 11-betahydroxysteroid dehydrogenase-2 (11-BOHD-2) was found to be one of the key factors for the existence of individual differences in the sensitivity to glycyrrhizin. The inhibition of 11-BOHD-2 by glycyrrhetic acid alters the cortisol/cortisone status and thus may result in pseudohyperaldosteronism.

[...]

A Dutch food consumption study (Kistemaker et al., 1998) revealed that the mean daily consumption by a regular consumer of liquorice is 11.5 g. Assuming an average content of 0.17% glycyrrhizin in liquorice products (Maas, 2000) this would provide a mean daily intake of 19 mg glycyrrhizin. According to this consumption study about 2% of regular consumers of liquorice ingest more than 100 mg glycyrrhizin per day.

In addition, it is known that glycyrrhizin may occur not only in liquorice but also, among other foodstuffs, in beverages, particularly teas, as well as chewing gum and medicines. Glycyrrhizinic acid and ammonium glycyrrhizinate are also used as chemically-defined flavouring substances. It must be recognised that in isolated cases the total intake of glycyrrhizin from liquorice or from all sources respectively may exceed 100 mg/day. Reliable estimates of total daily intake of glycyrrhizin by children are not available.

The recent data provide an improved basis for the estimation of a more accurate value of the safe daily intake of glycyrrhizin and confirm that the statement of the SKLM, that 100 mg glycyrrhizin per day represents an intake that should not be exceeded following regular consumption, is based on a correct assessment.

[...]

The SKLM [...] therefore reiterates its recommendation to label products that contain liquorice, glycyrrhizin or liquorice extract as a constituent. Furthermore, and depending on the glycyrrhizin content, information should be included concerning the acceptable amounts of consumption which should not be exceeded in order to avoid intakes of greater than 100 mg glycyrrhizin per day on regular consumption¹. Finally, it should be pointed out that excessive intakes should be avoided by individuals with hypertension.

¹ An example could be that the consumption of 25g/day of a product with a glycyrrhizin content of 0.2%-0.4% or of about 10 g/day of a product with a higher content could be regarded as acceptable.

Knowledge about groups of individuals with special sensitivity is still inadequate, in particular there are no data on the sensitivity of children. The SKLM therefore considers that research is needed to achieve a more precise definition of these groups, especially for elucidation of:

- the frequency of 11-BOHD-2 polymorphism
- the correlation of this polymorphism with hypertension due to glycyrrhizin
- the extent of constipation as a risk factor
- the sensitivity of children

Independent of the above, the SKLM recommends that there should be an analytical survey of glycyrrhizin in all those products which are likely to contain it in order to be able to estimate the total exposure of the consumer from all different sources (multiple exposure).

[...]

References

[...]

The original version of this opinion can be obtained through the Scientific Office.

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