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REFLECTION PAPER ON ETHANOL CONTENT IN HERBAL MEDICINAL PRODUCTS[1] AND TRADITIONAL HERBAL MEDICINAL PRODUCTS USED IN CHILDREN

Final

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[1] Throughout the reflection paper, unless otherwise specified, the term "herbal medicinal product" includes "traditional herbal medicinal product".

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1. INTRODUCTION

Herbal medicinal products may contain significant levels of ethanol arising from its use as an extraction solvent in liquid extracts and tinctures or when added as a diluent to liquid herbal preparations. The use of ethanol is necessary for extraction of some constituents that are important for efficacy.
Ethanol is metabolically active, therefore formulations without ethanol or with the lowest achievable level should be selected to avoid systemic exposure when the target population is children (1).

2. SCOPE

The scope of this paper is to reflect the need for safety limits for ethanol exposure by oral herbal medicinal products intended for the paediatric population. Establishing these limits is viewed as necessary to protect health and to allow safe free movement of goods within the EU. In addition, this will ensure a harmonised approach in assessment work among Member States as well as in the establishment by the HMPC of Community herbal monographs and of the list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products (respectively Article 16h (2,) and Article 16f (3) of Directive 2001/83/EC as amended).

3. PROBLEM STATEMENT

The safety evaluation of the ethanol content of herbal medicinal products for paediatric use is, at the moment, not harmonised between different EU Member States. Ethanol is often used as an extraction solvent or a diluent in herbal preparations and herbal medicinal products, respectively and can in some cases be present in substantial amounts, e.g., ethanol concentrations in excess of 60% (V/V) in finished oral liquid products. This is of toxicological concern in children with respect to both short-term and prolonged use of ethanol-containing herbal medicinal products that are mainly used and marketed on a non-prescription basis. It should also be noticed that a child may be given more than one herbal medicinal product containing ethanol concomitantly.

The lack of a common European guideline relating to safe limits for ethanol as part of the herbal medicinal products for the paediatric population has also led to different national labelling practices. The Recommendations on the ethanol threshold in oral liquid preparations administered to children have recently given in France stating that optional medical prescription drugs intended for paediatric use must have a concentration of ethanol less than 5% and/or the amount of ethanol in any medicinal product should not produce blood ethanol concentration greater than 0.125 g/L following the administration of only one dose (31).
The FDA has given labelling guidance on over-the-counter drug products containing ethanol, which are intended for oral administration. This guidance is based mainly on conclusions drawn from the publication in Pediatrics, 1984 by the American Academy of Pediatrics (4). In the European Community, the only requirements for ethanol labeling are found in the 'Guideline on excipients in the label and package leaflet of medicinal products for human use' (5). This guideline does not specifically recognise children or different age groups. Therefore, it is not considered sufficient guidance for herbal medicinal products intended for paediatric use. It should be noted that in many liquid herbal extracts, ethanol is part of the active substance and not an excipient. In the newly established 'Reflection paper: formulations of choice for the paediatric population' this problem is recognised, but no specific guidance is given (6, 7). However, recently a co work of CHMP, PDCO and HMPC has been initiated to produce a quality guideline on pharmaceutical development of medicines for paediatric use (32).

Concern over the exposure of children to ethanol and the effect which this exposure will have on public health has recently also been raised by the European Commission (8). Additionally, it has been reported that even the small amounts of ethanol ingested by infants of alcohol consuming mothers during breastfeeding could be detrimental for the child's psychomotor development at the age of one year (9). However, in a later study the same group was unable to replicate the finding in 18-month old toddlers (10). Although there is no compelling evidence that children would be more vulnerable to the toxic effects of ethanol than adults, it can be argued that children should be protected from the potential harmful effects of ethanol.

4. DISCUSSION

Available acute and chronic toxicity data of ethanol in the paediatric population is limited. Current knowledge on the metabolism of ethanol in children is based mainly on cases of acute poisonings or has been extrapolated from data produced in adults or from animal studies. Based on these studies, it can be estimated that the rate of serum ethanol clearance in children and adolescents is comparable to that reported in adults or somewhat faster (11). This is the case despite that ADH-activity (alcohol dehydrogenase liver-enzyme, mainly responsible for ethanol metabolism) in children has been reported to be low and may reach adult levels only after the age of 5 years (12).

The symptoms of ethanol poisoning in children resemble those in adults but may be more severe. It has been estimated that 0.4 ml/kg, i.e., approximately 0.3 g/kg of absolute ethanol, may cause acute toxic reactions in children (13, 14). Milder adverse reactions such as dizziness are expected to appear with much lower concentrations. The life-threatening blood ethanol concentration, usually reported to be approximately 3 g/L (3 ‰) in adults, may be lower in children, as it has been reported that already at blood ethanol concentrations of 1 g/L mortality in children may rise up to 50% (15, 33). One reason for the increased toxicity of ethanol in children may be the fact that they are more prone than adults to developing severe hypoglycaemia as a complication of acute ethanol intoxication (16, 17). Adverse effects on the Central Nervous System are commonly reported in children, arising with blood ethanol concentrations in the range of 0.01 – 1 g/L (6) It should also kept in mind that trauma is one of the major causes leading children to hospitalisation. Ethanol use is linked to a 3- to 7-fold increased risk of trauma. In adults, blood ethanol concentrations in the range of 0.15-0.3 g/L (0.15 – 0.3 ‰) have been reported to impair tasks that require a high degree of attention and motor coordination (18, 19, 20). The paediatric use of herbal medicinal products containing ethanol should not lead to blood ethanol concentrations affecting attention and motor coordination.

Risk evaluation of chronic toxicity of ethanol in children should be associated with routine use of herbal medical products containing ethanol. The effect of long-term exposure to ethanol has never been studied in a paediatric population. Studies and observations on FAS (foetal alcohol syndrome) and FAE (foetal alcohol effects) children, however, give direct evidence of the grave deleterious effects of chronic ethanol exposure, for example, on neurological and cognitive developmental processes (21, 22).

Chronic exposure to ethanol may lead to dependence the mechanism of which is poorly understood and may also be related to genetic factors (23) There are no studies on the addictive property of ethanol with paediatric population., however, adolescent alcohol use disorders with consequences have been documented (24, 25)

5. CONCLUSIONS

It is unrealistic to expect studies where safety thresholds for ethanol content in herbal medicinal products intended for paediatric use are directly demonstrated. The evaluation must stand on other bases. The following aspects should be considered:

- Ethanol administration to children should be minimised and the benefit/risk -ratio should be judged keeping in mind the target population. All herbal medicinal products containing ethanol, are should not be used in neonates and infants below 2 years unless adequate justification is given (e.g. residual solvent in dry extracts).
- The concomitant use of other medicinal products that contain ethanol should be avoided.
- The dose interval should be kept as long as possible, however it should be at least 4 hours to avoid accumulation. The whole treatment period should be as short as possible. For children below 6 years of age, adequate justification must be provided if the treatment exceeds one week.
- Appropriateness and safety of alternatives to ethanol should be considered and continued efforts should be made to have ethanol replaced in herbal liquid preparations intended for paediatric use.
- Harmful impairment of psychomotor functions can already occur when blood ethanol concentration is above 0.125 g/L. Therefore, the recommendation is that a 0.125 g/L blood ethanol concentration should not be exceeded following a single dose of herbal medicinal product containing ethanol (see Annex 1).

- Consideration should be given to herbal medicinal products containing more than 30 g of ethanol being packed with childproof closures (26).
- Information regarding the ethanol content of the herbal medicinal product should be provided in a clear and explicit manner in the package leaflet.
- Interactions for herbal combinations or concomitant medications likely to be used in paediatric population should be taken into account. Ethanol may enhance the absorption and pharmacological effect of some drugs, such as sedatives, and affect the elimination of others by inducing and/or inhibiting the cytochrome P450-dependent elimination pathways (27, 28). In addition, ethanol may, in the presence of, e.g., some antibacterials, cause a disulfiram-like reaction (29, 30)

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ANNEX 1

Theoretical calculations for safety limits of ethanol content in herbal medicinal products for paediatric population

Points to consider:

The following pharmacokinetic equation (1) is used to calculate maximum dose per intake as an absolute ethanol amount (g) predicted to produce a Potential ethanol Blood Level of 0.125 g/L as well as a potential lethal blood level of 3 g/L. The figures are presented in the table below.

$$\text{Blood ethanol level (‰)} = \frac{\text{ingested ethanol amount (g)}}{\text{(volume of distribution- coefficient)} \times \text{weight (kg)}} \quad (1)$$

where
Maximum Blood ethanol level = 0.125 g/L = 0.0125 % = 0.125 ‰
A toxic Blood ethanol level 1g/L = 0.1% =- 1 ‰
Volume of distribution = 0.6, which is based on the assumption of maximal distribution as well as on the approximated total body water compartment in children between 6 and 12 years of age ¤)

From the equation (1) follows that (2)

$$\text{Ingested ethanol amount (g)} = 0.6 \times \text{Weight (kg)} \times \text{Blood ethanol level (‰)} \quad (2)$$

Table 1 The maximum acceptable dose and a toxic dose per intake of absolute ethanol in herbal medicinal products for children between 6 and 12 years of age.

Age (years)	**6**	**8**	**10**	**12**
average weight (kg*)	20	25	30	38
maximum acceptable dose per intake absolute ethanol (g **)	1.5	1.8	2.2	2.8
toxic dose per intake absolute ethanol (g**)	12	15	18	22

* The average weight of a child, the values are drawn from European growth figures for boys and girls
** The doses in volumes (ml) can be calculated as follows (3):

$$\text{Volume (ml)} = \frac{\text{Ingested ethanol amount (g)}}{\text{Density}_{\text{ethanol}}\ \text{(g/ml)} \times \text{(degree)}} \quad (3)$$

where
$\text{Density}_{\text{ethanol}}$ = 0.789 g/ml
Degree, e.g. 5% V/V ethanol solution = 0.05

¤) Some of the ingested ethanol may undergo first-pass metabolism in the stomach but most of it is absorbed. Ethanol is practically insoluble in fat and distributes from the blood into tissues and fluids in proportion to their relative water content. The body water content varies individually and is age dependent and usually lower in children than in adults. Consequently, the same ethanol dose per body weight produces higher peak blood ethanol concentrations in children than in adults.