THE INTERNATIONAL FRAGRANCE ASSOCIATION

IFRA General Comments related to the CLH Report for Methyl Salicylate

Chemical name: Methyl Salicylate
EC Number: 204-317-7
CAS Number: CAS 119-36-8

Use of exposure data of Methyl Salicylate in cosmetics and medicinal products

Summary:

IFRA's comments are related to the use of exposure data of Methyl Salicylate in cosmetics and medicinal products as a basis and justification for deriving conclusions under the EU Regulation (EC) No 1272/2008 (CLP), with which IFRA strongly disagrees. Only end-use applications of fragrance substances covered by the scope of CLP should be considered and taken into account.

Rationale:

The aim of the CLP Regulation (Article 1 of Regulation (EC) No 1272/2008) is to ensure that the hazards presented by chemicals are clearly communicated to workers and consumers in the European Union through classification and labelling of substances and mixtures which are placed on the market.

The CLP Regulation also states that proposals for a harmonised classification should focus on hazard classes of highest concern i.e. substances classified for carcinogenicity, germ cell mutagenicity or reproductive toxicity categories 1A, 1B or 2, and for respiratory sensitisation. Proposals for other effects should be on a case-by-case basis.

Also, the CLP Regulation does not apply to substances and mixtures in the finished state and intended for the final user for which other Community legislation lays down more specific rules such as Regulation (EC) No 1223/2009 on cosmetic products and Directive 2001/83 relating to medicinal products for human use (see Article 1.2 of the CLP Regulation).

The French CLH dossier judges that action at Community level for skin sensitization is needed based on exposures from identified uses of Methyl Salicylate (see page 6 of the CLH dossier) which **fall outside of the scope of the CLP regulation** i.e. cosmetic products and topical medicinal products.

Indeed, substances with allergenic potential used in cosmetic products and placed on the market for consumers are adequately addressed and managed under the requirements of the Cosmetics legislation which is out of scope of the CLP Regulation. The consumer products containing fragrance substances affected by the CLP regulation are mainly household and detergent products, with a different exposure scenario compared to cosmetic products, providing significantly lower exposures.

Therefore, to set a final score of 6 for exposure to Methyl Salicylate (see page 31 of the CLH dossier) based on use and exposure data of cosmetics and medicinal products is not justified. For cosmetics in particular, the available concentration of use data (<0.6%) indicate a relatively low exposure (based on available data from 2003)**.** New data from the industry may be required to confirm concentration of use data for all cosmetic products.

The concentration/dose score of 2 in the CLH dossier is only based on an ointment, containing 12% of Methyl Salicylate. We consider this disproportionate and propose that a score of 0 should be used which

is appropriate for the low exposures. A total score of 2 for concentration/dose due to some topical medication is not warranted and can be considered completely exaggerated.

The use and exposure data should be related to the end uses of the substance in fragrance applications in the scope of the CLP e.g. laundry and dish washing products, cleaners in general etc.).

In essence, IFRA disagrees with the rationale of the Proposal for Harmonised Classification & Labelling of Methyl Salicylate because

- the use and exposure assumptions are focused on certain product categories (e.g. ointments) that in fact are not representative of the majority of exposures;
- and the major uses and exposures (in particular cosmetic products) actually fall outside of the remit of the CLP Regulation.

Sub-cutaneous applications

Summary:

IFRA's comments are related to the use of two rat studies with sub-cutaneous injection (FDA 2006c and 2006d) which are used to justify a proposal to classify Methyl Salicylate as a developmental toxic substance Repr. Cat 1B. Subcutaneous injection as route of administration is not a usual administration route and should be evaluated with caution under the CLP Regulation given the avoidance of typical 'first pass' metabolism. The developmental toxicity findings reported in rat studies using this route of administration are a consequence of maternal toxicity and are therefore not considered relevant for hazard classification purposes. Finally, the assigned reliability of Klimisch score 1 is not considered pertinent given the secondary source availability of the studies in question.

Rationale:

The proposal to classify Methyl Salicylate as a developmental toxic substance Repr. Cat 1B is in large part based on the results obtained in two rat studies using subcutaneous administration (FDA 2006c and 2006d). Developing conclusions based on such a route of administration needs caution since this route circumvents the opportunity for metabolism via the relevant exposure routes which have been shown to hydrolyse methyl salicylate into salicylic acid i.e. (i) the oral route and the 'first past' effect in the liver and (ii) the dermal route and skin metabolism. Consequently, the peak plasma levels of Methyl Salicylate achieved by the subcutaneous route of administration will be significantly higher than through oral and dermal exposure which do not avoid this metabolism. Therefore, from the metabolism and kinetic perspective, the results obtained for Methyl Salicylate by the subcutaneous route should not be compared to oral and dermal exposures. In addition, substances administered subcutaneously should be non-irritating and high percentage concentrations of Methyl Salicylate as applied in those studies are known to be irritating. Overall, the results obtained in these two studies are distorted and are not considered appropriate for hazard classification under the CLP regulation (see CLP Regulation, Annex 1, 1.1.1.5 "*For the purpose of classification for health hazards (Part 3) route of exposure, mechanistic information and metabolism studies are pertinent to determining the relevance of an effect in humans.*"

The oral exposure route is normally the preferred administration route for the hazard classification of chemicals. Since relevant and valid data for Methyl Salicylate via the oral route are available, they should be the basis for the hazard classification.

As per the specific developmental toxicity findings reported at 200mg/kg/day (FDA 2006d), these should be regarded as secondary to the maternal toxicity clearly observed at that dose and not test article related, and therefore, should not be considered for hazard classification purposes, in line with CLP Regulation Annex 1, 3.7.2.4. Furthermore, the occurrence of skeletal variations reported at 60mg/kg/day (FDA 2006d)

is inconsistent with the lack of those observations at 100mg/kg/day in a study designed to detect these effects (FDA 2006c).

Moreover, the proposed CLH assessment of the two studies with subcutaneous injection appears to be based on the results summarised in an NDA review report by the FDA (2006). IFRA considers that in order to make a robust evaluation for the purposes of harmonised classification under CLP, far more study details than those publicly available are needed, irrespective of the questionable relevance of the subcutaneous route of exposure of the studies as outlined above.

Unless a direct data source, such as the study report is used in the assessment, the reliability of the reference cannot be considered as Klimisch 1 and therefore, it is not appropriate to use such data to support a key argument for classification.