Comments to BSC on Proposed Studies of 2-Ethylhexyl *p*-methoxycinnamate

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Need for kinetic and penetration studies questionable

- Jimenez *et al.* showed that dermal penetration is minimal (<1%).
- **Less** EHMC is released into the stratum corneum from nanoencapsules than from without encapsulation.
  - Jimenez *et al.* state that EHMC "remained primarily on the skin surface" (82-90% for nanocapsulated versus 48-60% for oil-in-water emulsions alone).
- Intent of nanoparticles encapsulation is to reduce absorption not enhance it.
- Therefore, nanoencapsulation or even dermal absorption is not a valid rationale for the study of systemic effects of EHMC.

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Need for RACB study is questionable

- Specific studies to clarify putative reproductive effects confirmed the absence of endocrine disruptive properties of EHMC.
  - A uterotrophic and Hershberger assay were negative. Both studies indicate that EHMC is not an endocrine disruptor.
  - A study of hormonal effects following repeated oral dosing showed no biologically relevant changes in hormone levels.

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Need for RACB study is questionable

- Repeated dietary administration of EHMC (906 mg/kg) over a period of 4 weeks showed:
  - No changes in ovary weights and in estrus cycle duration;
  - No change in prolactin, follicle-stimulating hormone, luteinizing hormone, estradiol or progesterone serum levels;
  - T3 and TSH concentrations were unaffected by treatment whereas T4 was slightly **elevated** (44.77 ±7.94 nmol/l in control group versus 53.43 ±4.6 nmol/l in treated animals).
- Therefore, additional studies to clarify endocrine disruption are not warranted.

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Need for cancer study is questionable

- Carcinogenicity studies of EHMC were based on the potential to hydrolyze to 2-ethylhexanol (2-EH) and cinnamic acid (CA), both suspected of being tumor initiators.
  - 2EH is a weak carcinogen in rodents (Astill et al, 1996) and not genotoxic.
  - Cinnamates were recently reviewed and were not indicated to have any human health concerns.

- In a photocarcinogenicity study using hairless mice, EHMC was applied dermally at a 5% concentration as a reference compound over a period of 40 weeks (A. Fourtanier, 1996). EHMC delayed the median latent period for tumor development by 2 weeks. This contradicts the earlier Gallagher study (1984).

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Need for cancer study is questionable

- EHMC was reviewed by the EU Scientific Committee on Cosmetology in 1996.
  - Only minor findings in clinical pathology or adaptive and physiological processes at high dose levels, such as liver weight or kidney weight increases, could be detected in subchronic studies. No tissue changes were observed which might have indicated a potential oncogenicity after long-term exposure.

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