Public Comments on the Nomination of 2-Ethylhexyl p-Methoxycinnamate (EHMC)

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Additional studies not considered

- Studies published after the NCI's supporting document:
  - Kunz and Fent, 2006 (14 day: hormonal activity in fish; yeast reporter assay)
  - Seidlova-Wuttke et al., 2006 (chronic: hormonal and metabolic activity in rats)
  - Klammer et al., 2007 (5 day: thyroid function in rats)
  - Szwarcfarb et al., 2008 (2 day: hormone and neurotransmitter activity in rats)
- Other studies not cited in supporting document:
  - Trueman and Schupbach, 1983 (genotoxicity)
  - Young et al., 1987 (15 week: phototumorogenesis in mice)
  - Xu and Parsons, 1999 (cellular toxicology in culture)
  - Schreurs et al., 2002 (4 day: estrogenic activity in fish and reporter assay)
  - Schlumpf et al., 2004 (multi-generation: endocrine function, development in rats)
  - Heneweer et al., 2005 (estrogenic activity in cell culture)
  - Kunz et al., 2006 (estrogenic activity in fish)
  - Rachon et al., 2006 (cellular toxicology in culture)

The Board must conduct a thorough review of all existing data in order to make an informed decision regarding the need for extensive new studies.

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Studies by oral exposure unnecessary and irrelevant

- The NTP proposes both dermal and oral toxicokinetic studies of EHMC even though human exposure is expected to be exclusively dermal.
- The only rationale given for including oral exposure is the proposal to test *in utero* (typically done by oral exposure).
- A recent two-generation reproductive toxicity study using oral exposure (Schneider et al., 2005) reported:
  - No adverse effects on estrus cycle, sperm number, morphology or motility, differential follicle counts, mating, fertility, gestation or parturitions.
  - Toxicity (reduced food consumption; body weight, liver effects, stomach erosion) interfered with interpretation of effects on implantation rates and onset of puberty

New studies by oral exposure are therefore unlikely to provide additional, useful information but would double the number of animals used – *at minimum*.

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EHMC is especially well-suited to an epidemiological approach

- EHMC's long history and widespread use permits the conduct of large-scale, retrospective analyses.
- Likely endpoints for evaluation (changes in serum hormone levels, incidence of malignant melanoma and other skin cancers) have already been identified.
- Several large-scale, international, epidemiological studies have already begun to assess the health effects of sunscreens that include EHMC.

"… further (epidemiological) studies have to be performed in order to elucidate whether there is indeed a risk of using these UV filters for humans."

Heneweer et al., 2005

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Proposed studies are duplicative

- The proposed animal tests do not differ significantly from previous work on the estrogenic, toxic, and carcinogenic potential of EHMC. As a result, they do not address the ambiguities in the existing data that prompted this nomination.

  - Schneider et al., 2005 (multi-generation: reproduction in rats)
  - Schlumpf et al., 2004 (multi-generation: endocrine function, development in rats)
  - Schmutzler et al., 2001 (3 month: endocrine function)

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In vitro tests are more relevant

- Several standard *in vitro* tests for cytotoxicity, genotoxicity, mutagenicity and carcinogenicity have been optimized for the assessment of topically applied UV filters making them more precise and powerful tools for sunscreen ingredient evaluation than animal models:
  - Phototoxicity assays in yeast, 3T3 cells and 3D skin models (DiNardo et al., 1985; Flamand et al, 2006; Jones et al., 1999)
  - Photomutagenicity assays in bacteria and CHO cells (Chételat et al., 1993; Dean et al., 1991, 1992; Henderson et al., 1994; Utesch and Spittgerber, 1996)
  - Cell cycle and mitochondrial gene expression in cultured human cells (Xu and Parsons, 1999)

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Summary and Recommendations

- The extensive animal tests proposed will not provide additional useful data for the assessment of EHMC's toxicity.

- General and sunscreen-specific *in vitro* methods and epidemiological approaches were not considered.

We urge the NTP to reconsider the extensive animal testing proposed and instead to advocate appropriate *in vitro* assays, human clinical studies, and epidemiological analyses.

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