



NTP
National Toxicology Program

2-Ethylhexyl *p*-methoxycinnamate

Michael Wyde, Ph.D.

National Toxicology Program





2-Ethylhexyl methoxycinnamate (EHMC)

- Nominated by NCI for comprehensive toxicological characterization
 - Toxicity, carcinogenicity, characterization of photodegradation products
- Common active ingredient in sunscreens (ingredient name: Oxinoxate)
- Most widely used ultraviolet (UV) filter in topically applied sunscreens
- EHMC protects against UV-induced sunburn, photoageing, immunosuppression, and skin cancer by absorbing harmful UVB radiation
- FDA regulation – maximum 7.5% by weight in sunscreens
- Very limited toxicology data available
 - Weakly estrogenic
 - Reproductive effects



2-Ethylhexyl methoxycinnamate toxicity studies

- Not skin irritant or photosensitizer
- Not mutagenic in *Salmonella* assay
- Oral LD₅₀ in mice >8 g/kg
- Human data limited to absorption studies
 - <3% transdermal absorption in animal studies
- 12 week study there were slight alterations in thyroid hormones – decreased T4, increased TSH (low dose only)



Two-Generation Reproduction Study

- Concluded no evidence of selective influence on sexual landmarks of pups
- NOAEL for fertility and reproductive performance and systemic parental and developmental toxicity was 450 mg/kg
 - Slightly decreased implantation rate in F0 and F1 dams
- Statistically significant reproductive effects were disregarded
 - Reduced number of implantation sites, reduced litter size, delayed vaginal opening and preputial separation, increased number of stillborn pups, reduced viability index, reduced pup weight gain
 - Effects were consistent between generations
 - Significant reproductive effects observed at doses deemed a NOAEL



2-Ethylhexyl methoxycinnamate estrogenicity?

- Stimulate cell proliferation in MCF-7 cells
- Positive in *in vitro* transactivation assays via the ER
- Uterotrophic activity in immature rats – mixed results
- Estrogenic activity in other tissues
 - Expression of various estrogen-responsive genes *in vivo*
 - Cholesterol and LDL



Structure-activity relationship and potential metabolite formation

- Does 2-ethylhexyl moiety indicate potential carcinogenicity?
 - 2-ethylhexyl diester of phthalic acid and adipic acids carcinogenic in NCI/NTP bioassays
 - Not adequate data to implicate this group, just to raise the question
- Does metabolism of EHMC result in formation of 2-ethylhexanol or 2-ethylhexanoic acid?
 - Developmental toxicants



Proposed Research Program

- Comparative dermal and oral toxicokinetic and ADME studies to evaluate differential distribution and metabolism between route of exposure
- Oral (or dermal) subacute, subchronic, and chronic studies in rats and mice to characterize the toxicity and carcinogenicity with *in utero* exposures
 - Determination of male and female sex hormones and thyroid hormone levels
- Determine photodegradation and photoisomerization products
- Robust multigenerational study in the rat incorporating estrogen-sensitive endpoints



The Issue and the Impact

- EHMC use is widespread and chronic
 - Given the known dangers of UV radiation, sunscreens are typically applied for protection throughout one's lifespan
- Sensitivity of children
 - EHMC distributes in the stratus corneum (SC) in adults, but concerns about children where the SC is less likely to be protective
 - Children may have less-developed elimination capacity
- *in utero* exposures may occur
 - Studies on EHMC should take this exposure scenario into consideration
- Studies with EHMC have repeatedly demonstrated endocrine effects
 - Some effects have been debated
 - Indicates that further investigation and clarification of the reproductive effects of a potentially endocrine active compound is warranted
- Increase the scientific base on which regulatory agencies such as the FDA interpret potential toxicological events associated with exposure to sunscreens that contain EHMC