Comments on Draft Report 06 Dated March 21, 2021
NTP Developmental and Reproductive Toxicity Technical Report on the Modified One-Generation Study of 2-Ethylhexyl p-Methoxycinnamate (CASRN 5466 77-3) Administered in Feed to Sprague Dawley (Hsd:Sprague Dawley® SD®) Rats with Prenatal, Reproductive Performance, and Subchronic Assessments in F1 Offspring

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Issue: EHMC at concentrations ≤7.5% is used in sunscreens and other personal care products to protect the wearer from solar erythema (21 CFR § 352.10). Per the Environmental Working Group's Skin Deep® Database, EHMC is found in approximately 750 sunscreens, lip balms, and moisturizers.
Concern: It is somewhat confusing why NTP would choose to use the Environmental Working Group's database over the FDA National Drug Code (NDC) database which identifies all OTC sunscreen **drug** products currently registered for sale in the US (this is a legal requirement). Based on the FDA NDC database, as of September 21, 2021, there are 2,949 EHMC (also known as Octinoxate) products currently in the marketplace with only 205 products using EHMC alone (refer to excel file attached – products listed alphabetically by company name). This is a significant decrease from February 2018 (prior to Hawaii banning the sale of EHMC sunscreens) which at that time listed approximately 6,800 products.
Additionally, there are numerous other personal care products (skincare, haircare and other non-drug products) that use EHMC as noted in a Cosmetic Ingredient Review Priority list for 2016[1] the "FDA's Voluntary **Cosmetic** Registration Program (VCRP), received from FDA on February 12, 2015" identified 4,783 products that use ethylhexyl methoxycinnamate. The total number of drug and cosmetic products containing EHMC would appear to be approximately 7,732 or roughly 10 times what is reported by EWG.

In Summary, there are significantly more than "750 products" that use this chemical at concentrations ≤7.5%. The NTP report should be corrected to at least reflect what is currently in the FDA NDC database and perhaps make mention that the FDA Voluntary Cosmetic Registration Program which identifies numerous non-drug products that use EHMC . In addition, several of the references used in the report are over 30+ years old and, therefore, in light of more recent trends in research (2019 - 2021) it might be helpful to perhaps include a few newer perspectives (refer to Table 1 below). One exception included in this list is a 2015 paper by Manova et al, which indicates that children 4 years and younger are exposed to levels of EHMC above the level of concern for thyroid toxicity.

Issue: Under the conditions of this modified one-generation (MOG) study, there was **no evidence of reproductive** toxicity of 2-ethylhexyl p-methoxycinnamate (EHMC) in Hsd:Sprague Dawley® SD® rats at exposure concentrations of 1,000, 3,000, or 6,000 ppm. Mating and littering were not affected significantly by EHMC exposure.
Under the conditions of this MOG study, there was **equivocal evidence of developmental toxicity** of EHMC in Hsd:Sprague Dawley® SD® rats based on the observed postnatal effects on body weight that showed some indication of recovery by study end, delays in postnatal day 28-adjusted vaginal opening and balanopreputial separation, which could have influenced the apparent transient effects on body weight, and time in estrus was slightly longer in EHMC-exposed females relative to that of the control group. No other signals consistent with

alterations in estrogenic, androgenic, or antiandrogenic action were observed. **EHMC exposure did not induce any specific fetal malformations.**

Concern: The identification of the test levels used in the conclusion "**1,000, 3,000, or 6,000 ppm**" is exceptionally deceptive without any reference to some comparison that consumers are commonly exposed to levels as high as 75,000 ppm. EHMC use in sunscreens/antiaging products represents the highest use levels and greatest risk to humans. Other than the recent absorption studies conducted by Matta et. al.[2,3], there has not been toxicity studies conducted on actual consumer products containing EHMC. The maximum allowable level of EHMC is 7.5% which is used mainly in combination with other common sunscreen/antiaging actives, such as 3% Avobenzone + 15% Homosalate + 5% Octisalate + 10% Octocrylene + 6% Oxybenzone (2H4MBP) - totaling a possible allowable use level of actives in a product equal to 46.5% or 465,000 ppm. All of these actives have demonstrated, in the published literature, to possess some endocrine disrupting activity as well as may act synergistically with each another to cause toxicity[4-6]. Review of several SPF 50 or above products currently in the marketplace indicates a 35% - 45% active level of which EHMC is commonly used at 7.5%. Therefore, greater emphasis needs to be placed on how this data is summarized in the conclusion, which can be taken out of context by the press and others, possibly misleading consumers.

In summary, one should not simply state that "at the exposure concentrations " … "no evidence of reproductive toxicity" and "equivocal evidence of developmental toxicity" and "EHMC exposure did not induce any specific fetal malformations". More emphasis needs to be placed on "when EHMC was tested individually **at a very small fraction** of the concentration commonly used in sunscreen/antiaging products there was "no evidence of reproductive toxicity" and "equivocal evidence of developmental toxicity" and "EHMC exposure did not induce any specific fetal malformations". Additionally, it should also be noted that EHMC was not tested in conjunction with other OTC actives commonly used in sunscreen/antiaging products that may react synergistically with one another increasing the potential risk of reproductive and/or developmental toxicity. The shorter version of these statements would be that **this research does not represent the reproductive and/or developmental toxicity potential of EHMC, which maybe greater than what is reported in this document, in humans at the levels used in sunscreen/antiaging products**.

Additionally based on the Maximum Tolerated Dose Studies conducted to determine the dose levels in feed, it should be noted **in the conclusion** that levels of 20,000 ppm or 2% - which is less than one-third the human exposure - produced **maternally toxicity** and that levels of 10,000 ppm or 1% - again, a fraction of the human exposure - produced **fetal toxicity**. Lastly, per the comment in the discussion "pups in the 6,000 ppm groups weighed approximately 13%–15% less than the control groups; however, by PND 91, the body weights of pups exposed to 6,000 ppm were approximately 5%–7% lower than those of the control groups, demonstrating some reversibility/recovery of the effect on body weight." Although the signs of a potential "**rebound**" effect may be of some consolation, it should be noted that "In adulthood, every day of the animal is approximately equivalent to 34.8 human days (i.e., one rat month is comparable to three human years)[7]" meaning 91 days would be approximately equivalent to a 9 year old child! Again, please keep in mind that 6,000 ppm is 0.6% and EHMC is commonly used at 75,000 ppm or 7.5% in sunscreen/antiaging products.

References:

1) CIR EXPERT PANEL MEETING MARCH 16-17, 2015. Page 21 of 47 - https://www.cir-safety.org/sites/default/files/admin_2.pdf

2) Matta MK et al. Effect of sunscreen application under maximal use conditions on plasma concentration of sunscreen active ingredients: a randomized clinical trial. JAMA 2019; 321:2082-2091.

3) Matta MK et al. Effect of sunscreen application on plasma concentration of sunscreen active ingredients. JAMA 2020; 323:256-267.

4) Rehfeld A et al. Chemical UV Filters Mimic the Effect of Progesterone on Ca 2+ Signaling in Human Sperm Cells. Endocrinology 2016; 157:4297-4308.

5) Christiansen S et al. Mixtures of endocrine disrupting contaminants modelled on human high end exposures: an exploratory study in rats. Int J Androl 2012;35:303-16.

6) Jang GH et al. Sequential assessment via daphnia and zebrafish for systematic toxicity screening of heterogeneous substances. Environ Pollut 2016; 216:292-303.

7) Sengupta P. The Laboratory Rat: Relating Its Age With Human's. Int J Prev Med 2013; 4:624–630.

Table 1: Newer Papers Published on 2-Ethylhexyl p-Methoxycinnamate (EHMC)

Lead Author/Title/Reference	Observation(s)
Cahova J. The biological activity of the organic UV filter ethylhexyl methoxycinnamate in rainbow trout (Oncorhynchus mykiss). Sci Total Environ 2021; 774:145570.	"Histopathological examination revealed massive destruction of hepatic parenchyma at the highest concentration of EHMC. All these results support the finding of a stress load on the fish organism. In summary, although subchronic exposure to EHMC had no effect on behaviour, mortality or feed intake, this exposure resulted in the alteration of saccharide, lipid and protein metabolism and weakened antioxidant capacity."
Lorigo M. UV-B Filter octyl methoxycinnamate impaired the main vasorelaxant mechanism of human umbilical artery. Chemosphere 2021; 277:130302.	"Results also showed that long-term exposure to OMC induced a decreased vasorelaxation response on HUA due to an interference with the NO/sGC/cGMP/PKG pathway. Moreover, OMC seems to modulate the L-type Ca2" channels, the BKCa 1.1 a-subunit channels, and the PKG. Overall, since OMC compromises the vascular homeostasis of pregnant women it can be an inductor of pregnancy hypertensive disorders."
Verde I. Vasodilator effect of octyl methoxycinnamate on human umbilical arteries. Health and Society Vol. 1 No. 02 (2021). https://www.periodicojs.com.br/index.php/hs/article/view/295	"Here, we established that the OMC causes vasodilation of human arteries. This effect is analogous to the non-genomic effect caused by estradiol (E2), which occurs also by and endothelial-independent mechanism."
Carve M. Trends in environmental and toxicity research on organic ultraviolet filters: A scientometric review. Sci Total Environ 2021;773:145628.	"Emerging themes included improving the sensitivity of analytical detection methods for both OUVFs and their metabolites, consequences of OUVF transport to the marine environment, and concerns over prenatal exposure. Based on keyword analysis, benzophenone-3, 4-methylbenzylidene-camphor, 3-benzylidene camphor, and ethylhexyl-methoxycinnamate are the most studied OUVFs, and effects on estrogenic activity, gene expression, reproduction, and more recently, oxidative stress, have received most attention from a toxicological perspective."
Lambert FN. Effects of ultraviolet-filters on Daphnia magna development and endocrine-related gene expression. Aquat Toxicol 2021; 238:105915.	"We demonstrate that 4MBC, OMC, and BP3 affect development and long-term health in neonates of exposed parents at concentrations of 130 µg/L, 75 µg/L, and 166 µg/L, respectively."
Chu S. Effects of 2-ethylhexyl-4-methoxycinnamate (EHMC) on thyroid hormones and genes associated with thyroid, neurotoxic, and nephrotoxic responses in adult and larval zebrafish (Danio rerio). Chemosphere 2021; 263:128176.	"The hypothyroidism induced in the larval !sh by the exposure might be potentially associated with the neurotoxic potential of EHMC."
Vecchiato M. Organic pollutants in protected plain areas: The occurrence of PAHs, musks, UV-filters, flame retardants and hydrocarbons in woodland soils. Sci Total Environ 2021; 796:149003	"Moreover, these samples for the first time revealed the presence of personal care products, primarily 2-ethylhexyl-4-methoxycinnamate (EHMC) and tonalide (AHTN), in soils of protected woodlands, reaching respectively 3.4 ng g-1 and 5.0 ng g-1, together with the occurrence of both organophosphorus and brominated FRs, with total concentrations up to 15 ng g-1."
Su QZ. Decontamination efficiencies of post-consumer high-density polyethylene milk bottles and prioritization of high concern volatile migrants Resources, Conservation & Recycling 2021; 171:105640	"Nevertheless, other two high concern compounds, octocrylene, and 2-eth- ylhexyl-4-methoxycinnamate were not significantly reduced and thus deserve special attention when decontaminating rHDPE and evaluating its feasibility for food contact uses."
da Silva ACP. Ethylhexyl methoxycinnamate and butyl methoxydibenzoylmethane: Toxicological effects on marine biota and human concerns. Review: J Appl Toxicol 2021 Jun 7. doi: 10.1002/jat.4210.	"In this article, we reviewed the toxicological effects of EHMC and BMDM on aquatic ecosystems and the human consequences. According to the literature, EHMC and BMDM have been detected in water samples and sediments worldwide. Consequently, these compounds are also present in several marine organisms like fish, invertebrates, coral reefs, marine mammals, and other species, due to its bioaccumulation potential."
Lozano C. Toxicity of UV filters on marine bacteria: Combined effects with damaging solar radiation. Sci Total Environ 2020; 722:137803	"Octinoxate was the most toxic chemical at 1000 µg L-1 on growing cells."
Zhong X. Comparison of toxicological effects of oxybenzone, avobenzone, octocrylene, and octinoxate sunscreen ingredients on cucumber plants (Cucumis sativus L.). Sci Total Environ 2020; 714:136879	"On the basis of comprehensive evaluation, we speculated that the order of the four UV filters in terms of plant damage was OBZ > AVB > OMC > OCR. Because of the severe damaging effects of these UV filters on plant growth, the application of contaminated biosolids/reclaimed water in agriculture reduces agricultural production and may damage ecosystems."
Jentzsch F. Photolysis of mixtures of UV filters octocrylene and ethylhexyl methoxycinnamate leads to formation of mixed transformation products and different kinetics. Sci Total Environ 2019; 697:134048.	"The study shows that more attention should be paid to mixture-effects and mixture photo-transformation products that may cause further follow-up effects."
Zhou R. Bioaccumulation and biochemical effects of ethylhexyl methoxy cinnamate and its main transformation products in zebrafish. Aquat Toxicol 2019;214:105241.	"Results showed that both EHMC and 3,5DCl2HAcP can lead to the increase of malondialdehyde (MDA) and glutathione (GSH) contents, superoxide dismutase (SOD), catalase (CAT) and glutathione reductase (GR) activities in visceral mass compared with the corresponding control group, thus produced oxidative stress effect in organism and 3,5DCl2HAcP even showed stronger oxidative stress than EHMC."
Manova E. Aggregate consumer exposure to UV filter ethylhexyl methoxycinnamate via personal care products. Environ Int 2015;74:249-57.	"the predicted aggregate exposure exceeds the DNEL for thyroid-disrupting effects such as for children aged ≤4years, who might be particularly susceptible to endocrine disrupting events."