Issue: 2-Hydroxy-4-methoxybenzophenone (2H4MBP), also known as oxybenzone and benzophenone-3, is approved by the U.S. Food and Drug Administration for use in sunscreens and other personal care products in concentrations of <6%, either alone or in combination formulations, and as an indirect food additive in acrylic and modified acrylic plastics that come into contact with food.

Concern: To avoid confusion with the public “approved by FDA” should be removed. On February 26, 2019, FDA removed 2H4MBP and 11 other chemicals from Category I GRASE status to Category III “Insufficient data” for use in sunscreens based on the following concerns:

“For example, the available literature includes studies indicating that oxybenzone is absorbed through the skin to a greater extent than previously understood and can lead to significant systemic exposure, as well as data showing the presence of oxybenzone in human breast milk, amniotic fluid, urine, and blood plasma. The significant systemic availability of oxybenzone, coupled with a lack of data evaluating the full extent of its absorption potential, is a concern, among other reasons, because of questions raised in the published literature regarding the potential for endocrine activity in connection with systemic oxybenzone exposure.”

Also, FDA does not approve chemicals for use in “other personal care products” only Over-The-Counter drugs – please remove this statement. Also, 2H4MBP is commonly used at 6% (60,000 ppm) or less, not less than 6% “<6%” as noted – please correct.

Issue: Under the conditions of this modified one-generation (MOG) study, there was equivocal evidence of reproductive toxicity of 2-hydroxy-4-methoxybenzophenone (2H4MBP) in Hsd:Sprague Dawley® SD® rats based on a decrease in F2 litter size in both the prenatal and reproductive performance cohorts.

Concern: There is no identification of the test levels used in the study in the conclusion. 2H4MBP use in sunscreens/antiaging products represents the highest use level 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 2H4MBP. The maximum allowable level of 2H4MBP is 6% which is used in combination with other common sunscreen/antiaging actives, such as 3% Avobenzone + 15% Homosalate + 5% Octisalate + 10% Octocrylene + 7.5% Octinoxate (EHMC) - totaling a possible allowable use 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 toxicity³⁻⁶. Review of several SPF 50 or above products currently in the marketplace indicates a 35% - 45% active level of which 2H4MBP is commonly used at 6%. 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. For example: in the Scientific Committee on Consumer Safety (SCCS) opinion on benzophenone-3⁷ they state “it needs to be noted that the SCCS has regarded the currently available evidence for endocrine disrupting properties of BP-3 as inconclusive, and at best equivocal.” Unfortunately, there were 42 DART publications
(Table 1 below), several in humans, that were ignored in the review allowing one to believe that there are no endocrine disrupting effects associated with benzophenone-3.

In summary, one should not simply state that “there was equivocal evidence of reproductive toxicity” and “some evidence of developmental toxicity”. More emphasis needs to be placed on “when 2H4MBP was tested individually at one-half the concentration commonly used in sunscreen/antiaging products there was equivocal evidence of reproductive toxicity and some evidence of developmental toxicity. Additionally, it should be noted that 2H4MBP 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 2H4MBP, which maybe greater than what is reported in this document, in humans at the levels used in sunscreen/antiaging products.

Issue: “2-Hydroxy-4-methoxybenzophenone (2H4MBP) was obtained from Ivy Fine Chemicals (Cherry Hill, NJ) in a single lot (20100801), which was used for the dose range-finding and modified one-generation (MOG) studies ... The HPLC/UV analysis showed a single impurity with a peak area <0.1%, indicating an 2H4MBP purity of approximately 100.0%.”

Concern: Although most research utilizes the highest purity of a chemical available for testing, usually obtained from a specialty house, companies mostly purchase ingredients based on price not purity. A simple review of available grades of 2H4MBP in the marketplace demonstrates a purity range from 95% to 103%. This should raise concern since impurities can have a profound impact on the toxicity produced by a chemical and, therefore, chemicals should be selected based on what companies purchase and not the highest purity levels available. Perhaps a footnote can be made in this section of the report stating that “this ingredient may or may not represent the actually purity level of 2H4MBP that is used in consumer 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 30,000 ppm or 3% - which is half the human exposure - were found to produce maternally toxicity and that levels of 10,000 ppm or 1% - also a fraction of human exposure - were found to produce fetal toxicity based on the body weight data. Lastly, this data takes on a stronger significance when studies like Buckley et al. are considered who observed in a nine year study following the children of mothers who tested positive for 2H4MBP in their third trimester - “After adjustment, phenol biomarkers were not associated with percent fat mass. However, the association between benzophenone-3 and percent fat mass was modified by child's sex: benzophenone-3 concentrations were inversely associated with percent fat mass in girls (beta = −1.51, 95% CI = −3.06, 0.01) but not boys (beta = −0.20, 95% CI = −1.69, 1.26). Although we did not observe strong evidence that prenatal environmental phenols exposures influence the development of childhood adiposity, the potential antiadipogenic effect of benzophenone-3 in girls may warrant further investigation.”

References:
1) 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.


