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### A Review of the Endocrine Activity of Parabens and Implications for Potential Risks to Human Health

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#### Abstract:

Parabens are a group of the alkyl esters of p-hydroxybenzoic acid and typically include methylparaben, ethylparaben, propylparaben, butylparaben, isobutylparaben, isopropylparaben, and benzylparaben. Parabens (or their salts) are widely used as preservatives in cosmetics, toiletries, and pharmaceuticals due to their relatively low toxicity profile and a long history of safe use. Testing of parabens has revealed to varying degrees that individual paraben compounds have weakly estrogenic activity in some in vitro screening tests, such as ligand binding to the estrogen receptor, regulation of CAT gene expression, and proliferation of MCF-7 cells. Reported in vivo effects include increased uterine weight (i.e., butyl-, isobutyl-, and benzylparaben) and male reproductive-tract effects (i.e., butyl- and propylparaben). However, in relation to estrogen as a control during in vivo studies, the parabens with activity are many orders of magnitude less active than estrogen. While exposure to sufficient doses of exogenous estrogen can increase the risk of certain adverse effects, the presumption that similar risks might also result from exposure to endocrine-active chemicals (EACs) with far weaker activity is still speculative. In assessing the likelihood that exposure to weakly active EACs might be etiologically associated with adverse effects due to an endocrine-mediated mode of action, it is paramount to consider both the doses and the potency of such compounds in comparison with estrogen. In this review, a comparative approach involving both dose and potency is used to assess whether in utero or adult exposure to parabens might be associated with adverse effects mediated via an estrogen-modulating mode of action. In utilizing this approach, the paraben doses required to produce estrogenic effects in vivo are compared with the doses of either 17 $\beta$ -estradiol or diethylstilbestrol (DES) that are well established in their ability to affect endocrine activity. Where possible and appropriate, emphasis is placed on direct comparisons with human data with either 17 $\beta$ -estradiol or DES, since this does not require extrapolation from animal data with the uncertainties inherent in such comparisons. Based on these comparisons using worst-case assumptions pertaining to total daily exposures to parabens and dose/potency comparisons with both human and animal no-observed-effect levels (NOELs) and lowest-observed-effect levels (LOELs) for estrogen or DES, it is biologically implausible that parabens could increase the risk of any estrogen-mediated endpoint, including effects on the male reproductive tract or breast cancer. Additional analysis based on the concept of a hygiene-based margin of safety (HBMOS), a comparative approach for assessing the estrogen activities of weakly active EACs, demonstrates that worst-case daily exposure to parabens would present substantially less risk relative to exposure to naturally occurring EACs in the diet such as the phytoestrogen daidzein.