Genomic and Proteomic Biomarkers of Biological Responses to Exposure

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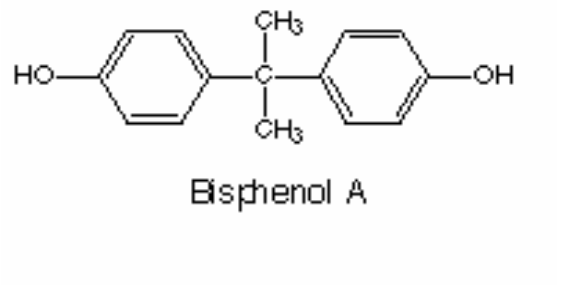
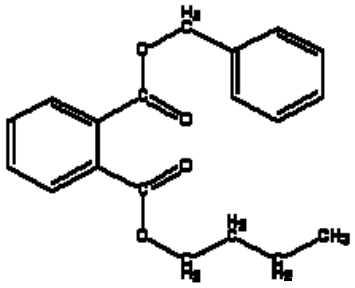
Fetuses, newborns, infants, and adolescents are uniquely susceptible populations to biochemical insult from environmental chemicals. Their increased susceptibility can arise from increased exposures, metabolism and excretion, and activation/detoxification mechanisms that render them more or less susceptible for toxicity. While some of these toxicities may be evident immediately, some exposures that take place during early critical periods of development can result in subtle alterations that are delayed in expression.

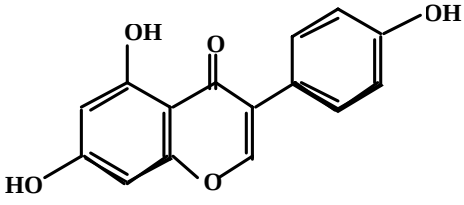
It is our goal to use sensitive and reproducible genomic and proteomic technologies for identification of biomarkers of exposure in girls (and rats as a model system) exposed to selected environmental chemicals [bisphenol A (BPA), phthalates (butyl benzyl phthalate (BBP), di-2-ethylhexyl phthalate (DEHP)) and genistein] that are measurable in the population and suspected to alter susceptibility for breast cancer. For this purpose, we are using a two-prong approach, humans and animals for our sources of blood serum and buffy coat, and buccal swabs. In rats we will investigate the mammary glands as well.



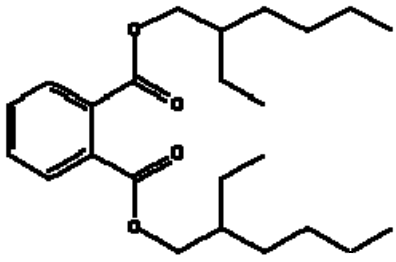
Bisphenol A



Butylbenzylphthalate (BBP)



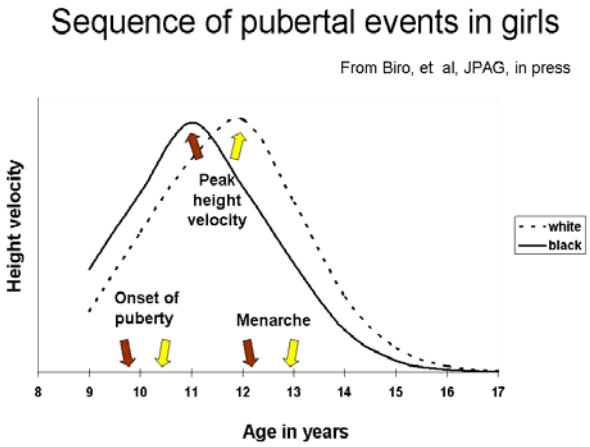
Genistein

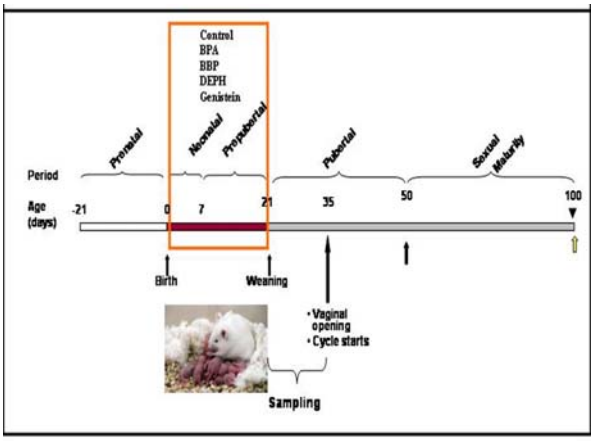


Di-2-ethylhexyl phthalate (DEHP)

In the human studies, we will target girls going through puberty who have elevated levels of one of the environmental chemicals selected, as determined by urine concentrations, but normal levels of other chemicals. Puberty consists of a series of changes in the hypothalamic-pituitary-

gonadal axis, as well as an increase in height velocity, changes in body composition, and attainment of fertility. What is unrecognized often is that these changes precede the development of secondary sexual characteristics, especially in girls. While the major factor that modulates variability in onset of puberty is genetics, some of the genetic influence may interact with environmental factors, including endocrine-disrupting chemicals. It is our intent to link puberty, biomarkers of exposure and biomarkers of susceptibility.





For the animal studies, we will treat rats sub-chronically with the same endocrine disrupting chemicals. In both humans and rats, we will identify genomic and proteomic biomarkers and chemical levels as a means of comparing patterns of response to environmental chemicals across species. The exposure period will be (pre)pubertal, using biological fluids from girls being evaluated for change in onset of puberty because of exposure to these chemicals. These samples are being collected at time of puberty as defined by breast and pubic hair development in girls and vaginal opening in rats. Genomic and proteomic signatures will be obtained *via* the use of customized low density gene microarrays and mass spectrometry (MS-TOF-TOF), respectively. Novel Bayesian statistical models and corresponding computational procedures will be used for identification of genomic and proteomic patterns informative about environmental exposures. (1U01ES016003-01)