WASHINGTON STATE UNIVERSITY

School of Molecular Biosciences
Biochemistry, Biophysics, Cell Biology, Genetics, Microbiology

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To the members of the DART IC:

I understand that you are considering whether to list bisphenol A (BPA) on California's Prop 65 list. I am writing to urge you to take this action. Studies from an increasing number of academic laboratories, including my own, have demonstrated that, in rodents, very low doses of the hormone-like chemical BPA can exert very powerful effects on the developing fetus and the neonate. These effects alter the reproductive ability of both males and females, affect the brain and behavior, lead to an increased risk of breast and prostate cancer in the adult animal, and cause metabolic changes that can lead to diseases like diabetes and heart disease.

My laboratory entered into BPA research in an unexpected way. An "accident" in our mouse facility led to leaching of the plasticizer bisphenol A (BPA) from caging material and water bottles, causing a sudden change in the data of several ongoing studies. Because the onset of leaching was abrupt - the result of inadvertent damaging of caging materials through the use of the wrong detergent – we were quickly able to detect changes in the results of individual experiments and determine the cause. Our studies involved analyses of periovulatory eggs, and the sudden exposure of our animals to the estrogenic chemical BPA caused a spike in meiotic disturbances in eggs from control females. Indeed, we observed changes in two separate sets of studies: an increase in chromosome alignment defects in cells undergoing the first meiotic division (which normally occurs just prior to ovulation), and an increased level of chromosomally abnormal eggs at the metaphase II stage (the stage at which an egg is ovulated). The changes in the data sets for both studies suggested that BPA exposure had the potential to disrupt the final stages of egg development.

Subsequently, four studies by others have examined various aspects of this same problem, with somewhat different results. The variability among the studies has been used by industry in an attempt to discredit our original findings by claiming that our results are not reproducible. The reasons for the variability in these studies and in other studies of this chemical are numerous and have been reviewed recently by us and by others. In our case, the claim is weak at best: All studies have a commonality, and that is the finding that BPA causes meiotic disturbances. There is, however, a point of contention, and that is whether or not these disturbances result in the production of chromosomally abnormal eggs. One of the studies by Eichenlaub-Ritter and colleagues found no link between BPA and aneuploidy, but did find an equally deleterious BPA effect; i.e., they postulated that oocytes exhibiting gross disturbances in chromosome behavior are prevented from completing the cell division. This difference, although biologically important, does nothing to diminish the significance of the effect of BPA on egg development. Neither an arrested egg nor an aneuploid egg are compatible with the production of a normal offspring, so the finer details of the BPA defect(s) are irrelevant to the larger discussion of the risk of BPA exposure. Thus, to dismiss the meiotic data because there is not complete accord is akin to throwing the baby out with the bathwater: the weight of evidence strongly suggests that BPA disrupts female meiosis.

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Although I believe the evidence for effects of BPA on the final stages of egg development is compelling, these results pale in light of our more recent studies. The earliest stages of egg development take place in the fetal ovary, and studies in humans have demonstrated that events that occur during this period set the stage for errors in the adult ovary that give rise to chromosomally abnormal eggs. We tested the effect of BPA exposure on the fetal stages of egg development by exposing pregnant mothers to low doses of BPA for several days and then analyzing the eggs developing in the ovaries of their female fetuses. The results were stunning: BPA caused major disturbances in the fetal ovary and, if exposed females were allowed to be born and mature, we found that 40% of the eggs they ovulated and the embryos they produced were chromosomally abnormal. This is a grandmaternal effect: By exposing mother, we are affecting the likelihood that her grandchildren will be chromosomally abnormal. The fact that a brief exposure during fetal development can dramatically impact the reproductive ability of the female has very serious implications for humans but, importantly, it would take us two generations to detect an effect like this in humans.

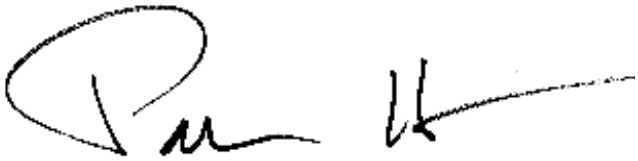
Over 200 papers from academic laboratories like mine have reported adverse effects as a result of "low dose" (i.e., doses within the range of human exposure) bisphenol A exposure. How – if these findings are true – can industry claim that this chemical is perfectly safe? In addition to trying to discredit the work of scientists like me, the American Chemistry Council and its chief spokesperson, Mr. Hentges claim that a few studies conducted by industry are more meaningful than all of the studies conducted by academic scientists. They make this claim because their studies use a very expensive standard testing protocol that is conducted under federally approved strict quality control guidelines called Good Laboratory Practice. This enables regulators to document the data in a court of law, but it is not any assurance of the *quality* of the science. Indeed, this standard study design has serious limitations, and is not suitable for studies of chemicals like BPA that have hormone like action. Although the 1996 Food Quality Protection Act passed by Congress mandated the development of new testing procedures, unfortunately, new and better standardized tests are not yet available. Importantly, the industry studies Mr. Hentges uses in his argument are deeply flawed, and concerns about the use of these studies by regulatory agencies are sufficiently serious that a number of scientists (myself included) felt compelled to write a commentary detailing the flaws and limitations for a leading journal in the field (see attached manuscript by Myers et al).

What should you believe - the results of studies conducted by an industry that makes billions of dollars from this chemical or the results of studies conducted by some of the countries best academic scientists using innovative new techniques? I don't think you should be forced to choose. I think you should consider all of the evidence. If you do, you will find that, as of August 2008, there were 218 studies of low dose effects of BPA; 189 reported significant adverse effects and 29 reported no evidence of adverse effects. Those of us who have been in this field for over a decade don't like those figures and we are very concerned.

In my opinion, the evidence against this chemical is strong and very damming. Academic scientists don't have the financial backing or the professional spokesmen that industry has, so our side of the story tends to be under-represented. However, a growing number of us have decided that we need to speak out about the flawed science that is being used to argue for the safety of this chemical. We banded together in a consensus statement two years ago (I have attached a copy of this document for you) and, more recently, we wrote a commentary detailing why the industry studies like those cited by Mr. Hentges as evidence of the safety of this chemical are deeply flawed (also attached).

If you have any further questions, I would be happy to talk to you by phone, email, or in person.

Yours sincerely,



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