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## Top US EPA scientist rejects Consumer Reports' BPA claim

Trevor Butterworth, November 10, 2009

Magazine's criticism of latest EPA study showing no adverse effects from BPA recycles "ad-hominem attack" repeatedly shown to be "without scientific merit," says EPA's Senior Reproductive Toxicologist.

Several days before Consumer Reports issued its dire warning about the presence of the chemical Bisphenol A (BPA) in canned foods, a major study by the Environmental Protection Agency (EPA), published in one of the leading peer-reviewed toxicology journals, *Toxicological Sciences*, concluded that exposure to BPA was not associated with many of the adverse effects the magazine alleged.

In the study, "In Utero and Lactational Exposure to Bisphenol A, in contrast to Ethinyl Estradiol, Does not Alter Sexually Dimorphic Behavior, Puberty, Fertility and Anatomy of Female LE Rats" (Ryan et al) researchers fed one group of pregnant rats a range of doses of BPA and another group a range of doses of the synthetic estrogen used in birth control pills ethinyl estradiol. The LE Rats demonstrated significant sensitivity to estradiol, and the researchers report reduced body weights, genital malformations and defeminization in pups whose mothers were gavaged (fed by tube) with the hormone. The pregnant rats gavaged with BPA showed no effects. The researchers also looked at behaviors controlled by estrogens – a topic of "some concern" for the National Toxicology Program (NTP) based on several papers with limited data. Again, the researchers found that estradiol produced clear effects but BPA did not.

Consumer Reports went to press too late to address this challenge to their argument, but on the magazine's [blog](#), Urvashi Rangan, Ph.D, disputed the EPA study findings.

*"It is not surprising that the authors did not find effects from BPA because this study used a specific type of rat (Long-Evans) that has been previously shown to be insensitive or unresponsive to low-dose exposures to BPA and even typical birth-control dosages of synthetic estrogen, which was used as a control in the experiment. The insensitivity to both was confirmed again in this study. In other, more estrogenic-sensitive lab animals, BPA has been shown to cause adverse effects at BPA dose levels used in this study."*

STATS asked one of the EPA authors, Dr. Earl Gray, about Dr. Rangan's claim. Gray is the EPA's Senior Reproductive Toxicologist, leading the agency's team that investigates endocrine disruption at critical development periods. He has Fifteen USEPA Scientific and Technological Achievement Awards, and he has received two gold medals and seven bronze medals for USEPA Service. In the past six years, he has authored or co-authored over 50 papers for peer-reviewed scientific publications.

The "insensitive rat" argument has been used for almost a decade to try to dismiss several well done rat studies that obtained negative results," Dr. Gray said via email. "It echoes the comments made about the 2002 rat study by Tyl et al."

"Several expert panels have addressed and dismissed this ad hominem attack as without scientific merit," said Gray.

“It demonstrates a lack of understanding about the basic biology of the cellular and molecular basis for tissue-specific responses in different strains of rats published in the last several years in journals like *Endocrinology*.... It also demonstrates a lack a familiarity with the literature on the effects of estrogens in the Long Evans rat, which has been widely used for decades to study estrogen action, specifically during the period of sexual differentiation.”

He added that,

“The statement that our rat strain is less sensitive to EE2 than humans also is not supported by the data. One must note that our rats are never directly exposed to BPA or EE2. Exposure is indirect, being transplacental or in the milk, whereas the human data we are referring to is direct exposure.

As for the Consumer Reports’ statement that the “‘type of rat (Long-Evans) that has been previously shown to be insensitive or unresponsive to low-dose exposures to BPA.....’ There are no data to support this speculation,” he said. “The LE rat has been used in only a handful of studies with BPA and only four of those studied female rats and of the four, only two used the oral route of exposure and these two studies only used high doses of BPA (100 and 200 mg/kg/d) after weaning. The oral studies did not include in utero exposure. Hence, this is an unfounded criticism.”

Dr. Gray also noted that they “explained in the discussion of our paper (Ryan et al. 2009) why the LE rat is an excellent model for the study of the effects of environmental estrogens because the sensitivity of this strain of rat, and others, is very similar to the sensitivity of humans to ethinyl estradiol.”

The choice of the Long Evans Hooded rat was significant, since some activists have previously claimed the findings of a previous multigenerational study using the Sprague Dawley rat (Tyl et al, 2002) were invalid due to the breed being insensitive

### **The National Toxicology Program on the sensitivity of rat strain**

CERHR [BPA Expert Panel](#), Section 4.4, Summary of Reproductive Toxicity Data:

The hypothesis has been advanced that the Charles River SD rat is insensitive to estrogens and other EDCs and therefore it should not be used for developmental EDC studies and the studies of the effects of BPA that used this strain should be discounted. In order to address this important issue Expert Panel members reviewed the literature on estrogen-sensitivity among rat strains and the following is a summary of our findings.

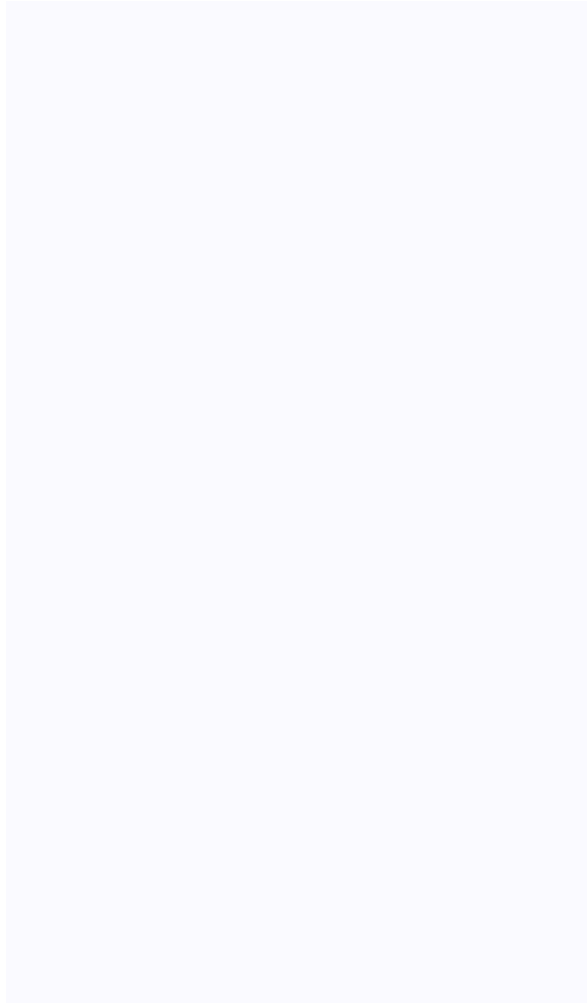
Different strains of rats show clear, robust reproducible differences in responses to potent estrogens and antiandrogens. Several traits have been shown to be estrogen sensitive in rats including prolactin regulation in the pituitary, thymic involution, uterine pyometra, and liver carcinogenesis to name a few. It is evident that the SD rat and other rat strains are less sensitive to the effects of estrogens than the F344 rat. However, for some traits, the reverse is true. In addition, while the SD was less sensitive than the F344 to estrogen, the reverse was true for sensitivity to tamoxifen.

The sensitivity to estrogens has been mapped to specific chromosomes for several traits. In no case has it been demonstrated that the SD strain is completely insensitive to any known estrogen. It is evident that different traits map to different chromosomes and the degree of estrogen sensitivity varies from tissue to tissue, likely depending upon the tissue-specific gene regulated by ER on the chromosome. Therefore, one cannot conclude that the SD is insensitive to estrogens and the results of BPA studies with BPA should be ignored. In fact, there are several papers reporting low dose effects that used the SD rat.

A comparison of the uterotrophic data from the OECD study with EE, BPA and other estrogens does not indicate that the SD rat is less sensitive to any estrogen versus the Wistar. In this study, oral EE at 1 microgram/kg/d for 3 days stimulated uterine weight whereas 0.3 micrograms/kg/d was uterotrophic when administered sc. In addition, in the pubertal female rat assay, EE, the antiestrogen tamoxifen and the estrogenic pesticide methoxychlor produced equivalent responses in the Long Evans and SD female rats. While some have hypothesized that the CrI: CD (SD) rat is more insensitive to estrogens than SD rats from other suppliers, there are no data supporting this assertion.”

to estrogens. As Newsweek [put](#) it in claiming that the activists were correct,

“...[R]esearch in 2002 used a strain of rat that is extremely insensitive to estrogen; it doesn't even show hormonal effects if it's given 100 times the dose of estrogen in human birth-control pills. Since BPA acts like an estrogen, finding no effect in this insensitive rat is about as illuminating as not finding an effect of rain on a waterproof watch. That doesn't tell you that water can't harm machinery.”



Gray also noted that the arguments against the Sprague Dawley rat are not supported by research either.

“[A] study conducted at the National Center for Toxicological Research for the NTP (Latendresse et al. 2009) administered EE2 in a dietary multigenerational study at 2, 10 or 50 ppb in diet (estimated to be 0.2, 1.1 or 5.8  $\mu\text{g}/\text{kg}/\text{d}$ ) to SD rats. These authors reported that EE2 reduced body weight of the females at 1.1 and 5.8  $\mu\text{g}/\text{kg}/\text{d}$ , altered the age at VO, induced abnormal estrous cycles at 5.8  $\mu\text{g}/\text{kg}/\text{d}$  and induced non-neoplastic uterine lesions at all doses. Thus they see adverse effects with chronic direct exposure to the SD rat at dosage levels like those used in humans for pharmaceutical purposes. A new study from another federal government laboratory also demonstrated the sensitivity of the SD rat was also very similar to humans.”