our experimentation could eventually be used to discredit our findings, should they happen not to agree with the original observations.

It seems important that all experiments in the rapidly expanding area of endocrine disruption toxicology should be carefully designed and fully reported. The use of concurrent positive and negative control groups also seems to be prudent. These needs are independent of who conducts or sponsors studies. Good science is good science. Finally, it should be noted that the only formal retraction of endocrine disruption data currently encountered derived from an academic laboratory (*15*), a salutary counterbalance to the assertions that stimulated this letter (*1–3*).

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Response

In a paper we published last year (*1*), we described biological effects *in vivo* on the rodent prostate caused by fetal exposure to very low doses of the environmental estrogen bisphenol A; this low-dose effect was predicted by a new *in vitro* assay. For the *in vivo* end point of prostate enlargement, the effect produced by bisphenol A mimicked the effect of fetal exposure to low doses of the natural and synthetic estrogens estradiol and DES, which were reported in another paper (*2*). Fetuses were exposed to bisphenol A by feeding pregnant female mice at average maternal doses of 2 and 20 µg/kg maternal body weight per day (2 and 20 ppb); these exposure levels produced enlarged prostates measured in subsequent adulthood. Our conclusion was that these doses of bisphenol A, up to 25,000 times lower than the previously reported NOAEL (no observed adverse effect level) for bisphenol A (*3*), were near and within reported ranges of current human exposures from different sources of this chemical (*4,5*). Three subsequent reports by two other groups have confirmed our finding of high estrogenic bioactivity of bisphenol A *in vivo* using end points (pituitary and mammary gland responses) that were different from ours (*6–8*).

We find perplexing the statement of Ashby and Odum that "many new findings in this area are either inadequately described or are based on inadequate test protocols. This makes it difficult to conduct faithful repeat experiments." The information that went into our experimental design is based on more than 50 years of combined experience in hormone action and control of development. It is impossible to put all of this information in any one paper, and experimental details that have been published previously are typically not repeated [for example, see (*9,10*)]. For these reasons, when we are interested in replicating an experiment, we contact the original authors, and other scientists have often contacted us for the same reason. For example, Ashby has contacted us on numerous occasions concerning experimental procedures for the replication of our studies. In addition, we recently ran a training session for laboratory personnel from a contract laboratory hired by the Society of the Plastics Industry to replicate our study with bisphenol A. Given this degree of cooperation with Ashby and others associated with the chemical industry, which is also true for Richard Sharpe (*11*), we are puzzled as to why Ashby and Odum would make the above statement. Considering the many questions they raise above in understanding the procedures of Colerangle and Roy (*8*), we would hope that they would also have contacted the original authors in that study.

Ashby and Odum also raised two specific questions about our studies (*1,2*). The first question concerned examination of prostate weight at 8 months of age in one study with prenatal exposure to estradiol and DES, while bisphenol A-exposed animals were examined at 6 months old of age. We had conducted a preliminary study comparing prostate weight in control CF-1 male mice (five to nine males/group) at 6, 7, 8, 9.5, and 12.5 months of age, which resulted in the following mean (± standard error) prostate weights (in milligrams): 42.1 ± 2.5, 40.8 ± 2.7, 45.1 ± 3.8, 41.1 ± 2.8, and 61.3 ± 2.8, respectively. These unpublished findings showed that between 9 and 12 months of age, male CF-1 mice experienced a significant increase in prostate weight, but between 6 and 9 months of age, there was no significant difference in prostate weight. We had initially waited until males were 8 months old to examine effects of prenatal treatment with estradiol and DES on the prostate due to concern that effects might only be seen in middle age (*12*). However, we have sought to reduce the age at organ collection in these studies to reduce costs. Relative to control males, an increase in prostate weight was seen at 6 months of age in the bisphenol A study and, more recently, was also found in 50-day-old CF-1 male mice exposed prenatally to low doses of ethinyl estradiol (*13*).

The second technical question concerned the combination of vehicle control and unhandled control animals into a single control group in our studies. In all of our experiments we conduct an initial analysis just with these two control groups. In every study that we have conducted, this initial analysis has revealed no statistical difference between the two groups (the F value was 0.7 and $p>0.4$ for this comparison in the bisphenol A study on prostate weight); these animals were then combined into one control group for comparison to chemical treatment groups. Ashby and Odum state, "that represents bad statistical practice." However, an initial comparison of multiple control groups is a common and appropriate procedure, although from some perspectives, there would be a decided advantage in not taking this approach. Specifically, the F ratio in analysis of variance is calculated as the product of variation between groups divided by variation within groups. The greater the number of groups with the same mean that are placed into an analysis of variance, the greater the reduction in the F ratio, and therefore the greater the probability of failing to find statistical significance. The procedure recommended by Ashby and Odum would thus increase the likelihood of falsely concluding that the test chemical had no effect.

The initial point made by Ashby and Odum involves the discovery of adverse effects for chemicals by academic laboratories and that the chemical industry is left to confirm unreplicated findings. It seems inappropriate to com-

plain that new results are published from unreplicated experiments when, to be considered a valid replication, it requires that the experiment must be conducted by different scientists who are informed of new knowledge from the initial publication. However, it is interesting that Ashby and Odum acknowledge that it is from academia that such new findings emanate. In 1992, a consensus statement was published by a diverse group of scientists who attended the first meeting devoted to the issue of endocrine disruption. There was consensus that "the effects are most often manifested in offspring, not in the exposed parent, and although critical exposure occurs during embryonic development, obvious manifestations may not occur until maturity" and that there is a "lack of multi-generational exposure studies that simulate ambient concentrations" of potential endocrine disruptors (*14*). Despite this consensus statement in 1992, we know of no prior efforts by industry to address these concerns about effects of endocrine disruptors raised at this meeting and in many subsequent publications. It appears that critical industry research on endocrine disruptors may not have been conducted because of the fear of finding new adverse effects. A related problem is that the credibility of industry-funded research will be an issue as long as the research can be terminated if it appears that new adverse effects will result in a loss of profitability. In contrast, in academic research the rapid dissemination of information is driven by the priority that is given to first publication of new experimental findings.

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