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Attn: TSCA 8(e) Coordinator

TSCA 8(e) Substantial Risk
Bisphenol-A
CAS No. 80-05-7

The enclosed communication titled *Exposure of adult female rats to environmental oestrogens during gestation and lactation results in reduced testis size and sperm production in the male off-spring in adult life* by R.M. Sharpe, J. Fisher, M. Millar, S. Jobling and J.S. Sumpter is submitted to the U.S. Environmental Protection Agency (EPA) pursuant to Section 8(e) of the Toxic Substances Control Act (TSCA) by;

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This abstract is from a (yet) unpublished presentation given at a European technical conference.

Please do not hesitate to contact me if you have any questions, (413) 448-4853.



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Stephen F. Austin

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Chemical Regulatory Programs

CS FT 9-9 AM 8:56

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Exposure of adult female rats to environmental oestrogens during gestation and lactation results in reduced testis size and sperm production in the male offspring in adult life

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Introduction

There is growing evidence that disorders of male reproductive development may be increasing in some countries, in association with a decline in sperm counts. It has been hypothesised (1) that these could have a common biological cause, perhaps resulting from increased exposure of the fetus/neonate to exogenous oestrogens.

To establish whether or not this is a realistic possibility, we have examined whether exposure of the fetal/neonatal rat to three recently identified 'environmental oestrogens' was able to adversely affect testis size and daily sperm production (DSP) in adulthood.

Materials & Methods

Adult female rats were exposed to one of 3 environmental oestrogens: octylphenol (OP), butyl benzyl phthalate (BBP) or bisphenol-A, which were added to the drinking water at a concentration of 1 mg/L. Negative controls received vehicle and positive controls had 0.1 mg/L diethylstilboestrol (DES) added to drinking water. Exposure lasted for 8-9 weeks (2 weeks prior to mating, during gestation and up until weaning on day 22). Based on water consumption, intake of the chemicals ranged from 100-350 µg/kg/day in the postnatal period. After weaning, male offspring remained untreated until autopsy at 90-95 days of age.

Results

Male offspring of mothers that had been exposed to OP or BBP had significantly reduced (5-13%; $p < 0.001$) final testis sizes in each of three separate studies of 5 or more litters. The consistency of this effect is most evident by comparing the mean testis weight of individual litters for treated and control animals (Figures 1 and 2), as this demonstrates that, against the background of the natural variation in testis size between litters, there is a relatively constant reduction in size induced by chemical exposure; comparable changes were found for relative testis size (2). A significant reduction in testis size was also induced by exposure to DES (not shown), though this effect was more variable and was complicated by significant adverse effects on litter size, bodyweight etc (2). Measurement of DSP (2) revealed a parallel reduction to that in testis size for the various treatment groups (Figure 3). So far, the effects of Bisphenol-A have not been studied in such detail, but preliminary results indicate a significant reduction ($p < 0.001$ in adult testicular size (controls: 2003 ± 178 mg, $N = 25$ Bisphenol-A: 1840 ± 140 mg, $N = 37$), whilst DSP has yet to be measured. In other studies in which exposure of the male offspring to OP or BBP was continued after weaning, no additional decrease in testis size was evident (not shown).

Discussion

These data show that exposure of male rats to environmental oestrogens via the placenta/milk during the period when Sertoli cells are proliferating in the testis (day 15 of gestation to postnatal day 15) (see Ref. 2), results in significantly smaller testes and reduced DSP in adulthood. Whilst this is unlikely to affect fertility, these findings raise the possibility of whether similar effects might occur in man. This is a difficult question to address, but detailed assessment of the level of exposure of man to the present, and other identified, environmental oestrogens may help to indicate whether or not such chemicals pose a significant risk to the developing testis of the human male.

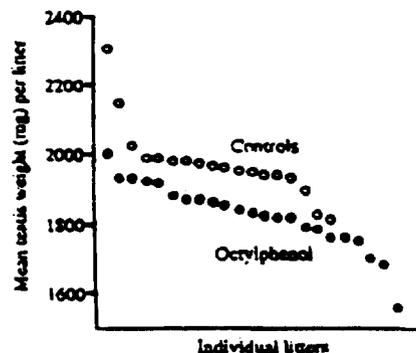


Figure 1. Effect of exposure to octylphenol (1 mg/L) during gestation and lactation on mean testis weight per litter in the male offspring in adulthood.

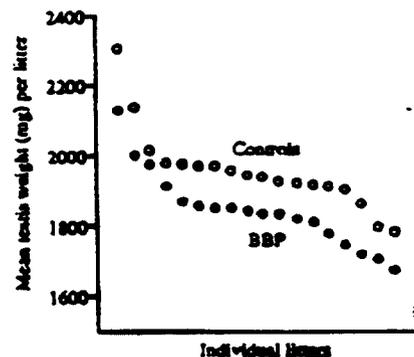


Figure 2. Effect of exposure to BBP (1 mg/L) during gestation and lactation on mean testis weights per litter in the male offspring in adulthood.

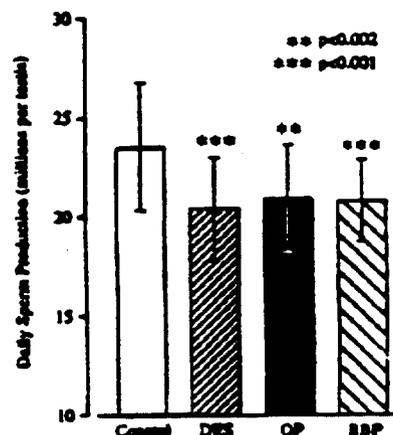


Figure 3. Effect of gestational/neonatal exposure to oestrogenic chemicals on daily sperm production (DSP) in adult life (Means \pm SD, $n = 19-40$ per treatment group).

References

1. Sharpe RM & Skolkebeck NE (1993) *Lancet* 1, 1392-1395.
2. Sharpe RM, Fisher J, Miller M, Jobling S and Sumpter JS (1995) *Environ Health Perspect* (In Press).