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Newbold, RR, WR Jefferson, and EP Banks. 2007.

Long-term Adverse Effects of Neonatal Exposure to Bisphenol A on the Murine Female Reproductive Tract. *Reproductive Toxicology* 24:253-258.

CONTEXT

Bisphenol A was first synthesized in 1891 and subsequently, in the 1930s, found to be estrogenic. Assays of the day indicated it was much weaker than another synthetic estrogen, diethylstilbestrol (DES), so it was not deemed useful for medical purposes. More than a decade later, polymer chemists discovered BPA molecules could be put together in molecular chains to form polycarbonate plastic.

It has since become ubiquitous, used in a wide array of consumer products such as in the clear rigid plastic above.

Additionally, BPA is used to form epoxy resins that line the majority of food cans sold in American supermarkets. It also lines soda cans, for example, holding products like Coca-Cola. BPA-based resins are also used to coat teeth to prevent cavities.

This widespread use has led to the reality that almost all people in developed countries, including the US, have measureable levels of biologically-active BPA in their tissues. Median levels in a series of studies are typically 1 - 2 nanograms per milliliter (ppb). In classic toxicology, these levels would not have stimulated concern, but the last ten years of research on endocrine disruption, especially BPA, have demonstrated numerous adverse effects of BPA at those levels in animal experiments.

Before this study by Newbold et al., none of the research has examined impacts of developmental exposure to BPA on reproductive tract effects in middle age, despite numerous studies in people and animals demonstrating strong effects of DES on reproductive tracts in adult women. This gap is especially troubling because of the unexplained commonness in women of uterine abnormalities like fibroids. Up to 20% of white women in the US and 50% of black women suffer from fibroids. They are an important contributor to infertility and the most common medical diagnosis leading to hysterectomy.

A new study with mice is the first to link low level neonatal exposure to bisphenol A to uterine diseases the women develop as they age, including fibroids, adenomyosis and cystic ovaries.

Some of the adverse conditions induced by BPA in mice have been previously described in daughters of mothers who took the drug diethylstilbestrol (DES), a synthetic estrogen which is structurally and functionally similar to bisphenol A. Extensive research on DES has shown that animal studies can be useful in predicting effects in people.

These new results add to a growing body of research showing that exposure to environmentally-relevant levels of BPA cause long-term adverse effects if exposure occurs during critical periods of development.

What did they do? Newbold et al. exposed neonatal mice to bisphenol A via subcutaneous injection, one per day, from days 1 through 5. They used three doses, 10, 100 or 1000 $\mu\text{g}/\text{kg}/\text{day}$ (parts per billion), dissolving the BPA in corn oil. Control animals received corn oil alone. At the age of 18 months, they dissected the animals to examine their ovaries and reproductive tract.

What did they find? Ovarian and reproductive tract abnormalities were more common in treated animals than controls.



A uterine fibroid removed from a woman Up to 20% of US white women and 50% of US black women experience fibroids. Hysterectomy is a common medical treatment.

respectively).

Cystic endometrial hyperplasia was more frequent in all treatment groups compared to controls, but only statistically significantly more frequent in the BPA-100 group (6% in controls vs. 45% in BPA-100; $p < 0.01$). This is a typical response to excessive estrogen stimulation. People with this condition are at increased risk to cancer.

Uterine leiomyomas (fibroids) were also more common in BPA treated animals. None were found in controls (18) whereas 1 out of 20 animals in the BPA-10 group developed them, 2 out of 20 in the BPA-100 and 1 out of 16 in the BPA-1000 group. One of the animals in the BPA-100 group with fibroids had multiple lesions.

Stromyl polyps were seen in all groups, with the highest number (5 out of 20) in the BPA-100 group.

Another defect seen in BPA-treated animals but not in controls were enlarged mesonephric duct remains.

What does it mean? This is the first study of BPA to report abnormalities in the reproductive tract of middle-aged mice following neonatal exposure. The two lower doses used are low enough to be environmentally-relevant. The results are not surprising, given that similar effects have been in DES-exposed mice and that DES is structurally and functionally similar to BPA. They are important because decades of research with DES has shown that effects found in mice are highly predictive of effects found in people. They are also important because similar abnormalities are common in middle-aged women and little is known about the causes of most cases. They are important contributors to human infertility and disease.

While low and high dose treatments did not differ from controls in the number of cystic ovaries, animals receiving 100 $\mu\text{g}/\text{kg}/\text{day}$ had almost twice as many (39% in controls vs 70% in treated; $p < 0.05$).

Para-ovarian cysts were not observed in any controls but were seen in all groups of the treated animals (4% , 10% and 6% in animals in the 10, 100 and 1000 treatment groups, respectively).

Progressive proliferative lesion did not occur in controls but was seen in all groups exposed to BPA (13%, 15% and 6% in BPA-10, BPA-100 and BPA-1000,

One recurrent pattern in the results presented by Newbold et al. was that in several cases, the intermediate dose of 100 ppb produced larger effects than either the lower or the higher dose. The sample sizes in the experiment were small, limiting the strength of that observation, but it resembles non-monotonic dose-response patterns seen in other experiments with endocrine disrupting compounds like BPA.

Resources:

Flake, GP, J Andersen and D Dixon. 2003. Etiology and pathogenesis of uterine leiomyomas: A review. *Environmental Health Perspectives* 111: 1037-1054.

Newbold R. 2004. Lessons Learned from Perinatal Exposure to Diethylstilbestrol (DES). *Toxicology and Applied Pharmacology* 199: 142-150.

Wikipedia. Diethylstilbestrol

Wikipedia. Fibroids.