Bisphenol A bioaccumulates in the serum of pregnant mice

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Introduction. Bisphenol A (BPA) is a xenoestrogen present in the environment that induces increases in uterine wet weight and stimulates prolactin release in rodents, and stimulates proliferation of estrogen-responsive MCF-7 human breast cancer cells. Fetal exposure to BPA at lower doses, concentrations below detection limits of standard analytical methods, can enlarge the prostate in male rodents and accelerate puberty in female mice. BPA is widely used in the manufacture of polycarbonates and epoxy resins, and is present in many consumer products including the inner lining of food cans and dental composites and sealants; since BPA can and does leach from these sources, human exposures may be significant. We report here the bioaccumulation of BPA in serum of pregnant female mice, assessed by using HPLC separation of products in serum after feeding tritium-labelled BPA.

Methods. In Experiment 1, pregnant mice were fed BPA in oil at 20 ug/kg body weight, either once or multiple times (7-8 daily doses), ending on day 18 of gestation. Maternal blood was collected at 1, 3, 6 or 24 hours after the final dose. Experiment 2 examined effects of different doses of BPA (2 ug/kg, 20 ug/kg or 100 mg/kg), as well as differing numbers of doses (1, 4 or 8 daily doses ending on day 17 of gestation), to study bioaccumulation. Radiolabelled BPA (2, 6 or 20 uCi /dose) was used to permit detection of lower concentrations than those detectable by UV absorption. Because the BPA levels in serum were low and the identity of the peak observed by HPLC could not be confirmed using GC-mass spectrometry, we instead bioassayed HPLC fractions for estrogenic activity using MCF-7 breast cancer cell proliferation, and confirmed that the labelled peak tentatively identified as BPA was in fact estrogenic.

Results. Analysis of maternal serum indicated that BPA was cleared rapidly from the blood over the first 3 hours, but the concentration then appeared to stabilize at a level that was maintained to 24 hours after exposure. This stable concentration was influenced by the number of doses given. Specifically, 7-8 doses resulted in maintained blood BPA levels that were around 5 times higher than those in animals given a single dose, up to nearly 0.5 ng/ml (2.2 nM). The effect of BPA dose on serum BPA levels was directly proportional from 2 ug/kg to 100 mg/kg body weight, with higher doses resulting in higher serum BPA levels at 24 hours after the last treatment. Interestingly, substantial individual variation in BPA levels was observed, with around 10% of the animals showing approximately 10-fold higher BPA levels than their treatment group averages. This individual variation in the bioaccumulated level may identify a sensitive subpopulation that is more susceptible to endocrine disruption by BPA. Together these data indicate that while most BPA may initially be cleared rapidly, the parent compound remains in circulation, and that with repeated exposure, the stable circulating concentration of BPA increases.

Conclusions. While prior work in adults has not reported bioaccumulation of BPA, our data indicate significant bioaccumulation in the blood of pregnant females. BPA in maternal serum may not only represent a risk to the pregnant mother, but also a significant source of exposure to the fetus at a time when the reproductive tract is developing, and when the fetus is most vulnerable to permanent, non-

reversible changes. We hypothesize that the bioaccumulation of BPA in maternal circulation may be responsible for the high sensitivity of the fetus to the estrogenic activity of BPA.

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