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Toxicity Study of Bisphenol A, Nonylphenol, and Genistein in Rats Neonatally Exposed to Low Doses

Kanji Yamasaki*, and Satoko Ishii

Chemicals Evaluation and Research Institute, 1-4-25 Kouraku, Bunkyo-ku, Tokyo 112-0004, Japan

Due to reports that a considerable number of compounds may have endocrine-disrupting activity in humans and animals, the Organization for Economic Co-operation and Development (OECD) revised the original OECD Test Guideline No. 407 assay and introduced in vivo screening tests in 2008 to detect endocrine-mediated effects. These effects are one of the important parameters in assessing the risk assessment of chemicals in the REACH program. Recently, risk assessments of Bisphenol A (BPA) have conducted [1,2], and several countries such as Canada, Denmark and France have adopted a national ban on baby bottles made from polycarbonate plastic [3]. On the other hand, neonatal exposure assay has been reported as an assay for detection of endocrine effects in the early life stages of rats and mice, and the endocrine effects of estrogenic compounds, such as clomiphene, diethylbestrol, ethynylestradiol, 17β-estradiol, tamoxifen, BPA, and some phytoestrogens have been detected by this assay [4-11]. Therefore, this assay is considered to be a useful method of detecting endocrine-mediated effects. However, since few studies have been reported to detect endocrine effects of weakly estrogenic compounds designed, we performed the neonatal exposure assays of the weakly estrogenic compounds, BPA, nonylphenol, and genistein.

Pregnant female rats on 13 days after mating were purchased from Charles River Japan, Inc. (Shiga, Japan), and the pups that were subsequently born were used in this study. All animals were cared for according to the principles outlined in the guide for animal experimentation prepared by the Japanese Association for Laboratory Animal Science. Rats were subcutaneously injected with 0, 0.1, 1 or 10 μg/rat/day of each chemical for 5 days starting on Postnatal Day 1 (PND 1). A positive control group injected with diethylstilbestrol was also established. Animals were killed by exsanguination under ether anesthesia on PND 50. The following were assessed: clinical signs, body weight changes, ano-genital distance, vaginal opening, preputial separation, estrous cycling, organ weight changes, and histological changes.

No abnormities were detected in clinical signs, body weights, ano-genital distance, vaginal opening, preputial separation, estrous cycling, and histological changes. Seminal vesicle weight was significantly lower in all genistein groups, and ventral prostate weight was higher in the 10 μg BPA group. No changes were observed in rats given nonylphenol. On the other hand, various endocrine-mediated effects in each parameter were detected in the diethylstilbestrol groups.

The estrogenic compounds DES, ethynylestradiol, clomiphen, tamoxifen, BPA, and 17β-estradiol, all of which except BPA appear to be strongly estrogenic compounds based on their receptor binding affinities and the results of uterotrophic assays [12-14], were administered to neonatal rats for a short time, and endocrine-mediated effects were detected [4-6,8-11]. Although there are few neonatal exposure data for weakly estrogenic compounds, there is an interesting study in which BPA was given to pregnant mice at doses of 10 and 100 mg/kg on gestational days 10-18 and resulted in no abnormalities in offspring, but in which abnormalities such as vaginal epithelial stratification and abnormal estrous cycles were detected in mice given BPA at dose of 15 and/or 150 μg/mouse for 5 days starting on PND 1 [10]. The investigators suggested that greater ER binding of estrogen occurs in the postnatal female reproductive tracts than in the prenatal reproductive tract and some placental barrier activity of BPA may be caused by the greater binding of estrogenic compounds to ERs in the postnatal period. These suggestions demonstrate that neonatal exposure studies are useful means to detect the endocrine-mediated effects of some estrogenic compounds. We therefore used the neonatal exposure assay to test weakly estrogenic compounds.

The uterotrophic property of BPA, nonylphenol, and genistein was detected in the rat immature uterotrophic assay [15], and abnormal estrous cycles and thyroid dysfunction have been observed in rats given BPA 600 mg/kg in a 28-day repeated toxicity test according to OECD enhanced TG 407 [16]. Thus, some endocrine-mediated changes caused by BPA, nonylphenol and genistein at high dose levels were already known. Vaginal epithelial stratification was observed in mice given 150 μg/kg BPA and abnormal estrous cycles in mice given 15 and 150 μg/mouse BPA for 5 days beginning on PND 1 [10], but no abnormal changes in reproductive function or histological changes in reproductive organs were observed in rats given 300 μg/kg BPA on the same schedule [17]. No abnormalities were also detected in male rats given 8 mg/kg nonylphenol by intraperitoneal injection from PND 1-10 [18]. On the other hand, neonatal exposure to phytoestrogens, such as coumestrol and equol, inhibited uterine gland formation but reproductive organ structure in male rats was not altered by the neonatal exposure of coumestrol [7,19]. Although seminal vesicle weight was lower in all genistein groups, and ventral prostate weight was higher in the 10 μg BPA group, no abnormal histological findings were detected in these groups. The results of the present study demonstrate that no serious changes occurred in the rats given BPA, nonylphenol, or genistein.

To investigate the endocrine-mediated effects of neonatal administration of low doses of weakly estrogenic compounds, BPA, nonylphenol and genistein were subcutaneously injected to male and female rats in doses of 0.1, 1, and 10 μg/rat/day for 5 days starting on PND 1. No significant changes were observed until PND 50 in the rats given each compound.

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***Corresponding author:** Kanji Yamasaki, Chemicals Evaluation and Research Institute, 1-4-25 Kouraku, Bunkyo-ku, Tokyo 112-0004, Japan, Tel: +81-3-5804-6136; Fax: +81-3-5804-6149; E-mail: yamasaki-kanji@ceri.jp

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