Maternal Exposure to Low Doses of Bisphenol A Has No Effects on Development of Female Reproductive Tract and Uterine Carcinogenesis in Donryu Rats

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Abstract. Effects of maternal exposure to low doses of bisphenol A (BPA), including those comparable with human exposure levels, on growth and development of the female reproductive system and uterine carcinogenesis in Donryu rats were investigated. Dams were administered BPA (0, 0.006 and 6 mg/kg/day) daily by gavage from gestation day 2 up to the day before weaning (postnatal day 21 at offspring). The serum levels of BPA were significantly elevated in the dams receiving 6 mg/kg/day, however, BPA levels in the milk of dams, and those in the serum and liver of offspring were similar between control and treated groups. The treatment did not exert any influences on uterine development including weight, gland genesis and estrogen receptor α expression, vaginal opening and gonadotropin secretion in the female offspring up to puberty. After maturation, no effects were evident with regard to estrous cyclicity in female offspring treated with BPA. In addition, the treatment had no effects on age-related morphological changes of the reproductive and endocrine organs and uterine carcinogenesis until 15 months of age. The results demonstrate that maternal exposure to BPA at levels comparable to human exposure did not have any effects on the female reproductive system of offspring in rats. In addition, BPA was also found in the serum, milk and liver of control dams and pups, and low levels of BPA were detected in drinking water and pellet diet. The present study showed that the experimental animals were also exposed to environmental BPA in the animal room.

Key words: Bisphenol A, Low doses, Female reproductive system, Toxicity, Uterine carcinogenesis (J. Reprod. Dev. 50: 349–360, 2004)

Bisphenol A (BPA), volume chemical used in the manufacture of polycarbonate plastics, has been found in canned foods packed in lacquer subjects, containers and composite dental sealants [1]. BPA is reported to be an endocrine disrupting chemical (EDC) with weak estrogenic activity in both in vitro and in vivo systems [2], binding to both estrogen receptor (ER)α and ERβ with low affinity and causing reporter gene transactivation in vitro [3, 4]. Uterotropic effects of BPA at high doses (3 daily oral applications of 400, 600 or 800 mg/kg/day) were reported in immature female rats [5], and significant increases in the luminal epithelial height and the thickness of both stromal and myometrial layers of the uterus were also observed in ovariectomized mice injected 0.8–8 mg/day of BPA for 4 days [6]. A study conducted by the National Toxicology Program (NTP) in the USA demonstrated that maternal exposure to high doses of BPA, at 0.5 or 1.0% in feed (approximately daily intakes of 875 and 1750 mg/kg/day), reduced the number of live pups per litter and litters per pair in
first generation mice [7]. However, pre- and/or postnatal high dose BPA exposure did not have any apparent adverse effects on pubertal development in female rats or reproductive functions in rats and mice [8–10].

On the other hand, perinatal treatment with BPA at much lower doses has been reported to influence growth and male reproductive organ parameters such as weights of the testis, prostate, preputial glands and epididymis, and the efficiency of sperm production in rodents [11–15]. However, other investigators have reported no treatment-related effects of low doses of BPA given to pregnant mice [16–18] and to rats in a three generation reproductive toxicity study [19].

In female rodents, inappropriate perinatal exposure to endogenous and/or exogenous estrogens is known to induce serious and irreversible effects on the reproductive system [20–24]. Perinatal and/or postnatal effects of EDCs on the reproductive organs in rodents are very complex and the underlying mechanisms remain to be fully determined. Recently, some investigators have reported ‘delayed’ influences of perinatal exposure to estrogens or EDCs on the female reproductive system which are manifested after puberty or sexual maturation [25–27]. In fish, the ovo-testis can serve as a good indicator of estrogenic effects of EDCs [28]. For assessment to human health, it is very important to investigate the effects of low doses of EDCs, including BPA, on the reproductive organs at levels comparable to human exposure. Although there is as yet no consensus regarding the endpoint markers for detecting perinatal effects of estrogens or EDCs with estrogenic activity: lowering of gonadotropin levels at prepuberty, anovulation, polycystic ovary, persistent estrus, early vaginal opening, abnormal development of uterus such as inhibition of uterine gland-genesis and abnormal expression of ERα, and increased uterine or vaginal carcinogenicity [10, 20–25, 27, 29, 30]. In particular, induction of uterine cancers by perinatal exposure to estrogens or EDCs with estrogenic activity is the most striking event, since natural occurrence of uterine cancer is generally rare in rats. Our co-workers found that uterine endometrial adenocarcinomas spontaneously developed in aged Donryu rats with a high incidence, and that the tumors showed a number of morphological and biological similarities to humans, such as ovarian hormonal imbalance leading to elevation of the serum estrogen/progesterone ratio [31–33]. Therefore, we selected this rat strain in the present study for the experimental animal.

In the investigations of maternal exposure to EDCs, especially with low dose exposure, it is very important to examine the biotransfer of chemicals from dams to offspring, because the effects of EDCs on the target organs are fundamentally related to serum EDCs level [34]. Although there has been much speculation about the potential adverse effects of low dose exposure to estrogenic EDCs including BPA [15–17], little information is available regarding test compound transfer from dams to offspring via the placenta or milk.

The purpose of the study was to investigate the effects of maternal exposure to low doses of BPA, at levels comparable to human exposure, on the growth and development of the female reproductive tracts, and also uterine carcinogenesis in rats observed from prepuberty up to 15 months of age, using the many endpoint markers reported previously. In addition, we monitored the transfer of BPA to offspring via the placenta and milk.

Materials and Methods

Animals

Forty-six pregnant female Crj:Donryu rats at gestation day (GD) 2, verified by plugs and sperm in the vagina and judged pregnant by the breeder, were purchased from Charles River Japan (Kanagawa, Japan).

Treatment of BPA

Animals were allocated into three groups: 0 mg/kg/day (control group, 12 dams), 0.006 mg/kg/day BPA (Tokyo Kasei Kagaku, Tokyo, Japan)(15 dams) group and 6 mg/kg/day BPA (19 dams). The concentration of 0.006 mg/kg was selected as relevant to provide the 63 ppb that is defined as the average daily intake from canned food in human beings [35]. The 6 mg/kg was selected as appropriate to simulate the maximum dose level (80 ppm) detected in plastic plates for children [35]. BPA was suspended in 0.05% carboxymethylcellulose solution (CMC; Wako Pure Chemicals, Osaka, Japan) for dosing. The dams
were orally administered BPA or the vehicle, 0.05% CMC (2 ml/kg body weight), every morning from GD 2 to the day before weaning (21 days after delivery) by gavage. The treatment period was selected to observe the effects of maternal treatment with BPA for as long as possible.

**Examination of dams**

Body weights of dams were checked once a week during the pregnancy and lactating periods. All dams were observed at least twice a day for morbidity, mortality and treatment-related clinical signs. The day of birth was designated postnatal day (PND) 0. After delivery, dams with offspring were housed in plastic cages containing wooden chips, and litter sizes were adjusted to 8–10 pups/dam at PND 4 or 6. All dams were euthanatized at weaning (PND 21) and the numbers of implantation sites in the uterus were recorded after complete necropsy. The uterus, vagina, ovaries, pituitary, adrenals, liver and kidneys were fixed in 10% neutral buffered formaldehyde solution, routinely processed and examined histopathologically.

**Examination of offspring**

Body weights, sex, external abnormalities and the number of offspring: The number and sex of offspring were checked at PNDs 1. At PNDs 1, 7, 14 and 21, body weights and external abnormalities were examined.

Uterine development: Three to 5 animals from different dams per group were euthanatized at PNDs 10, 14, 21 and 28 and 8 weeks of age to investigate uterine development in female offspring except uterine weights at PND 10 and uterine gland genesis at 8 weeks. After the uteri were weighed, uterine gland-genesis in the uterus was histopathologically quantified as follows. The uterus, vagina, ovaries, pituitary, adrenals, liver and kidneys were fixed in 10% neutral buffered formaldehyde solution, routinely processed and examined histopathologically.

Hormone profiles: Blood from the animals used for examination of uterine development was collected by decapitation and the serum was stored at –80°C until assay. Up to PND 14, pooled serum samples from the animals examined for uterine growth and gland genesis were used. Serum follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels at PNDs 10, 14, 21 or 28 were measured using NIDDK-rat-FSH and -LH radioimmunoassay (RIA) kits (NIAMDD; NIH, Bethesda, MD, USA), and compared among three groups, according to the method reported previously [36,37].

Uterine carcinogenicity study: For initiation of carcinogenesis, female pups (35, 36 or 35 animals in 0, 0.006 or 6 mg/kg group, respectively) at 11 weeks of age were administered a single dose of 20 mg/kg N-ethyl-N’-nitro-N-nitrosoguanidine (ENNG; Nacalai Tesque Inc., Tokyo, Japan) into a uterine horn using a stainless steel catheter via the vagina, as reported previously [38]. The ENNG-treatment is reported to exert no toxic or carcinogenic effect on tissues or organs other than the uteri in rats [38]. At the termination of the experiment, all surviving animals (15 months of age) (24, 30 and 30 animals in 0, 0.006 and 6 mg/kg groups, respectively) underwent histopathological examination. Animals found dead and sacrificed when moribund were also examined similarly. After complete necropsy, the reproductive and representative organs were fixed in 10% neutral buffered formalin, and then routinely processed. Each uterus was cut into about 12 slices in cross-section for hematoxylin and eosin staining. Endometrial proliferative lesions were classified into three degrees of hyperplasia (slight, moderate or severe) and adenocarcinomas, according to our categories described previously [39]. In addition,
adenocarcinomas were subdivided into well, moderately and poorly differentiated types, and also classified as to the degree of invasion: limited to the uterus, invading into the serosa and/or surrounding adnexae, and with distant metastasis, in accordance with the simplified FIGO histopathological grades for human uterine cancers [40].

Histopathological examination: The ovaries, vagina and other representative organs including liver, kidneys, brain and endocrine organs were fixed in 10% neutral buffered formaldehyde solution at PNDs 10, 14 21, 28 and 8 weeks of age for histopathological examination.

**Serum and tissue concentrations of BPA in dams and their offspring**

In dams, BPA concentrations in the serum at weaning (PNDs 21) of their offspring and in milk collected in the stomachs of their pups at PNDs 10 and 14 were analyzed by gas chromatography mass spectrometry (QT-5050; Shimadzu, Kyoto, Japan) using the modified method reported previously [34]. Samples of milk were pooled from each litter for analysis.

In offspring, BPA concentrations in the serum and the liver were sequentially measured at PNDs 10, 14, and 21 in the same manner as their dams.

**Housing conditions including measurement of environmental BPA**

Animals were maintained in an air-conditioned animal room under constant conditions of 24 ± 2°C and 55 ± 10% humidity with a 12 h light/dark cycle (light, 0800–2000 h; dark, 2000–0800 h). All pups were weaned at PND 21 and female offspring in the same treatment group were housed 3 or 4 pups per cage. Commercial pellet diet and drinking water were available ad libitum, and animals drank tap water stored in plastic containers throughout the study. Animal care and use followed the NIH Guide for the Care and Use of Laboratory Animals.

To examine environmental BPA, concentrations of environmental BPA in the animal room, samples of fresh tap water, drinking water stocked in plastic containers used for water supply to the animals and in fresh pellet diet were determined using high performance liquid chromatography (HPLC). For tissue preparation, an internal standard (dimethylbutylidene-bisphenol) was added to tap water and drinking water samples and evaporated to dryness for sample preparation. Pellet diet samples were grained, added to distilled water and 2 N sodium hydroxide and sharked for 1 hr. The samples were centrifuged and the aqueous layer was added to an internal standard and 2 N hydrogen chloride. The mixture was extracted twice with ethyl acetate and the organic solvent layers were evaporated to dryness. Both the residue of water and pellet diet samples were dissolved in 60% acetonitrile solution and subjected to HPLC analysis. HPLC was carried out using a M-600 pump (Waters, USA), MightySil RP-18GP (Kanto Kagaku Co. Ltd, Tokyo, Japan) and a F-1080 fluorescence detector (Hitachi Co., Tokyo, Japan) [41].

**Statistical analysis**

Values for incidences were statistically analyzed using Fisher’s exact probability test. Other data were analyzed using ANOVA, and post hoc comparisons between BPA-treated and control groups were made with the Dunnett’s t-test. P values less than 0.05 were considered to be statistically significant.

**Results**

The body weights were similar in the control and treated groups during the BPA-treatment period (GD2 to PND 21), and no treatment-related clinical signs were observed in dams (data not shown). Table 1 summarizes data for reproductive ability of dams. There were no significant differences among the groups in all parameters: gestation period, the number of implantation sites, the average number of offspring per litter, and the body weights of offspring at birth. No external abnormalities were detected in any offspring. The body weights of female offspring were similar among control and treated groups from puberty up to 15 months of age.

The days of vaginal opening of offspring are shown in Table 1. No significant inter-group differences were found. After vaginal opening, precise 4-day cyclicity was observed in all animals. Table 2 shows uterine weights and uterine gland genesis from PNDs 10 up to 8 weeks of age. At PNDs 14, 21, 28 and 8 weeks of age, uterine weights did not differ among three groups. Sequential changes in the number of uterine glands in the
treated groups at PNDs 10, 14, 21 and 28 were similar to those in the control group. No obvious morphological changes, including expression of ERα and the labeling index for cell proliferation activity in the uterus were observed in either of the BPA-treated groups before puberty (Fig. 1). In all of the 3 groups, persistent estrus, characterized by vaginal smears exhibiting nucleated epithelial and/or cornified cells, began to appear after 5 months of age and then gradually increased with age, so that
all animals were affected by persistent estrus at 11 months of age (Fig. 2). In endocrine tissues and representative organs such as those of the alimentary, urinary, respiratory and nervous systems, treatment-related lesions were not morphologically detected.

The average numbers and SD values of ova at 8 weeks of age were 13.3 ± 1.0, 13.0 ± 2.8 and 12.7 ± 1.2 in control, 0.006 and 6 mg/kg BPA-treated groups, respectively, with no significant differences.

Serum gonadotropin levels for BPA-treated and control rats in the immature period are shown in Fig. 3. During the immature period, serum FSH and LH levels were comparable among the BPA and control groups, the differences at each PND being not significant.

The incidences of uterine preneoplastic and
neoplastic lesions at the termination of the experiment are shown in Table 3. There were no significant differences or treatment-related tendencies among the groups. Sub-classification of adenocarcinomas with regard to their differentiation and invasion status also revealed no inter-group variation. Most of the ovaries in all groups showed atrophy with small cystic atretic follicles and an absence of any corpus luteum (Table 3). Various non-neoplastic and neoplastic lesions including mammary or pituitary tumors were observed of animals in all groups, but again the incidences were not significant among the three groups. In addition, the animals found dead or euthanatized when moribund showed no treatment related changes histopathologically.

Table 3. Proliferative lesions in the uteri and histopathology of the ovary at 15 months of age

<table>
<thead>
<tr>
<th>Dose</th>
<th>0 mg/kg/day</th>
<th>0.006 mg/kg/day</th>
<th>6 mg/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of female offspring examined</td>
<td>24</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td><strong>Uterus:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperplasia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slight</td>
<td>4 (21)(^a)</td>
<td>6 (20)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Moderate</td>
<td>5 (21)</td>
<td>6 (20)</td>
<td>14 (47)</td>
</tr>
<tr>
<td>Severe</td>
<td>3 (13)</td>
<td>5 (17)</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Endometrial adenocarcinoma</td>
<td>8 (33)</td>
<td>10 (33)</td>
<td>6 (20)</td>
</tr>
<tr>
<td>Sub-classification of adenocarcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Differentiation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well-differentiated</td>
<td>8</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Moderately- or poorly-differentiated</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Invasion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited to the uterus</td>
<td>8</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Invading into the serosa</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Ovary:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrophy with cystic follicles and absence of corpus luteum</td>
<td>24</td>
<td>30</td>
<td>29</td>
</tr>
</tbody>
</table>

\(^a\) Values in parentheses indicate percentage of incidence.

Serum and tissue concentrations of BPA are shown in Table 4. BPA was detected in all serum and tissues examined in all groups of the present study. In dams, serum BPA was significantly
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Table 4. BPA concentration (ppb) in the serum, milk and liver of dams and pups

<table>
<thead>
<tr>
<th>Sample</th>
<th>Age of examination</th>
<th>Doses of BPA (ppb)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0 mg/kg</td>
</tr>
<tr>
<td><strong>Dam:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum</td>
<td>PND 21 of offspring</td>
<td>3 ± 0 (5)</td>
</tr>
<tr>
<td>Milk</td>
<td>PND 10 of offspring</td>
<td>28 ± 9 (3)</td>
</tr>
<tr>
<td></td>
<td>PND 14 of offspring</td>
<td>255 ± 78 (4)</td>
</tr>
<tr>
<td><strong>Offspring:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum</td>
<td>PND 10</td>
<td>Females</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males</td>
</tr>
<tr>
<td></td>
<td>PND 14</td>
<td>Females</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males</td>
</tr>
<tr>
<td></td>
<td>PND 21</td>
<td>Females</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males</td>
</tr>
<tr>
<td>Liver</td>
<td>PND 10</td>
<td>Females</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males</td>
</tr>
<tr>
<td></td>
<td>PND 14</td>
<td>Females</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males</td>
</tr>
<tr>
<td></td>
<td>PND 21</td>
<td>Females</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Males</td>
</tr>
</tbody>
</table>

Table 5. Environmental BPA

<table>
<thead>
<tr>
<th>Instruments or diet</th>
<th>Concentration of BPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh tap water</td>
<td>0 ± 0 ng/ml (3)</td>
</tr>
<tr>
<td>Drinking water stored in plastic containers</td>
<td>2.56 ± 2.51 ng/ml (3)</td>
</tr>
<tr>
<td>Pellet diet (on opening)</td>
<td>40.06 ± 2.59 ng/g (3)</td>
</tr>
<tr>
<td>Pellet diet (several days after opening)</td>
<td>39.70 ± 0.56 ng/g (3)</td>
</tr>
</tbody>
</table>

Values are means ± SD. Values in parentheses indicate numbers of samples.

Elevated in the 6 mg/kg group as compared to the controls. BPA levels in the milk, however, did not significantly vary among the BPA-treated and control groups. In the offspring, there were no differences in BPA levels in the serum and liver among BPA-treated and control animals from PND 10 up to PND 21.

The concentrations of environmental BPA in the animal room specimens are shown in Table 5. BPA was not detected in fresh tap water, but was identified in drinking water stored in the plastic containers. BPA was also detected in fresh pellet diet at levels several times higher than in the stocked water.

Discussion

The present study was performed to investigate the effects of maternal exposure to low doses of BPA, at levels comparable with human exposure, on growth and development of the female reproductive system and uterine carcinogenesis in Donryu rats. Unappropriate maternal and/or neonatal exposure to estrogens has been well known to exert irreversible influence directly and indirectly on the reproductive system. The typical influences called ‘androgenization’ are characterized by lowering of the gonadotropin levels in puberty, anovulation, polycystic ovary and persistent estrus immediately after vaginal opening, resulting from direct modulation of the hypothalamic-pituitary-gonadal axis [21, 23]. Androgenized uteri showed abnormal development such as inhibition of uterine glandogenesis or abnormal expression of ERα, and these effects were detectable until maturation [20, 29]. In addition, perinatal exposure to high-doses...
estrogens or EDCs with estrogenic activity induced a ‘delayed’ influence with a different phenotype from that of typical androgenization and is probably caused by delayed modulation of the hypothalamic-pituitary-ovarian control system [25–27]. For instance, first 5 days exposure after birth to 100 mg/kg p-tert-octylphenol, this dose is estrogenic [42] and extremely higher (about \(10^6\)) than waste water, caused a ‘delayed’ influence which was characterized by accelerated appearance of atrophic ovary compared to controls. This was manifested by an early occurring and a long-term continuing persistent estrus status, whereas no abnormalities could be found with regard to growth and development of the reproductive organs and the hypothalamic-pituitary-gonadal control system up to maturation [27]. In the present study, the treatment did not exert any influences on the reproductive ability of the dams and also on the uterine growth and development of BPA-treated offspring with reference to ER\(\alpha\) expression, cell proliferating activity and gland genesis in the uterus, estrous cyclicity, vaginal opening and hormonal secretion up to sexual maturation. These results demonstrate no influence of low doses of BPA on the hypothalamic-pituitary-gonadal control system and the reproductive system up to puberty. After maturation, no disruption of ovarian function reflected by vaginal cytology was also noted, indicating no ‘delayed’ modulation effects on the reproductive system under the present experimental conditions. Vaginal cytology or its morphological feature in the vagina might be useful for assessment of the individual hormone milieu including dysfunction of the hypothalamic-pituitary-ovarian axis, as previously reported [43].

The most striking examples of changes caused by prenatal exposure to EDCs in the reproductive system of humans and rodents are uterine or vaginal cancers [29, 30, 44, 45]. Many studies have also demonstrated the induction of uterine endometrial adenocarcinomas in rats by perinatal treatment with estrogenic compounds [27, 46]. Uterine endometrial adenocarcinoma is one of the most common malignant tumors in women and has increased in number in recent years, although some epidemiological aspects remain unclear [47, 48]. The Donryu strain rat is a high-incidence strain for spontaneous endometrial adenocarcinoma development with aging, and the tumors have morphological and biological similarities to those found in humans [30, 31]. In this strain, earlier occurrence of ovarian atrophy with cystic atretic follicles but without corpus luteum leads to ovarian hormonal imbalance, resulting in prolonged elevation of the serum estrogen/progesterone ratio and then early onset of persistent estrus [33]. Under such characteristics, spontaneous uterine cancer development is ascribed to the age-dependent modulation of the ovarian hormonal control, as similarly evidenced in humans [49]. We also reported that neonatal exposure of Donryu rats to high-dose p-tert octylphenol enhanced uterine carcinogenesis with prolonged persistent estrus status [27]. The present study clearly demonstrated that maternal treatment with low doses BPA did not affect ovarian function manifesting as vaginal cytology throughout the experiment or susceptibility to uterine carcinogenesis. It might be recommended that relatively long-term comprehensive studies of endocrinological and morphological aspects are necessary for determination of perinatal effects of EDCs.

When considering about effects of maternal exposure to low doses of EDCs on the offspring, the subject of most concern is transfer of EDCs from dams to pups through the placenta and/or milk and subsequent modification of toxicokinetics [50], however, the data about transfer of test compounds are quite limited. BPA is known to form its major metabolite, bisphenol A glucuronide in the liver and is excreted very quickly via feces and urine [51–53]. In the present study, serum BPA levels were elevated in the dams given 6 mg/kg BPA, but BPA was not elevated in the milk, serum or liver of offspring. Surprisingly, however, BPA was detected in the serum and tissues of all the animals examined, including the controls. Furthermore, environmental BPA was found in the drinking water and more prominently in the diet. The increase in the serum of dams at 6 mg/kg group might be related to the BPA-treatment; however the influences of biotransfer of 0.006 mg/kg BPA could not be decided in the present study due to the environmental BPA. In the animal room, there were a number of instruments made with BPA such as plastic cages and water containers, and pellet diet and wood chips are packed in plastic wrapping. Therefore, the presence of environmental BPA in the present study is not considered to have been an incidental contamination, and indicates the possibility that
animal studies using rats or mice are always exposed to environmental BPA. While the influence of long-term exposure to environmental BPA on experimental animals remains to be determined, the possibility that major effects on the female reproductive system occur is unlikely, since the present data were similar to those of relevant studies previously reported in rats [10, 54] and our background data [55, 56]. In addition, any abnormalities, which are defined as effects of perinatal exposure to estrogens or EDCs with estrogenic activity on the female reproductive system, or suggested disruption of the hypothalamic-pituitary-gonadal axis were not detected in the present study [10, 20–27, 29].

In conclusion, transplacental and lactational exposure to BPA at levels comparable to human exposure did not exert any adverse influence on the female reproductive system such as uterine growth and development, and uterine carcinogenesis. Maternal exposure to BPA did not result in appreciable transfer to the offspring, although serum BPA levels in dams treated with 6 mg/kg BPA group were significantly elevated. The situation, however, is complicated, because low doses of environmental BPA were detected in the drinking water and diet.

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References


