ビスフェノールAの低用量影響に関する文献の概要一覧 （2012～1997）

| No. | Year | Reference | Species | Stage | Exposure Period | Route | Dose | Endpoints | Effects |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2012 | Batista TM, Alonso-Magdalena P, Vieira E, Amaral ME, Cederroth CR, Nef S, Quesada I, Carneiro EM, Nadal A (2012). Short-term treatment with bisphenol-A leads to metabolic abnormalities in adult male mice. PLoS One. 7, e33814. | OF1 mice | 3 months old［♂］ | for 8 days twice a day | Subcutaneous | 100 μg/kg bw/day | 【obesity】Plasma analysis, glucose, Insulin tolerance test, Insulin signaling assay, Whole-body energy homeostasis | Mice treated with BPA were insulin resistant and had increased glucose-stimulated insulin release. BPA-treated mice had decreased food intake, lower body temperature and locomotor activity compared to control. In skeletal muscle, insulin-stimulated tyrosine phosphorylation of the insulin receptord b subunit was impaired in BPA-treated mice. This impairment was associated with a reduced insulin-stimulated Akt phosphorylation in the Thr308 residue. Both skeletal muscle and liver displayed an upregulation of IRS-1 protein by BPA. The mitogen-activated protein kinase (MAPK) signaling pathway was also impaired in the skeletal muscle from BPA-treated mice. In the liver, BPA effects were of lesser intensity with decreased insulin-stimulated tyrosine phosphorylation of the insulin receptor b subunit. |
| 2 | 2012 | Bauer, S.M., Roy, A., Emo, J., Chapman, T.J., Georas, S.N., and Lawrence, B.P. (2012). The effects of maternal exposure to bisphenol A on allergic lung inflammation into adulthood. Toxicol Sci 130, 82-93. | C57BL/6 mice | Pregnant and lactating dams | GD 6-PND 21 | Oral | 0.5, 5, 50, 500 μg/kg bw/day | 【immune】Mucosal sensitization: PND 16-18, Peritoneal sensitization: PND 13, ［♂♀］ | In the mucosal sensitization model, female offspring that were maternally exposed to 50, 500 μg BPA/kg bw/day displayed enhanced airway lymphocytic and lung inflammation, compared to offspring of control dams. Peritoneally sensitized, female offspring exposed to 0.5, 5, 50 μg BPA/kg bw/day presented dampened lung eosinophilia, compared to vehicle controls. These subtle, yet persistent changes due to developmental exposure to BPA did not lead to significant differences in overall airway responsiveness. |
| 3 | 2012 | Brannick, K.E., Craig, Z.R., Himes, A.D., Peretz, J.R., Wang, W., Flaws, J.A., and Raetzman, L.T. (2012). Prenatal exposure to low doses of bisphenol A increases pituitary proliferation and gonadotroph number in female mice offspring at birth. Biol Reprod 87, 82. | mice on a mixed FVB, C57BL/6 background | Pregnant dams | E 10.5-18.5 | Oral | 0.5, 50 μg/kg bw/day | 【pituitary, gonadotroph】Gonadotroph cell number or parameters of hormone synthesis in the pituitary: PND 1 ［♂♀］ | Pituitaries from female offspring exposed in utero to either dose of BPA had increased proliferation, as assessed by mKi67 mRNA levels and immunohistochemistry. Gonadotroph number also increased in treated females. Females exposed to 0.5 μg/kg bw/day of BPA showed a significant increase in both luteinizing hormone (Lhb) and follicle stimulating hormone (Fshb) mRNA, females exposed to the higher dose of 50 μg/kg bw/day of BPA showed a significant decrease in mRNA levels of both Lhb and Fshb. Female mice exposed to 0.5 μg/kg bw/day BPA had increased mRNA levels of gonadotropins and the GnRH receptor (Gnrhr), females treated with 50 μg/kg bw/day BPA had decreased gonadotropin mRNA levels, Gnrhr and Nr5a1. Male pituitaries showed no change in the parameters tested. |
| 4 | 2012 | Cao J, Mickens JA, McCaffrey KA, Leyrer SM, Patisaul HB (2012). Neonatal Bisphenol A exposure alters sexually dimorphic gene expression in the postnatal rat hypothalamus. Neurotoxicology. 33, 23-36. | Long-Evans rats | Neonatal pups ［♂♀］ | PND 0-2 | Subcutaneous | 50, 50,000 μg/kg bw/day | 【brain】In situ hybridization in the anterior and mediobasal hypothalamus: PND 4, 10 | ERb expression was significantly reduced in both BPA exposure groups by PND 10 with the Anteroventral periventricular nucleus (AVPV) expression virtually eliminated in both sexes. BPA had no effect on ER expression in females but the low dose resulted in elevated ERb expression in the male caudal hypothalamic ventromedial nucleus (VMNvl) by PND 10. Kiss1 expression was diminished by BPA in the anterior hypothalamus, especially in females. |
| 5 | 2012 | Chao, H.H., Zhang, X.F., Chen, B., Pan, B., Zhang, L.J., Li, L., Sun, X.F., Shi, Q.H., and Shen, W. (2012). Bisphenol A exposure modifies methylation of imprinted genes in mouse oocytes via the estrogen receptor signaling pathway. Histochem Cell Biol 137, 249-259. | CD-1 mice | Neonatal pups ［♀］ | Experiment 1: PND 7-14, Experiment 2: PND 5, 10, 15, 20 | Subcutaneous | 20, 40 μg/kg bw/day | 【reproductive system】Methylation of imprinted genes (sodium bisulfite genomic DNA sequencing) during oocyte growth and meiotic maturation: Experiment 1 (PND 15), Experiment 2 (PND 21) | Hypomethylation of imprinted gene Igf2r and Peg3 during oocyte growth, and enhanced estrogen receptor (ER) expression at the levels of mRNA and protein. |
| 6 | 2012 | D'Cruz SC, Jubendradass R, Mathur PP (2012). Bisphenol A induces oxidative stress and decreases levels of insulin receptor substrate 2 and glucose transporter 8 in rat testis. Reprod Sci. 19, 163-172. | Wistar rats | 90 days old ［♂］ | for 45 days | Oral | 0.005, 0.5, 50, 500 μg/kg bw/day | 【testis】 Glucose metabolism in testis, Oxidative stress | The levels of plasma glucose and insulin were significantly increased, whereas the testicular glucose level significantly decreased following exposure to BPA. A dose-dependent increase in the level of hydrogen peroxide (H2O2) and a significant decline in the activities of hexokinase and phosphofructokinase was observed in the testis of rats treated with BPA. Western blot analyses of insulin receptor substrate 2 (IRS-2) and glucose transporter 8 (GLUT-8) in the testis showed a decline in the levels of these proteins following BPA administration. Immunolocalization of GLUT-8 protein in the testis revealed decreased expression of this protein in spermatocytes and developing spermatids of rats exposed to BPA. |
| 7 | 2012 | D'Cruz SC, Jubendradass R, Jayakanthan M, Rani SJ, Mathur PP (2012). Bisphenol A impairs insulin signaling and glucose homeostasis and decreases steroidogenesis in rat testis: an in vivo and in silico study. Food Chem Toxicol. 50, 1124-1133. | Wistar rats | 90 days old ［♂］ | for 45 days | Oral | 0.005, 0.5, 50, 500 μg/kg bw/day | 【testis】Insulin signaling molecules, glucose transporter-2 (GLUT-2) Steroidogenesis in testis | Decreased levels of insulin, insulin receptor, insulin receptor substrate-1, phosphoinositide 3-kinase and GLUT-2. Dose-dependent decrease in the activities of antioxidant enzymes, 3-b-hydroxysteroid dehydrogenase, 17-b-hydroxysteroid dehydrogenase, Steroidogenic Acute Regulatory Protein and testosterone were also observed. |
| 8 | 2012 | Doshi, T., D'Souza, C., Dighe, V., and Vanage, G. (2012). Effect of neonatal exposure on male rats to bisphenol A on the expression of DNA methylation machinery in the postimplantation embryo. Journal of biochemical and molecular toxicology 26, 337-343. | Holtzman rats | Neonatal pups ［♂］ | PND 1-5 | Subcutaneous | 400 μg/kg bw/day | 【reproductive system】Fertility assessment with normally cycling adult females: PND 75, Expression analysis of DNA methyltransferases of E 20 embryos sired by BPA-treated male | A significant increase was observed in the time taken for copulation in females mated with BPA-treated males. The number of copulated females showing resorptions significant increased, ultimately leading to subfertility. Neonatal exposure of male rats to BPA down regulates the gene expression of DNA methyltransferases and related transcription factors in resorbed embryos as compared with the viable embryo. |
| 9 | 2012 | Eilam-Stock T, Serrano P, Frankfurt M, Luine V (2012). Bisphenol-A impairs memory and reduces dendritic spine density in adult male rats. Behav Neurosci. 126, 175-185. | Sprague-Dawley rats | 60 days old ［♂］ | On the day of testing | Subcutaneous | 40 μg/kg bw | 【brain】Object recognition test, Object placement test, Golgi impregnation, Dendritic spine density analysis | BPA significantly impaired both visual and spatial memory and decreased dendritic spine density on pyramidal cells in CA1 and the medial prefrontal cortex (mPFC). Additionally, BPA significantly decreased postsynaptic density-95 (PSD-95), a synaptic marker, in the hippocampus and increased cytosolic cAMP-responsive element-binding protein transcription factor (pCREB), a transcription factor, in mPFC. |
| 10 | 2012 | Ferguson, S.A., Law, C.D., and Abshire, J.S. (2012). Developmental treatment with bisphenol A causes few alterations on measures of postweaning activity and learning. Neurotoxicol Teratol 34, 598-606. | Sprague-Dawley rats | Pregnant dams-Pups | GD 6-21 and PND 1-21 | Oral | 2.5, 25.0 μg/kg bw/day | 【behavior】Open field test: PND 40-42, Startle response on the first trial block: PND 54, ［♂♀］ | Males of the BPA groups were significantly more active in open field assessments. Males of both BPA groups exhibited a significantly decreased startle response |
| 11 | 2012 | He Z, Paule MG, Ferguson SA (2012). Low oral doses of bisphenol A increase volume of the sexually dimorphic nucleus of the preoptic area in male, but not female, rats at postnatal day 21. Neurotoxicol Teratol. 34, 331-337. | Sprague-Dawley rats | Pregnant dams-Pups | GD 6-21 and PND 1-21 | Oral | 2.5, 25.0 μg/kg bw/day | 【brain】Volume of the rodent sexually dimorphic nucleus of the preoptic area (SDN-POA): PND 21 ［♂♀］ | Males treated with 2.5 or 25.0 μg/kg bw/day BPA had significantly larger SDN-POA volumes than same-sex vehicle controls. |
| 12 | 2012 | Inagaki, T., Frankfurt, M., and Luine, V. (2012). Estrogen-induced memory enhancements are blocked by acute bisphenol A in adult female rats: role of dendritic spines. Endocrinology 153, 3357-3367. | Sprague-Dawley rats | 3 months old ［♀］ | On the day of testing | Subcutaneous | 1, 4, 40, 120, 240, 400 μg/kg bw | 【behavior, brain】Hippocampal-dependent memory: Object placement test, Object recognition test, Golgi impregnation and spine density analysis | BPA (1–400 μg/kg bw) did not alter recognition memory, but 1 and 40 μg/kg bw BPA, respectively, blocked 17b-E2-dependent increases in place and visual memory. When ovariectomized rats were tested with 17b-E2, 1 μg/kg bw BPA blocked place memory, but up to 40 μg/kg bw did not block visual memory. BPA, given to cycling rats at 40 μg/kg bw, blocked visual, but not place, memory during proestrus when 2 h intertrial delays were given. Spine density was assessed at times of memory consolidation (30 min) and retention (4 h) after 17b-E2 or BPA +17b-E2. In prefrontal cortex, BPA did not alter E2-dependent increases. In the hippocampus, BPA blocked E2 increases in basal spines at 4 h and was additive with E2 at 30 min. |

| No. | Year | Reference | Species | Stage | Exposure Period | Route | Dose | Endpoints | Effects |
|---|---|---|---|---|---|---|---|---|---|
| **13** | 2012 | Jones BA , Watson NV (2012). Perinatal BPA exposure demasculinizes males in measures of affect but has no effect on water maze learning in adulthood. Horm Behav. 61, 605-610. | Long-Evans rats | Pregnant and lactating dams | GD 7-PND 14 | Oral | 5, 50, 500, and 5,000 μg/kg bw/day | 【behavior】 Morris water maze test, Elevated plus maze test, Forced swim test: PND 90-150 [♂♀] | No effect of BPA was observed in the Morris Water Maze, but on both the Elevated Plus Maze and Forced Swim Test, low doses (5 μg/kg bw/day) of BPA eliminated sex differences found between controls. |
| **14** | 2012 | Kass, L., Altamirano, G.A., Bosquiazzo, V.L., Luque, E.H., and Munoz-de-Toro, M. (2012). Perinatal exposure to xenoestrogens impairs mammary gland differentiation and modifies milk composition in Wistar rats. Reprod Toxicol 33, 390-400. | Wistar rats | Pregnant and lactating F0 dams | GD 9-PND 21 | Drinking water | 0.7, 64 μg/kg bw/day | 【mammary gland】 Milk: nursing F1 dams on LD14, Mammary gland differentiation: pregnant F1 dams on GD 18, 21 | The amount of b-casein in milk samples from F1 nursing mothers at LD 14 was lower in all of the experimental groups compared to the control group. On GD 21, F1 pregnant dams treated with BPA showed a reduced mammary gland histological differentiation score that did not differ from that of the control group on GD 18. The reduced scores on GD 21 were mostly due to the presence of less distended alveoli. |
| **15** | 2012 | Kendziorski JA, Kendig EL, Gear RB, Belcher SM (2012). Strain specific induction of pyometra and differences in immune responsiveness in mice exposed to 17a-ethinyl estradiol or the endocrine disrupting chemical bisphenol A. Reprod Toxicol. 34, 22-30. | C57BL/6 mice, CD-1 mice | 6-7 weeks old [♂♀] | from 6-7 weeks old till the end of testing | Diet | 4.0, 32.8, 4,168 (C57BL/6), 4.1, 41.7, 4,182 (CD1) μg/kg bw/day | 【uterus】Fertility and Fecundity, Uterine pathology: 19-23 weeks old [♀] | No effect on fertility or fecundity in the C57BL/6 strain for any dose of BPA was observed. In the CD1 strain 4 μg/kg bw/day and 41 μg/kg bw/day BPA treatment groups, an increase in latency of mating and a decrease in productive mating was noted. In the C57BL/6 strain, pyometra occurred in the 33 μg/kg bw/day BPA treatment groups. At the effective concentration of BPA, histological analysis revealed pathological alterations of uterine morphology associated with a >5.3-fold increase in macrophage numbers in non-pyometra uteri of C57BL/6 mice exposed to BPA. Pyometra did not occur in CD1 mice exposed to different dietary doses of BPA. |
| **16** | 2012 | Komada M, Asai Y, Morii M, Matsuki M, Sato M , Nagao T (2012). Maternal bisphenol A oral dosing relates to the acceleration of neurogenesis in the developing neocortex of mouse fetuses. Toxicology. 295, 31-38. | C57BL/6J mice | Pregnant dams | E 8.5-13.5 | Oral | 20, 200 μg/kg bw/day | 【brain】Histopathological analysis: E 14.5 [♀] | 200 μg/kg bw/day: Cortical plate was hyperplastic and the number of neural stem/progenitor cells was decreased after the exposure to BPA. In particular, the maternal BPA oral dosing related to the effects on intermediate progenitor cells (IPCs, neural progenitor cells) in the subventricular zone (SVZ) of dorsal telencephalon. Exposure to BPA associated the promotion of the cell cycle exit in radial glial cells (RGCs, neural stem cells) and IPCs, and decreased the proliferation resulting from the prolong cell cycle length of IPCs in the SVZ. |
| **17** | 2012 | Losa-Ward, S.M., Todd, K.L., McCaffrey, K.A., Tsutsui, K., and Patisaul, H.B. (2012). Disrupted organization of RFamide pathways in the hypothalamus is associated with advanced puberty in female rats neonatally exposed to bisphenol A. Biol Reprod 87, 28. | Wistar rats | Neonatal pups [♂♀] | PND 0-3 | Subcutaneous | 50, 50,000 μg/kg bw/day | 【gonadotropic】Gonadotropin releasing hormone (GnRH) in neurons, [♀] : PND 17, 21, 24, 28, 33, [♂] : PND 21, 33 | Neonatal low dose BPA exposure to females was accompanied by advanced vaginal opening and decreased RFamide related peptide 3 (RFRP3) cell numbers, fiber density and gonadotropin releasing hormone (GnRH) innervation. |
| **18** | 2012 | Marmugi A, Ducheix S, Lasserre F, Polizzi A, Paris A, Priymenko N, Bertrand-Michel J, Pineau T, Guillou H, Martin PG , Mselli-Lakhal L (2012). Low doses of bisphenol A induce gene expression related to lipid synthesis and trigger triglyceride accumulation in adult mouse liver. Hepatology. 55, 395-407. | CD-1 mice | 6 weeks old [♂] | for 28 days | Diet | 5, 50, 500, 5,000 μg/kg bw/day | 【obesity】Plasma Insulin, Liver Transcriptome, Histopathological analysis of liver [♂] | Data analysis revealed a specific impact of low doses of BPA on the hepatic transcriptome, more particularly on genes involved in lipid synthesis. The effect of BPA on the expression of de novo lipogenesis followed a nonmonotonic dose-response curve, with more important effects at lower doses than at the higher dose. In addition to lipogenic enzymes (Acc, Fasn, Scd1), the expression of transcription factors such as liver X Receptor, the sterol regulatory element binding protein-1c, and the carbohydrate responsive element binding protein that govern the expression of lipogenic genes also followed a nonmonotonic dose-response curve in response to BPA. Consistent with an increased fatty acid biosynthesis, determination of fat in the liver showed an accumulation of cholesteryl esters and of triglycerides. |
| **19** | 2012 | Matsuda, S., Matsuzawa, D., Ishii, D., Tomizawa, H., Sutoh, C., Nakazawa, K., Amano, K., Sajiki, J., and Shimizu, E. (2012). Effects of perinatal exposure to low dose of bisphenol A on anxiety like behavior and dopamine metabolites in brain. Progress in neuro-psychopharmacology & biological psychiatry 39, 273-279. | C57BL/6J mice | Pregnant dams | GD 10–20 | Subcutaneous | 0.25 μg/kg bw/day | 【behavior, brain】Open field test: P4W, P8W [♂♀] , Dopamine and DOPAC in dorsal hippocampus, amygdala, medulla oblongata: P9W [♂♀] | In males, BPA decreased the time spent in the center area of the open field in both juveniles and adults. BPA increased dopamine levels in the dorsal hippocampus and medulla oblongata and decreased the DOPAC/Dopamine ratio in the dorsal hippocampus amygdala and medulla oblongata in adults. The activity of monoamine oxidase-B, the enzyme that metabolizes dopamine into DOPAC, was reduced in the medulla oblongata. In females, those changes were not observed. |
| **20** | 2012 | Nakamura K, Itoh K, Dai H, Han L, Wang X, Kato S, Sugimoto T, Fushiki S (2012). Prenatal and lactational exposure to low-doses of bisphenol A alters adult mice behavior. Brain Dev. 34, 57-63. | ICR/jcl mice | Pregnant and lactating dams | GD 0-PND 21 | Subcutaneous | 20 μg/kg bw/day | 【behavior】Open field test, Elevated plus maze test, Morris water maze test: P3W, P10W-P13W, [♂♀] | The total distance in the elevated plus maze test at PND 21 and in the open-field test at PND 70 was significantly decreased in the BPA-exposed males group. |
| **21** | 2012 | Nanjappa MK, Simon L , Akingbemi BT (2012). The Industrial Chemical Bisphenol A (BPA) Interferes with Proliferative Activity and Development of Steroidogenic Capacity in Rat Leydig Cells. Biol Reprod. 86, 135 | Long-Evans rats | Pregnant and lactating dams | GD 12-PND 21 | Oral | 2.5, 25 μg/kg bw/day | 【testis】Leydig cell differentiation: PND 21, 35, 90, Primary Leydig cultures: progenitor Leydig cells (PLCs) at PND 21 | Perinatal exposure of male rats to BPA (2.5, 25 μg/kg bw/day) increased Leydig cell numbers at PND 90. Exposure of male rats to BPA (2.5, 25 μg/kg bw/day) induced proliferative activity in PLCs. Perinatal exposure of male rats to BPA increased PCNA, cyclin D3, IGF1RB, EGFR, AMHR2 protein, phosphorylation (p-MAPK3/1) in PLCs. Exposure to BPA (2.5, 25 μg/kg bw/day) caused greater LHCGR, ERa and AR protein levels in PLCs. Leydig cell (PND 21, 35, 90) testosterone production was decreased exposure to BPA (2.5, 25 μg/kg bw/day). LHCGR and HSD17B3 protein were decreased in BPA (2.5, 25 μg/kg bw/day)-exposed adult Leydig cells at PND 90. |
| **22** | 2012 | Pant, J., Pant, M.K., and Deshpande, S.B. (2012). Bisphenol A attenuates phenylbiguanide-induced cardio-respiratory reflexes in anaesthetized rats. Neurosci Lett 530, 69-74. | Charles Foster strain rats | adult [♀] | for 30 days | Oral | 2 μg/kg bw/day | 【cardio, respiratory】Effect on cardio-respiratory parameters | In BPA treated group, the phenylbiguanide-induced heart rate and respiratory frequency changes were attenuated significantly. |
| **23** | 2012 | Patisaul, H.B., Sullivan, A.W., Radford, M.E., Walker, D.M., Adewale, H.B., Winnik, B., Coughlin, J.L., Buckley, B., and Gore, A.C. (2012). Anxiogenic effects of developmental bisphenol a exposure are associated with gene expression changes in the juvenile rat amygdala and mitigated by soy. PLoS One 7, e43890. | Wistar rats | Pregnant and lactating dams-Pups | GD 6-PND 20 and PND 21-40 | Drinking water | 18.2(♂), 22.4(♀) μg/day (1 mg/L) | 【behavior】Light/dark box test, Elevated plus maze test: PND 24–28, PND 60–70, Gene Expression Analysis in amygdalar: PND 34, [♂♀] | BPA induced anxiogenic behavior in juveniles and loss of sexual dimorphisms in adult exploratory behavior, but only in the animals reared on the soy-free diet. Expression analysis revealed a suite of genes, including a subset known to mediate sociosexual behavior, associated with BPA-induced juvenile anxiety. Esr2 (ERb) and Gad2 expression were significantly down-regulated by BPA in both sexes compared to Soy-free controls. Tac2 and Mc4r were significantly down-regulated by BPA exposure in females. |
| **24** | 2012 | Pelch KE, Carleton SM, Phillips CL , Nagel SC (2012). Developmental exposure to xenoestrogens at low doses alters femur length and tensile strength in adult mice. Biol Reprod. 86, 69. | C57BL/6 mice | Pregnant and lactating dams | GD 11-PND 12 | Pumps s.c. | 10 μg/kg bw/day | 【bone】Bone geometry, Torsional strength: P10W [♀] , P13W [♀] , P23 W [♂] | Increased adult femur length in males (P23W). Developmental exposure to BPA tended to decrease energy to failure in females (P13W), but had no effect on energy to failure in males. |

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|---|---|---|---|---|---|---|---|---|---|
| **25** | 2012 | Roy A, Bauer SM , Lawrence BP (2012). Developmental exposure to bisphenol A modulates innate but not adaptive immune responses to influenza A virus infection. PLoS One. 7, e38448. | C57BL/6 mice | Pregnant and lactating dams | GD 6-PND 21 | Oral | 50 μg/kg bw/day | 【immune】Immune response to infection with influenza A virus, Pulmonary inflammation, Cytokine/chemokine gene expression levels in lung tissues: P6W–P8W［♂♀］ | Significantly less severe pulmonary inflammation 7 days after infection (during early virus clearance phase) in mice exposed to BPA. A general pattern of reduced expression of genes for the cytokine TNF-a and the chemokines RANTES (CCL5), IP-10 (CXCL10), and MCP-1 (CCL2) in lungs of infected mice exposed to BPA, however, statistical significance of this reduction was only found for some of these genes. Reduced expression levels of genes for interferon (IFN)-g and inducible nitric oxide synthase (iNOS) in the lungs of BPA exposed mice. |
| **26** | 2012 | Tang WY, Morey LM, Cheung YY, Birch L, Prins GS, Ho SM (2012). Neonatal exposure to estradiol/bisphenol A alters promoter methylation and expression of Nsbp1 and Hpcal1 genes and transcriptional programs of Dnmt3a/b and Mbd2/4 in the rat prostate gland throughout life. Endocrinology. 153, 42-55. | Sprague-Dawley rats | Neonatal pups［♂］ | PND 1, 3, 5 | Subcutaneous | 10 μg/kg bw/day | 【prostate】Estrogen-reprogrammable epigenetic marks, methylation changes in the prostate gland: Bisulfite genomic sequencing, Methylation-specific PCR: PND 10, 90, 200 | Hypomethylation of the promoter of nucleosome binding protein-1 (Nsbp1), unlike Pde4d4, is an early and permanent epigenetic mark of neonatal exposure to BPA that persists throughout life, unaffected by events during adulthood. In contrast, hippocalcin-like 1 (Hpcal1) is a highly plastic epigenetic mark whose hypermethylation depends on both type of early-life exposure and adult-life events. Four of the eight genes involved in DNA methylation/demethylation showed early and persistent overexpression that was not a function of DNA methylation at their promoters, including genes encoding de novo DNA methyltransferases (Dnmt3a/b) and methyl-CpG binding domain proteins (Mbd2/4) that have demethylating activities. |
| **27** | 2012 | Tharp, A.P., Maffini, M.V., Hunt, P.A., VandeVoort, C.A., Sonnenschein, C., and Soto, A.M. (2012). Bisphenol A alters the development of the rhesus monkey mammary gland. Proc Natl Acad Sci U S A 109, 8190-8195. | Rhesus monkey (Macaca mulatta) | Pregnant mothers | GD 100–165 | Oral | 400 μg/kg bw/day | 【mammary gland】Histopathological analysis, Morphometric analysis of mammary gland： PND 1-3 | The density of mammary buds was significantly increased in BPA-exposed monkeys, and the overall development of their mammary gland was more advanced compared with unexposed monkeys. |
| **28** | 2012 | Wolstenholme, J.T., Edwards, M., Shetty, S.R., Gatewood, J.D., Taylor, J.A., Rissman, E.F., and Connelly, J.J. (2012). Gestational exposure to bisphenol a produces transgenerational changes in behaviors and gene expression. Endocrinology 153, 3828-3838. | C57BL/6J (B6) mice | Dams | from 7–10 days before pairing with a male, over the last 10 days of gestation | Diet | 20 μg/day | 【behavior】Transgenerational alterations ( F1, F2 and F4) of behavior and gene expression, Juvenile social interactions: PND 20, Elevated plus maze test: PND 24, Microarray analysis of brain : E 18.5, ［♂♀］ | Juveniles in the first generation exposed to BPA in utero displayed fewer social interactions as compared with control mice, whereas in later generations (F2 and F4), the effect of BPA was to increase these social interactions. Brains from embryos (E 18.5) exposed to BPA had lower gene transcript levels for several estrogen receptors, oxytocin, and vasopressin as compared with controls; decreased vasopressin mRNA persisted into the F4 generation, at which time oxytocin was also reduced but only in males. |
| **29** | 2012 | Xu, X., Hong, X., Xie, L., Li, T., Yang, Y., Zhang, Q., Zhang, G., and Liu, X. (2012). Gestational and lactational exposure to bisphenol-A affects anxiety- and depression-like behaviors in mice. Horm Behav 62, 480-490. | ICR m ice | Pregnant dams or Lactating dams | GD 7-20 or PND 1-14 | Oral | 400, 4,000 μg/kg bw/day | 【behavior】Open field test, Dark/light transition test, Elevated plus maze test, Forced swim test: PND 56［♂♀］ | The results indicated that both gestational and lactational exposures to BPA at low levels increased anxiety- and depression-like behavior in mice of both sexes. Western blot analyses showed that both gestational and lactational exposures inhibited the expression of the AMPA receptor subunit GluR1 in the hippocampus and amygdala in mice of both sexes. |
| **30** | 2012 | Zhang HQ, Zhang XF, Zhang LJ, Chao HH, Pan B, Feng YM, Li L, Sun XF, Shen W (2012). Fetal exposure to bisphenol A affects the primordial follicle formation by inhibiting the meiotic progression of oocytes. Mol Biol Rep. 39, 5651-5657. | CD-1 mice | Pregnant dams | 12.5-18.5 dpc | Oral | 20, 40, 80 μg/kg bw/day | 【germ cell】 Oocyte cyst breakdown, Primordial follicle assembly, Follicle development: PND 3, 5, 7. Meiosis prophase I assay: 15.5, 17.5, 19.5 dp., DNA methylation ( bisulfite sequencing) analysis of oocytes: 13.5, 15.5, 17.5 dpc［♀］ | A dose-response relationship was observed with increased BPA exposure level associated with more oocytes in germ cell cyst and less primordial follicle at PND 3. Progression to meiosis prophase I of oocytes was delayed in the 80 μg/kg bw/day treated group. Decreased mRNA expression of specific meiotic genes including Stra8, Dmc1, Rec8 and Scp3 were observed. |
| **31** | 2012 | Zhang, X.F., Zhang, L.J., Feng, Y.N., Chen, B., Feng, Y.M., Liang, G.J., Li, L., and Shen, W. (2012). Bisphenol A exposure modifies DNA methylation of imprint genes in mouse fetal germ cells. Mol Biol Rep. 39(9): 8621-8628. | CD-1 mice | Pregnant dams | 0.5-12.5 dpc | Oral | 40, 80, 160 μg/kg bw/day | 【germ cell】 DNA methylation of imprinting genes, the expression of specific genes in fetal germ cells: 12.5 dpc ［♂♀］ | DNA methylation of imprinting genes, Igf2r, Peg3 and H19, was decreased with the increase of BPA concentration in fetal mouse germ cells. The relative mRNA levels of Nobox were lower in BPA-treated group compared to control in female fetal germ cells, but in male fetal germ cells, a significant higher in Nobox expression was observed in BPA-treated group compared to control. After BPA exposure, the mRNA expression of specific meiotic genes (Stra8, Dazl) in 160 μg/kg bw/day group were significantly lower than that of the control group. |
| **32** | 2011 | Adewale, H.B., Todd, K.L., Mickens, J.A., and Patisaul, H.B. (2011). The impact of neonatal bisphenol-A exposure on sexually dimorphic hypothalamic nuclei in the female rat. Neurotoxicology 32, 38-49. | Long-Evans rats | Neonatal pups ［♀］ | PND 0-3 | Subcutaneous | 50, 50,000 μg/kg bw/day | 【brain】Development of sexually dimorphic hypothalamic regions: PND 181-202 | Both doses of BPA increased the number of oxytocin-immunoreactive neurons within the paraventricular nucleus, but no significant effects were seen on serotonin-immunoreactive fiber density or ERa-immunoreactive neuron number in any of the areas analyzed. |
| **33** | 2011 | Cabaton NJ, Wadia PR, Rubin BS, Zalko D, Schaeberle CM, Askenase MH, Gadbois JL, Tharp AP, Whitt GS, Sonnenschein C , Soto AM (2011). Perinatal exposure to environmentally relevant levels of bisphenol A decreases fertility and fecundity in CD-1 mice. Environ Health Perspect. 119, 547-552. | CD-1 mice | Pregnant and lactating F0 dams | GD 8-PND 16 | Pumps s.c. | 0.025, 0.25, 25 μg/kg bw/day | 【reproductive system】Forced breeding experiment: F1［♀］ P8W | The forced breeding experiment revealed a decrease in the cumulative number of pups, observed as a nonmonotonic dose-response effect, and a decline in fertility and fecundity over time in female mice exposed perinatally to BPA. |
| **34** | 2011 | Doshi, T., Mehta, S.S., Dighe, V., Balasinor, N., and Vanage, G. (2011). Hypermethylation of estrogen receptor promoter region in adult testis of rats exposed neonatally to bisphenol A. Toxicology 289, 74-82. | Holtzman rats | Neonatal pups［♂］ | PND 1-5 | Subcutaneous | 2.4 μg/kg bw/day | 【testis】DNA methylation profile of estrogen receptor promoter region, DNA methylation machinery in testis : PND 125 | Bisulfite sequencing revealed significant hypermethylation of ERa promoter to varying extents from 40% to 60%, and ERb promoter region with varying extent from 20% to 65%. Approximately 2-fold increase in Dnmt3a and Dnmt3b expression at transcript and protein level was also observed. |
| **35** | 2011 | Durando M, Kass L, Perdomo V, Bosquiazzo VL, Luque EH , Munoz-de-Toro M (2011). Prenatal exposure to bisphenol A promotes angiogenesis and alters steroid-mediated responses in the mammary glands of cycling rats. J Steroid Biochem Mol Biol. 127, 35-43. | Wistar rats | Pregnant dams | GD 8-23 | Pumps s.c. | 25, 250 μg/kg bw/day | 【mammary gland】Mammary gland angiogenesis, Steroid hormone pathways: PND 50, 110, ［♀］ | At PND 50, all BPA-treated animals had lower serum levels of progesterone, while estradiol levels remained unchanged. The higher dose of BPA increased mammary ERa and decreased SRC-3 expression at PND 50 and PND 110. SMRT protein levels were similar among groups at PND 50, whereas at PND 110, animals exposed to 250 μg/kg bw/day BPA showed a lower SMRT expression. In the control and 25 μg/kg bw/day BPA groups, SMRT increased from PND 50 to PND 110. At PND 50, an increased vascular area associated with higher VEGF expression was observed in the 250 μg/kg bw/day BPA-treated rats. At PND 110, the vascular area was still increased, but VEGF expression was similar to that of control rats. |
| **36** | 2011 | Jain S, Kumar CH, Suranagi UD , Mediratta PK (2011). Protective effect of N-acetylcysteine on bisphenol A-induced cognitive dysfunction and oxidative stress in rats. Food Chem Toxicol. 49, 1404-1409. | Wistar rats | 6-8 weeks old ［♂］ | for 28 days | Oral | 2, 20 μg/kg bw/day | 【behavior, brain】Step-down latency, Morris water maze test, Brain malondialdehyde, Glutathione levels | A significant reduction in step-down latency, and prolongation of latency in spatial navigation task were observed in BPA (2, 20 μg/kg bw/day) treated group. The co-administration of N-acetylcysteine treatment also attenuated the BPA-induced increased malondialdehyde levels and decreased glutathione levels in brain. |
| **37** | 2011 | Jenkins S, Wang J, Eltoum I, Desmond R , Lamartiniere CA (2011). Chronic oral exposure to bisphenol A results in a nonmonotonic dose response in mammary carcinogenesis and metastasis in MMTV-erbB2 mice. Environ Health Perspect. 119, 1604-1609. | FVB/N mice: MMTV-erbB2 transgenic | 8 weeks old ［♀］ | for 28 weeks | Drinking water | 0.5, 5, 50, 500 μg/kg bw/day | 【carcinogenesis】Mammary gland: Cell proliferation index: 112 days old), Apoptotic index, Histopathological analysis: 252 days old | Only low doses of BPA significantly decreased tumor latency and increased tumor multiplicity, tumor burden, and the incidence of metastasis. All BPA doses significantly increased the cell proliferation index, but only the higher doses also increased the apoptotic index in the mammary gland. At the molecular level, BPA 5 μg/kg bw/day, but not 500 μg/kg bw/day, increased phosphorylation of erbB2, erbB3, insulin-like growth factor 1 receptor, and Akt in the mammary gland. |

| No. | Year | Reference | Species | Stage | Exposure Period | Route | Dose | Endpoints | Effects |
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| **38** | 2011 | Jones BA, Shimell JJ , Watson NV (2011). Pre- and postnatal bisphenol A treatment results in persistent deficits in the sexual behavior of male rats, but not female rats, in adulthood. Horm Behav. 59, 246-251. | Long-Evans rats | Pregnant and lactating dams | GD 7-PND 14 | Oral | 5, 50, 500, 5,000 μg/kg bw/day | 【behavior】 Sexual behavior : PND 90-120 [♂♀] | Males receiving low dose perinatal BPA (50 μg/kg bw/day) showed persistent deficits in sexual behavior in adulthood. Males receiving the highest dose (5 mg/kg bw/day), however, were indistinguishable from controls with respect to consummatory sexual behaviors but showed decreased latencies to engage in those behaviors when sexually naive, with significant non-linear, or U-shaped, dose-response relationships observed on the first and last day of testing. Adult female sexual behavior was not affected by early BPA administration at any dose tested. |
| **39** | 2011 | Kunz N, Camm EJ, Somm E, Lodygensky G, Darbre S, Aubert ML, Huppi PS, Sizonenko SV, Gruetter R (2011). Developmental and metabolic brain alterations in rats exposed to bisphenol A during gestation and lactation. Int J Dev Neurosci. 29, 37-43. | Sprague-Dawley rats | Pregnant and lactating dams | GD 6-PND 20 | Drinking water | 70 μg/kg bw/day | 【brain】Cerebral structural development, Metabolite concentrations analysis of NMR in hippocampus, Histopathological analysis: PND 20 | Localized proton magnetic resonance spectroscopy (1H MRS) showed significant increase in glutamate concentration in the hippocampus as well as in the Glu/Asp ratio. Quantitative histological analysis revealed that the density of NeuN-positive neurons in the hippocampus was decreased in the BPA-treated offspring when compared to controls. The density of GFAP-positive astrocytes in the cingulum was increased in BPA-treated offspring. |
| **40** | 2011 | Lawson, C., Gieske, M., Murdoch, B., Ye, P., Li, Y., Hassold, T., and Hunt, P.A. (2011). Gene expression in the fetal mouse ovary is altered by exposure to low doses of bisphenol A. Biol Reprod 84, 79-86. | C57BL/6J | Pregnant dams | 11 dpc | Oral | 20 μg/kg bw | 【ovary】Gene expression changes in ovary: 12, 12.5, 13.5, 14.5 dpc | The first changes in gene expression in the fetal ovaries from exposed fetuses were evident within 24 h of exposure, and the most extensive changes correlated with the onset of meiosis. Furthermore, gene ontology analysis suggested that BPA acts to down-regulate mitotic cell-cycle genes. |
| **41** | 2011 | Prins, G.S., Ye, S.H., Birch, L., Ho, S.M., and Kannan, K. (2011). Serum bisphenol A pharmacokinetics and prostate neoplastic responses following oral and subcutaneous exposures in neonatal Sprague-Dawley rats. Reprod Toxicol 31, 1-9. | Sprague-Dawley rats | Neonatal pups [♂] | PND 1, 3, 5 | Oral or Subcutaneous | 10 μg/kg bw/day | 【prostate】Prostatic response to 16 weeks of T+E treatment as adults: PND 200 | Prostates from aged rats given s.c. or oral BPA neonatally and T+E implants as adults exhibited nearly identical, heightened susceptibility to prostate intraepithelial neoplasia incidence and score as compared to neonatal oil-controls. |
| **42** | 2011 | Rivera, O.E., Varayoud, J., Rodriguez, H.A., Munoz-de-Toro, M., and Luque, E.H. (2011). Neonatal exposure to bisphenol A or diethylstilbestrol alters the ovarian follicular dynamics in the lamb. Reprod Toxicol 32, 304-312. | Sheep | Neonatal pups [♀] | PND 1-14 | Subcutaneous | 50 μg/kg bw/day | 【ovary】Histopathological analysis of ovarian follicular: PND 30 | BPA showed a decline in the stock of primordial follicles with stimulation of follicular development. BPA reduced ovarian weight and increased the number of multioocyte follicles. BPA promoted proliferation of granulosa/theca cells in antral follicles, and increased both the number of antral atretic follicles and p27 expression. Neonatal exposure to BPA reduced the primordial follicle pool by stimulating their initial recruitment and subsequent follicle development until antral stage. |
| **43** | 2011 | Varayoud, J., Ramos, J.G., Bosquiazzo, V.L., Lower, M., Munoz-de-Toro, M., and Luque, E.H. (2011). Neonatal exposure to bisphenol A alters rat uterine implantation-associated gene expression and reduces the number of implantation sites. Endocrinology 152, 1101-1111. | Wistar rats | Neonatal pups [♀] | PND 1, 3, 5, 7 | Subcutaneous | 50, 20,000 μg/kg bw/day | 【reproductive system】Evaluation of reproductive performance: GD 18, Assessment of uterine gene expressions, ovarian steroid serum levels: GD 5 | In both BPA groups, not only did the number of rats with more than one resorption site increase, but also the number of resorption sites per rat tended to be higher than in the control group. The ER and PR mRNA levels in samples of rats neonatally exposed to both BPA groups were significantly lower compared with those of control animals. A clear decrease in Hoxa10 expression was detected in both BPA groups. |
| **44** | 2011 | Weber Lozada, K., and Keri, R.A. (2011). Bisphenol A increases mammary cancer risk in two distinct mouse models of breast cancer. Biol Reprod 85, 490-497. | FVB/N mice | Pregnant and lactating dams | 8 dpc-PND 21 | Oral | 25, 250 μg/kg bw/day | 【carcinogenesis】Vaginal opening, Mammary development experiment: P3W, P5W, P8W, Tumor susceptibility experiment: P5W, P6W, [♀] | Both low- and high-dose BPA cohorts had a statistically significant increase in susceptibility to DMBA-induced tumors compared to vehicle-treated controls. |
| **45** | 2011 | Wei J, Lin Y, Li Y, Ying C, Chen J, Song L, Zhou Z, Lv Z, Xia W, Chen X , Xu S (2011). Perinatal exposure to bisphenol A at reference dose predisposes offspring to metabolic syndrome in adult rats on a high-fat diet. Endocrinology. 152, 3049-3061. | Wistar rats | Pregnant and lactating dams | GD 0-PND 21 | Oral | 50, 250, 1,250 μg/kg /day | 【obesity】Blood parameters, Oral glucose tolerance test, Insulin tolerance test: P15W, P26W, [♂♀] | On a normal diet, perinatal exposure to 50 μg/kg bw/day BPA resulted in increased body weight, elevated serum insulin, and impaired glucose tolerance in adult offspring. Severe metabolic syndrome, including obesity, dyslipidemia, hyperleptindemia, hyperglycemia, hyperinsulinemia, and glucose intolerance, was observed in high-fat-fed offspring perinatally exposed to 50 μg/kg bw/day BPA. No adverse effect of perinatal BPA exposure at 250 and 1,250 μg/kg bw/day was observed no matter on a normal diet or a high-fat diet. |
| **46** | 2011 | Wolstenholme JT, Taylor JA, Shetty SR, Edwards M, Connelly JJ , Rissman EF (2011). Gestational exposure to low dose bisphenol a alters social behavior in juvenile mice. PLoS One. 6, e25448. | C57BL/6J (B6) mice | Pregnant dams | from 7 days before pairing with a male, over the last 10 days of gestation | Diet | 5 μg/daily (73.5 μg/kg bw/day) | 【behavior, brain】Embryo brain: E18.5, Juvenile social interactions: PND 21, Social behaviors test, Elevated plus maze test: PND 22, Social preference test: PND 24, [♂♀] | In addition BPA increased display of nose-to-nose contacts, play solicitations and approaches in both sexes. In all these cases interactions were produced by differences between control and BPA females. mRNA for the glutamate transporter, Slc1a1, was enhanced by exposure to BPA in female brains. BPA changed the expression of DNA methyltransferase genes, Dnmt1 and Dnmt3a. |
| **47** | 2011 | Wu JH, Jiang XR, Liu GM, Liu XY, He GL, Sun ZY (2011). Oral exposure to low-dose bisphenol A aggravates testosterone-induced benign hyperplasia prostate in rats. Toxicol Ind Health. 27, 810-819. | Sprague-Dawley rats | 9 weeks old [♂] | for 4 weeks | Oral | 10, 30, 90 μg/kg bw/day | 【prostate】Histopathological analysis of prostate: 13 weeks old | Benign prostatic hyperplasia was induced by testosterone and then treated with BPA for 4 weeks. Prostate weight and volume in rats treated with low dose BPA (10 μg/kg bw/day) was higher than that of model control, and BPA significantly increased the relative weight of prostate. For prostate lobes, BPA 10 μg/kg bw/day significantly increased relative weight of ventral prostate (VP), weight and relative weight of dorsolateral prostate (DLP). And histopathology results showed that height of epithelial cell (HEC) of VP and DLP in BPA group were significantly higher than that of model control. |
| **48** | 2011 | Xu X, Tian D, Hong X, Chen L, Xie L (2011). Sex-specific influence of exposure to bisphenol-A between adolescence and young adulthood on mouse behaviors. Neuropharmacology. 61, 565-573. | ICR mice | 4 weeks old [♂♀] | 31-87 days old | Oral | 40, 400 μg/kg bw/day | 【behavior】Open field test, Elevated plus maze test, Morris water maze test, Step-down test: about 91 days old [♂♀] | In open field tests, rearing and grooming sex differences were abolished by BPA exposure. In the elevated plus maze test, the number of open arm entries, the time spent in open arms, and the number of unprotected head dips in the center area were reduced in males but increased in females by BPA at 40 or 400 μg/kg bw/day, thus eliminating or reversing sex differences in these behaviors. In the Morris water maze task, exposure to BPA at 40 μg/kg bw/day significantly extended the average escape pathlength to the hidden platform in males, but no significant influence was found in females; thus, the sex differences in spatial learning and memory were abolished. In the step-down test, the latency to step down from the platform 24 h after receiving a footshock was shortened by BPA exposure in males but not in females; thus, a sex difference was induced in passive avoidance memory in mice. |
| **49** | 2011 | Xu, X., Li, T., Luo, Q., Hong, X., Xie, L., and Tian, D. (2011). Bisphenol-A rapidly enhanced passive avoidance memory and phosphorylation of NMDA receptor subunits in hippocampus of young rats. Toxicol Appl Pharmacol 255, 221-228. | Sprague-Dawley rats | Neonatal pups [♂] | PND 18 | Subcutaneous | 50, 500 μg/kg bw | 【behavior, brain】Step-down passive avoidance task, NMDA receptor subunits expressions in hippocampus: PND 18 [♂] | Compared with the control, 1 h after treatment, BPA (50, 500 μg/kg bw) markedly extended the latency to step down after footshock, the extension effect on the latency to step down was disappeared 24 h after treatment of BPA. Compared with the vehicle-treated control, the phosphorylation levels of NR1 and NR2B were increased by approximately 2 times by BPA at 50 and 500 μg/kg bw in hippocampus within 1 h. Pre-treatment with an estrogen receptors antagonist, ICI182,780, or an ERK-activating kinase inhibitor, U0126, significantly attenuated BPA-induced phosphorylations of NR1, NR2B, and ERK within 1 h. |
| **50** | 2011 | Yu C, Tai F, Song Z, Wu R, Zhang X , He F (2011). Pubertal exposure to bisphenol A disrupts behavior in adult C57BL/6J mice. Environ Toxicol Pharmacol. 31, 88-99. | C57BL/6J mice | Neonatal pups [♂♀] | PND 23-30 | Subcutaneous | 50 μg/kg bw/day | 【behavior】 Social interaction, Open field test, Elevated plus maze test: PND 60-70 [♂♀] | Compared to controls, pubertal exposure to BPA significantly altered female exploratory and anxiety behavior. Moreover, BPA-treated female mice displayed increased levels of affiliation to female stimulus mice and decreased levels of affiliation to male stimulus mice |

| No. | Year | Reference | Species | Stage | Exposure Period | Route | Dose | Endpoints | Effects |
|---|---|---|---|---|---|---|---|---|---|
| **51** | 2011 | Zhou, R., Bai, Y., Yang, R., Zhu, Y., Chi, X., Li, L., Chen, L., and Sokabe, M. (2011). Abnormal synaptic plasticity in basolateral amygdala may account for hyperactivity and attention-deficit in male rat exposed perinatally to low-dose bisphenol-A. Neuropharmacology 60, 789-798. | Sprague-Dawley rats | Pregnant and lactating dams | GD 10-PND 7 | Subcutaneous | 2 μg/kg bw/day | 【brain】Synaptic properties of GABAergic/dopaminergic systems in basolateral amygdala: PND 28［♂］ | A single electrical stimulation of the capsule fibers evoked multispike responses with an enhanced primary population spikes (1st-PS) in the BPA-rats. A single train of high-frequency stimulation of the fibers induced NMDA receptor (NMDAR) dependent long-term potentiation (LTP) in BPA-rats, but not in control rats. Also, paired-pulse inhibition (PPI, GABA-dependent) in control rats was reversed to paired-pulse facilitation in BPA-rats. Perfusion of slices obtained from BPA-rats with the GABAA receptor (GABAAR) agonist muscimol blocked the multispike responses and LTP, and recovered PPI. By contrast, the dopamine D1 receptor antagonist SCH23390 abolished LTP and attenuated the increased amplitude of 1st-PS in BPA-rats. |
| **52** | 2010 | Alonso-Magdalena P, Vieira E, Soriano S, Menes L, Burks D, Quesada I, Nadal A (2010). Bisphenol A exposure during pregnancy disrupts glucose homeostasis in mothers and adult male offspring. Environ Health Perspect. 118, 1243-1250. | OF1 mice | Pregnant dams | GD 9-16 | Subcutaneous | 10, 100 μg/kg bw/day | 【obesity】Blood glucose homeostasis, Analysis of glucose and insulin sensitivity, pancreatic islet function: F0 ［♀］, F1［♂］, 6 months old | BPA exposure aggravated the insulin resistance produced during pregnancy and was associated with decreased glucose tolerance and increased plasma insulin, triglyceride, and leptin concentrations relative to controls. Insulin-stimulated Akt phosphorylation was reduced in skeletal muscle and liver of BPA-treated pregnant mice relative to controls. BPA exposure during gestation had long-term consequences for mothers: 4 months post-partum, treated females weighed more than untreated females and had higher plasma insulin, leptin, triglyceride, and glycerol levels and greater insulin resistance. At 6 months of age, male offspring exposed in utero had reduced glucose tolerance, increased insulin resistance, and altered blood parameters compared with offspring of untreated mothers. The islets of Langerhans from male offspring presented altered Ca2+ signaling and insulin secretion. BrdU (bromodeoxyuridine) incorporation into insulin-producing cells was reduced in the male progeny, yet b-cell mass was unchanged. |
| **53** | 2010 | Betancourt AM, Eltoum IA, Desmond RA, Russo J , Lamartiniere CA (2010). In utero exposure to bisphenol A shifts the window of susceptibility for mammary carcinogenesis in the rat. Environ Health Perspect. 118, 1614-1619. | Sprague Dawley CD rats | Pregnant dams | GD 10-21 | Oral | 25, 250 μg/kg bw/day | 【carcinogenesis, mammary gland】DMBA-induced mammary gland carcinogenesis: PND 50, 100 | Prenatal exposure of the dam to BPA 250 μg/kg bw/day combined with a single exposure of female offspring to DMBA on PND 100, but not on PND 50, significantly increased tumor incidence while decreasing tumor latency compared with the control group. Prenatal exposure of the dam to BPA 250 μg /kg bw/day, in the absence of DMBA to the female offspring, increased cell proliferation and elicited differential effects at the protein level at PND 100 compared with PND 50. Differentially regulated proteins in the mammary gland included ER-a, progesterone receptor-A, Bcl-2, steroid receptor coactivators, epidermal growth factor receptor, phospho-insulinlike growth factor 1 receptor, and phospho-Raf. |
| **54** | 2010 | Betancourt AM, Mobley JA, Russo J , Lamartiniere CA (2010). Proteomic analysis in mammary glands of rat offspring exposed in utero to bisphenol A. J Proteomics. 73, 1241-1253. | Sprague Dawley CD rats | Pregnant dams | GD 10-21 | Oral | 25, 250 μg/kg bw/day | 【mammary gland】Mammary gland proteomic analysis using 2-DE, MALDI-TOF-TOF, LC-MS/MS: PND 21, 50 | Western blot analysis of key downstream signaling proteins demonstrated increased phospho-AKT, c-Raf, phospho-ERKs-1 and 2, but decreased TGF-b in mammary glands of 50 day old rats exposed prenatally to BPA. |
| **55** | 2010 | Bosquiazzo, V.L., Varayoud, J., Munoz-de-Toro, M., Luque, E.H., and Ramos, J.G. (2010). Effects of neonatal exposure to bisphenol A on steroid regulation of vascular endothelial growth factor expression and endothelial cell proliferation in the adult rat uterus. Biol Reprod 82, 86-95. | Wistar rats | Neonatal pups［♀］ | PND 1, 3, 5, 7 | Subcutaneous | 50, 20,000 μg/kg bw/day | 【reproductive system】Uterine response to hormonal stimuli in OVX rats after progesterone plus E2 treatment : PND 93 | Rats neonatally exposed to BPA (both groups) showed a decreased induction of uterine endothelial proliferation and a decreased Vegf mRNA expression in response to ovarian steroid treatment. In rats neonatally exposed to BPA (50 μg/kg bw/day), although ERa expression was lower in subepithelial cells than in controls, a higher expression of silencing mediator of retinoic acid and thyroid hormone receptor (NCOR1, also known as SMRT) corepressor was evidenced in the same compartment. |
| **56** | 2010 | Braniste, V., Jouault, A., Gaultier, E., Polizzi, A., Buisson-Brenac, C., Leveque, M., Martin, P.G., Theodorou, V., Fioramonti, J., and Houdeau, E. (2010). Impact of oral bisphenol A at reference doses on intestinal barrier function and sex differences after perinatal exposure in rats. Proc Natl Acad Sci U S A 107, 448-453. | Wistar rats | adult［♀］ | for 15 days | Oral | 0.5, 5, 50, 500, 5,000 μg/kg bw/day | 【colon】Colonic paracellular permeability: Chambers Experiments | BPA dose-dependently decreased basal colonic paracellular permeability (CPP), with a half-maximal inhibitory dose of 5.2 μg/kg bw/day. |
| **57** | 2010 | Goncalves CR, Cunha RW, Barros DM , Martinez PE (2010). Effects of prenatal and postnatal exposure to a low dose of bisphenol A on behavior and memory in rats. Environ Toxicol Pharmacol. 30, 195-201. | Wistar rats | Pregnant dams , Lactating dams or Pregnant and lactating dams | PRE: GD 0-20, LAC: PND 0-21, PRE-LAC: GD 0-PND 21 | Oral | 40 μg/kg bw/day | 【behavior】 Step-down inhibitory avoidance task, Open field test, Object recognition test, Morris water maze: P16W［♂♀］ | In the PRE-LAC group, exposure to BPA impaired both short-term and long-term memory in inhibitory avoidance and the object recognition task, and also affected locomotor activity and spatial memory. Some sex-specific behavioral characteristics disappeared in the LAC group. Sex-specific memory and behavior impairment were caused by BPA exposure during brain organogenesis and differentiation. |
| **58** | 2010 | Jones, L.P., Sampson, A., Kang, H.J., Kim, H.J., Yi, Y.W., Kwon, S.Y., Babus, J.K., Wang, A., and Bae, I. (2010). Loss of BRCA1 leads to an increased sensitivity to Bisphenol A. Toxicol Lett 199, 261-268. | C57BL/6 mice: Brca1 conditional knockout | 3 months old ［♀］ | for 4 weeks | Pumps s.c. | 0.25 μg/kg bw/day | 【carcinogenesis, mammary gland】 Histopathological analysis of mammary gland :120 days old | BPA administration stimulates mammary gland epithelial tissue/cell proliferation leading to hyperplasia in Brca1 mutant mice compared to wild-type control mice. |
| **59** | 2010 | Martini M, Miceli D, Gotti S, Viglietti-Panzica C, Fissore E, Palanza P, Panzica G (2010). Effects of perinatal administration of Bisphenol A on the neuronal nitric oxide synthase expressing system in the hypothalamus and limbic system of CD1 mice. J Neuroendocrinol. 22, 1004-1012. | CD-1 mice | Pregnant and lactating dams | GD 11-PND 8 | Oral | 10, 20, 40 μg/kg bw/day | 【brain】Neuronal nitric oxide synthase (nNOS) immunohistochemistry in brain : 2 months old［♂♀］ | Significant effects of BPA exposure were detected for the number of neuronal nNOS immunoreactive cells in the medial preoptic nucleus and in the ventromedial subdivision of the bed nucleus of the stria terminalis, in a sex-oriented and dose-dependent way. |
| **60** | 2010 | Matsuda, S., Saika, S., Amano, K., Shimizu, E., and Sajiki, J. (2010). Changes in brain monoamine levels in neonatal rats exposed to bisphenol A at low doses. Chemosphere 78, 894-906. | Sprague-Dawley rats | Neonatal pups［♂］ | PND 2 | Intracranial | 0.1, 1.0, 10 μg/kg bw/day | 【brain】Brain function, Monoamine concentrations in hippocampus: PND 9, PND 30 | Significant increases of serotonin (5-HT) in hippocampus, 5-hydroxyindole-3-acetic acid (5-HIAA) and 5-HIAA/5-HT in brain stem, dopamine (DA) and DOPAC in striatum were observed at 28 days after the injection on PND 2. At 7 day after the injection, increases in 5-HT and norepinephrine (NE) and decreases in DOPAC and 5-HIAA were observed in hippocampus. |
| **61** | 2010 | Monje L, Varayoud J, Munoz-de-Toro M, Luque EH, Ramos JG (2010). Exposure of neonatal female rats to bisphenol A disrupts hypothalamic LHRH pre-mRNA processing and estrogen receptor alpha expression in nuclei controlling estrous cyclicity. Reprod Toxicol. 30, 625-634. | Wistar rats | Neonatal pups［♀］ | PND 1, 3, 5, 7 | Subcutaneous | 50, 20,000 μg/kg bw/day | 【brain, reproductive system】Neural network that controls estrous cyclicity, Histopathological analysis of hypothalamus: PND 100［♀］ | At PND 100, BPA (50 μg/kg bw/day)-females showed alterations in estrous cyclicity and BPA (20 mg/kg bw/day)-females were incapable of producing an estradiol-induced LH surge. By real-time PCR, hypothalamic expression of mature LH-releasing hormone (LHRH) mRNA was increased in BPA (50 μg/kg bw/day) and decreased in BPA (20 mg/kg bw/day)-females. Furthermore, unprocessed intron A-containing LHRH RNA was decreased in the cytoplasm of hypothalamic cells of both groups. Immunohistochemistry revealed that ERa protein was up-regulated in anteroventral periventricular and down-regulated in arcuate nucleus of both groups. |

| No. | Year | Reference | Species | Stage | Exposure Period | Route | Dose | Endpoints | Effects |
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| **62** | 2010 | Nakamura K, Itoh K, Yoshimoto K, Sugimoto T , Fushiki S (2010). Prenatal and lactational exposure to low-doses of bisphenol A alters brain monoamine concentration in adult mice. Neurosci Lett. 484, 66-70. | ICR/Jcl mice | Pregnant and lactating dams | GD 0-PND 21 | Subcutaneous | 20 μg/kg bw/day | 【brain】Level of neurotransmitters (5-HT, DA, 5-HIAA, DOPAC) in brain: P3W, P12W, P14W-P15W, ［♂♀］ | The levels of dopamine and its metabolite significantly increased in the caudate/putamen and dorsal raphe nucleus, whereas serotonin and its metabolite increased in the caudate/putamen, dorsal raphe nucleus, thalamus and Substantia nigra in the BPA-exposure group at both P3W and/or P14W-P15W. |
| **63** | 2010 | Poimenova A, Markaki E, Rahiotis C , Kitraki E (2010). Corticosterone-regulated actions in the rat brain are affected by perinatal exposure to low dose of bisphenol A. Neuroscience. 167, 741-749. | Wistar rats | Pregnant and lactating dams | GD 0-PND 21 | Oral | 40 μg/kg bw/day | 【behavior, brain】Plasma corticosterone levels, corticosteroid receptors (GR, MR) in hippocampi, Y-maze test: PND 46［♂♀］ | BPA treated females had higher corticosterone levels than control females and BPA males and lower GR levels than BPA males, under basal conditions. Following the mildly stressful experience of Y-maze, corticosterone levels were increased in BPA-treated animals of both sexes, compared to the controls. GR levels were also increased in BPA-treated females compared to males. No effect of BPA was observed on MR levels, whereas the Y-maze experience significantly decreased receptors' levels in both female groups. The animals' performance in the task was also evaluated. BPA exposure significantly impaired the spatial recognition memory in both sexes, and modified the behavioural coping in a sex-dependent manner. Female BPA-treated offspring exhibited increased "anxiety-like" behaviour and dramatic loss of exploration attitude during the task, in comparison to males. |
| **64** | 2010 | Ryan KK, Haller AM, Sorrell JE, Woods SC, Jandacek RJ, Seeley RJ (2010). Perinatal exposure to bisphenol-A and the development of metabolic syndrome in CD-1 mice. Endocrinology. 151, 2603-2612. | CD-1 mice | Pregnant and lactating dams | GD 0-PND 21 | Diet | 0.25 μg/kg bw/day | 【obesity】Body length: P4W, Glucose tolerance tests: P8W［♂♀］ | Weanling mice exposed to BPA during gestation and lactation are heavier compared with control mice. BPA mice are longer than controls at 4 weeks old, but these differences are no longer apparent when the mice reach adulthood (7 weeks old), even when tested on a high-fat diet. |
| **65** | 2010 | Signorile PG, Spugnini EP, Mita L, Mellone P, D'Avino A, Bianco M, Diano N, Caputo L, Rea F, Viceconte R, Portaccio M, Viggiano E, Citro G, Pierantoni R, Sica V, Vincenzi B, Mita DG, Baldi F, Baldi A (2010). Pre-natal exposure of mice to bisphenol A elicits an endometriosis-like phenotype in female offspring. Gen Comp Endocrinol. 168, 318-325. | BALB-C mice | Pregnant and lactating dams | GD 1-PND 7 | Subcutaneous | 100, 1000 μg/kg bw/day | 【endometriosis】Histopathological analysis of pelvic organs: 3 months old［♀］ | In the adipose tissue surrounding the genital tracts of a consistent number of treated animals, endometriosis-like structure with the presence of both glands and stroma and expressing both estrogen receptor and HOXA-10. Moreover, cystic ovaries, adenomatous hyperplasia with cystic endometrial hyperplasia and atypical hyperplasia were significantly more frequent in treated animals respect to the controls. Finally, BPA was found in the livers of exposed moms and female offspring. |
| **66** | 2010 | Tian YH, Baek JH, Lee SY, Jang CG (2010). Prenatal and postnatal exposure to bisphenol A induces anxiolytic behaviors and cognitive deficits in mice. Synapse. 64, 432-439. | ICR mice | Neonatal pups［♀］ | PND 7-36 | Oral | 100, 500 μg/kg bw/day | 【behavior, brain】Open field test, Elevated plus-maze test, Y-maze teat, Novel object teat: P5W | In the open field test, BPA treatment (100 μg/kg bw/day) increased movement in the central zone. BPA treatment (500 μg/kg bw/day) also increased the time spent in the open arms in the Elevated plus-maze test. BPA-treated mice showed decreased alternation behavior in the Y-maze at both of doses, indicating working memory impairment. BPA-treated mice (100 μg/kg bw/day) also showed decreased novel object recognition as expressed by central locomotion and frequency in the central zone. BPA treatment increased D2 receptor binding in the caudate putamen (CPu) but decreased DAT binding. BPA treatment also decreased NMDA receptor binding in the frontal cortex and CA1, CA3, and DG of the hippocampus. |
| **67** | 2010 | Xu XH, Wang YM, Zhang J, Luo QQ, Ye YP , Ruan Q (2010). Perinatal exposure to bisphenol-A changes N-methyl-D-aspartate receptor expression in the hippocampus of male rat offspring. Environ Toxicol Chem. 29, 176-181. | Sprague-Dawley rats | Pregnant and lactating dams | GD 7-PND 21 | Oral | 50, 500, 5,000, 50,000, 200,000 μg/kg bw/day | 【brain】NMDA receptor subunits NR1, NR2A, 2B, ERb, and aromatase cytochrome P450 protein expressions of hippocampus: PND 4, 7, 14, 21, 56, ［♂］ | Western-blotting analyses showed that perinatal exposure to BPA significantly affected the expression of NMDA receptor (NMDAR) subunits. At the lower doses of 0.05 to 50 mg/kg bw/day, BPA concentration dependently inhibited the expression of NMDAR subunits. However, at the higher dose (200 mg/kg bw/day), the effects of BPA on these subunits were different, with a stronger inhibition of NR1 expression and a slighter inhibition of NR2A, 2B expression when compared with those at the lower dosage of BPA. In addition, perinatal exposure to BPA inhibited the expression of ERb protein, but increased P450arom protein expression in a concentration-dependent manner, especially during the early postnatal period (the first 1-3 postnatal weeks). No significant influence of BPA on P450arom was observed at PND 56. |
| **68** | 2010 | Xu, X.H., Zhang, J., Wang, Y.M., Ye, Y.P., and Luo, Q.Q. (2010). Perinatal exposure to bisphenol-A impairs learning-memory by concomitant down-regulation of N-methyl-D-aspartate receptors of hippocampus in male offspring mice. Horm Behav 58, 326-333. | ICR mice | Pregnant and lactating dams | GD 7-PND 21 | Oral | 50, 500, 5,000, 50,000 μg/kg bw/day | 【behavior, brain】Morris water maze spatial memory task, Step-down passive avoidance task, NMDA receptor (NMDAR) subunits NR1, NR2A, NR2B, ERb in hippocampus: PND 21, 56, ［♂］ | BPA at 0.5, 5, and 50 mg/kg bw/day significantly extended the escape length to find the hidden platform in Morris water maze, and BPA at 0.5 or 5 mg/kg bw/day markedly decreased the percentage of time spent in the quadrant where the platform had been during training both in PND 21 and PND 56 mice. In the PND 21, a dosage-dependent down-regulation of the expression of NR1 was observed in the BPA groups (0.05-50 mg/kg bw/day), while the expressions of NR2A and 2B were significantly down-regulated by the higher dose of BPA (5-50 mg/kg bw/day). In the PND 56, all of the BPA-exposed mice displayed marked down-regulation of the NMDAR subunits NR1, NR2A, and 2B in hippocampus. Significantly inhibited the expressions of NMDAR subunits NR1, NR2A, and 2B in the hippocampus. The expressions of ERb in both PND 21 and PND 56 mice were markedly down-regulated by BPA at 0.5, 5, and 50 mg/kg bw/day. |
| **69** | 2009 | Adewale, H.B., Jefferson, W.N., Newbold, R.R., and Patisaul, H.B. (2009). Neonatal bisphenol-A exposure alters rat reproductive development and ovarian morphology without impairing activation of gonadotropin-releasing hormone neurons. Biol Reprod 81, 690-699. | Long-Evans rats | Neonatal pups［♀］ | PND 0-3 | Subcutaneous | 50, 50,000 μg/kg bw/day | 【reproductive system, brain】Testing for sexual receptivity, Histopathological analysis of hypothalamus, ovary: PND 182-202 | Exposure to the low dose of BPA advanced pubertal onset. A total of 67% of females exposed to the high BPA dose were acyclic by 15 week after vaginal opening compared with 14% of those exposed to the low BPA dose, none of the control animals. Severity of deficits within the BPA-treated groups increased with dose and included large antral-like follicles and lower numbers of corpora lutea. Sexual receptivity, examined after ovariectomy and hormone replacement, was normal in both groups. |
| **70** | 2009 | Jenkins, S., Raghuraman, N., Eltoum, I., Carpenter, M., Russo, J., and Lamartiniere, C.A. (2009). Oral exposure to bisphenol A increases dimethylbenzanthracene-induced mammary cancer in rats. Environ Health Perspect 117, 910-915. | Sprague Dawley CD rats | Lactating dams | PND 2-20 (a total of 15 treatments on Monday through Friday only) | Oral | 25, 250 μg/kg bw/day | 【carcinogenesis, mammary gland】DMBA-induced mammary gland carcinogenesis, Mammary dissections: PND 21, 50 | The combination of DMBA treatment with lactational exposure to BPA demonstrated a dose-dependent increase in mammary tumor multiplicity and reduced tumor latency compared with controls. In the absence of DMBA treatment, lactational BPA exposure resulted in increased cell proliferation and decreased apoptosis at 50 but not 21 days postpartum (shortly after last BPA treatment). Using Western blot analysis, steroid receptor coactivators (SRCs) 1-3, Akt, phosphorylated Akt, progesterone receptor A (PR-A), and erbB3 proteins were significantly up-regulated at PND 50. |
| **71** | 2009 | Monje, L., Varayoud, J., Munoz-de-Toro, M., Luque, E.H., and Ramos, J.G. (2009). Neonatal exposure to bisphenol A alters estrogen-dependent mechanisms governing sexual behavior in the adult female rat. Reprod Toxicol 28, 435-442. | Wistar rats | Neonatal pups［♂♀］ | PND 1, 3, 5, 7 | Subcutaneous | 50, 20,000 μg/kg bw/day | 【behavior】 Estrogen-dependent gene expression in hypothalamus, Sexual behavior : PND 100 OVX ［♀］ | In BPA-exposed females, ERa expression was down-regulated in both the medial preoptic (MPN) and ventromedial nucleus (VMHvl), while repressor of estrogen receptor activity (REA) expression was up-regulated in the VMHvl. PR protein expression was significantly decreased in the VMHvl of BPA (50 μg/kg bw/day)-treated females only. BPA-exposed females displayed significantly lower levels of proceptive behavior. |
| **72** | 2009 | Nakagami, A., Negishi, T., Kawasaki, K., Imai, N., Nishida, Y., Ihara, T., Kuroda, Y., Yoshikawa, Y., and Koyama, T. (2009). Alterations in male infant behaviors towards its mother by prenatal exposure to bisphenol A in cynomolgus monkeys (Macaca fascicularis) during early suckling period. Psychoneuroendocrinology 34, 1189-1197. | Cynomolgus monkeys (Macaca fascicularis) | Pregnant mothers | GD 20-160 | Pumps s.c. | 10 μg/kg bw/day | 【behavior】Social behaviors between infants and their mothers during the suckling period: PND 31-60, 61-90 | Prenatal exposure to BPA altered the behaviors of male infants significantly; BPA-exposed male infants behaved as female infants. And it also affected some of female infant behaviors. |

| No. | Year | Reference | Species | Stage | Exposure Period | Route | Dose | Endpoints | Effects |
|---|---|---|---|---|---|---|---|---|---|
| **73** | 2009 | Newbold, R.R., Jefferson, W.N., and Padilla-Banks, E. (2009). Prenatal exposure to bisphenol A at environmentally relevant doses adversely affects the murine female reproductive tract later in life. Environ Health Perspect 117, 879-885. | CD-1 mice | Pregnant and lactating dams | GD 9-16 | Subcutaneous | 0.1, 1, 10, 100, 1,000 μg/kg bw/day | 【reproductive system, carcinogenesis】 Histopathological analysis of ovary/oviduct, uterus: 18 months old | Ovarian cysts were significantly increased in the 1 μg/kg bw/day group; ovarian cyst-adenomas were seen in the other three BPA-treated groups but not in corn-oil controls. We observed increased progressive proliferative lesions of the oviduct after BPA treatment, similar to those described in response to DES. Further, although not statistically different from the controls, prominent mesonephric (Wolffian) remnants and squamous metaplasia of the uterus, as well as vaginal adenosis, were present in BPA-treated mice, similar to lesions reported following DES treatment. More severe pathologies observed in some BPA-treated animals included atypical hyperplasia and stromal polyps of the uterus; sarcoma of the uterine cervix; and mammary adenocarcinoma. We did not observe these lesions in controls. |
| **74** | 2009 | Salian, S., Doshi, T., and Vanage, G. (2009). Impairment in protein expression profile of testicular steroid receptor coregulators in male rat offspring perinatally exposed to Bisphenol A. Life Sci 85, 11-18. | Holtzman rats | Pregnant and lactating F0 dams | GD 12-PND 21 | Oral | 1.2, 2.4 μg/kg bw/day | 【testis】 Immunohistochemical localization of SRC-1, GRIP-1, p/ClP, NCaR in testis: F1, F2, F3 generations, PND 125 | A significant reduction in the expression of SRC-1 and NCoR, with a parallel increase in the expression of p/CIP and GRIP-1, was observed in the testes of rats exposed perinatally to BPA. A similar pattern was observed in the testes of F2 and F3 rats. |
| **75** | 2009 | Salian, S., Doshi, T., and Vanage, G. (2009). Neonatal exposure of male rats to Bisphenol A impairs fertility and expression of sertoli cell junctional proteins in the testis. Toxicology 265, 56-67. | Holtzman rats | Neonatal pups ［♂］ | PND 1-5 | Subcutaneous | 100, 200, 400, 800, 1,600 μg/kg bw/day | 【reproductive system】Fertility assessment with normally cycling adult females: PND 75, Immunohistochemical localizationin testicular for Cx-43, ZO-1, N-cadherin: PND 15, 30, 45, 90, Epididymal sperm count and motility: PND 125, ［♂］ | Females mated with male rats that were exposed neonatally to various concentrations of BPA showed a significant increase in post-implantation loss and a decrease in litter size. There were significant changes in sperm count along with hormonal imbalances in the rats exposed neonatally to BPA. 400 μg/kg bw/day of BPA was determined as the lowest dose that was capable of impairing male fertility. A significant reduction in the expression of Cx-43 (PND 45 and 90) and increases in the expression of N-cadherin (PND 45 and 90) and ZO-1 (PND 90) were observed in the testes of rats exposed neonatally to effective dose of BPA. There was an altered expression pattern of Cx43 amongst the sloughed cells in the testes of the experimental rats as compared to controls. |
| **76** | 2009 | Salian, S., Doshi, T., and Vanage, G. (2009). Perinatal exposure of rats to Bisphenol A affects the fertility of male offspring. Life Sci 85, 742-752. | Holtzman rats | Pregnant and lactating F0 dams | GD 12-PND 21 | Oral | 1.2, 2.4 μg/kg bw/day | 【reproductive system】Fertility assessment with normally cycling adult females: F1, F2, F3 generation, PND 75, Immunohistochemical localization of testicular steroid receptors: F1, F2, F3 generation, PND 125, ［♂］ | A significant increase in post implantation loss and a decrease in litter size and sperm count and motility were observed in the F1 male offspring. A reduction in the testicular expression profile of testicular steroid receptors was observed. These effects were very prominent in the subsequent F2 and F3 generations. |
| **77** | 2009 | Somm, E., Schwitzgebel, V.M., Toulotte, A., Cederroth, C.R., Combescure, C., Nef, S., Aubert, M.L., and Huppi, P.S. (2009). Perinatal exposure to bisphenol A alters early adipogenesis in the rat. Environ Health Perspect 117, 1549-1555. | Sprague-Dawley rats | Pregnant and lactating dams | GD 6-PND 21 | Drinking water | 70 μg/kg bw/day | 【obesity】Histopathological analysis, Gene expression of perigonadal adipose tissue: PND 21 ［♂♀］ | On PND 1, the weight of male and female BPA-exposed pups was increased. On PND 21, body weight was increased only in females, in which parametrial white adipose tissue (pWAT) weight was increased about 3-fold. This excess of pWAT was associated with adipocyte hypertrophy and overexpression of lipogenic genes such as C/EBP-a (CAAT enhancer binding protein alpha), PPAR-g (peroxisome proliferator-activated receptor gamma), SREBP-1C (sterol regulatory element binding protein-1C), LPL (lipoprotein lipase), FAS (fatty acid synthase), and SCD-1 (stearoyl-CoA desaturase 1). In addition, gene expression of SREBP-1C, FAS, and ACC (acetyl-CoA carboxylase) was also increased in liver from BPA-exposed females at PND 21, without a change in circulating lipids and glucose. After weaning, perinatal BPA exposure predisposed to overweight in a sex- and diet-dependent manner. |
| **78** | 2008 | Moral, R., Wang, R., Russo, I.H., Lamartiniere, C.A., Pereira, J., and Russo, J. (2008). Effect of prenatal exposure to the endocrine disruptor bisphenol A on mammary gland morphology and gene expression signature. J Endocrinol 196, 101-112. | Sprague Dawley CD rats | Pregnant dams | GD 10–21 | Oral | 25, 250 μg/kg bw/day | 【mammary gland】Mammary gland morphology, Gene expression by microarray, real-time RT-PCR: PND 21, 35, 50, 100 ［♀］ | BPA exposure induced changes in the mammary gland that were time and dose specific. High-dose exposure resulted in architectural modifications, mainly in the number of undifferentiated epithelial structures of the breast tissue. Low and high doses of BPA changed the gene expression signature of the mammary gland following a different fashion: low dose had the highest effect by PND 50, while high dose had a highest influence on gene expression by PND 100. Both doses presented a significant cluster of up-modulated genes related to the immune system at the age of maximal changes. |
| **79** | 2008 | Patisaul, H.B., and Bateman, H.L. (2008). Neonatal exposure to endocrine active compounds or an ERb agonist increases adult anxiety and aggression in gonadally intact male rats. Horm Behav 53, 580-588. | Long-Evans rats | Neonatal pups ［♂］ | PND 0-3 | Subcutaneous | 50 μg/kg bw/day | 【behavior】Anxiety testing: PND 56-61, Aggression testing: PND 121 | Fewer open arm entries, and spent significantly less time in the open arms. Time spent in the closed arms was significantly increased. Significantly increased adult (PND 68) body weight. |
| **80** | 2008 | Vandenberg, L.N., Maffini, M.V., Schaeberle, C.M., Ucci, A.A., Sonnenschein, C., Rubin, B.S., and Soto, A.M. (2008). Perinatal exposure to the xenoestrogen bisphenol-A induces mammary intraductal hyperplasias in adult CD-1 mice. Reprod Toxicol 26, 210-219. | CD-1 mice | Pregnant and lactating dams | GD 8- PND 16 | Pumps s.c. | 0.25, 2.5, 25 μg/kg bw/day | 【mammary glands】 Histopathological analysis of mammary glands: 3, 9, 12–15 months old | BPA-exposed females demonstrated altered mammary phenotypes including the appearance of alveolar buds. Additionally, intraductal hyperplasias were observed exclusively in BPA-exposed females. These lesions had the appearance of "beaded" ducts, with epithelial cells present inside the ductal lumen and increased proliferation indexes compared to normal ducts. |
| **81** | 2008 | Varayoud, J., Ramos, J.G., Bosquiazzo, V.L., Munoz-de-Toro, M., and Luque, E.H. (2008). Developmental exposure to Bisphenol A impairs the uterine response to ovarian steroids in the adult. Endocrinology 149, 5848-5860. | Wistar rats | Neonatal pups ［♀］ | PND 1, 3, 5, 7 | Subcutaneous | 50, 20,000 μg/kg bw/day | 【uterus】Hoxa10 and Hoxa11 mRNA in uterine expression: PND 8, Uterine response to hormonal stimuli in OVX rats after progesterone plus E2 treatment : PND 93 | At PND 8, real time RT-PCR assays showed a decrease in Hoxa10 and Hoxa11 expression in both treated groups. Low dose of BPA but not high dose of rats failed to up-regulate ERa in response to P+E. The ovarian steroid induction of Hoxa10 mRNA expression was significantly attenuated in neonatally both BPA-exposed rats compared with controls exposed to corn oil. Regarding Hoxa11 mRNA, rats neonatally exposed to high dose of BPA showed no differences compared with controls, whereas in the low dose of BPA, a significant down regulation was observed. |
| **82** | 2008 | Yan, H., Takamoto, M., and Sugane, K. (2008). Exposure to Bisphenol A prenatally or in adulthood promotes TH2 cytokine production associated with reduction of CD4+CD25+ regulatory T cells. Environ Health Perspect 116, 514-519. | BALB/c mice | Dams | from 2 weeks before mating to 7 dpc (total 3 weeks) | Drinking water | 0.03, 0.3, 3 μg/kg bw/day | 【immune】Th1/Th2 immune responses (Footpad swelling): PND 10 ［♂］ | Mice exposed to BPA prenatally showed a dose-dependent increase in footpad swelling after being infected with L. major. Mice prenatally exposed to BPA showed increased production of not only IL-4 but also IFN-g. The percentages of CD4+CD25+ cells were decreased. |
| **83** | 2008 | Yaoi, T., Itoh, K., Nakamura, K., Ogi, H., Fujiwara, Y., and Fushiki, S. (2008). Genome-wide analysis of epigenomic alterations in fetal mouse forebrain after exposure to low doses of bisphenol A. Biochem Biophys Res Commun 376, 563-567. | ICR/Jcl mice | Pregnant dams | GD 0-14.5 | Subcutaneous | 20 μg/kg bw/day | 【brain】Genome-wide effect of maternal exposure to BPA on the epigenome in forebrain: E 12.5, 14.5 | Maternal exposure to BPA can cause both hyper- and hypomethylation at the promoter-associated CpG islands of multiple unique loci in the developing mouse forebrain |
| **84** | 2007 | Durando, M., Kass, L., Piva, J., Sonnenschein, C., Soto, A.M., Luque, E.H., and Munoz-de-Toro, M. (2007). Prenatal bisphenol A exposure induces preneoplastic lesions in the mammary gland in Wistar rats. Environ Health Perspect 115, 80-86. | Wistar rats | Pregnant dams | GD 8-GD 23 | Pumps s.c. | 25 μg/kg bw/day | 【carcinogenesis, mammary gland】N-nitroso-N-methylurea (NMU)-induced mammary gland carcinogenesis: PND 110, 180 | At puberty, animals exposed prenatally to BPA showed an increased proliferation/apoptosis ratio in both the epithelial and stromal compartments. During adulthood (PND 110 and PND 180), BPA-exposed animals showed an increased number of hyperplastic ducts and augmented stromal nuclear density. Moreover, the stroma associated with hyperplastic ducts showed signs of desmoplasia and contained an increased number of mast cells, suggesting a heightened risk of neoplastic transformation. Administration of a subcarcinogenic dose of NMU to animals exposed prenatally to BPA increased the percentage of hyperplastic ducts and induced the development of neoplastic lesions. |

| No. | Year | Reference | Species | Stage | Exposure Period | Route | Dose | Endpoints | Effects |
|---|---|---|---|---|---|---|---|---|---|
| **85** | 2007 | Gioiosa, L., Fissore, E., Ghirardelli, G., Parmigiani, S., and Palanza, P. (2007). Developmental exposure to low-dose estrogenic endocrine disruptors alters sex differences in exploration and emotional responses in mice. Horm Behav 52, 307-316. | CD-1 mice | Pregnant and lactating dams | GD 11-PND 8 | Oral | 10 μg/kg bw/day | 【behavior】 Novelty-seeking test, Free-exploratory open-field test, Elevated plus maze test: PND 70 [♂♀] | The main results are sex differences in control mice on a number of behavioral responses at both ages and in all experimental paradigms, while perinatal exposure to BPA decreased or eliminated such sex differences. |
| **86** | 2007 | Miyawaki, J., Sakayama, K., Kato, H., Yamamoto, H., and Masuno, H. (2007). Perinatal and postnatal exposure to bisphenol a increases adipose tissue mass and serum cholesterol level in mice. J Atheroscler Thromb 14, 245-252. | ICR mice | Pregnant and lactating dams-Pups | GD 10-PND 30 | Drinking water | 260, 2,720 μg /kg bw/day | 【obesity】Body weight, Adipose tissue weight, Serum lipid levels: PND 31 [♂♀] | In females, the mean body weight increased in both groups. The mean adipose tissue weight increased in the low dose group. The mean total cholesterol level increased. In males, the mean body weight and mean adipose tissue weight increased in the high dose group. The mean triacylglycerol level increased in the low dose group. |
| **87** | 2007 | Murray, T.J., Maffini, M.V., Ucci, A.A., Sonnenschein, C., and Soto, A.M. (2007). Induction of mammary gland ductal hyperplasias and carcinoma in situ following fetal bisphenol A exposure. Reprod Toxicol 23, 383-390. | Wistar-Furth rats | Pregnant dams | E 9-PND 1 | Pumps s.c. | 2.5, 25, 250 and 1,000 μg /kg/day | 【mammary gland】Induction of mammary gland ductal hyperplasias and carcinoma: PND 50, 95 | Exposure of fetuses to all BPA doses resulted in a significant 3–4 fold increase in the incidence of hyperplastic ducts relative to the controls at PND 50. At PND 95 the percentage of hyperplastic ducts was lower overall than the PND 50 animals, only the incidence of hyperplastic lesions observed in the BPA 2.5 μg/kg bw/day group was significantly higher than those of the vehicle-exposed controls. In addition to the increased number of hyperplastic ducts, cribriform-like structures were also observed in the mammary glands of BPA (250, 1,000 μg/kg bw/day) rats at PND 50 and PND 95. |
| **88** | 2007 | Nakamura, K., Itoh, K., Sugimoto, T., and Fushiki, S. (2007). Prenatal exposure to bisphenol A affects adult murine neocortical structure. Neurosci Lett 420, 100-105. | ICR/Jcl mice | Pregnant dams | E 0.5- 14.5 | Subcutaneous | 20 μg/kg bw/day | 【brain】BrdU labeled cells in cortex: P3W, P12W | The BrdU-positive cells labeled at E14.5 were significantly increased in the Vth and VIth cortical layers of BPA-treated mice at P3W, whereas they were confined to the IVth layer of control mice, though such differences disappeared at P12W. The thalamocortical projections demonstrated by DiI-labeling were abnormal at P3W and P12W in BPA-treated mice. |
| **89** | 2007 | Newbold, R.R., Jefferson, W.N., and Padilla-Banks, E. (2007). Long-term adverse effects of neonatal exposure to bisphenol A on the murine female reproductive tract. Reprod Toxicol 24, 253-258. | CD-1 mice | Neonatal pups [♀] | PND 1-5 | Subcutaneous | 10, 100, 1000 μg/kg bw/day | 【reproductive system】Histopathological analysis of ovaries and reproductive tract tissues: 18 months old | There was a statistically significant increase in cystic ovaries and cystic endometrial hyperplasia in the BPA-100 μg/kg bw/day group as compared to Controls. Progressive proliferative lesion of the oviduct and cystic mesonephric (Wolffian) duct remnants were also seen in all of the BPA groups. More severe pathologies of the uterus following neonatal BPA treatment included adenomyosis, leiomyomas, atypical hyperplasia, and stromal polyps. |
| **90** | 2007 | Ohshima, Y., Yamada, A., Tokuriki, S., Yasutomi, M., Omata, N., and Mayumi, M. (2007). Transmaternal exposure to bisphenol A modulates the development of oral tolerance. Pediatr Res 62, 60-64. | BALB-C mice: OVA-TCR-Tg [♂] , Wild [♀] | Pregnant and lactating F0 dams | GD 0-PND 21 | Diet | 10, 100 μg/kg bw/day | 【immune】Antigen-specific responses: mononuclear cells from spleens of F1 [♂] OVA-TCR-Tg: PND 21 | Oral administration of both high and low doses of ovalbumin (OVA) suppressed OVA-specific cell proliferation and cytokine production in both BPA-exposed and nonexposed control mice, but the OVA-mediated suppression was significantly more diminished by the BPA exposure. The accumulation of CD4+CD25+Foxp3+ T cells was diminished in the BPA-exposed offspring. Moreover, after low dose OVA administration, serum OVA-specific IgG1 and IgG2a levels were higher in the BPA-exposed offspring than in nonexposed ones. |
| **91** | 2007 | Vandenberg, L.N., Maffini, M.V., Wadia, P.R., Sonnenschein, C., Rubin, B.S., and Soto, A.M. (2007). Exposure to environmentally relevant doses of the xenoestrogen bisphenol-A alters development of the fetal mouse mammary gland. Endocrinology 148, 116-127. | CD-1 mice | Pregnant dams | E 8-18 | Pumps s.c. | 0.25 μg/kg bw/day | 【mammary glands】 Immunohistochemistry of mammary gland : E18 | Significantly increased ductal area and ductal extension in exposed fetuses and obliterated positional differences. In the stroma, BPA exposure promoted maturation of the fat pad and altered the localization of collagen. Within the epithelium, BPA exposure led to a decrease in cell size and delayed lumen formation. |
| **92** | 2007 | Wadia, P.R., Vandenberg, L.N., Schaeberle, C.M., Rubin, B.S., Sonnenschein, C., and Soto, A.M. (2007). Perinatal bisphenol A exposure increases estrogen sensitivity of the mammary gland in diverse mouse strains. Environ Health Perspect 115, 592-598. | CD-1, C57BL/6J mice | Pregnant dams | GD 8-PND 2 | Pumps s.c. | 0.25 μg/kg bw/day | 【mammary gland】Sensitivity of the mammary glands to E2 at puberty: PND 35 [♀] | Both strains exhibited similar responses to E2. Perinatal BPA exposure altered responses to E2 at puberty for several parameters in both strains, although the effect in CD-1 was slightly more pronounced. |
| **93** | 2006 | Della Seta, D., Minder, I., Belloni, V., Aloisi, A.M., Dessi-Fulgheri, F., and Farabollini, F. (2006). Pubertal exposure to estrogenic chemicals affects behavior in juvenile and adult male rats. Horm Behav 50, 301-307. | Sprague-Dawley rats | Neonatal pups [♂♀] | PND 23-30 | Oral | 40 μg/kg bw/day | 【behavior】Behavioral testing: PND 45, 90, Hormone assays: PND 37, 105, [♂] | Exposure to BPA altered the temporal pattern of male sexual activity, reducing performance, in the adult animals. Short-term behavioral effects were observed in the treated animals with BPA: the exploratory drive, directed to a stimulus object and to the environment, as well as to conspecifics, was reduced in the juveniles. Modifications in the circulating Testosterone (T) levels were observed after treatments: T was reduced in the juveniles. The decrement persisted in the adult animals but reached significance. |
| **94** | 2006 | Fujimoto, T., Kubo, K., and Aou, S. (2006). Prenatal exposure to bisphenol A impairs sexual differentiation of exploratory behavior and increases depression-like behavior in rats. Brain Res 1068, 49-55. | Wistar rats | Pregnant dams | during the final week of pregnant | Drinking water | 15 μg/kg bw/day | 【behavior】Open-field test: P6W, Elevated plus maze test: P7W, Passive avoidance test: P8W, Forced swimming test: P9W, [♂♀] | Prenatal exposure to BPA mainly affected male rats and abolished sex differences in rearing behavior in the open-field test and struggling behavior in the forced swimming test. BPA increased the immobility of male rats in the forced swimming test. The avoidance learning and behaviors in the elevated plus maze were not affected. |
| **95** | 2006 | Ho, S.M., Tang, W.Y., Belmonte de Frausto, J., and Prins, G.S. (2006). Developmental exposure to estradiol and bisphenol A increases susceptibility to prostate carcinogenesis and epigenetically regulates phosphodiesterase type 4 variant 4. Cancer research 66, 5624-5632. | Sprague-Dawley rats | Neonatal pups [♂♀] | PND 1, 3, 5 | Subcutaneous | 10 μg/kg bw/day | 【carcinogenesis, prostate】Prostate gland susceptibility, Hormonal carcinogenesis: P28W, DNA methylation analysis in prostates: PND 10, 90, 200 | Neonatal exposure to BPA significantly increased the intraepithelial neoplasia incidence and score following adult exposure to elevated testosterone plus estradiol. BPA exposure followed by adult hormones also significantly increased proliferation in regions with high-grade intraepithelial neoplasia with high basal rates of apoptosis. Although methylation frequency at CpGs sites 49 to 56 progressively increased in the oil-control prostates as the animals aged, reaching 100% methylation by day 200, these sites remained relatively hypomethylated in aging prostates exposed neonatally to BPA. |
| **96** | 2006 | Nakamura, K., Itoh, K., Yaoi, T., Fujiwara, Y., Sugimoto, T., and Fushiki, S. (2006). Murine neocortical histogenesis is perturbed by prenatal exposure to low doses of Bisphenol A. Journal of neuroscience research 84, 1197-1205. | ICR/Jcl mice | Pregnant dams | E 0-16.5 | Subcutaneous | 20 μg/kg bw/day | 【behavior, brain】 Morphology and the expression of some genes related to brain development in neocortex: E 12.5, 14.5, 16.5 | The BrdU-labeled cells, analyzed 2 days after BrdU injection, were decreased in the ventricular zone of BPA-treated mice at E 14.5 and E1 6.5, whereas they were increased in the cortical plate at E 14.5 as compared with those in control mice. The expression of Math3, Ngn2, Hes1, L1CAM, and THRa was significantly upregulated at E 14.5 in the BPA-treated group. |
| **97** | 2006 | Narita, M., Miyagawa, K., Mizuo, K., Yoshida, T., and Suzuki, T. (2006). Prenatal and neonatal exposure to low-dose of bisphenol-A enhance the morphine-induced hyperlocomotion and rewarding effect. Neurosci Lett 402, 249-252. | ddY mice | Pregnant and lactating dams | GD 0-PND 21 | Diet | (0.03, 3, 2,000 μg/g diet) | 【behavior, brain】 Morphine-induced rewarding effect , hyperlocomotion: P7W [♂] | On rewarding effect, treatment with morphine produced a significant place preference in the mice chronically treated with low- and high-dose of bisphenol-A, but not middle-dose of bisphenol-A. In mice chronically treated with low- and high-dose of bisphenol-A, but not middle-dose of bisphenol-A, the hyperlocomotion induced by morphine was dramatically potentiated as compared to that in control. Additionally, the treatment with bisphenol-A produced an up-regulation of dopamine receptor function to activate G-protein in the mouse limbic forebrain. |
| **98** | 2006 | Rubin, B.S., Lenkowski, J.R., Schaeberle, C.M., Vandenberg, L.N., Ronsheim, P.M., and Soto, A.M. (2006). Evidence of altered brain sexual differentiation in mice exposed perinatally to low, environmentally relevant levels of bisphenol A. Endocrinology 147, 3681-3691. | CD-1 mice | Pregnant and lactating dams | GD 8-PND 16 | Pumps s.c. | 0.025, 0.25 μg/kg bw/day | 【behavior, brain】Brain sexual differentiation: PND 22–24 [♂♀] , Open field test: P6W–P9W [♂♀] | The significant sex differences in tyrosine hydroxylase (TH) neuron number observed in control offspring were diminished or obliterated in offspring exposed to BPA primarily because of a decline in TH neuron number in BPA-exposed females. Significant sex differences in the vehicle-exposed offspring that were not observed in the BPA-exposed offspring on sexually dimorphic behaviors in the open field. |

| No. | Year | Reference | Species | Stage | Exposure Period | Route | Dose | Endpoints | Effects |
|---|---|---|---|---|---|---|---|---|---|
| **99** | 2006 | Ryan, B.C., and Vandenbergh, J.G. (2006). Developmental exposure to environmental estrogens alters anxiety and spatial memory in female mice. Horm Behav 50, 85-93. | C57BL/6 mice | Pregnant and lactating dams | GD 3-PND 21 | Oral | 2, 200 μg/kg bw/day | 【behavior】Elevated-plus maze test, Light/dark preference chamber test: PND 42 [♀] | Animals in BPA 200 μg/kg bw/day groups reached puberty at a significantly earlier age than the vehicle control group. The BPA 200 μg/kg bw/day group spent marginally less time in the open arms than controls, although this difference did not reach significance. The BPA 200 μg/kg bw/day-treated animals spent less time in the lighted section than did the control animals. |
| **100** | 2005 | Della Seta, D., Minder, I., Dessi-Fulgheri, F., and Farabollini, F. (2005). Bisphenol-A exposure during pregnancy and lactation affects maternal behavior in rats. Brain Res Bull 65, 255-260. | Sprague-Dawley rats | Pregnant and lactating dams | GD 0-PND 21 | Oral | 40 μg/kg bw/day | 【behavior】Maternal behavior: PND 3-4, 8-9 [♂♀] | Different maternal behavioral patterns towards male and female pups of control mothers, with more ano-genital licking to males than to females. Exposure of mothers to BPA modified their behavior, reducing specific components of maternal behavior, both active and passive, irrespective of the sex of pups and the period of observation |
| **101** | 2005 | Laviola, G., Gioiosa, L., Adriani, W., and Palanza, P. (2005). D-amphetamine-related reinforcing effects are reduced in mice exposed prenatally to estrogenic endocrine disruptors. Brain Res Bull 65, 235-240. | CD-1 mice | Pregnant dams | GD 11-18 | Oral | 10 μg/kg bw/day | 【behavior】Amphetamine conditioned place preference: PND 60 [♂♀] | A clear-cut profile of D-amphetamine-induced conditioned place preference was only shown by oil-exposed females, whereas exposure to bisphenol-A resulted in little or no place conditioning. |
| **102** | 2005 | Markey, C.M., Wadia, P.R., Rubin, B.S., Sonnenschein, C., and Soto, A.M. (2005). Long-term effects of fetal exposure to low doses of the xenoestrogen bisphenol-A in the female mouse genital tract. Biol Reprod 72, 1344-1351. | CD-1 mice | Pregnant dams | GD 9-23 | Pumps s.c. | 0.025, 0.25 μg/kg bw/day | 【reproductive system】Histopathological analysis, Morphometric analysis of uterus: 3 months old | They include decreased wet weight of the vagina, decreased volume of the endometrial lamina propria, increased incorporation of bromodeoxyuridine into the DNA of endometrial gland epithelial cells, and increased expression of ERa and progesterone receptor in the luminal epithelium of the endometrium and subepithelial stroma. |
| **103** | 2005 | Munoz-de-Toro, M., Markey, C.M., Wadia, P.R., Luque, E.H., Rubin, B.S., Sonnenschein, C., and Soto, A.M. (2005). Perinatal exposure to bisphenol-A alters peripubertal mammary gland development in mice. Endocrinology 146, 4138-4147. | CD-1 mice | Pregnant and lactating dams | GD 9-PND 4 | Pumps s.c. | 0.025, 0.25 μg/kg bw/day | 【mammary gland】Histopathological analysis, Morphometric analysis of mammary gland： PND 20, 30, 120 | In their intact 30 days old littermates, the area and numbers of terminal end buds relative to the gland ductal area increased whereas their apoptotic activity decreased. There was a positive correlation between ductal length and the age at first proestrus; that was reduced as the BPA dose increased. There was also a significant increase of progesterone receptor-positive ductal epithelial cells that were localized in clusters. Lateral branching was significantly enhanced at 4 months old in mice exposed to BPA 25 ng/kg bw/day. |
| **104** | 2005 | Porrini, S., Belloni, V., Della Seta, D., Farabollini, F., Giannelli, G., and Dessi-Fulgheri, F. (2005). Early exposure to a low dose of bisphenol A affects socio-sexual behavior of juvenile female rats. Brain Res Bull 65, 261-266. | Sprague-Dawley rats | Pregnant and lactating dams | GD 0-PND 21 | Oral | 40 μg/kg bw/day | 【behavior】Behavioral testing: PND 35, 45, 55 [♀] | Early administration of BPA was responsible for a significant increase of exploration (including social investigation), as well as a decrease of play with males and social grooming at 45 days of age, indicating a general decrease of playful interactions. |
| **105** | 2005 | Razzoli, M., Valsecchi, P., and Palanza, P. (2005). Chronic exposure to low doses bisphenol A interferes with pair-bonding and exploration in female Mongolian gerbils. Brain Res Bull 65, 249-254. | Mongolian gerbils | 12-13 weeks old [♀] | From day of pairing to day 21 of cohabitation ( total 3 weeks) | Oral | 2, 20 μg/kg bw/day | 【behavior】Pairs' behavior: from day of pairing throughout day 21, Free exploratory test: 21 days after pairing [♀] | BPA affected male-female social interactions by increasing social investigation. BPA reduced several exploratory parameters, indicating a decreased exploratory propensity of females. |
| **106** | 2005 | Timms, B.G., Howdeshell, K.L., Barton, L., Bradley, S., Richter, C.A., and vom Saal, F.S. (2005). Estrogenic chemicals in plastic and oral contraceptives disrupt development of the fetal mouse prostate and urethra. Proc Natl Acad Sci U S A 102, 7014-7019. | CD-1 mice | Pregnant dams | GD 14-18 | Oral | 10 μg/kg bw/day | 【prostate】Morphology using computer-assisted 3D reconstruction, Histochemical analysis of prostate: GD 19 | In male mouse fetuses, BPA produced an increase in the number and size of dorsolateral prostate ducts and an overall increase in prostate duct volume. Histochemical staining of sections with antibodies to proliferating cell nuclear antigen and mouse keratin 5 indicated that these increases were due to a marked increase in proliferation of basal epithelial cells located in the primary ducts. The urethra was malformed in the colliculus region and was significantly constricted where it enters the bladder, which could contribute to urine flow disorders. |
| **107** | 2004 | Negishi, T., Kawasaki, K., Suzaki, S., Maeda, H., Ishii, Y., Kyuwa, S., Kuroda, Y., and Yoshikawa, Y. (2004). Behavioral alterations in response to fear-provoking stimuli and tranylcypromine induced by perinatal exposure to bisphenol A and nonylphenol in male rats. Environ Health Perspect 112, 1159-1164. | F344/N rats | Pregnant and lactating dams | GD 3-PND 20 | Oral | 100 μg/kg bw/day | 【behavior】Open field test: P8W, Spontaneous motor activity: P12W, Passive avoidance test: P13W, Elevated plus maze test: P14W, Active avoidance test: P5W, Monoamine-disruption test: P22W–P24W, [♂] | A passive avoidance test (13 weeks old) showed that BPA-treated offspring tended to delay entry into a dark compartment. An active avoidance test at 15 weeks of age revealed that BPA-treated offspring showed significantly fewer avoidance responses. BPA-treated offspring significantly increased the number of failures to avoid electrical unconditioned stimuli within 5-sec electrical shock presentation compared with the control offspring. In a monoamine-disruption test using tranylcypromine (Tcy), a monoamine oxidase inhibitor, BPA-treated offspring at 22-24 weeks of age failed to show a significant increment in locomotion in response to Tcy, whereas control offspring significantly increased locomotion behavior after Tcy injection. |
| **108** | 2004 | Yoshino, S., Yamaki, K., Li, X., Sai, T., Yanagisawa, R., Takano, H., Taneda, S., Hayashi, H., and Mori, Y. (2004). Prenatal exposure to bisphenol A up-regulates immune responses, including T helper 1 and T helper 2 responses, in mice. Immunology 112, 489-495. | DBA/1 J mice | Pregnant dams | GD 0-18 | Oral | 3. 30, 300, 3,000 μg/kg bw/day | 【immune】Immunization with hen egg lysozyme (HEL): PND 77 [♂♀] , Measurement of HEL-specific antibodies, Th1 and Th2 responses of spleen: PND 98 [♂♀] | Production of anti-HEL IgG was increased, in a dose-related manner, in mice fetally exposed to BPA (300, 3,000 μg/kg bw/day). Treatment with BPA (30, 300, 3,000 μg/kg bw/day) was followed by a significant increase in anti-HEL IgG2a. Exposure to BPA (300, 3,000 μg/kg bw/day) was followed by a dose-related increase in IFN-g. Significant augmentation of IL-4 was seen in mice prenatally treated with 300 or 3,000 μg/kg bw/day of BPA. |
| **109** | 2003 | Adriani, W., Seta, D.D., Dessi-Fulgheri, F., Farabollini, F., and Laviola, G. (2003). Altered profiles of spontaneous novelty seeking, impulsive behavior, and response to D-amphetamine in rats perinatally exposed to bisphenol A. Environ Health Perspect 111, 395-401. | Sprague-Dawley rats | Pregnant and lactating dams | GD 0-PND 21 | Oral | 40 μg/kg bw/day | 【behavior】Novelty preference test: PND 35-45, Impulsivity test, Open field test with amphetamine: adult, [♂♀] | BPA-exposed females spent significantly less time in exploration of the novel side, whereas no effect was found in the male group. A reduced level of impulsive behavior was evidenced in BPA-treated rats. The frequency of inadequate responding (during the length of the delay) also provided a measure of restless behavior. Interestingly, the profile of BPA-treated males was feminized, strongly resembling that of control females. In the response to an amphetamine challenge, the drug-induced increment activity was significantly less marked in BPA-treated male rats compared with controls. |
| **110** | 2003 | Carr, R., Bertasi, F., Betancourt, A., Bowers, S., Gandy, B.S., Ryan, P., and Willard, S. (2003). Effect of neonatal rat bisphenol A exposure on performance in the Morris water maze. J Toxicol Environ Health A 66, 2077-2088. | Fischer 344 rats | Neonatal pups [♂♀] | PND 1-14 | Oral | 100, 250 μg/kg bw/day | 【behavior】Swim channel test : PND 33, Morris water maze: PND 34, [♂♀] | Acquisition of maze performance was significantly better in control males than in control females. Treatment with low BPA disrupted this normal gender-dependent pattern of acquisition, while treatment with high BPA did not. In a probe trial (PND 40), females treated with high BPA spent significantly less time in the escape quadrant. |
| **111** | 2003 | Kubo, K., Arai, O., Omura, M., Watanabe, R., Ogata, R., and Aou, S. (2003). Low dose effects of bisphenol A on sexual differentiation of the brain and behavior in rats. Neurosci Res 45, 345-356. | Wistar rats | Pregnant and lactating dams | GD 0-PND 21 | Drinking water | 30, 300 μg/kg bw/day | 【behavior, brain】Open field test: P6W, Sexual behavior: P11W-P12W [♂♀] , Reproductive organ weights, Sperm counts and serum Hormone levels: P12W [♂] , Measurements of sexually dimorphic nuclei: P14W [♂♀] | BPA abolished and inverted the sex differences of the open-field behavior and the locus coeruleus volume, respectively, without affecting the reproductive system. |

| No. | Year | Reference | Species | Stage | Exposure Period | Route | Dose | Endpoints | Effects |
|---|---|---|---|---|---|---|---|---|---|
| **112** | 2002 | Aloisi, A.M., Della Seta, D., Rendo, C., Ceccarelli, I., Scaramuzzino, A., and Farabollini, F. (2002). Exposure to the estrogenic pollutant bisphenol A affects pain behavior induced by subcutaneous formalin injection in male and female rats. Brain Res 937, 1-7. | Sprague-Dawley rats | Pregnant dams or Lactating dams | GD 0-21 or PND 0-21 | Oral | 40 μg/kg bw/day | 【pain test】Pain test : P22W［♂♀］ | BPA-prenatal treatment induced an increase in licking duration in females and in flexing duration in both sexes in the first half of the test (0-30 min after formalin injection). BPA-postnatal treatment induced a decrease in paw-jerk frequency in males and females during the second part of the test (30-60 min after formalin injection). |
| **113** | 2002 | Dessi-Fulgheri, F., Porrini, S., and Farabollini, F. (2002). Effects of perinatal exposure to bisphenol A on play behavior of female and male juvenile rats. Environ Health Perspect 110 Suppl 3, 403-407. | Sprague-Dawley rats | Pregnant and lactating dams | from day 10 before mating to PND 21: 40 μg/kg bw/day, GD 14-PND 6 : 400 μg/kg bw/day | Oral | 40, 400 μg/kg bw/day | 【behavior】Behavioral testing: PND 35, 45, 55［♂♀］ | An early action of BPA on several behavioral categories in both males and females, in particular, a masculinization of female behavior in two behavioral categories (play with females and sociosexual exploration). |
| **114** | 2002 | Farabollini, F., Porrini, S., Della Seta, D., Bianchi, F., and Dessi-Fulgheri, F. (2002). Effects of perinatal exposure to bisphenol A on sociosexual behavior of female and male rats. Environ Health Perspect 110 Suppl 3, 409-414. | Sprague-Dawley rats | Pregnant dams or Lactating dams | GD 0-21 or PND 0-21 | Oral | 40 μg/kg bw/day | 【behavior】Intruder test, Sexual orientation test, Sexual activity test: PND 100［♂♀］ | An intruder test revealed in males but not in females an increase in defensive behavior due to prenatal exposure of BPA. In males, an increase of the number of intromissions due to BPA was evident only in the postnatal exposure group, and significant effects only in the perinatal exposure increased latency to intromission and genital sniff duration, on sexual behavior. In females, BPA produced a small increase in sexual motivation and receptive behavior. |
| **115** | 2002 | Honma, S., Suzuki, A., Buchanan, D.L., Katsu, Y., Watanabe, H., and Iguchi, T. (2002). Low dose effect of in utero exposure to bisphenol A and diethylstilbestrol on female mouse reproduction. Reprod Toxicol 16, 117-122. | ICR/Jcl mice | Pregnant F0 dams | GD 11-17 | Subcutaneous | 2, 20 μg/kg bw/day | 【reproductive system】 Vaginal opening, Estrous cycle, Reproductive ability: F1［♀］ PND 0-120 | The age at vaginal opening was significantly earlier in all exposed females except for 2 μg/kg bw/day BPA females compared to oil controls. Body weight at vaginal opening was lower than controls in all exposed females. The first vaginal estrus was earlier in all exposed females except for the 2 μg/kg bw/day BPA group females compared to controls. |
| **116** | 2002 | Palanza, P.L., Howdeshell, K.L., Parmigiani, S., and vom Saal, F.S. (2002). Exposure to a low dose of bisphenol A during fetal life or in adulthood alters maternal behavior in mice. Environ Health Perspect 110 Suppl 3, 415-422. | CD-1 mice | Pregnant dams (F0, F1) | GD 14-18 | Oral | 10 μg/kg bw/day | 【behavior】Maternal behavior: F1［♀］ LD 2–15, Measurements of the offspring's postnatal development: F2 PND 2-15 | Dams exposed to BPA either as fetuses or in adulthood spent less time nursing their pups and more time out of the nest compared with the control group. Females exposed to BPA both as fetuses and in adulthood did not significantly differ from controls. No alterations in postnatal reflex development were observed in the offspring of the females exposed to BPA. |
| **117** | 2001 | Markey, C.M., Luque, E.H., Munoz De Toro, M., Sonnenschein, C., and Soto, A.M. (2001). In utero exposure to bisphenol A alters the development and tissue organization of the mouse mammary gland. Biol Reprod 65, 1215-1223. | CD-1 mice | Pregnant dams | GD 9-21 | Pumps s.c. | 25, 250 μg/kg bw/day | 【mammary gland】Histopathological analysis, Morphometric analysis on mammary gland: PND 10, 1, 6 months old | Mammary glands of BPA-exposed mice showed differences in the rate of ductal migration into the stroma at 1 months old and a significant increase in the percentage of ducts, terminal ducts, terminal end buds, and alveolar buds at 6 months old. The percentage of cells that incorporated BrdU was significantly decreased within the epithelium at 10 days old and increased within the stroma at 6 months old. |
| **118** | 2001 | Ramos, J.G., Varayoud, J., Sonnenschein, C., Soto, A.M., Munoz De Toro, M., and Luque, E.H. (2001). Prenatal exposure to low doses of bisphenol A alters the periductal stroma and glandular cell function in the rat ventral prostate. Biol Reprod 65, 1271-1277. | Wistar rats | Pregnant and lactating dams | GD 8-PND 21 | Pumps s.c. | 25, 250 μg/kg bw/day | 【prostate】Proliferation and differentiation of epithelial and stromal cells on ventral prostate: PND 30 | Prenatal exposure to BPA increases the fibroblastic:smooth muscle cells ratio and decreases the number of Androgen receptor-positive cells of periductal stroma of the ventral prostate. No changes in proliferation patterns were observed in epithelial and stromal compartments; however, the expression of prostatic acid phosphatase was diminished in prostate ductal secretory cells of rats in utero exposed to BPA. |
| **119** | 1999 | Farabollini, F., Porrini, S., and Dessi-Fulgherit, F. (1999). Perinatal exposure to the estrogenic pollutant bisphenol A affects behavior in male and female rats. Pharmacol Biochem Behav 64, 687-694. | Sprague-Dawley rats | Pregnant and lactating dams | from 10 days before mating to PND 21: 40 μg/kg bw/day, GD 14-PND 6: 400 μg/kg bw/day | Oral | 40, 400 μg/kg bw/day | 【behavior, brain】Motor activity, Hole-board test (Exploration), Elevated plus maze test: PND 85［♂♀］ | In treated males both the motivation to explore and anxiety are reduced, while in females, motor activity and motivation to explore are depressed. |
| **120** | 1997 | Nagel, S.C., vom Saal, F.S., Thayer, K.A., Dhar, M.G., Boechler, M., and Welshons, W.V. (1997). Relative binding affinity-serum modified access (RBA-SMA) assay predicts the relative in vivo bioactivity of the xenoestrogens bisphenol A and octylphenol. Environ Health Perspect 105, 70-76. | CF1 mice | Pregnant dams | GD 11-17 | Oral | 2, 20 μg/kg bw/day | 【prostate】 Prostate weight: 6 months old | Increased their adult prostate weight relative to control males |

BPA: bisphenol A

dpc: days post coitum

E: embryonic day

GD: gestational day

LD: lactatinal day

PND: postnatal day

PW: postnatal week

s.c. : subcutaneous