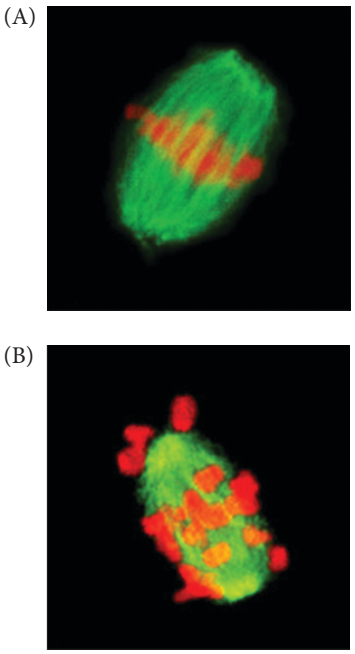

FIGURE 24.13 Bisphenol A causes meiotic defects in maturing mouse oocytes. (A) Chromosomes (red) normally line up at the center of the spindle during first meiotic metaphase. (B) Short exposures to BPA cause chromosomes to align randomly on the spindle. Different numbers of chromosomes then enter the egg and polar body, resulting in aneuploidy and infertility. (From Hunt et al. 2003, courtesy of P. Hunt.)

from the plastic and the female mice housed in the cages showed meiotic abnormalities in 40% of their oocytes (the normal level of such abnormalities is about 1.5%). When BPA was administered to pregnant mice under controlled circumstances, Hunt and her colleagues (2003) showed that short, low-dose exposure to BPA was sufficient to cause meiotic defects in maturing mouse oocytes (**FIGURE 24.13**). This effect was also seen in primates. Exposure of fetal female monkeys to low doses of BPA (at levels comparable to that found in human serum) caused ovarian and meiotic abnormalities similar to those observed in mice. There were several abnormalities of ovarian function, including abnormal meiotic chromosome behavior and aberrant follicle formation (Hunt et al. 2012).

BPA crosses the human placenta and accumulates in concentrations that can alter development in laboratory animals (Ikezuki et al. 2002; Schönfelder et al. 2002). Indeed, women exposed to high levels of BPA during pregnancy had an 83% higher rate of miscarriages than women who had not been so heavily exposed (Lathi et al. 2014). In model organisms, BPA at environmentally relevant concentrations can cause abnormalities in fetal gonads, prostate enlargement, low sperm counts, and behavioral changes when these fetuses become adults (vom Saal et al. 1998, 2005; Palanza et al. 2002; Kubo et al. 2003). When vom Saal and colleagues (1997) gave pregnant mice 2 parts per billion BPA—that is, 2 nanograms per gram of body weight—for the 7 days at the end of pregnancy (equivalent to the period when human reproductive organs are developing), male offspring showed an increase in prostate size of about 30% (Wetherill 2002; Timms et al. 2005). Female mice exposed to low doses of BPA in utero had reduced fertility and fecundity as adults (Cabaton et al. 2007).

This lower fertility may be the result of several actions in addition to the above-mentioned effects on developing eggs. First, BPA and other endocrine disruptors are found to prevent the sex-specific maturation of those parts of the mouse brain regulating ovulation (Ruben et al. 2006; Gore et al. 2011). Second, female mice exposed in utero to low doses of BPA (2000 times lower than the dosage considered safe by the U.S. government) had alterations in the organization of their uterus, vagina, breast tissue, and ovaries, as well as altered estrous cycles as adults (Howdeshell et al. 1999, 2000; Markey et al. 2003). And third, BPA alters the gamete-specific methylation pattern of imprinted genes in mouse embryos and placentas (Susiarjo et al. 2013).

WEB TOPIC 24.7 TESTICULAR DYSGENESIS The amount of sperm produced by human males appears to have declined rapidly during the past 50 years. There is evidence that estrogen-enhancing endocrine disruptors are causing this decline.

BPA AND CANCER SUSCEPTIBILITY BPA appears to make breast tissue more sensitive to estrogens, and it is thought that in utero exposure to BPA may predispose women to breast cancer later in life. Fetal exposure to BPA caused the development of early-stage cancer in the mammary glands of one-third of the rats exposed to environmentally relevant doses of BPA later in life (Murray et al. 2006). None of the control rats developed such cancers. Furthermore, daily gestational exposure to as little as 25 ng BPA per kilogram of body weight, followed at puberty by a "subcarcinogenic dose" of a chemical carcinogen, resulted in the formation of tumors *only* in those animals exposed to BPA (Durando et al. 2006). Indeed, altered mammary development had already manifested during fetal life in BPA-exposed mice, and at puberty, the mammary glands produced more terminal buds and were more sensitive to estrogen, which may have predisposed these mice toward breast cancer as adults (Muñoz-de-Toro et al. 2005). Moreover, exposure of female monkey fetuses to low doses of BPA (at levels comparable to those found in human blood serum) caused changes in mammary development similar to those seen in BPA-exposed mice (**FIGURE 24.14**). In the above experiments, BPA was shown to be a factor that predisposed the rats to develop a cancer when they encountered estrogenic chemicals later in life. However, new studies with a different strain of rats have shown that when rat embryos are exposed to relatively small doses of BPA (levels considered safe by the EPA), they can develop palpable postnatal tumors without