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# Development of a physiologically based pharmacokinetic model for bisphenol A in pregnant mice

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**Abstract**

Bisphenol A (BPA) is a weakly estrogenic monomer used to produce polymers for food contact and other applications, so there is potential for oral exposure of humans to trace amounts via ingestion. To date, no physiologically based pharmacokinetic (PBPK) model has been located for BPA in pregnant mice with or without fetuses. An estimate by a mathematical model is essential since information on humans is difficult to obtain experimentally. The PBPK model was constructed based on the pharmacokinetic data of our experiment following single oral administration of BPA to pregnant mice. The risk assessment of bisphenol A (BPA) on the development of human offspring is an important issue. There have been limited data on the exposure level of human fetuses to BPA (e.g. BPA concentration in cord blood) and no information is available on the pharmacokinetics of BPA in humans with or without fetuses. In the present study, we developed a physiologically based pharmacokinetic (PBPK) model describing the pharmacokinetics of BPA in a pregnant mouse with the prospect of future extrapolation to humans. The PBPK model was constructed based on the pharmacokinetic data of an experiment we executed on pregnant mice following single oral administration of BPA. The model could describe the rapid transfer of BPA through the placenta to the fetus and the slow disappearance from fetuses. The simulated time courses after three-time repeated oral administrations of BPA by the constructed model fitted well with the experimental data, and the simulation for the 10 times lower dose was also consistent with the experiment. This suggested that the PBPK model for BPA in pregnant mice was successfully verified and is highly promising for extrapolation to humans who are expected to be exposed more chronically to lower doses.


*Keywords:* Risk assessment; Bisphenol A; PBPK model; Offspring

## Introduction

Bisphenol A (4,4′-isopropylidene-2-diphenol, BPA) is used as a monomer for the production of polycarbonate and epoxy resins, and also as a stabilizer or antioxidant for many types of plastics in many consumer products, including food-ware, food-can linings, baby bottles and dental composite fillings and sealants. The use of these products raises the potential of oral exposure of humans directly to trace amounts of BPA, released from these products or via water contaminated with BPA that has leached out of plastic wastes in landfill (Yamamoto et al., 2001).

There has been concern about the estrogenic potential of BPA. Gaido et al. (1997) confirmed the weak estrogenicity of BPA in a yeast-based steroid hormone receptor gene transcription assay, showing BPA to be approximately 15,000 times less potent than 17β-estradiol, and Kuiper et al. demonstrated that BPA binds to human estrogen receptors and stimulates the transcriptional activity of both estrogen receptor subtypes (Kuiper et al., 1997, 1998). The estrogenicity of BPA is attributed to its weak *in vitro* agonist activity, in the order of 1/10 000 of that of estrogen, and differences in the binding to ERa and ERb (Matthews et al., 2001). BPA also exerts an estrogen-like effect *in vivo* on the estrus cycle of rats (Laws et al., 2000), on the development of the reproductive tract and mammary gland in female mice offspring (Nikaido et al., 2004), and on the size of reproductive organs, as well as sperm production, of male mice offspring by prenatal exposure to BPA (Nagel et al.,

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1997; vom Saal et al., 1998), although these observations are still controversial (Cagen et al., 1999; Yoshida et al., 2004).

Attention has been renewed on the effect of prenatal or neonatal exposure to BPA on the development of the nervous system (Kabuto et al., 2004; Shikimi et al., 2004) and behavior of offspring (Carr et al., 2003; Negishi et al., 2004). The effect of prenatal exposure to BPA on the immune system (Yoshino et al., 2004) and the disruption of thyroid hormone functions (Moriyama et al., 2002; Seiwa et al., 2004) in mice have also been reported.

Based on such an accumulated information in test animals on the reproductive and developmental effect of BPA, the endocrine-like effect on humans due to BPA has been under discussion.

In this study, we developed a physiologically based pharmacokinetic (PBPK) model describing the pharmacokinetics of BPA in a pregnant mouse with the prospect of future extrapolation to humans. Clarifying the controversial issues on the low-dose effects of BPA is vital (Gray and Cohen, 2004; Gray et al., 2004). The PBPK model was constructed based on the pharmacokinetic data of the experiment we executed on the pregnant mice following single oral administration of BPA (Kawamoto et al., 2005). The model was verified and given a trial for the extrapolation to the lower and prolonged exposure that is expected in humans.

Recently, other investigators have reported on developing a PBPK model for BPA in non-pregnant rats and humans (Shin et al., 2004). Their model was basically constructed to simulate pharmacokinetics of BPA in steady state after multiple i.v. injections. In contrast, the PBPK model we developed is in pregnant animals with oral administration, which is the most likely exposure route for humans. Our model can simulate the characteristic pharmacokinetics of orally administered BPA in a non-steady state and estimate the prenatal exposure level to BPA.

The present study was designed to develop a physiologically based pharmacokinetic (PBPK) model for BPA in pregnant

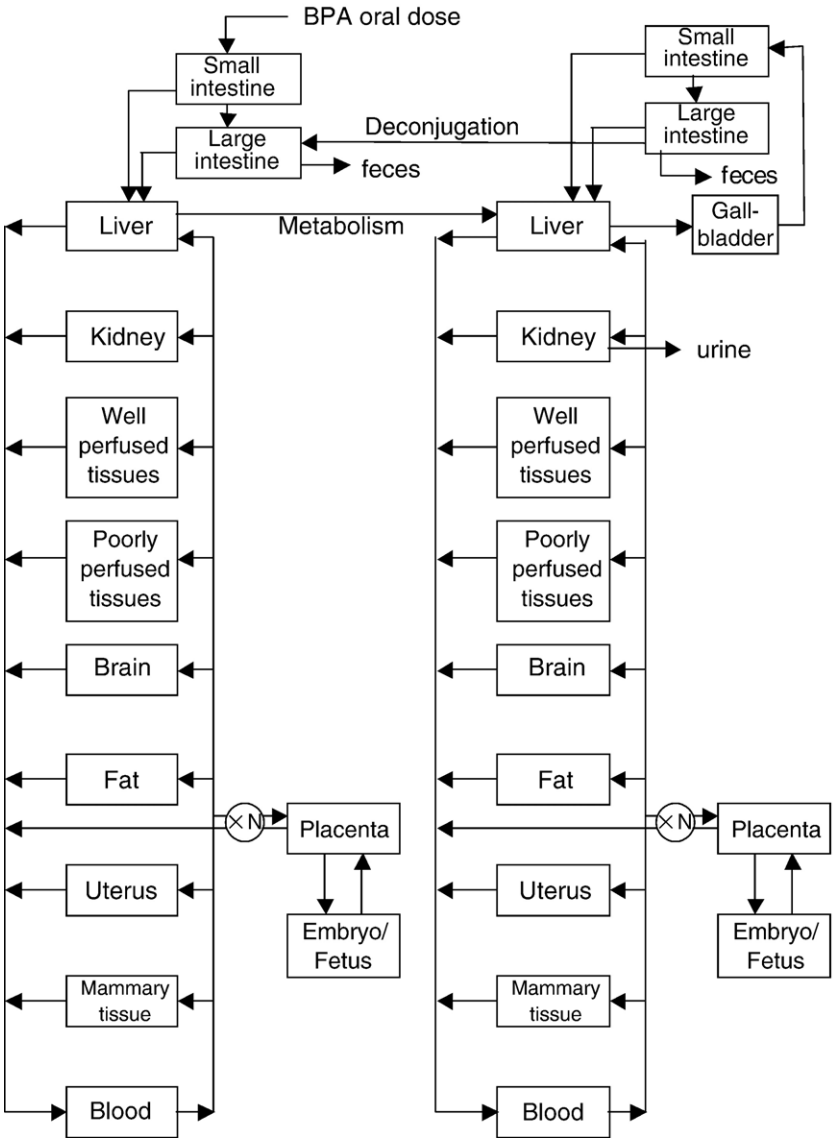


Fig. 1. The schematic diagram of the PBPK model for BPA in pregnant mice.