DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration

Memorandum

AD

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From William L. Roth, Ph.D.; Vanee Komolprasert, Ph.D.

Subject Compact Summary of Bisphenol A (BPA) Pharmacokinetics

To Michelle Twarowski, Ph.D.

The attached review is a compact summary of information on the pharmacokinetic properties of bisphenol A (**BPA** : 2,'2-bis(4-hydroxyphenyl)propane CAS No. 80-05-7) currently available to the FDA. Most of the studies discussed here were reviewed by the Center for the Evaluation of Risks to Human Reproduction of the National Toxicology Program (NTP-CERHR), in a publication titled "*Report on the Reproductive and Developmental Toxicity of Bisphenol A*" (draft - December 2006). Our procedure in completing the Compact Summary was to examine each of the sources available, tabulate doses, methods, and results of similar studies for comparison, and finally to create graphs or tables to make the overall properties more easily comprehendible.

We have attempted to compute and tabulate low level coefficients which characterize kinetic processes (absorption - k_a, tissue extraction - ϵ_j, glucuronidation - k_g (= V_{max}/K_m), elimination - k_e). This may allow direct computation of many of the endpoints reported in the original literature surveyed. The NTP_CERHR report tabulates only the reported endpoints, such as Tmax, Cmax, AUC, volume of distribution, many of which which are actually **variables** - dependent on dose, sampling time, route of administration, animal age and weight, etcetera. None of the latter variables have much predictive value.

This work was greatly facilitated by preliminary literature searches and document retrieval conducted by Dr. Mary Shackelford.

/s/ /s/

William L. Roth, Ph.D.

/s/ /s/

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Attachments

Toxicokinetics of Bisphenol A

Bisphenol A (BPA) or 2, 2'-bis(4-hydroxyphenyl)propane (CAS Reg. No. 80-05-7) is a monomer widely used in the manufacture of resins with a wide range of applications, e.g. polycarbonate (PC) and plastic coatings in the food packaging industry. It is currently listed in 21 CFR as a component for adhesives (175.105), for polymer coating (177.300), and for use in polymers for manufacture of food contact articles (177.1440, 1580, 2280, 2440, and 2800). BPA has been shown to have a weak estrogenic activity in vitro and in vivo. Despite its low estrogenic potency there is concern that, because of its slow clearance from fetal tissues, BPA might reach biologically significant levels in humans that could compromise public health safety.

Executive Summary

Pharmacokinetic studies of BPA conducted in mice, rats, monkeys and humans all indicate rapid intestinal absorption, and very rapid conjugation of BPA with UDP-glucuronic acid, forming BPA-glucuronide (BPAG). BPAG formation is followed by a slower process of elimination of the BPAG. Human (and monkey) BPAG elimination is rapid ($t_{1/2}$ = 3-4 hr) and primarily to the urine. Elimination of BPAG in rodents is complicated by the fact that it is routed primarily into the bile, rather than the urine (as in primates), and consequently enters the intestines, where bacterial glucuronidases hydrolyze BPAG to re-form free BPA, which can be re-absorbed. The extent of re-absorption of BPA from rat intestines may be less than 50 %, but is sufficiently large to make kinetic measurements in the rat confusing. The half-life for BPAG may be a few hours, but could be as long as 17 hours. Further analysis of the available data sets is required to separate contributing processes (absorption, distribution, metabolism, elimination) which can be deduced from different sets of plasma and tissue disappearance data.

BPA appears in the milk of lactating animals in substantial quantities Although BPA in milk is found to be primarily in the form of BPAG, it could be hydrolyzed by intestinal (bacterial) glucuronidases to form free BPA which would be rapidly absorbed by the neonate, which has a low glucuronidating capability at birth which develops with age.

Some free BPA appears to enter the fat and other tissues, where it may have an extended residence time without glucuronidation. BPA has been shown to cross the placenta and enter the fetus in rats, mice, monkeys and humans. Depending on the author and sampling methodology, concentrations of fetal BPA residues have been reported as much lower or as much higher than in the mother. Fetal-stage animals do not have the ability to conjugate BPA rapidly, so the residence time of free BPA in the conceptus should be longer than in maternal circulation. Further analysis of the available data sets is needed in order to clarify this issue and assess any risk of endocrine disruption in the fetus / neonate.

Physiologically-based pharmacokinetic models have been developed for prediction of BPA levels in blood and tissues, but these models need to incorporate additional physiological detail for the gastrointestinal tract and better data on BPA conjugation kinetics to be fully successful.

Summaries of Pertinent Studies

Rat Studies

Twelve studies were identified which contained useful pharmacokinetic data from rats.

Miyakoda et al (1999) treated pregnant (GD 19)Wistar rats with an oral dose of 10 mg/kg BPA followed by sampling of blood and fetuses at 1, 3 and 24 hours. Total BPA was measured by methanol extraction, acetylation, and GC/MS-SIM analysis. At the earliest time point (1 hr), the ratio of maternal plasma to fetal tissue was 3:1. This ratio was reversed at 24 hr post-dose (see Table 3). The authors concluded that transfer of BPA from maternal circulation to the fetus is rapid and that BPA residues remain in the fetuses longer than in maternal blood.

Miyakoda et al. (2000) repeated the experiment described above, but also treated 10 week old male rats with 10 mg/kg BPA, taking blood and testis samples. Plasma was separated from blood to allow hydrolysis by β-glucuronidase as well as extraction of total BPA. Tissues were homogenized in acetate buffer and hydrolyzed (or not) as plasma samples. Analysis of both types of samples was conducted by extraction, acetylation, and GC/MS. The difference between these two types of samples was used as a measure of BPA-glucuronide (BPAG). Extracts of fetuses showed no difference between total BPA and hydrolyzed extracts (no BPAG - all free BPA). Maternal blood samples showed glucuronide:free BPA ratios of 5-10. Ratios in testis samples were between 1 and 5 (glucuronide:free). The authors concluded that BPA glucuronide could not readily pass through tissue barriers from the blood.

Pottenger et al. (2000) studied the pharmacokinetics and metabolism of ^{14}C-labeled BPA following single oral, intraperitoneal (ip) and subcutaneous (sc) doses of 10 and 100 mg/kg given to Fischer-344 rats (males vs. females) for a 7-day period. They measured concentrations of BPA, BPA-metabolites, and total BPA-derived ^{14}C in blood, plasma, tissues, urine, and feces using HPLC/UV, LC/MS and liquid scintillation counting methods. The study showed that BPA was primarily eliminated in feces (52-85%), with smaller amounts appearing urine (13-34%). The tissue residual after 7 days was 1-2% of the dose. BPA- glucuronide was the major conjugate in urine (60-87%), followed by free BPA (3-12%) and BPA-sulfate (2-7%). The authors suggested that BPA was metabolized by intestinal and hepatic UDP glucuronosyl transferase (UGT) to form BPA-glucuronide, the major metabolite in plasma (68-100%) following oral administration, as compared to 27-69% and 17-49% following ip and sc administration, respectively.

Snyder et al. (2000) compared the metabolism and disposition of ^{14}C-labeled BPA in adult female F-344 and Sprague-Dawley (SD) rats following a single oral dose of 100 mg/kg body weight. Total ^{14}C was also measured in milk and PND14 neonate carcasses at 1, 8 and 24 hr post-dose. The study results were consistent with those of Pottenger et al. (2000) in that BPA was the major component detected in feces. The fraction of unconjugated BPA in the feces was 50% in F-344 rats versus 70% in SD rats. Urinary elimination correspondingly increased (42%) in F-344 rats compared to SD rats (21%). BPA-glucuronide was the major metabolite present in milk and plasma, with a milk:plasma ratio of 0.2 - 0.5 from 1 to 24 hours post-dose. Less than 0.1 % of the dose was found in the neonates at 24 hr.

Takahashi et al. (2000) treated pregnant (GD 18) F-344 rats with 1000 mg/kg BPA dissolved in propylene glycol by oral gavage. Maternal blood, livers, kidneys and fetuses were removed at intervals between 10 min and 48 hours post dose. BPA residues were measured by methanol extraction and HPLC /UV analysis. Since measurements were of BPA, the ratio of tissue:blood ($T:B_j$) AUCs should approximate partition coefficients ($T:B_{liv} = 53$; $TB_{kid} = 6.4$; $TB_{fetus} = 1.75$) Terminal half-lives, which probably represent BPAG, were reported as 2-5 hours. BPA appearance and disappearance in the liver and kidney were slower than in the plasma. Concentrations of BPA in fetuses were lower than in maternal tissues only at early time points.

Upmeier et al. (2000) treated female DA/Han rats with 10 mg/kg (intravenous - IV) as well as 10 and 100 mg/kg (oral) doses of unlabeled BPA dissolved in a 1,2-propanediol vehicle. Blood samples were drawn from the retroorbial plexus at multiple time points between 1 and 360 minutes post-dose. Analysis of free BPA was performed by GC/MS after extraction into diisopropyl ether. A three compartment model was used to fit parameters for the plasma curve. The distribution phase (for free BPA) $t_{1/2}$ was estimated at 5 min ($k_{uptake} = 0.138$/min), followed by two additional phases with $t_{1/2} = 479$ min (8 hours) and 38 hours. BPA disappearance was highly variable between individual rats - absorption appeared to be rapid in all cases but curve shapes were highly variable.

Yoo et al. (2000) injected male S-D rats with either bolus doses of 0.2 - 2 mg/kg BPA followed by blood, tissue and excreta sampling, or used a 2 hr continuous infusion (0.5 mg/kg-hr) followed by blood and tissue sampling. Pharmacokinetic parameters computed from the serum concentrations showed no change over the dosage range, with a distribution phase $t_{1/2} = 4\text{-}8$ ($\pm$ 3) min and elimination phase $t_{1/2} = 38\text{-}62$ ($\pm$ 24) min. Partition ratios computed from this data are shown in Table 3 of this review.

Yoo et al. (2001) also treated male and female (lactating) S-D rats with 0.1 mg/kg (IV) and 10 mg/kg (Oral) doses of BPA dissolved in PEG-saline. Serial blood samples were collected from a jugular catheter at time points between 5 and 180 minutes post-dose. Three groups of lactating rats received 4 hr infusions or IV bolus injections of BPA at total doses ranging from 0.5 to 2.0 mg/kg. Blood and milk samples were drawn between 0 and 4 hr post-dose. All samples were extracted with methylene chloride, hydrolyzed, reconstituted and analyzed by reverse-phase HPLC. This procedure measured free BPA only. The distribution phase $t_{1/2}$ was estimated at 6.1 $\pm$ 1.3 min, and a second phase $t_{1/2}$ computed as 52 minutes. Milk:serum BPA concentration ratios (2.4 - 2.7) were relatively constant across the dose range tested (see Table 3).

Domoradzki et al (2003) (Dow Chemical laboratory) extended studies of Pottenger et al. (2000) to determine the pharmacokinetics and metabolism of ^{14}C-labeled BPA in pregnant S-D rats following a single oral dose of 10 mg/kg body weight. The authors noted that pharmacokinetics and metabolism of BPA in pregnant rats in any stage of pregnancy and in non-pregnant rats were identical. The study showed similar results to those of Pottenger et al. (2000) in that free BPA was primarily eliminated in feces (65-78% of dose), with 14-22% in urine, and 1-6% remaining in tissues after 96 hours. No elimination rates (k_e) or half-lives were computed. The authors reported that 83-89% of the BPA content of the feces was unconjugated, and 2-3% was in the form of BPA-glucuronide. The urinary content was 62-70% BPA-glucuronide and 19-23% free BPA. The sum of BPA-glucuronide and free BPA concentrations in the placentae and fetuses

were lower than that found in maternal plasma, indicating no selective concentration of BPA or BPA-glucuronide in either yolk sac/placenta or embryo/fetus relative to maternal plasma or tissues. These results are inconsistent with Miyakoda et al. (1999) and Snyder et al (2000)

In a second study Domoradzki et al (2004) studied the pharmacokinetics of BPA in 4 - 21 day post-natal (PND) rats, using the same 10 mg/kg dose and oral route. This study showed that PND 4 neonates had much less ability to glucuronidate BPA than PND 7 or PND 21 rats, but also demonstrated that significant glucuronidation capability was present in PND 4 rats .

Kim et al. (2004) (FDA laboratory) studied the distribution of ^{14}C-BPA in abdominal tissues (liver, kidney, fat, stomach, small intestine, uterus & ovaries) and plasma of female F-344 rats, plus several neuroendocrine organs. Doses of 0.1, 10, and 100 mg/kg BPA were administered via gastric intubation as a solution in corn oil. After dosing, animals were anesthetized with pentobarbital (50 mg/kg) to allow blood samples and tissue to be taken rapidly at times of 5, 15, 30 min, 1, 4, 8, 12, 24, and 48 hours post-dose. Samples were processed for measurement of total radioactivity only - no separation of metabolites was reported. A half-life of about 17 hours was reported for BPA residues in plasma. Concentrations of BPA and its metabolites (total radioactivity) appeared to be elevated relative to plasma only in the liver during the in vivo portion of the study. In a second experiment, tissue slices were taken from BPA-naive animals, and incubated in physiological buffers with ^{14}C-BPA for 90 minutes. BPA residues were elevated in many tissues relative to buffer (partition coefficient), but no plasma-buffer partitioning experiments were available for computation of tissue:plasma partitioning ratios.

Kurebayashi et al. (2005) performed a whole body autoradiography (WBA) study of pregnant rats, injecting 100 or 500 μg ^{14}C-BPA /kg BW by IV and oral routes. Serial blood and excreta samples were taken from one group of rats for 168 hr, blood and milk from lactating rats with neonates for 48 hr, while a third group were sacrificed at 30 min, 24 hr and 72 hours for WBA. The milk:plasma concentration ratio was about 1: 5 from 8 - 42 hr. BPA was not detectable in fetal tissues until GD 18, at that time concentrations of ^{14}C in fetal tissues were approximately equal to corresponding maternal tissues. Elimination half-lives (^{14}C) ranged from 13 -22 hr.

Two authors studied the biliary excretion of BPA in rats. Kurebayashi et al. (2003) injected male and female Fischer 344 rats with 0 1 mg/kg [ring-^{14}C(U)]-BPA dissolved in isotonic phosphate buffer (pH 7.4) via oral and IV routes. One group of rats were housed in metabolism cages for collection of urine and feces, while another group was anesthetized with ether for collection of serial jugular blood samples. A third group of rats were implanted with bile duct cannulas, and placed in Bollman cages for collection of bile. Most of the intravenous dose was eliminated via the bile (66 % ♂, 58 % ♀) within 24 hours. The same pattern was followed after an oral dose but with a smaller amount absorbed systemically. Urinary elimination was much smaller - 8.4 ± 1.8 % IV dose for males. Non-cannulated rats excreted a smaller percentage of the dose than did cannulated rats - apparently the appearance of biliary BPA in the feces is delayed and / or partially reabsorbed. Elimination half-lives for blood were 39 - 45 hours.

Inoue et al. (2005) studied biliary excretion in perfused rat livers. Their study is described with others under *In Vitro Studies* (below).

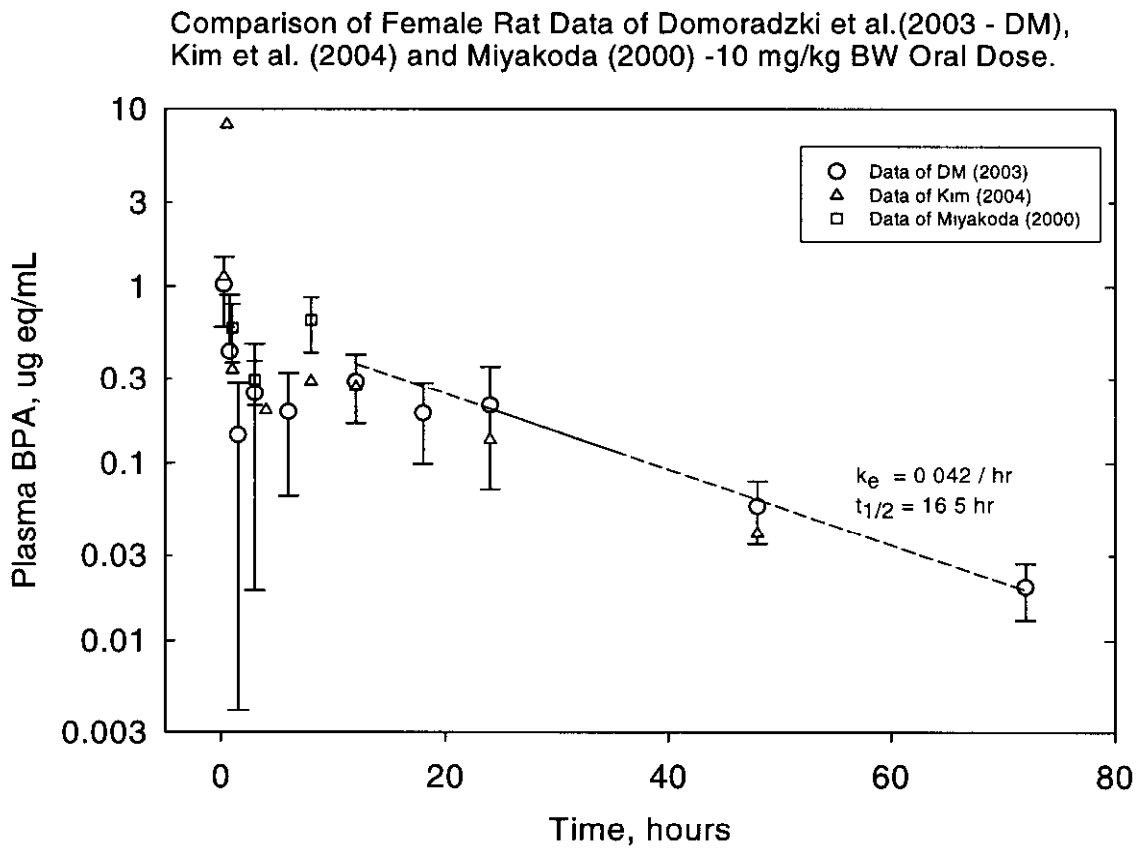

Figure 1 Appearance and disappearance of total BPA residues from female rats in independent studies following single oral doses of 10 mg/kg BPA. Note the concordance between these studies in showing a biphasic curve despite using different methods of detection (^{14}C, ^{14}C, GC-MS, respectively).

Mouse Studies

Only two studies were found that contained useful ADME data from mouse experiments.

Uchida et al. (2002) measured BPA concentrations in pregnant mice (GD 17) after a single sc injection of 100 mg/kg bw at times for a 24-h period, using a GC/MS method. The authors also used six pregnant mice, non-treated, as controls, but did not clearly present the results in comparison with the treated mice. The authors detected BPA in tissues as early as 30 min postdosing, which was consistent with the results of Zalko et al (2003). BPA concentrations in fetal serum and liver were higher than those of mothers, expected to be correlated with the presence of ER in fetal uterus (Iguchi, 1992).

Zalko et al. (2003) determined BPA-derived residues in pregnant CD-1 mice after subcutaneous injection of a single dose of 25 μg/kg ^{3}H-labeled BPA (actual dose of 20-25 μg/kg) for a 24- hr period. They noted that BPA was extensively metabolized to form a glucuronic acid conjugate of BPA, several double conjugates, and conjugated methoxylated compounds, demonstrating the formation of potential reactive intermediates. Metabolic balance results at 24 hr postdosing

showed that BPA residues were mainly in the digestive tract (45%), compared to 21% in feces, 6% in urine, 4% in fetus, 3% in carcass, 2.5% in liver, 2% in bile and < 1% in other tissues. The major component in feces was free BPA, which the authors believed to be the result of deconjugation of biliary glucuronides into BPA by intestinal bacteria. BPA glucuronide was the major component detected in urine, along with glucuronide conjugate of hydroxylated BPA, and several double-conjugated metabolites of BPA. The authors also conducted an oral dosing experiment, giving mice 25 μg/kg ^{3}H-labeled BPA and found no qualitative difference in metabolites between mice dosed by sc or oral route. In CD-1 mice, transport of BPA into the placenta and fetus occurred rapidly, as seen in Figure 2 at 0.5 hr postdosing. At this time point, calculated BPA-glucuronide concentrations in fetuses were similar to that of free BPA, indicating the passage of BPA through the placenta followed by glucuronidation, forming higher concentrations of BPA-glucuronide in amniotic fluids than that of free BPA. Elimination half-life could not be determined from this data set, since it has all of the hallmarks of enterohepatic recirculation, but no measurements after recirculation ends (24 hr - see Figure 1).

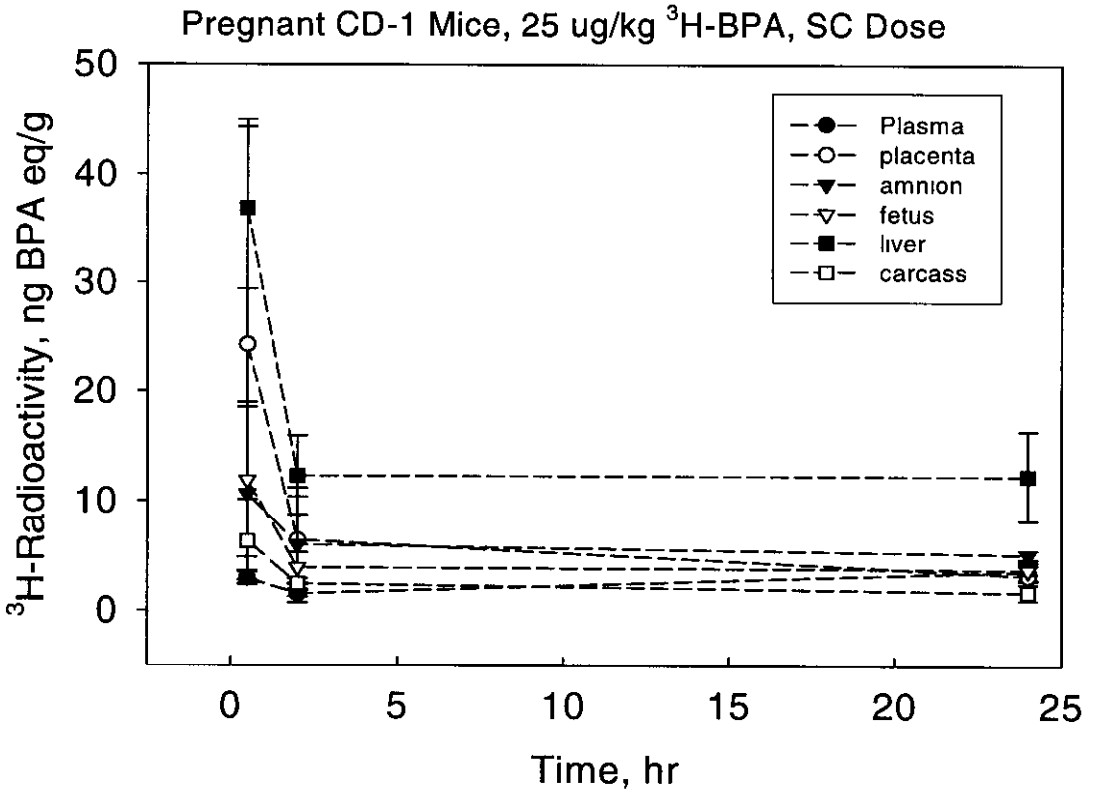

Figure 2 Disappearance of ^{3}H-BPA derived radioactivity from selected tissues of pregnant mice after a subcutaneous (SC) 25 ug/kg dose of BPA. Note that the highest concentrations are initially reached in the liver, closely followed by the placenta. Concentrations in the uterus are actually higher than the liver (not shown). Data shown here are derived from Zalko et al. (2003).

Monkey Studies

Three authors conducted studies in monkeys. Kurebayashi et al. (2002) injected cynomolgus monkeys with 100 ug/kg [ring $^{14}C(U)$] labeled BPA by both intravenous and oral routes, in volumes of 1 mL/kg BW. Dosing was followed by blood sampling and excreta collection for 72 hours. Total radioactivity was counted in all excreta and blood samples. Plasma samples were extracted with methanol ± glucuronidase treatment, followed by radio-HPLC analysis. Intravenous dosing resulted in 98 % of the dose being excreted in the urine. After oral dosing, 97 % of the dose was found in the urine, indicating that nearly 100 % of the BPA dose was rapidly absorbed. The terminal half-life reported for elimination of total radioactivity (primarily BPAG) after oral dosing was 9.7 ± 3 hours, while that observed after IV dosing was 14 ± 3 hours. No tissue samples were obtained, but the authors speculate that the longer half-life for the IV route is the result of unconjugated BPA partitioning into fat, versus first pass conjugation of BPA in the portal blood after intestinal absorption. This reviewer notes that virtually all of the BPA dose had been converted to glucuronide within the first hour post-dose (see Figures 3 and 4, below), and that the rapid phase ($t_{1/2}$ = 42 min) appeared not to be free BPA, but rather a distribution phase for BPAG . Formation of BPAG is apparently too rapid to be observed in this data set, and is likely to be too rapid to be evaluated in the whole animal. Mathematical modeling based on data generated from in vitro preparations (see Pritchett et al., below) is probably the only means available to accurately predict blood-tissue transport of free BPA and BPAG at early time points.

Using two Japanese monkeys on GD 150 of pregnancy sc injected with a single dose of 50 mg BPA/kg bw, the authors found that BPA was detected 1 h postdosing in all organs including fetal liver, kidney, brain, and umbilical cord of treated monkeys. The results again indicated that BPA can pass through the placenta to the fetus (Uchida et al., 2002).

Negishi et al. (2004) conducted a species comparison study with F-344 rats, female cynomolgus monkeys and chimpanzees. Oral doses of 10 and 100 mg/kg BPA were administered to rats and cynomolgus monkeys, while only the 10 mg/kg dose was given to chimpanzees. Blood samples were taken at 6 time points over a 24 hour time period post dose. Individual rats were euthanized for each timed blood sample, while six serial blood samples were taken from each monkey. Blood samples were extracted with methanol, and analyzed using a proprietary ELISA (antigen to bound BPA) kit. This study did not discriminate between BPA and its conjugates. Results from the oral route administration were not suitable for half-life estimation or other kinetic analyses.

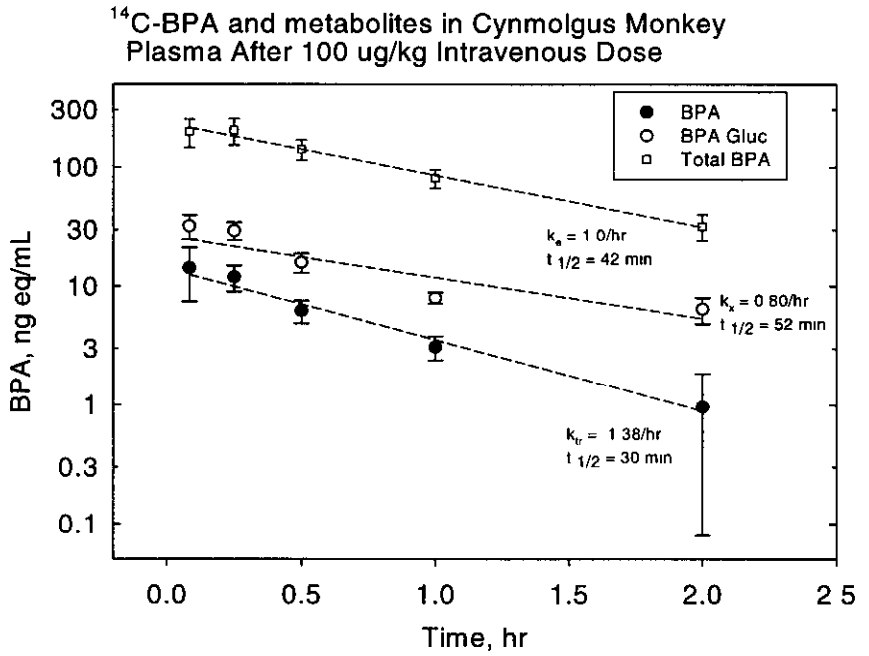

Figure 3 Phase 1 disappearance data following intravenous dosing of monkeys. BPA is converted to BPAG in a process that is complete by the time of first sampling.

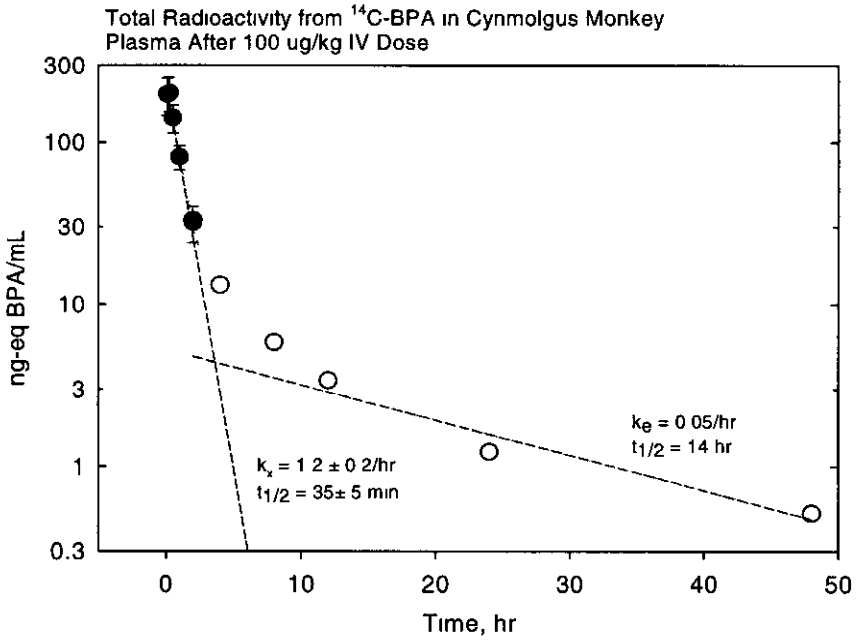

Figure 4 Disappearance of BPA-derived radioactivity following intravenous dosing of monkeys with a low dose (100 ug/kg BW). The rapid phase (1) data slope (residual), derived by subtracting phase two simulation from phase 1 data in Figure 2, is not significantly different from the slope derived from raw phase 1 data points. Data from Kurebayashi et al. (2002).

Human Studies

Although measurements of BPA in human blood and tissues have been conducted by several laboratories over the last decade, studies providing data relevant to the pharmacokinetics of BPA in humans have all been published since 2002. These are described below.

Völkel et al. (2002) gave human volunteers capsules of 5 mg/person (64-82 ug/kg BW) deuterated BPA (d_{16}) tracer and followed the appearance and disappearance of BPA glucuronide from blood at 12 time points distributed over a 24 hour period. using a sensitive GC/MS method. This study showed equal rates of absorption and elimination for males and females over the 24 hour time period, with a terminal elimination rate of 0 206/hr or half-life of 3.37 hr.

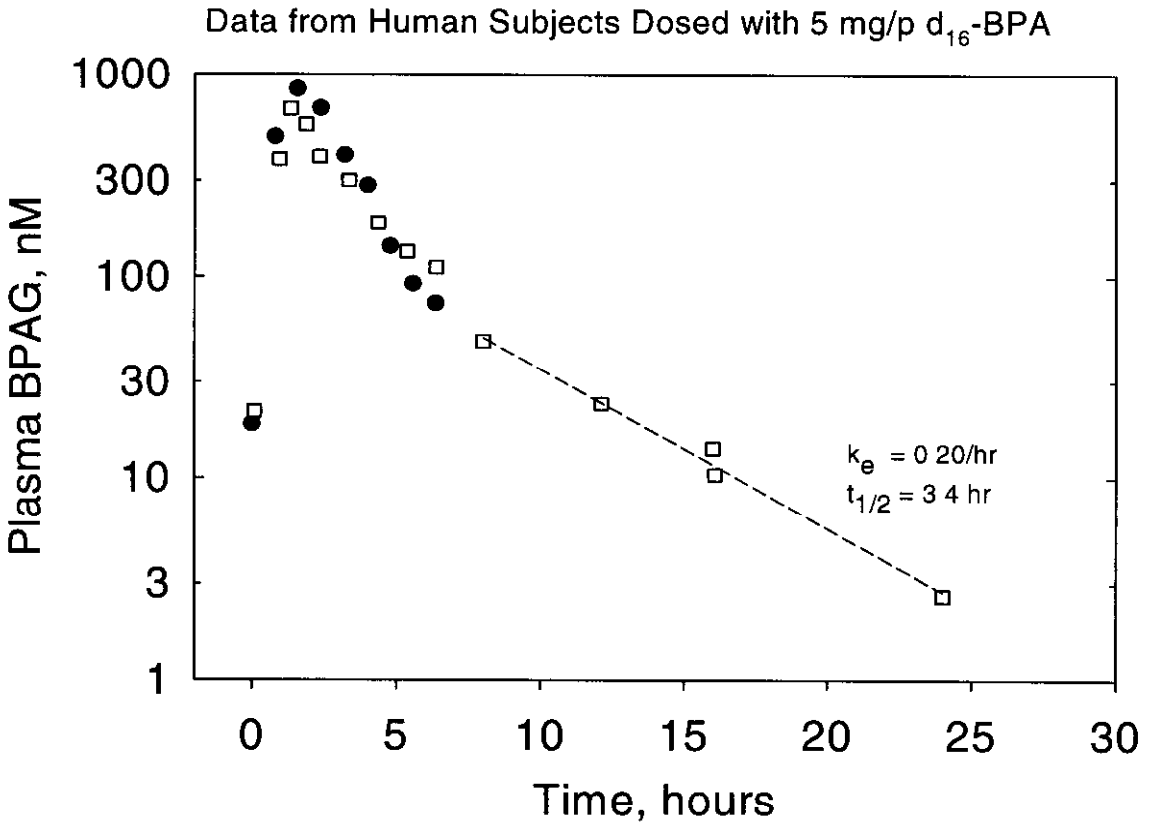

Figure 5 Disappearance of BPAG from plasma of human subjects (Völkel et al., 2002) after oral dosing with 5 mg/p d_{16}-BPA. Experiment 1 (males, ●) and experiment 2 (both genders, □). A much more detailed curve fit was provided by the authors

Kim et al. (2003) added to the information above by measuring levels of BPA and BPA conjugates in human urine (both genders) using an HPLC method with fluorescence detection. These authors noted a significantly lower fraction of BPA glucuronide in urine from females vs males, (1.0 ± 0.34 vs 2.34 ± 0.85 ng/mL) and a corresponding increase of BPA sulfate (0.49 ± 0.27 vs 1.20 ± 0.32 ng/mL). Free BPA (0.56 - 0.58 ± 0.14 ng/mL) and total BPA (2.76 - 2.82 ± 0.73 ng/mL) levels in urine followed a similar distribution for both genders.

Schönfelder et al. (2002) measured BPA in plasma samples from human mothers at the time of delivery, as well as BPA in samples of placenta and neonatal plasma. Concentrations were higher in the placenta than in maternal or neonatal plasma, and suggested higher levels of BPA in maternal than fetal plasma, but the concentrations measured were highly variable (1.1 - 20 ng/mL) in all cases and would include the possibility of 1:1 partitioning between the maternal and fetal compartments within the error range for the mean (2.54 ± 1.58).

Table 1
BPA - Basic Kinetic Characteristics by Species

Species	F (fraction absorbed) reported	*Range of $t_{1/2}$ (k_e = elimination)	Elimination Routes
Mouse	?	< 5 hr (total BPA)	primarily fecal
Rat	80 - 100 %	1 hr (free BPA) 14 - 21 hr (BPAG)	50 - 80 % fecal 20 - 40 % urinary
Monkey	80 + %	1 hr (free BPA) 10 - 14 hr (BPAG)	80 - 90 % urinary 5 - 10 % fecal
Human	84 + %	3.4 - 17 hr (BPAG) k_e = .04 - 0.2 /hr	80 - 90 % urinary 10 + % fecal

* These parameters represent the range reported in studies reviewed here, or estimated by us from the data

In Vitro Studies

A number of studies have been conducted *in vitro* with perfused organs (intestines and liver), cultured cells (hepatocytes) and subcellular preparations (microsomes, purified proteins, etc.). Studies of this type can be very useful for interspecies extrapolation, but must be used with more or less sophisticated mathematical models for accurate prediction.

Kawade and Onishi (1981) measured the postnatal development of UDP-glucuronosyl transferase in human livers from 16 weeks of gestation through 8 weeks post-natal age. A plot of this data is shown in Figure 6. The activity measured was towards bilirubin and may not translate directly into BPA glucuronidation activity

Yokota et al. (1999) tested isoforms of rat liver UDP glucuronosyl transferase for activity towards BPA in vitro. It was determined that UGT 2B1 had the highest activity towards BPA, although other isoforms were also active towards BPA. Data is interesting but of limited use.

Elsby et al. (2001) Incubated hepatocytes prepared from female Wistar rats, or microsomes prepared from human and rat livers with a range of concentrations of BPA to study in vitro metabolism and enzyme kinetics using HPLC-MS for analysis of metabolic products. The only major metabolite detected was BPAG. BPA-sulfate and 5-OH-BPA-sulfate were detected as minor metabolites. Human glucuronidation parameters were $V_{max} \approx 5.5 \pm 0.4$ nmol/min/mg-protein and $K_m \approx 70.0 \pm 8.3$ μM. Rat parameters were $V_{max} = 31.6 \pm 8.1$ and $K_m = 27 \pm 1.2$ μM.

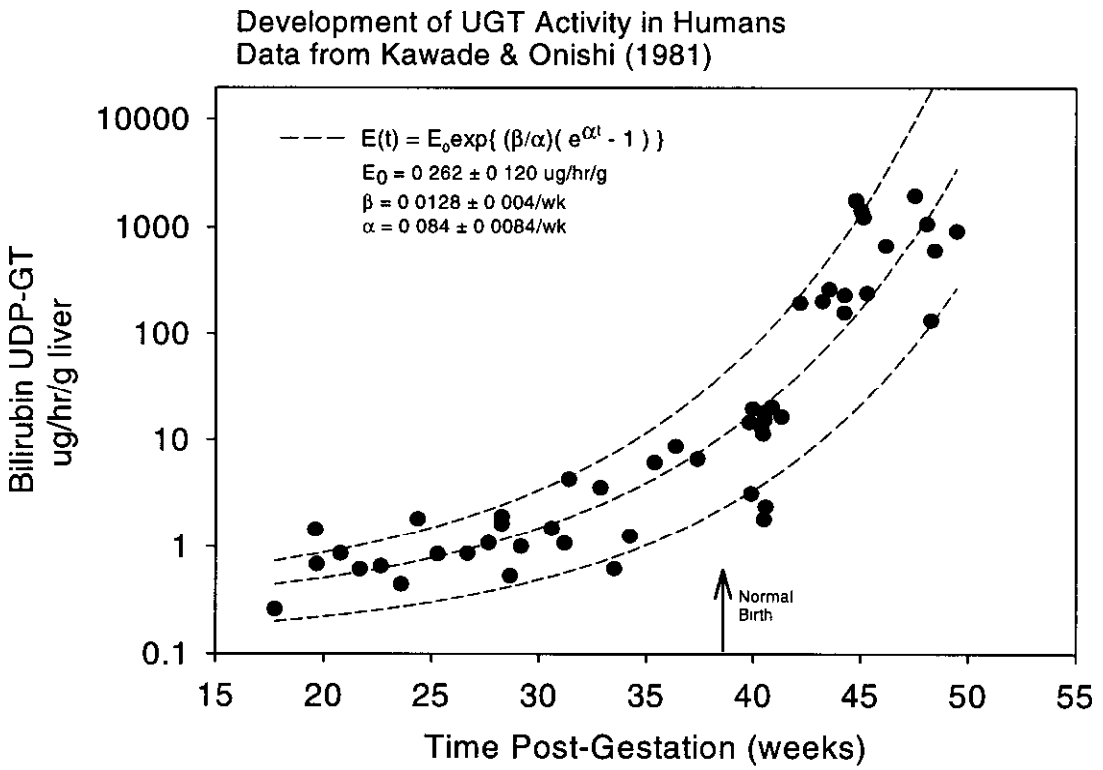

Figure 6 Development of UDP-glucuronosyl transferase activity towards bilirubin measured in human liver samples. A Stirling growth model (E(t)) was used by this reviewer to fit the development of enzyme activity.

Matsumoto et al (2002) measured rat microsomal UDPGT activity towards multiple xenoestrogens at several stages of pregnancy. Activity in the dams were found to decrease with the duration of the pregnancy. This data could be used in a PBPK model, with normalization.

Sakamoto et al. (2002) dosed Sprague-dawley rats with BPA in olive oil and measured free BPA and BPA-glucuronide in two sections of the small intestine (I , II) the cecum (III) and colon (IV) over a 12 hour period. BPA-glucuronide appeared rapidly in the small intestinal segments of the lumen, but then disappeared - replaced by free BPA - in the cecum and colon. This experiment and pH-dependent experiments with tissue and lumen extracts showed that the β-glucuronidase activity present in the small intestine is of tissue origin, and is not active at normal intestinal lumen pH, while the predominant activities in cecum and colon are of bacterial origin, and have pH optima (5-8) in the range of normal intestinal contents.

Inoue et al. (2003), tested perfused intestinal segments for the ability to absorb and glucuronidate BPA in an everted, flow-through system. BPA-glucuronide appeared on both the mucosal and serosal sides of the intestinal segment. Appearance of this conjugate on the mucosal side was about 10 x faster than serosal appearance, which raises some question as to the relevance of this test system to an intact intestine. This data could be used to scale intestinal vs hepatic UDPGT activity in a PBPK model of the rat, if the results were correlated with confirming perfusion measurements performed in intact intestines *in situ*.

Inoue et al. (2005) perfused Sprague-Dawley rats (male, nonpregnant female and GD 20 female) and Eisai hyperbilirubinemic rats with BPA via the portal vein. Bile ducts and the caudal vena cava were cannulated to facilitate measurement of BPA transport and conjugation to the glucuronide Extraction was very high, but the perfusion Females appeared to produce about 30 % more glucuronide than males, but transport into the bile was reduced by more than 50 % in livers of pregnant females as compared with nonpregnant females and male rats. Eisai rats are deficient in multidrug resistance-associated protein (MRP2). These rats were able to form the glucuronide, but it appeared only in venous blood.

Pritchett et al. (2002) studied the metabolism of BPA in hepatocyte preparations derived from both genders of : CD1 mice, F-344 and Sprague-Dawley rats, and 5 anonymous adult human liver samples. BPA-glucuronide was the major metabolite formed by hepatocytes from all species tested, except that male F-344 rats. Hepatocytes from this strain of rat formed a diconjugate (glucuronide sulfate) as the major metabolic product after initial formation of the mono glucuronide. The diconjugate was not found by in vivo studies of F-344 rats. Table 2 shows that the maximal velocities / 10^6 cells was similar across species, if trending lower for human hepatocytes. These values were extrapolated to whole liver conjugation rates, and could be used in a kinetic model to predict pharmacokinetics in humans. No K_m values were reported, and as a consequence, first-order rate coefficients cannot be calculated without supplementary data.

Table 2
Glucuronidation of BPA by Hepatocytes at 20 uM BPA

Species	Vmax nmol/min/10^6 cells	Maximum Hepatic Activity umol/hr
F-344 Rat, female (0.20-0.25 kg BW)	0.92	46 5 (186 /kg BW)
F-344 Rat, male (0.25-0.30 kg BW)	0.72	61.8 (206 /kg BW)
S-D Rat, female (0.20-0.25 kg BW)	0 78	54 5 (218 /kg BW)
S-D Rat, male (0.25-0.3 kg BW)	0 90	79.9 (266 /kg BW)
CD-1 Mouse, female (0.025-0.03 kg BW)	1.0	13.8 (460 /kg BW)
CD-1 Mouse, male (0.03-0 04 kg BW)	1.64	23.6 (590 /kg BW)
Human, female (60 kg)	0.42 - 0.40	3042 - 5070 *
Human, male (70 kg)	0.30 - 0.34	4436 - 5028 *

* Human rates and total capacities recomputed by this reviewer assuming 60 kg female, 70 kg male Liver/BW = 2 57 %, and using data from graph (publication Figure 5) at 180 min incubation

Estrogen Receptor Binding Studies

Snyder et al. (2000) also transfected human hepatoma cells (HepG2) with plasmids encoding either human estrogen receptor α (ERα) or receptor β (ERβ), with each incorporating a luciferase reporter plasmid so that ligand binding by ERα or ERβ could be detected by luminescence. The HepG2 cells without ER-plasmid were also used to measure BPA metabolism in the same culture system used to detect ER binding. EC50 values determined for ERα by estradiol and BPA were 1.9×10^{-9} M and 6.4×10^{-7} M , respectively(~ 300 x lower affinity for BPA). BPA-glucuronide showed no significant binding affinity for either ERα or ERβ. The HepG2 cells showed no ability to glucuronidate BPA, thus indicating that this was a relatively "clean" system for the evaluation of ligand binding to the estrogen receptor.

Matthews et al. (2001) Used three methods (two *in vitro* and one *in vivo*) to measure estrogenicity of BPA. Human estrogen receptor (hER) was incorporated into MCF-7 cells by plasmid transfection, followed by incubation with a range of concentrations of estradiol and BPA to determine reporter gene (luciferase) expression. A competitive binding assay (^{3}H-E2 vs ligand) was also conducted with mouse uterine ER preparations. Both methods showed an affinity of BPA for ER (7.1×10^{-7} M) consistent with that of Snyder et al. (2000). Treatment of mice with BPA caused no effect in a uterotrophic assay below 200 mg/kg-BW. It is concluded that rapid metabolism of BPA prevents estrogenic effects in the *in vivo* test system.

Physiologically-Based Models

Four attempts have been made to create physiologically-based models of the fate of BPA. Although one attempt was made to extrapolate to humans (Teeguarden et al., 2005), none of these models have been completely successful in predicting the rat ADME data used to develop them. None of these authors attempted to predict the rodent enterohepatic recirculation of BPA.

Two models were published almost simultaneously - Hutter et al. (2004) and Shin et al. (2004) Both of these models are relatively simple equilibrium partitioning models, which do not attempt to track the tissue distribution of the metabolite BPAG. The model of Hutter incorporates a one compartment GI tract (k_a = 0.8/hr), with no gastric delay and no enterohepatic recycling. The lack of additional, flow-limiting compartments required Hutter et al. to limit the absorption to a fraction (0.50 - 0.60) of the total dose. Metabolic parameters for glucuronidation (V_{max} , K_m) were obtained by trial-and-error fit of the model to literature data. The overall model was calibrated from two data sets (Kim et al., 2004, Pottenger et al., 2000).

The model of Shin et al.(2004) is similar to the model of Hutter et al. (2004), but adds partitioning compartments for the lung, and stomach tissue. The Shin model does not include the stomach in the GI tract for delay or any other purpose associated with absorption. Elimination rates were obtained by trial-and-error fit of the model to literature data ($t_{1/2}$ = 76.8 min ; k_e = 0 54/hr), and were compared to metabolism rate estimates in an allometric scaling paper by Cho et al. (2002) The Shin et al. (2004) model was developed using BPA concentration data primarily from their own laboratories, and did not consider BPA data collected independently.

Teeguarden et al. (2005) developed an equilibrium partitioning model for the rat calibrated with

data from several laboratories, including Pottenger et al. (2000), Upmeier et al. (2000), and Csanady et al. (2002). Conversion of the Teeguarden model for prediction of human BPA disposition was calibrated using data of Völkel et al. (2002). Like the models of Hutter et al. (2004) and Shin et al. (2004), the Teeguarden model contains only a single absorption compartment in its GI tract, with no biliary input or BPAG hydroylic capability, and consequently no ability to model enterohepatic recirculation - critical for modeling ADME of BPA in the rat. Figure 1 it can be seen that three independent laboaratories have each found a biphasic plasma concentration curve, with the second peak occuring from 6-18 hours post-dose. BPAG from the bile is hydrolyzed in the cecum to re-form BPA, which is largely reabsorbed These models may be useful for predicting human BPA disposition, since human elimination of BPAG is primarily via the urine (Table 1 and Völkel et al, 2002). The human model extension was not validated with an independent human data set.

Table 3
Partitioning of BPA in Rats

Organ / Volume	Concentration Ratio [a] relative to Plasma	Alternate Source [b]	Alternate Source [c]	Models :Hutter ; Teeguarden
Serum / Plasma	1.00	1.00	1.00	1 00
Muscle / Carcass		0.8 ± 0.1	0.21 - 0.95	0.5 ; 1.35
Milk	2.4 - 2.7 [d]	nd	0.19 - 0.52	nd ; nd
Liver	1.95 ± 1.0	5.7 ± 2.2	4.4 - 5.9	1.46
Kidney	4.91 ± 0.2	4.4 ± 0.7	0.65 - 1.28	6.4 ; nd
Lung	5.72 ± 1.9	5.5 ± 0.5	0.38 - 0.45	nd ; nd
Fat		0.7 ± 0.6	0.21 - 0.23	3.6 ; nd
Spleen	2.88 ± 1.2	2.8 ± 0.8	nd	nd ; nd
Heart	3.31 ± 1.7	3.4 ± 1.0	nd	nd ; nd
Brain	0.75 ± 0.46	4.4 ± 0.6	nd	6.2 ; nd
Thyroid	4.25 ± 1.9	nd	nd	nd ; nd
Testes	2.80 ± 1.4	3.4 ± 0.5	nd	nd ; nd
Placenta / Uterus	nd	nd	nd	7.5 ; 1.35
Fetus (Miyakoda et al., 1999 & 2000)	0.8 - 2.1	nd	nd	nd ; nd

[a] from Yoo et al. (2000) from 2 hr infusion
[b] from Shin et al. (2004) from 3 hr infusion Also used for model.
[c] computed from Snyder et al (2000), bolus dose, Table 3
[d] from Yoo et al (2001) from 4 hr infusion.

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Bisphenol A ADME
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Author	Type of study	Species	Half-life	Mass Balance	Route of Admin	Dose	Chemical species	Bio Samples	Analytcial methods
Cho (2002)	Allomet Model	Multiple species	Ammometric model prediction only	no					
Cuughtrie (1988)	In Vitro UGT	Rat, Human	no	no	In Vitro	NA	Enzyme UDPGT	Rat liver dead infant liver	Elextrophoresis, immunoblot
Csanady (2002)	In Vitro Binding, partition coefficient	Rat, Human	no	no	In Vitro	0 25 mmol/L	BPA	Blood, tissues	HPLC/UV
Domoradzki (2004)	ADME - neonatal	Rat	yes - multiple ages	no	Oral	1, 10/ mg/kg	BPA, BPAG	Plasma, tissues	HPLC/Radioactivity Detection, LSS, LC/MS
Domoradzki (2003)	DME, PK	Nonpregnant vs Pregnant Rats	no	no	Oral	10 mg/bw	BPA, BPAG	Blood, yolk sac/placenta, embryo/fetus	HPLC-ESI-MS, LSS
Hutter (2004)	PBPK - review	Human models	model only	yes					
Inoue (2003)	In vitro perfusion	Rat intestine	no	yes	In vitro perfusion, intestine, colon	10, 50, 100 microM	BPA, BPAG	Intestine, colon	HPLC/UV at 222 nm
Inoue (2004)	In Vitro - perfusion, ME	Rat liver	no	yes	Liver perfusion	10 and 50 microM	BPA, BPAG	Liver	HPLC
Kim, Y H (2003)	Analysis	Human	no	no	no	no	Enzyme, BPA, BPAG, BPAS	Urine	HPLC/FD, GC/EI-MS
Kim, C S (2004)	Oral ADME	Rat	yes	yes					
Kurebayashi (2002)	Oral ADE	monkey (Male/Female)	yes	yes	Oral, IV	100 mg/kg	BPA, BPAG	Plasma	HPLC /UV at 254 nm, LSC
Kurebayashi (2003)	IV & Oral ADME	Male Rat	yes	yes	Oral, IV, IP	0 1, 100 mg/kg (Oral), 0 1 mg/kg (IV)	BPA, BPAG, BPAS	Plasma, urine, feces	HPLC-ESI-MS
Kurebayashi (2005)	IV & Oral ADME					0 1 mg/kg (IV), 10 mg/kg (oral)			
Matsumoto (2002)	In Vivo UGT	Adult Rat	no	no	In vitro	no	UDPGT	Liver, fetus	Immunoblot, Northern blot, HPLC
Miyakoda (1999)	D only	Pregnant Rat	no	no	Oral	10 mg/kg	BPA	Blood plasma, fetuses	GC/MS
Miyakoda (2000)	In Vivo - DM only	Pregnant Rat	no	no	Oral	10 mg/kg	BPA, BPAG	Fetus, testis, blood plasma	GC/MS
Negishi (2004)	AE	Monkey	Calculable from info	no					
Pritchett (2002)	In Vitro M only	Mice, Rat, Human	no - but useful kinetic information	no	In Vitro	10, 20 and 35 microM	BPA, BPAG, BPAS	Hepatocytes	LC/MS-MS

Pottenger (2000)	ADME	Rat	Calculable from info	yes	Oral, IP, SC	10, 100 mg/kg	BPA, BPAG, BPAS	plasma, tissue, urine, feces	HPLC-ESI-MS, GC/MS
Schönfelder (2002)	D only	pregnant Human	no	no	no	no	BPA	Fetus, placenta, plasma	GC/MS
Shibata (2002)	In vitro UGT	Rat	no	no	Oral	2 mg every 2 days for 2-4 weeks	UGT, BPAG, metabolite glucoronides	Liver	HPLC, immunoblot, Northern blot
Shin (2002)	ADME & model	Rats	model only (five compartments)	yes	IV	3 mg/kg	BPA	Placenta, Fetus, Serum, Amniotic fluid	HPLC/Fluorescence
Shin (2004)	ADME & PBPK model	Rats, Humans	Complex model only	yes	IV, Oral	Rat mutiple dose of 0 5 mg/kg (IV), Human 5 mg/person (Oral) and multiple dose of 100 mg/d	BPA	Blood intestine, stomach, liver, kidney, lung, spleen, heart, testis, brain, muscel, adipose	HPLC/Fluorescence
Snyder (2000)	ADME & ER binding	Lactating Rats	Calculable from info	yes	Oral	100 mg/kg bw	BPA, BPAG	Plasma, milk, urine, feces+ (liver, abdominal and sc fat, kidney, lung, intestine + contents, carcass for labeled C)	HPLC/PDA, radiochemical detection, NMR
Strassburg (2007)	In vitro UGT	Humans w/ age	no	no	In vitro	no	UGT	Liver tissues (6-24 months, 25-75 years)	Western blot
Takahashi (2000)	ADME	Pregnant Rats	yes	Calculable from info	Oral	1 g/kg in PG	BPA	blood, liver, kidney, fetues	HPLC/ UV at 227 nm
Teeguarden (2005)	Model & In vitro binding, PBPK	Rats & Human	model only	yes	Oral, IV data from others	10, 100 mg/kg		Plasma	
Uchida (2002)	SC ADME	Pregnant Mice, monkeys	Calculable ?	no	SC	100 mg/kg bw (Mice), 50 mg/kg (Monekys)	BPA,	Mice Serum, brain, uterus, liver, placenta and testis, Monkeys Serum, amd most organs	GC/MS
Upmeier (2000)	IV & Oral ADME	Female Rate	yes	no	IV, Oral	10 mg/kg (IV), 10 &100 mg/kg bw (Oral)	BPA	Blood	GC/MS
Völkel (2002)	AME	Human	Yes, Calculable from info	no	Oral	5 mg/person	BPA, BPAG	Blood, Urine	GC/MS, LC/MS-MS
Völkel (2005)	M only	Human	no	no					
Yokota (1999)	In vitro UGT and M only	Rats	no	no	In Vitro	UGT2B1	UDP-G acid, BPAG	Liver, kidney, lung, small intestine, testis, brain	Nothern blot, cDNA cloning and UGTs expression
Yoo (2001)	Oral & IV ADME	Pregnant Rats	yes, Calculable from info	Calculable from info	Oral, IV	0 1 mg/kg (IV), 10 mg/kg (oral)	BPA	Serum, milk	HPLC/Fluorescence
Zalko (2003)	SC, ADME	Pregnant Mice	Calculable from info	Calculable from info	SC, Oral	25, 50 microg/kg (IV), 25 microg/kg (Oral)	BPA, metabolites (Glu moiety)	Blood/Amniotic fluid, Liver, Fetus, Placenta, Tisues, Urine, Feces, Carcass	HPLC/UV at 270 nm, HPLC-ESI-MS