

BISPHENOL A: INFORMATION SHEET

PHARMACOKINETICS OF BISPHENOL A

SUMMARY

One of the questions that can be asked about any chemical is: what happens to that chemical in the body? A “pharmacokinetic” study is how that question is answered. Pharmacokinetic studies measure how much of the chemical is absorbed and distributed into the body, metabolized to other compounds, and eliminated or retained. These measurements can provide key information to perform a safety assessment of the chemical.

Recently, a pharmacokinetic study (Pottenger *et al*, 2000) was conducted on bisphenol A in rats. Bisphenol A is used in the manufacture of polycarbonate plastic and epoxy resins. The study demonstrated that bisphenol A was rapidly metabolized to a hormonally inactive form and excreted. Another study that compared bisphenol A metabolism in rat, mice and human liver cells showed similar metabolism across the species (Pritchett *et al*, 2001). Taken all together, the studies indicate that rapid metabolism and excretion would also occur following any possible human exposure.

The pharmacokinetic study also showed that concentrations of bisphenol A in the blood were much lower for oral doses than for other routes of administration, such as injection in the abdominal cavity (intraperitoneal) or under the skin (subcutaneous). The oral route of exposure is the most relevant route of possible human exposure. Consequently, safety assessments comparing possible levels of human exposure to no-effect or lowest effect levels should be based on laboratory animal studies using the oral route of exposure. Studies based on other routes of exposure, such as intraperitoneal or subcutaneous injection, will not be comparable to possible human exposures and will not produce realistic safety assessments.

THE POTTENGER PHARMACOKINETIC STUDY

- Groups of healthy, adult laboratory rats (Fisher 344 rats, five males and five females per dose per route of administration) were given a single dose of bisphenol A, and absorption, metabolism, excretion and retention were measured over a seven-day period. The bisphenol A used was custom synthesized with radioactive carbon-14 (radiolabeled) to allow easy tracking of intact material and any metabolites. An analytical method specifically developed for this study was used to measure bisphenol A concentrations in blood.

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- Two doses of bisphenol A were studied: a high dose (100 milligrams bisphenol A per kilogram of test animal body weight) and a ten-fold lower dose (10 milligrams per kilogram body weight). Each dose was mixed in an edible oil (corn oil) to provide bisphenol A in an easily administered and readily absorbable form.
- Three routes of administration were examined: oral, where bisphenol A was given using a feeding tube (gavage); intraperitoneal, where the dose was injected into the abdominal cavity; and subcutaneous, where the dose was injected directly under the skin.
- Concentrations of bisphenol A and metabolites were measured in blood, feces and urine collected from the test animals over a 7-day period. The animals were then sacrificed and residual concentrations of bisphenol A and metabolites in tissues were determined.
- Results were calculated for each group (sex, dose level and route of administration) of test animals.

KEY RESULTS

- The highest bisphenol A concentrations in blood were observed in the first hour following administration of oral or intraperitoneal doses and within four hours following subcutaneous doses.
- Bisphenol A was rapidly cleared from the blood (below the limit of quantitation) within 72 hours for intraperitoneal or subcutaneous injection and within approximately 18 hours for oral gavage. The limit of quantitation was 0.1% of the initial dose administered, which is equal to 0.01 and 0.1 micrograms bisphenol A per gram of blood for blood samples from low and high doses, respectively.
- Metabolites of bisphenol A were detected in the blood of test animals. Highest concentrations of metabolites in blood were reached within one hour of dosing. Metabolite concentrations in blood were below the limit of quantitation within 7 days for intraperitoneal or subcutaneous injection and within 72 hours for oral gavage.
- Fecal excretion was the major route of elimination with urinary excretion as a secondary route. Total excretion was similar for male and female rats (86-96%) but males excreted more bisphenol A in the feces (74-83%) than females (52-72%) while females excreted more bisphenol A in the urine (21-34%) than males (13-16%).

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- Bisphenol A was excreted in the feces mostly as unmetabolized bisphenol A (86-99% of the radiolabeled material in the feces). The major forms of bisphenol A in urine were the monoglucuronide of bisphenol A (69-87% and 57-68% of the radiolabeled material in the urine from females and males, respectively) and bisphenol A itself (8-10% of the radiolabeled material). A glucuronide is a common type of metabolite formed by liver metabolism. Bisphenol A monoglucuronide is inactive in a short-term test (uterotrophic assay) in which bisphenol A is active, indicating that metabolism of bisphenol A results in a metabolite that is hormonally inactive (Fennell *et al*, 2000; Matthews *et al*, 2001).
- A number of other metabolites of bisphenol A were detected in feces and urine. None of these metabolites represented more than 10% of the radiolabeled material in feces or urine.
- After the 7-day observation period, residual amounts of bisphenol A and metabolites in the animals were quite low, ranging from a maximum of 1.3% of the test dose for subcutaneous injection, 0.8% for intraperitoneal injection and 0.4% for oral gavage. Residual concentrations in body fat and sex organs were no higher than in other tissues.
- Recent data from the University of Arizona with liver cells from rats, mice and humans show similar metabolism of bisphenol A across the species (Pritchett *et al*, 2002). Consequently, bisphenol A intake from any possible human exposure would be rapidly metabolized to a hormonally inactive form and excreted from the body (Fennell *et al*, 2000; Matthews *et al*, 2001; Pottenger *et al*, 2000).
- The metabolism and toxicokinetics of BPA in humans has also been measured directly by exposing human volunteers to oral doses of 5 mg of deuterated BPA (d₁₆-BPA). The glucuronide was the only metabolite detected in urine and blood, and free d₁₆-BPA was not detected in either urine or blood. The applied doses were completely recovered in urine as the glucuronide and the clearance of the glucuronide from blood to urine proceeded with a terminal half-life of less than 6 hours (Völkel *et al*, 2002).

CONCLUSIONS

- Bisphenol A was rapidly adsorbed into the blood and metabolized following intraperitoneal or subcutaneous injection, or oral exposure (gavage). Bisphenol A was efficiently excreted from the bodies of both female and male laboratory rats. The excreted material is primarily bisphenol A itself and bisphenol A monoglucuronide, a metabolite that is biologically inactive.

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- Bisphenol A did not accumulate in body fat or sex organs of either male or female test animals given either 10 or 100 milligrams per kilogram body weight of bisphenol A administered by oral exposure, or intraperitoneal or subcutaneous injection.
- The results of a study comparing rat, mice and human liver cells (Pritchett *et al*, 2002) demonstrate that the results of the pharmacokinetic study in rats also apply to humans. Consequently, bisphenol A intake from any possible human exposure would be rapidly metabolized to a hormonally inactive form and excreted from the body.
- The rapid metabolism of BPA to the glucuronide and clearance from the body in humans has been confirmed in a test on human volunteers.
- In the pharmacokinetic study of Pottenger *et al* (2000), lowest concentrations of bisphenol A in blood were observed following oral exposure, the most relevant route of administration for a safety assessment of bisphenol A. Consistent with this observation, lower bioactivity of bisphenol A following oral exposure has also been observed (Ashby and Tinwell, 1998; Jekat *et al*, 2000, Matthews *et al*, 2001).
- This finding of different levels of bioavailability and bioactivity of bisphenol A depending on the route of exposure provides important guidance for conducting a safety assessment of bisphenol A. Specifically, safety assessments comparing possible levels of human exposure to no-effect or lowest effect levels should be based on laboratory animal studies using oral routes of exposure since this is the most relevant route of human exposure. Studies based on other routes of exposure, such as intraperitoneal or subcutaneous injection, will not be comparable to possible human exposures and will not produce realistic safety assessments.

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