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Importance of Metabolism to Risk Evaluation of Environmental Chemicals

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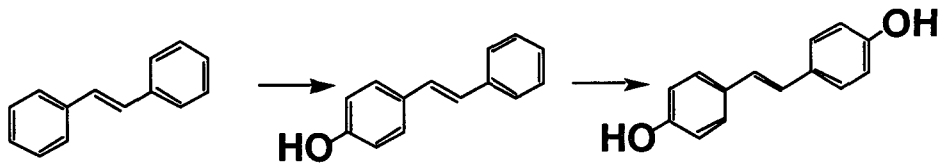
Introduction

More than 16 million of chemical substances are exist on the earth now, and the number of the compounds are continuously increase. We are surrounded innumerable environmental chemicals with daily life. Some of the compounds obtain toxic characters via changing structure in environment or metabolism in animals including human being. On the other hand, toxic compounds can be also converted to non-toxic metabolite. We should pay attention to metabolites of environmental chemicals.

trans-Stilbene (1)

trans-Stilbene is used as an industrial raw material for stilbene dyes and fluorescent brightening agent. Estrogenic activity of *trans*-stilbene in the presence or absence of a rat liver microsomal oxidation system was examined. *trans*-Stilbene itself did not show estrogenic activity. When *trans*-stilbene was incubated with liver microsomes of 3-methylcholanthrene-treated rats in the presence of NADPH, the extract of the incubation mixture exhibited an estrogenic effect. In contrast, little effect was obtained when liver microsomes of untreated or phenobarbital-treated rats were used. These facts suggest that *trans*-stilbene is metabolically activated by rat liver microsomes, especially those from 3-methylcholanthrene-treated rats. The metabolites of *trans*-stilbene were *trans*-4-hydroxystilbene and *trans*-4,4'-dihydroxystilbene. These compounds showed strong estrogenicity.

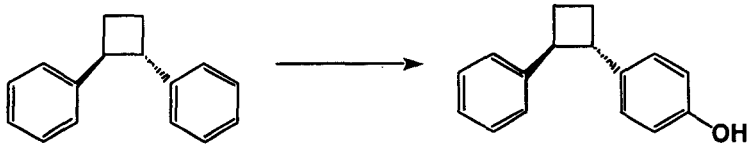


***trans*-Stilbene**

trans-1,2-Diphenylcyclobutane (2)

Polystyrene has been used to manufacture food containers for takeout, such as coffee cups, meat trays. Styrene oligomers, such as trans-1,2-diphenylcyclobutane (TCB) and cis-1,2-diphenylcyclobutane (CCB) are incorporated into polystyrene resin as impurities.

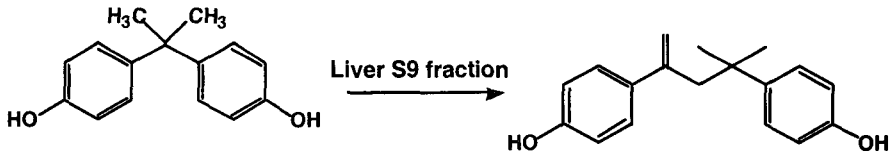
TCB and CCB themselves exhibited no estrogenic activities. When TCB was incubated with liver microsomes of phenobarbital-treated rats in the presence of NADPH, an active metabolite was formed. The metabolite showed strong estrogenic activity.



TCB

Bisphenol A (3)

Bisphenol A (BPA) is a weak estrogen that is widely used as a component of polycarbonate and epoxy plastics. Thus, BPA is regarded as one of the endocrine disrupting chemicals (EDCs) ingested by humans in daily life. Estrogenicity of BPA in vitro is less potent than that of in vivo. This discrepancy between in vitro and in vivo suggests that an active metabolite may be formed in vivo. We have shown that a metabolite of BPA is a very potent estrogenic compound formed by liver S9 fractions of several animal species, including human.



Bisphenol A

Potent estrogen

Conclusion

Here we demonstrate some examples of metabolic conversion for environmental chemicals. These types of research have not been done so much. Much further work is needed to identify potentially hazardous proestrogens in our environment.

References

1) Sugihara, K., Kitamura, S., Sanoh, S., Ohta, S., Fujimoto, N., Maruyama, S., Ito, A., Metabolic activation of the proestrogens trans-stilbene and trans- stilbene oxide by rat liver microsomes. Toxicol. Appl. Pharmacol. 167, 46-54 (2000)
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3) Yoshihara, S., Mizutare, T., Makishima, M., Suzuki, N., Fujimoto, N., Igarashi, K., Ohta, S. Potent estrogenic metabolites of bisphenol A and bisphenol B formed by rat liver S9 fraction: their structures and estrogenic potency. Toxicol. Sci. 78, 50-59 (2004)