

Effects of Bisphenol A on Human Health

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Abstract: When examining substances suspected to be endocrine disruptors, it is important to recognize that these can be divided into persistent organic pollutants and estrogenic chemicals. Beside bisphenol A, estrogenic chemicals include synthetic estrogens and phytoestrogens in food. Most estrogenic chemicals have many properties in common; they are biodegradable and not bioaccumulable. However, estrogenic potencies vary largely from substance to substance. Many animal experiments, including multigenerational reproductive toxicity studies, have been conducted on bisphenol A, and the no-observed-effect level (NOEL) in humans is estimated to be 0.05 mg/kg/day. The NOEL can be estimated for synthetic estrogens and phytoestrogen because they have frequently been used in humans. Based on the current situation regarding usage, I believe bisphenol A is safe to use.

Key words: Endocrine disruptors; Bisphenol A; Estrogenic chemicals; Tolerable daily intake; No observed effect level

Introduction

Approximately 0.35 million tons of bisphenol A are produced in Japan each year, and most are used as raw materials for polycarbonate resin and epoxy resin.

Bisphenol A might be ingested by humans through polycarbonate used as milk bottles and as dishes used at schools or through epoxy resin used for cans. Such cans are usually coated with epoxy resin on the inside, from which very low levels of bisphenol A may migrate.

I believe it is safe to use bisphenol A for these uses based on the reasons explained below.

Tolerable Daily Intake of Bisphenol A

The tolerable daily intake (TDI) that will not adversely affect humans is 0.05 mg/kg/day. So for someone who weighs 50 kg, the total daily intake is 2.5 mg, which means that bisphenol A will be ingested at concentration of 2.5 ppm in a food if a person were to eat 1 kg of food in a day.

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When bisphenol A is detected in dishes used at schools, as we occasionally hear on the news, the levels are usually no more than 1/1,000 of 2.5 ppm.

The TDI for bisphenol A was established as follows. First, various types of studies, such as chronic/carcinogenicity studies and reproductive toxicity studies, were conducted. Based on the results of these studies, the no-observed-effect level (NOEL) was estimated to be 5 mg/kg/day. Since TDI in humans is calculated by multiplying the NOEL in animals by uncertain factor of 1/100, the figure 0.05 mg/kg/day is obtained as the TDI for bisphenol A in humans.¹⁾

However, people frequently ask the question, "Shouldn't the TDI be lowered since the current TDI was established long ago, and since bisphenol A acts as a estrogen?"

To this I respond that the TDI for bisphenol A was determined also based on reproductive toxicity studies, which are the most appropriate test for assessment of the toxicity caused by estrogenic actions.

Moreover, the same TDI is used in the United States and Europe, and there have been no indications that this might change.

Achievements in Occupational Health

It is reasonable to assume that people who work at companies that manufacture bisphenol A are exposed to bisphenol A at a much greater level than others are, especially since bisphenol A exists as a powder, and people are likely to be exposed to it at high levels when packaging it into bags or pouring it out of bags into reactors.

However, despite the fact that bisphenol A has been manufactured and used for more than 40 years, only several cases of impairment in such employees have been reported. These were only cases of irritation to eye, nose, and throat due to exposure to high levels of dust and photosensitization in skin. Systemic impairment, such as reproductive toxicity and liver

toxicity, have not been reported.²⁾

Thus, it can be said that bisphenol A will pose no hazard to humans as long as the current TDI and handling instructions are observed.

There are Two Types of Endocrine Disruptors Suspected

When examining substances suspected to be endocrine disruptors, it is important to recognize that these can be divided into persistent organic pollutants and estrogenic chemicals.

Persistent organic pollutants include PCB, DDT, dioxin, and tributyl-tin compounds.

Estrogenic chemicals are substances that possess estrogenic activity, and include diethylstilbestrol, synthetic estrogens, genistein, which is contained in soybeans, as well as bisphenol A and nonyl phenol.

Persistent organic pollutants are not biodegradable, and will remain in the environment for a long time once they are released in the environment. Since they are bioaccumulable, they can adversely affect birds and humans that eat fish in the food chain even when the levels in the environment are very low.

The harmful effect of these persistent organic pollutants has been known even before the endocrine disruptors issue began to attract attention, and these pollutants has been strictly controlled. As a result, the pollution has already being improved.

Estrogenic chemicals, on the other hand, are biodegradable and not bioaccumulable. Adverse effects through the food chain are, therefore, not a threat. When absorbed in the body, they are easily metabolized, and most are excreted within a day.

The only thing people need to be careful concerning estrogenic chemicals is the fact that they may exhibit estrogenic actions, and that some of them, like bisphenol A, are commonly used in our daily life.

There are some that fuel nervousness among people by causing them to think that estrogenic chemicals might also cause like incidents that

were associated with dioxin and PCB.

It is important that people understand that bisphenol A is an estrogenic chemical that possesses completely different properties from dioxin.

Estrogenic Chemicals

Estrogenic chemicals have the following in common.

- (1) They have similar chemical structures. Molecular weight ranges from 200 to 300, and the structures contain one or more phenolic hydroxyl groups.
- (2) When absorbed into the body, they are rapidly excreted after becoming water-soluble through glucuronidation.
- (3) They bind with estrogen receptors, and exhibit estrogenic actions.
- (4) They lose their estrogenic activities through glucuronidation.

While these chemicals share many properties, as shown above, there are great differences among their estrogenic potencies. Results of a

comparison of the estrogenic potencies that were made in rats using uterotrophic assay are shown in Table 1.³⁾ Lowest-observed-effect level (LOEL) is the dose at which the weight of the uterus increased significantly, and is based on the results of oral administration studies. Relative activity is the inverse number of the relative LOEL.

Estrogenic action does not necessarily lead to toxicity. Whether or not the estrogenic actions might be toxic must be examined through reproductive toxicity studies. Minimum toxic dose in reproductive toxicity studies and those in any studies are compared in Table 2.³⁾ "Any studies" are toxicity studies, such as chronic tests and reproductive studies, and the values for "any toxicity" in the table represent the lowest value among all minimum toxic doses. As suggested in Table 2, the toxicity of a substance with strong estrogenic potency, for example, diethylstilbestrol, is caused by the estrogenic actions. With respect to bisphenol A, general toxicity, such as adverse effects on the liver, is observed at levels lower than those at

Table 1 Comparison of the Estrogenic Potency³⁾

Name of substance	LOEL (mg/kg/day)	Relative potency (E2 = 1)
Diethylstilbestrol	0.001	50
Ethinyl estradiol	0.002	25
Estradiol (E2)	0.050	1
Genistein	28	0.0018
Bisphenol A	200	0.00025

Table 2 Comparison of the Minimum Toxic Dose in Animal Studies³⁾

Name of substance	Reproductive toxicity (mg/kg/day)	Any toxicity (mg/kg/day)
Diethylstilbestrol	0.0075	0.0075
Ethinyl estradiol	0.010	0.010
Estradiol	0.16	0.16
Genistein	67	67
Bisphenol A	437	50

Table 3 NOEL and Intake in Humans³⁾

Name of substance	Intake (mg/day)	Relative potency (E2 = 1)	Adjusted intake (mg/day)
DES (Estimated NOEL in men)	2.0	50	100
DES (Estimated NOEL in women)	0.1	50	5
EE (NOEL)	0.035	25	0.88
GE (Actual intake)	15	0.0018	0.027
BPA (Tolerable intake)	2.5	0.00025	0.0006
BPA (Actual intake)	<0.025	0.00025	<0.000006

DES: Diethylstilbestrol EE: Ethinyl estradiol GE: Genistein BPA: Bisphenol A

which estrogenic actions can cause any toxicity. As such, substances like bisphenol A should not be considered as endocrine disruptors.

Adverse Effects and NOEL in Humans

In considering how a substance might affect human health, it is important to examine case studies. Examples are shown in Table 3, from which it can be deduced that there are NOEL in humans.³⁾

A famous case is that of a child who was born to a mother who had taken diethylstilbestrol during pregnancy. Abnormality in genitalia and vaginal cancer occurred in the child. Regarding this matter, a very reliable epidemiological investigation was conducted,^{4,5)} which showed that there was little or no effect when the dose was small. It can also be estimated that there is no effect on the offspring if the actual intake of the mother is no more than 2 mg/day when the child is a boy and 0.1 mg/day when the child is a girl.

Ethinyl estradiol is used as a birth-control pill, and its NOEL is 0.035 mg/day. What happened in the case example of diethylstilbestrol could also happen with this pill, too, if a woman continues to take it without realizing that she is pregnant. However, it is thought that congenital abnormalities will not occur even in such cases.

The average daily intake of genistein contained in soybeans is about 15 mg in Japan. People who eat fermented soybeans, *natto*, every morning will have ingested 20 mg of genistein in breakfast alone. Of course, however, this is within NOEL, as one can expect from the fact that consumption of soy poses no adverse effects.

The TDI for bisphenol A, on the other hand, is 2.5 mg, and the actual daily intake is less than 1/100 of the tolerable daily intake.

Relative potency is shown in Table 1. Adjusted daily intake is obtained by multiplying the daily intake by relative potency.

Table 3 also shows that the TDI for bisphenol

A and the actual daily intake are small enough compared with other NOEL, suggesting that bisphenol A is very unlikely to be harmful in humans.

Low-Dose Effects

Some think that substances with hormonal activity can pose a threat to health even at a low dose. Recently, this issue has been of great interest to many.

The growing interest in this issue came about with a report by Dr. vom Saal. In this report, he reported that the weight of prostates increased by 30% in male fetuses of pregnant mice to whom bisphenol A was orally administered at 0.002 mg/kg/day or 0.02 mg/kg/day.⁶⁾

In response, an international group of bisphenol A manufacturers conducted a large-scale study using more animals and parameters, and verified that there was no such effect.⁷⁾

A three-generation reproductive toxicity study was also conducted using rats to further verify the safety of bisphenol A. A wide range of doses ranging from 0.001 mg/kg/day to 500 mg/kg/day was used to determine the effects at low doses. Also, many parameters were added so that effects related to estrogenic actions could be observed in detail. Results of this study confirmed the accuracy of the current TDI.⁸⁾

The Ministry of Health, Labour and Welfare has also conducted a two-generation reproductive toxicity study using rats to verify the effects at low doses, and confirmed that there are no effects.⁹⁾

Conclusion

In conclusion, I wish to convey the impression I have received through my involvement with issues regarding endocrine disruptors.

There is a saying, "Do not use anything suspicious." This is very reasonable, and I, as one representing a manufacturer, do not intend to sell anything that is suspicious. However, the

difficulty lies in the reality that whether or not a substance is suspicious is not determined by manufacturers such as ours or by public offices, but ultimately by consumers. This is the case because newspapers and TV programs, which have an overwhelming influence on the public, tend to take interest only in views that fuel anxiety.

If you are interested in finding out more about bisphenol A than what I have explained, as one in charge of safety at a manufacturer of bisphenol A, I would be delighted if you visited our Web site where you will find more information.^{10,11)}

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* Papers written by Mr. Nishikawa in the *Aromatics* can also be found at “South Wave”.
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