3.Polyvinyl chloride

Polyvinyl chloride is used in food containers, vinyl sheet, agricultural vinyl sheet and building materials because its hardness is easily adjusted. This plastic is generally formed by repeated polycondensation, using ethylene monomer and ethylene dichloride as materials. Polyvinyl chloride is originally hard, but can be softened by adding di(2-ethylhexyl) phthalate (DEHP) or others as a plasticizer. Phthalate used as plasticizer is suspected of being an endocrine disruptor. The Japan Toy Association has stated that teething rings and pacifiers made in Japan do not contain polyvinyl chloride.

●Annual food-related use (investigated by Japan Hygienic Olefine and Styrene Plastics Association, unit: 1,000 ton)

Production: 2,510; domestic sales: 2,510, including food-related use: 110; volume of resin using diethylhexyl phthalate, for food-related use: 40

(1) Elution of phthalate

Reportedly, phthalate is detected in dairy products and drinks. Examination of foods packed in plastic containers showed di(2-ethylhexyl) phthalate (DEHP) volumes to be approximately 10 to 100 ppb, as shown in Table 3[*127*128].

In studies on phthalate contained in vinyl chloride toys, dibutyl phthalate, dioctyl phthalate, dihepthyl phthalate and dinonyl phthalate ranged from 0.2 to 24%[*129]. In another study, phthalates at concentrations from 10 to 40% were found using a similar measuring method[*130]. In a study of diisononyl phthalate (DINP) elusion from vinyl chloride toys into saliva, with the cooperation of 20 volunteers, DINP levels were from 1.38 to 2.44 μg/min[*131].

(2) Safety of phthalate

1. Screening

- In vitro study

Some studies reported ER-binding capacity in human mammary carcinoma cell line and rat uterus as follows:

1) Transcription activation capacities of phthalates (as mediated by ER in human mammary carcinoma cell line (MCF-7)) were compared with the

maximum activity (10^{-8} to 10^{-9} M) in estradiol (E_2). Dibutylbenzyl phthalate (10^{-6} to 10^{-4} M) and dibutylphthalate (10^{-5} to 10^{-4} M) increased in the activity, but diethylhexyl phthalate (10^{-4} M) showed no such action[*132].

2) In a study of estrogenic activity in terms of proliferation potency of human mammary carcinoma cell line (MCF-7) dibutyl phthalate, diamyl phthalate, dimethyl isophthalate, dimethyl telephthalate and dinonyl phthalate were evaluated to have no estrogenic activity, but the estrogenic activity of benzylbutyl phthalate was 0.0003 times that of estradiol (E_2) as 100[*119].

3) In a study using mouse peroxisome proliferation activity receptor, monoethylhexyl phthalate (10^{-5} to 10^{-4} M), a metabolite of diethylhexyl phthalate, showed increase in the activity, but diethylhexyl phthalate (10^{-5} M) did not[*133].

(Reference data)

In a study on binding to rat uterin ER, 50% inhibition concentration of estradiol (E_2) (a positive control) was 10^{-9} M, and dibutyl phthalate and diisooctyl phthalate showed 9% and 15% inhibition respectively at 10^{-3} M, while diisononyl phthalate, diisodecyl phthalate and dioctyl phthalate had no influence[*134].

- In vivo study

Utero-trophic assay etc. in phthalates have been reported.

In a study using male and female mice given diethylhexyl phthalate subcutaneously (1 to 100 ml/kg, at days 1, 5 and 10), pregnancy ratio decreased in groups given 10 ml/kg or more, and testis weight decreased in groups given 15 to 20 ml/kg. However, uterine weight did not change[*135].

(Reference data)

In a study of ovariectomized female mice given the above chemical subcutaneously (1,000 mg/kg, for 3 days), dibutyl phthalate and diisooctyl phthalate exhibited 9% and 15% inhibition, respectively, at 10^{-3} M, while diisononyl phthalate, diisodecyl phthalate and dioctyl phthalate did not show any influence on uterine weight nor on amounts of progesteron receptor volume[*134].

2. Repeat dose tests etc.

As regards diethylhexyl phthalate, etc., subchronic toxicity studies in mice and rats have been reported:

1) In a 4-week oral dose study in mice given a mixture of diocyl phthalate and styrene (13:1, 0.02, 0.03, 0.05 × LD_{50}), the immune system was influenced, e.g., decrease in numbers of lymphoid cells and monocytes in the spleen[*136].
2) In both single oral dose (5,000 mg/kg) and 14-day repeat oral dose (1,500 mg/kg) toxicity studies in rats with diethylhexyl phthalate, any neurotoxicity was not detected[*137].
3) In a 12-day toxicity study in adult rats fed a mixed diet containing diethylhexyl phthalate (2 g/kg), prolonged estrous cycle, inhibition of ovulation and decrease in serum estradiol were found[*138].
4) In a 10-day repeat oral dose toxicity study in male rats aged 4 and 15 weeks with diethylhexyl phthalate (2,800 mg/kg), atrophy of the seminiferous tubules and decrease in the prostate weight were found in 4-week group, whereas there was no alteration in 15-week group[*139].
5) In a mid-term hepatic carcinogenicity study in rats fed a mixed diet containing diethylhexyl phthalate (30, 300, 3,000 and 12,000 ppm), at 48 weeks hyperplastic nodules developed in 3,000- and 12,000-ppm dose groups. At 52 weeks, the hyperplastic nodules had developed in all animals of the 12,000-ppm dose group, with hepatocellular carcinoma in 9 of 12 cases[*140].

(Reference data)

In a 13-week oral dose study in marmosets (the primate) with diethylhexyl phthalate (100, 500 and 2,500 mg/kg), decrease in body weight gain was found in 2,500-mg/kg dose group, and increases in liver microsome protein and p-450 content per unit of weight were found in male 500- and 2,500-mg/kg dose groups. Testicular atrophy was not found[*141].

3. Pharmacodynamics

(Reference data)

A distribution study on testis was performed with radio-labelled diethylhexyl phthalate. In a single oral dose testis toxicity study in rats with oral diethylhexyl phthalate (700, 1,000, 1,400, 2,000 and 2,800 mg/kg), degeneration of the spermatocyte and expansion of smooth-surfaced endoplasmic reticulum in the junction of Sertoli cells etc. were found in 2,800-mg/kg group. Slight expansion of smooth-surfaced endoplasmic reticulum was

observed also in the groups with 700- and 1,000-mg/kg. In a single oral dose study with the ^{3}H labelled diethylhexyl phthalate, testis and liver distribution were examined, and it was revealed that diethylhexyl phthalate affected localization of β-actin in Sertoli cells in the testis[*142].

(3) Conclusion

ER-binding capacity of phthalates differed with the kind of ester; it has been reported that diethylhexyl phthalate did not bind to ER at a low concentration. In another report concerning utero-trophic assay in rats, uterine hypertrophy was not found.

As shown above, we do not have scientific information that diethylhexyl phthalate at the level eluting from polyvinyl chloride seriously influences human health; therefore, it would not be necessary to prohibit use of polyvinyl chloride at present. However, in a 10-day repeat dose toxicity study in rats, atrophy of the seminiferous tubule and decrease in prostate weight were found. Therefore, we should conduct further researches such as two-generation reproductive studies. Safety performance should be assessed on the basis of examination of exposure levels of tableware and toys infants may take into their mouth as well as international trends.

(4) Future research

- Two-generation reproductive study in rats; pharmaco-dynamic study in rats etc. (bioaccumulation, transfer to fetus and milk)
- Concentration research in human umbilical cord blood and breast milk and research for organ distribution
- Research for elution volumes from tableware and toys