Commentary

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An Overview of Phthalate Ester Carcinogenicity Testing Results: The Past

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This paper presents a short review of the available carcinogenicity tests which have been carried out on various phthalate esters prior to the availability of the National Cancer Institute bioassay studies. All of these studies suffer from diverse limitations in design or reporting when compared to more recent experimental protocols and reports.

There are three papers related to di(2-ethylhexyl) phthalate, one to di-*n*-butyl phthalate, two to butyl benzyl phthalate, one to ethyl phthalyl ethyl glycolate and another to butyl phthalylbutyl glycolate (*1*).

Di(2-ethylhexyl) Phthalate (DEHP)

The first experiment was carried out in 1953 in Sherman rats. Groups of 32 male and 32 female rats were administered 0.04, 0.13 or 0.4% DEHP in the diet for a maximum of two years. The doses were equivalent to 0. 20, 60 and 200 mg/kg body weight/day, respectively. Controls (number unspecified) received basal diet alone. After one year, 42% of the control rats and the same percentage of rats at the highest dose level survived. The various groups were reduced to a maximum of eight males and eight females per group at the end of one year. Two groups of 32 males and 32 females (F_1 progeny) were generated from the control and high dose P generation and at 15 days of age were maintained at a dose level of 0.4% DEHP in the diet for one year, at which time the animals were killed. Some tumors were observed in the animals surviving longer than a year, but they were equally scattered among the different groups, so that, on the basis of this experiment, it was not possible to conclude either a negative or positive carcinogenic response to this chemical (*2*). The small number of animals, poor survival and limited reporting make this experiment inadequate in terms of a carcinogenicity bioassay.

The second experiment was carried out by Harris et al. (*3*) on Wistar rats. Groups of 43 males and 43 female rats were fed DEHP at a dose of 0, 0.1% and 0.5% in the diet for a maximum of two years, which corresponded to an intake of about 0, 70 and 250 mg/kg body weight/day, respectively. In this experiment, groups of animals were sacrificed at various times, namely, at 3, 6, 12, and 24 months, the number of animals sacrificed being four, four, 10 and 24 rats, respectively. Pathological examination, however, was not carried out for all animals sacrificed, but only in eight males and eight females per group at 12 months, and in one to a maximum of four rats in the treated and control groups at two years. No tumors were observed. In addition to the limited pathology examination carried out, this study has the same limitations as the previous experiment in regard to the possibility of assessing the carcinogenicity of this chemical.

An experiment in 1974 by Onda et al. cited by Omori (*4*) which was originally reported as an abstract in Japanese, mentions the induction of renal cysts in the F_1 and F_2 generations of ddY or ICR mice treated with 10 or 100 mg/kg body weight/day DEHP, but it is not clear if the treatment of the animals was carried out only in the parent generation, or if it was continued also into F_1 and F_2 generations. This experiment could not be evaluated for carcinogenicity.

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Di-*n*-butyl Phthalate

A similar experiment cited by Omori (*4*) on di-*n*-butyl phthalate reported less severe effects on the kidney; this study also cannot be used for an evaluation of carcinogenicity.

Butyl Benzyl Phthalate

An experiment was carried out on butyl benzyl phthalate by Theiss et al. (*5*) on male strain A/St mice aged 6-8 weeks, in which mice were given IP injections of 160, 400 or 800 mg/kg body weight three times/week for 8 weeks. The animals were killed at 24 weeks and examined for the number of lung tumors detected macroscopically. The numbers of lung tumors per mouse were 0.1-0.25 in treated groups, compared with 0.39 in the corresponding vehicle controls. A negative effect in this test system cannot be taken as evidence for the absence of a carcinogenic effect.

Butyl benzyl phthalate was administered to a group of 20 male and 20 female Wistar rats at a dose of 5 mg/kg body weight/day (exact route and length of treatment unspecified). There was 100% survival at two years. Nontumorous pathological changes were reported to occur in the kidney as well as atrophy of the testes, but no tumors were observed. No details were given concerning control rats, which makes this experiment (*6*) difficult to evaluate.

Ethyl Phthalylethyl Glycolate

Ethyl phthalylethyl glycolate was administered to Wistar rats at doses of 0.05, 0.5 and 5% in the diet for a period of two years. No difference in survival occurred between the two lowest dose groups and the controls (exact survival times not reported), whereas none of the animals in the 5% dose group survived longer than 72 weeks. In this experiment, no tumors were observed, but some kidney pathology was observed in the highest dose group (*7*). The lack of details on survival makes this experiment impossible to evaluate.

Butyl Phthalylbutyl Glycolate

Butyl phthalylbutyl glycolate was administered to groups of 20 Sherman rats (sex unspecified) at three dose levels (200, 2000 and 20,000 mg/kg body weight) in the diet for two years. A group of 40 controls received the basal diet. Although no tumors were reported to occur, more than 80 rats were killed before the end of the observation period, and it is difficult to assess the number of animals surviving or at risk to develop tumors (*8*).

In conclusion, these various experiments do not allow any evaluation of the carcinogenicity of these chemicals in mice or rats.

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