TOX II

Developmental Toxicity of 3,3',4,4',5-Pentachlorobiphenyl in Mice

Mineo Yasuda, Keisuke Yamashita, Toshio Takagi, Ichita Miwa and Mizuyo H. Tsugane
Department of Anatomy, Hiroshima University School of Medicine
Kasumi 1-2-3, Minami-ku, Hiroshima 734, Japan

1. Introduction

Environmental pollution with PCBs has been a great social concern in Japan. The public has been warned against potential health effects of coplanar PCBs. 3,3',4,4',5-Pentachlorobiphenyl (PeCB) is one of such compounds, and is considered as a ligand of the Ah receptor, which mediates toxic action of dioxins. Its developmental toxicity was established in chick embryos[1], however, to the best of our knowledge, its adverse effects on mammalian embryos have not been reported. The present study aimed at studying effects of 3,3',4,4',5-PeCB on mouse embryos, and estimating its Toxic Equivalency Factor (TEF).

2. Materials and Methods

Colony-bred Jcl:ICR mice from CLEA Japan, Inc. (Tokyo) were used. Mature females were mated with males overnight. Copulation was ascertained by the presence of a vaginal plug on the following morning, and the day was designated as gestational day (GD) 0. At GD12.5, 3,3',4,4',5-PeCB (Cambridge Isotope Laboratories, originally solved in isooctane at a concentration of 100 μg/ml, and diluted with corn oil) was orally given by gavage at dose levels between 25 and 800 μ g/kg body weight. Control mice received the vehicle (a mixture of isooctane and corn oil). The dams were killed by cervical dislocation at GD18.5, and fetuses were removed by caesarean section. The number of implantation sites and resorptions was recorded. The live fetuses were sexed, weighed, and examined for external abnormalities including cleft palate. After fixation in Bouin's solution, the mandible of fetuses was removed, and rugae on the oral surface of the secondary palate were examined in fetuses without cleft palate under a dissecting microscope. Abnormal patterns of the palatal rugae were recorded according to the definition by Yasuda, et al.[2]. Abdominal organs were examined by Wilson's method[3], and enlargement of the renal pelvis was diagnosed as hydronephrosis.

3. Results

No maternal death was induced by administration of 3,3',4,4',5-PeCB. Preliminary results of our fetal examination were illustrated in Fig 1. 3,3',4,4',5-PeCB did not show any obvious embryolethal action in the tested dose range. However, it induced cleft palate, abnormal patterns of palatal rugae, and hydronephrosis in a dose related manner. ED50s for cleft palate, abnormal patterns of palatal rugae, and hydronephrosis were estimated to be about 300 μg/kg, 250 μg/kg, and 80 μg/kg, respectively. The cleft was limited to the secondary palate. The most common abnormal pattern of palatal rugae was shortness (Fig. 2) . The enlargement of the renal pelvis became severer as the dose increased. No other major malformations were induced by 3,3',4,4',5-PeCB.

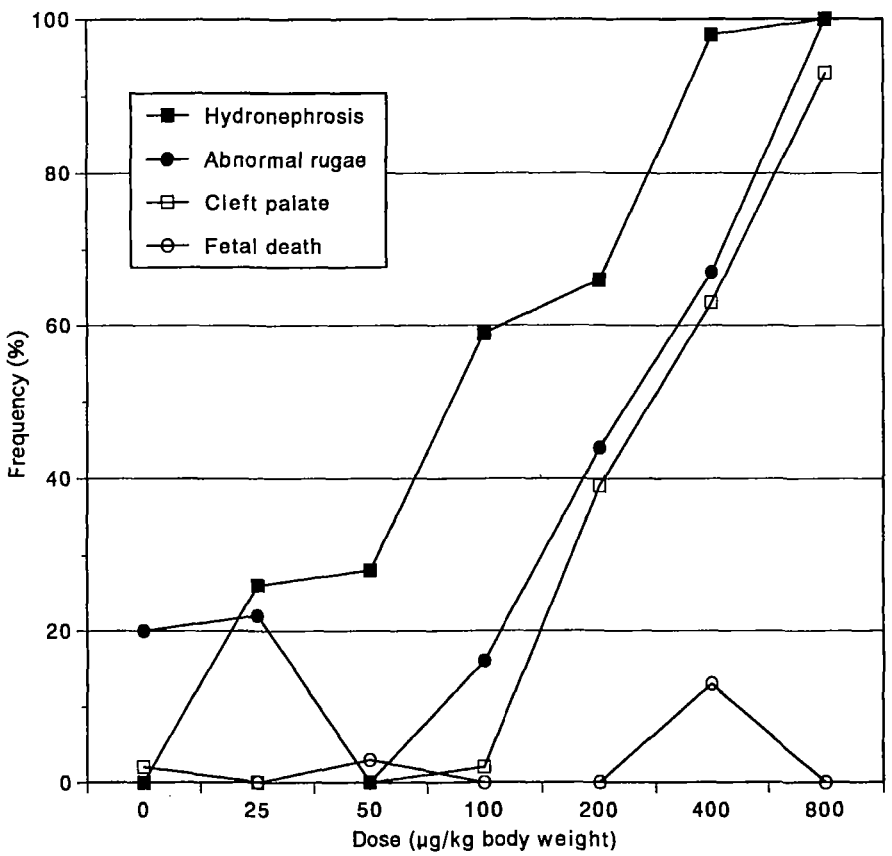

Fig. 1. Relationship between 3,3',4,4',5-PeCB dose and frequencies of fetal death, cleft palate, abnormal palatal rugae, and hydronephrosis.

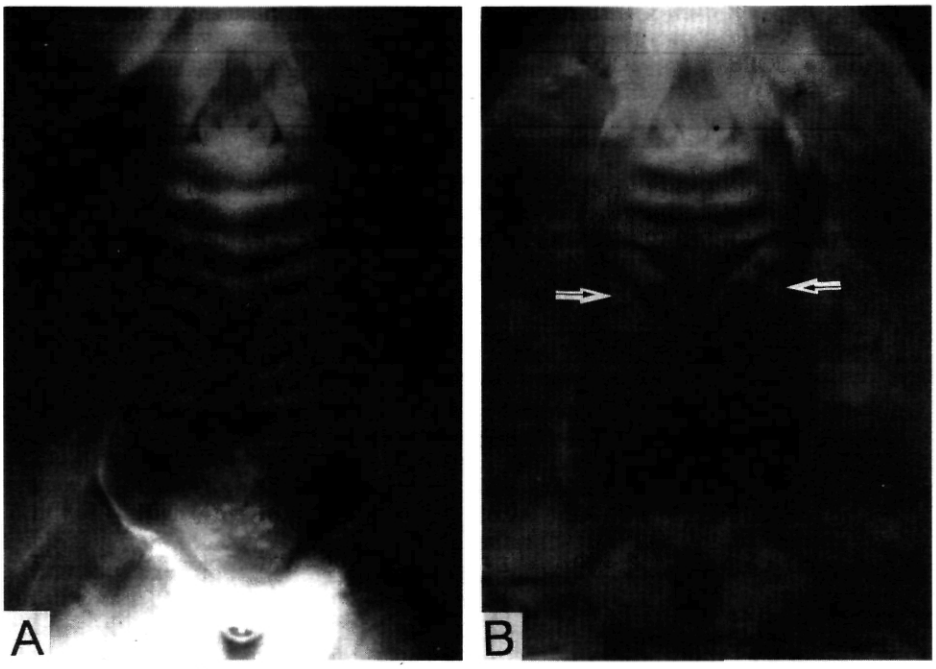

Fig. 2. A: Palatal rugae in a control fetus. B: Palatal rugae in a fetus treated with 3,3',4,4',5-PeCB at 800 μg/kg. Note shortness of bilateral ruga 5 (arrows).

4. Discussion

The present study clearly demonstrated that 3,3',4,4',5-PeCB is a potent teratogen in mice. From the results of our previous experiments with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) given to Jcl:ICR mice at GD12.5[4), 5)], its ED50s for cleft palate, abnormal patterns of palatal rugae, and hydronephrosis were estimated to be around 30 μ g/kg, 20 μ g/kg, and 15 μ g/kg, respectively. When these values were divided by the values obtained in the present experiment with 3,3',4,4',5-PeCB, a TEF value of about 0.1 was obtained. This value corresponds closely with the TEF recommended by WHO[6)], which estimated the TEF mainly from induction of AHH and EROD activities.

The similarity in the spectrum of induced malformations, i.e. cleft palate and hydronephrosis, between TCDD and 3,3',4,4',5-PeCB strongly suggests that the mechanisms for induction of these malformations are similar for these compounds. The common abnormal pattern of palatal ruga anomaly, shortness, was frequently observed in fetuses treated with either TCDD or 3,3',4,4',5-PeCB.

We have advocated observation of the pattern of palatal rugae in developmental toxicity studies in mice[5] and rats[7]. Usefulness of this method was verified also in the present experiment.

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5. References

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