ASSESSMENT OF THE CLEFT PALATE INDUCTION BY SEVEN PCDD/F CONGENERS IN THE MOUSE FETUS

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Introduction

Polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) are highly toxic compounds found in almost every part of the environment. Toxic equivalency factor (TEF) is set for such congeners as ratios of potency to the most potent 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)[1)], so that effects of combined exposure by the congeners could be effectively assessed. The TEF values set by WHO has been used as standard and these values are based mainly of in vitro experiments. On the other hand, one of the most diagnostic indicators of dioxin-like toxicity is the teratogenic response in the mouse[2-7)]. TCDD is known to induce cleft palate and hydronephrosis in mice. The objective of this study is to assess the potency of top seven congeners to induce cleft palate in a dioxin-sensitive mouse strain C57BL/6.

Methods and Materials

Seven congeners used in this experiment were purchased from Radian International, Cambridge Isotope Laboratories, Inc. Female C57BL/6 mice were obtained from SLC Co. (Hamamatsu, Japan). Chemicals except for PCDD were initially dissolved in a small volume of acetone (benzen for PCDD) and subsequently adjusted to a working concentration in corn oil. The mice were given rodent chow (CRF-1, Oriental Co. Atsugi, Japan) and distilled water *ad libtum* and housed under controlled conditions of temperature and light (12-h light; 12-h dark cycle). On GD 12.5, the mice were given single oral administration of congeners with dosage levels set according to WHO TEF values (Table 1), i.e., 2,3,7,8-TCDD,2.5-10ìg/kg; 1,2,3,7,8-PCDD,2.5-10ìg/kg; 2.3,4,7,8-PCDF,20-80ìg/kg; 2,3,7,8-TCDF, 50-200ìg/kg; 1,2,3,4,7,8-HxCDD,50-200ìg/kg; 1,2,3,7,8.9-HxCDD,100-400ìg/kg; 1,2,3,7,8-PCDF,50-400ìg/kg. On GD18, the dams were killed and fetuses were examined to evaluate the incidence of cleft palate.

Results and Discussion

The results are summarized in Table 1 and Fig. 1. As a whole, the ED50 of the PCDD and TCDF tested are in good accordance with the WHO TEF values. However, there are slight discrepancy, for example, 1,2,3,7,8-PCDD which shares the top TEF value with 2,3,7,8-TCDD was less potent in this experiment. This data on cleft palate inducibility could be used for re-evaluation of TEF values of the dioxins.

Table 1. Comparison of ED50 values and WHO-TEFs

Congener tested in this study	ED50 (ìg/kg)	WHO-TEF[1)]
2,3,7,8-TCDD	10	1
1,2,3,7,8-PCDD	25	1
2,3,4,7.8-PCDF	65	0.5
2,3,7,8-TCDF	150	0.1
1,2,3,4,7,8-HxCDD	170	0.1
1,2,3,7,8,9-HxCDD	350	0.1
1,2,3,7,8-PCDF	220	0. 05

ED50s are estimated from our dose-response curves for cleft palate induction in mice by dioxins

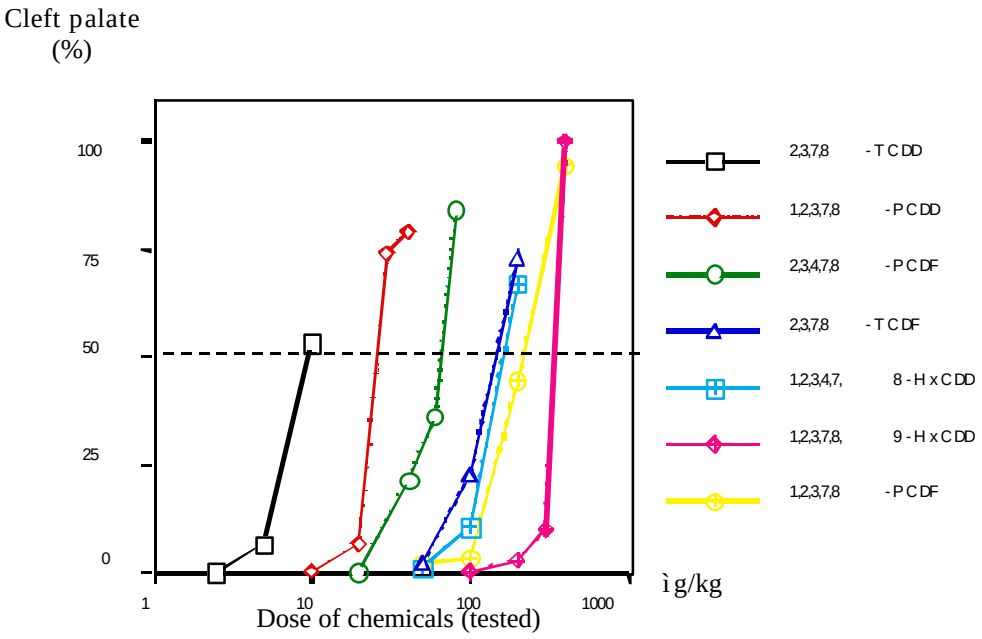

Fig.1. Dose-response curves for cleft palate frequency in mice by dioxins

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