

A Critical Review of the Developmental Toxicity and Teratogenicity of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin: Recent Advances Toward Understanding the Mechanism*

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ABSTRACT A specific teratogenic response is elicited in the mouse as a result of exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD; dioxin). The characteristic spectrum of structural malformations induced in mice following exposure to TCDD and structurally related congeners is highly reproducible and includes both hydronephrosis and cleft palate. In addition, prenatal exposure to TCDD has been shown to induce thymic hypoplasia. These three abnormalities occur at doses well below those producing maternal or embryo/fetal toxicity and are thus among the most sensitive indicators of dioxin toxicity. In all other laboratory species tested, TCDD causes maternal and embryo/fetal toxicity but does not induce a significant increase in the incidence of structural abnormalities even at toxic dose levels. Developmental toxicity occurs in a similar dose range across species; however, mice are particularly susceptible to development of TCDD-induced terata. Recent experiments using an organ culture were an attempt to address the issue of species and organ differences in sensitivity to TCDD. Human palatal shelves examined in this *in vitro* system were found to approximate the rat in terms of sensitivity for induction of cleft palate. Investigators have suggested that altered regulation of growth factors and their receptors may involve inappropriate proliferation and differentiation of target cells, ultimately producing TCDD-induced terata. Why the teratogenic effects of TCDD are so highly species and tissue specific, and which animal species most accurately predicts the response of the human embryo/fetus, at the levels of exposure experienced by humans, still remains to be clarified.