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Comparative developmental toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in the hamster, rat and guinea pig

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Abstract

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is a persistent environmental contaminant capable of causing a wide variety of adverse health effects including teratogenesis and altered development. The objective of this study was to compare the developmental toxicity of TCDD in the hamster, rat and guinea pig, which in mature animals exhibit a relatively low, medium and high sensitivity to TCDD, respectively. A single oral dose of TCDD was administered to pregnant rats (0, 1.5, 3.0, 6.0 or 18.0 μg/kg) on gestation day 10, pregnant hamsters (0, 1.5, 3.0, 6.0 or 18.0 μg/kg) on gestation day 9 and pregnant guinea pigs (0, 0.15 or 1.5 μg/kg) on gestation day 14 with fetal analysis on gestation day 20, 15 and 56, respectively. The developmental toxicity of TCDD in the three species included increased fetal mortality, alterations to fetal body weight, body length, organ weight and significant changes to the fetal white blood cell differential counts. Additionally, teratogenic responses were observed in the hamster and rat consisting of cleft palate, kidney congestion, hydronephrosis and intestinal hemorrhaging. Furthermore, the results from this study demonstrate that despite the up to 5000-fold interspecies variability to the acute lethal potency of TCDD observed in mature guinea pigs, rats and hamsters, the developing fetus is uniquely vulnerable to gestational TCDD exposure and displays approximately a 10-fold variability in fetal lethal potency in these species. Together, these results will assist efforts to reduce the uncertainty in the risk assessment for TCDD in sensitive populations, such as the developing embryo and fetus.

Keywords: 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin; Developmental toxicology; Teratogenic response; Altered white blood cell differential; Hamster; Rat; Guinea pig; Hematopoiesis; Cytochrome P450

1. Introduction

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is the prototypical congener of a group of structurally related compounds belonging to the large family of halogenated aromatic hydrocarbons. TCDD and related compounds, polychlorinated dibenzofurans and coplanar polychlorinated biphenyls, are persistent environmental contaminants. In humans, laboratory animals and wildlife, exposure to these compounds results in a wide

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variety of toxic manifestations including a wasting syndrome, chloracne, immunosuppression, thymic atrophy, altered development, teratogenesis and tumor promotion (Birnbaum and Tuomisto, 2000; Mandal, 2005).

Evidence suggests that most of the toxic manifestations induced by TCDD occur through the activation of the aryl hydrocarbon receptor (AhR). The AhR is a ligand-activated transcription factor and member of the basic helix–loop–helix/Per-Arnt-Sim (bHLH/PAS) superfamily (Denison and Nagy, 2003). Upon ligand binding, AhR translocates into the nucleus and binds its dimerization partner AhR nuclear transporter (ARNT) (Hoffman et al., 1991; Probst et al., 1993; Reyes et al., 1992). After dimerization, the activated AhR/ARNT complex binds dioxin-response elements (DREs), located in the 5′ region upstream of responsive target genes, and acts as a transcription factor resulting in a variety of differential changes in gene expression (Hanlon et al., 2005; Martinez et al., 2002; Tijet et al., 2006; Vezina et al., 2004). Alterations in gene expression are in turn associated with a range of altered biological and toxicological responses.

Mature laboratory animals display a wide interspecies variability with respect to the toxic effects observed after TCDD exposure. There is upwards of a 5000-fold difference in the acute lethal potency between the guinea pig, rhesus monkey, rat, mouse and hamster with reported LD_{50} values of 0.6–2, 1–70, 22–60, 114–536 and 1157–5051 μg/kg, respectively (McNulty, 1984; Olson et al., 1990). However, when compared to mature animals, the developing embryo and fetus are uniquely vulnerable to TCDD and related compounds. The potency of TCDD appears to be similar across species when administered during gestation resulting in the observed fetal LD_{100} being significantly lower than reported maternal LD_{50} values (Peterson et al., 1993).

Exposure to TCDD during gestation can have significant effects on fetal development. Studies in rats and in mice have found TCDD to be a potent embryo/fetal toxin, developmental and teratogenic agent (Birnbaum, 1995; Peterson et al., 1993; ten Tusscher and Koppe, 2004). For example, in rats an *in utero* exposure to less than 1 μg/kg TCDD results in a significant number of reproductive abnormalities including disruption of brain sexual differentiation and an increase incidence of cleft phallus, a persistent thread of tissue across the vaginal opening (Gray et al., 1997; Ikeda et al., 2005; Mably et al., 1992a,b,c). Mice gestationally exposed to TCDD not only have developmental and embryotoxic effects, but also have a teratogenic response characterized by the induction of cleft palate, hydronephrosis and thymic atrophy (Couture et al., 1990a). Higher mammalian species, such as monkeys, are also sensitive to gestational TCDD exposure and exhibit developmental, embryotoxic and teratogenic responses (Giavini et al., 1983; McNulty, 1984; Negishi et al., 2006; Yasuda et al., 2005).

To complete a human risk assessment for a compound, a majority of data is extrapolated from animal models to define limits of exposure. In the case of the developmental toxicity due to an *in utero* exposure to TCDD, there has been extensive use of the rat and mouse as model systems. Other animal models, such as the hamster and guinea pig, are under utilized since the developmental and embryotoxic effects of TCDD resultant from an *in utero* exposure are not fully characterized. The objective of this study was to evaluate the developmental and embryotoxic potential of TCDD in the hamster, rat and guinea pig, which exhibit a relatively high, medium and low LD_{50} dose in mature animals. The results from this study further define TCDD as a developmental, embryotoxic and teratogenic agent and additionally show that the toxic potency of TCDD in the fetus is markedly lower than in the mature animals, particularly in the hamster and rat.

2. Materials and methods

2.1. Chemicals

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) (purity >99%) was a gift from Dow Chemical Co. (Midland, MI) and dissolved in 1,4-dioxane (J.T. Baker Chemical Co., Phillipsburg, NJ). Concentrations of TCDD in the dosing solutions were validated via gas chromatography with electro-chemical detection (GC-ECD). All other chemicals and reagents used were obtained from commercial sources and were of the highest quality available.

2.2. Animals

Timed pregnant Holtzman rats, Golden Syrian hamsters and Hartley guinea pigs were purchased from Harlan Co. (Indianapolis, IN). All animals were housed individually and allowed access to food and water *ad libitum*. Animal cages were maintained under controlled temperature (25 °C) and light conditions (12/12 h light–dark). All animal protocols were reviewed and approved by the Institutional Use and Animal Care Committee at the University at Buffalo.

2.3. Experimental design

Pregnant rats, 22 day gestation period, received a single oral dose of either a corn oil vehicle control or TCDD in corn oil (0, 1.5, 3.0, 6.0, or 18.0 μg/kg) via gastric gavage on gestation day 10 and were sacrificed on gestation day 20. Pregnant hamsters,