DEVELOPMENTAL TOXICITY OF 2,3,7,8-TETRACHLORODIBENZO-*p*-DIOXIN (TCDD) IN HAN/WISTAR (KUOPIO) AND LONG-EVANS (TURKU AB) RATS.

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Secondary palate and kidneys are the target organs of TCDD teratogenicity. Hydronephrosis and cleft palate are typically seen in mice, but in rats embryo/fetal toxicity is the main response. The developmental toxic potential of TCDD has been shown not to follow the differences in sensitivity across species[1]. Two rat strains, outbred Han/Wistar (Kuopio; H/W) and Long-Evans (Turku AB; L-E), have an over 300-fold difference in their LD_{50}-values for TCDD, H/W being more resistant[2]. To gain further insight into the relationship between TCDD acute toxicity and teratogenicity, we assessed the developmental effects of TCDD in the TCDD-resistant (LD_{50} >3000 μg/kg) H/W and TCDD-sensitive L-E (LD_{50} about 10 μg/kg) rat strains.

An oral dose of 0, 1 or 10 μg/kg TCDD in corn oil was given to mated female H/W rats on gestation day 8 or 12. In L-E rats, an oral dose of 0, 1 or 5 μg/kg TCDD was given on gestation day 8 to mated females. The day on which sperm was detected in vaginal smears was considered day 0 of gestation. Females were killed on gestation day 20 and the uterine contents and ovaries were immediately examined. Fetuses were preserved in Bouin's solution and assessed for visceral anomalies[3]. Very early resorptions were visualized as described by Salewsky[4]. Dilatation of renal pelvic cavity and ureter were graded[5] and classified as hydronephrosis only if extensive pelvic dilatation was associated with ureter dilatation.

Maternal toxicity (decreased corrected maternal body weight gain) appeared at 10 μg/kg dose in H/W rats and at both dose levels (1 and 5 μg/kg) used in L-E rats. Absolute and relative thymus weights decreased dose-dependently in both strains, but relative liver weights increased only in the high dose group in H/W and in low dose group in L-E rats.

The number of living fetuses per litter decreased in the high dose group whether administered on day 8 or 12 in H/W rats. A more severe decrease in the number of living fetuses per litter was found in L-E rats. In L-E rats, the numbers of resorptions and late fetal deaths were increased at 5 μg/kg (Table 1). Edematous dead fetuses and a slightly increased number of resorptions were found in H/W rats at 10 μg/kg. Fetal body weights slightly decreased, and an increased incidence of hydronephrosis was found in the high dose groups of H/W rats. In L-E rats, mean fetal body weights decreased at 5 μg/kg and cleft palate occurred in 70 % of fetuses. Gastrointestinal hemorrhaging was observed only in H/W fetuses.

In conclusion, the administration of a dose of 5 μg/kg TCDD on gestation day 8 was fetotoxic and embryo/fetolethal in TCDD-sensitive L-E rats and the administration of a dose of 10 μg/kg TCDD on gestation day 8 or 12 was fetotoxic and fetolethal in the TCDD-

resistant H/W rat strain. Cleft palate was induced in L-E rats and hydronephrosis, but not cleft palate, was induced in H/W fetuses. The present data show that sensitivity to the acute lethality of TCDD does not correlate with susceptibility to its developmental toxicity.

TABLE 1. Litter data after administration of TCDD on gestation day 8 in H/W and L-E rats.
(Number of litters = 9-17)

	Dose group (μg/kg)					
	H/W			L-E		
Parameter	0	1	10	0	1	5
Living fetuses (%) a)	88.8	88.5	64.1 #	92.9	88.3	23.2 #
Resorptions (%)	11.2	11.5	21.7	17.1	11.7	70.2 #
Late fetal deaths (%)	0.0	0.0	14.1	0.0	0.0	5.5
Living fetuses/litter b)	9.5	11.1	6.6	10.4	9.0	2.5 +
Nonlive implants/litter	1.2	1.4	3.7	0.8	1.2	8.1 +
Affected fetuses c)/litter	1.2	2.0	4.7 #	1.1	1.7	8.1 +
Postimplantation loss (%)	16.7	11.5	38.5 +	6.9	16.9	77.6 +
Reduced thymus size d)	0.0	1.0	25.4 #	0.0	9.2	80.5 #
Dilatation of renal pelvis	0.0	4.0	27.1 #	0.0	4.0	2.4
Hydronephrosis	0.0	3.0	11.9 #	0.0	3.5	0.0
Cleft palate	0.0	0.0	0.0	0.0	0.0	71.4 #
Other malformations	0.0	2.0	2.2	3.4	2.1	0.0
Edema, severe	0.0	0.0	6.8 Φ	0.0	0.0	0.0
Gastrointestinal hemorrhaging	0.0	4.0	18.6 #	0.0	0.0	0.0

* $p \leq 0.05$, Scheffé's test, compared with the dose group of 0 μg/kg
\# $p \leq 0.01$, Chi^2-test, compared with the dose group of 0 μg/kg
Φ $p \leq 0.05$, Chi^2-test, compared with the dose group of 0 μg/kg
\+ $p \leq 0.05$, Mann-Whitney U-Wilcoxon Rank Sum W Test, compared with the dose group of 0 μg/kg
a) % of implantations
b) mean number in litter
c) resorptions, fetal deaths, hydronephrosis or other malformations
d) % of live fetuses

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