Multiple Dose (Subchronic) Toxicity of Heptachlorodibenzo-*p*-dioxin

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ABSTRACT
A multiple dose 90-day (subchronic) toxicity study was conducted in the spirit of GLPs for heptachlorodibenzo-*p*-dioxin (hepta-CDD). Preliminary results indicate little, if any, difference in the toxicity of hepta-CDD after single 30-day (acute) and multiple 90-day (subchronic) exposure to hepta-CDD. This confirms the validity of the suggested TEF of 0.007 (Stahl et al.[1]) for multiple 90-day (subchronic) exposure to hepta-CDD.

INTRODUCTION
Single dose 30-day (acute) toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (tetra-CDD), 1,2,3,7,8-pentachlorodibenzo-*p*-dioxin (penta-CDD), 1,2,3,6,7,8-hexachlorodibenzo-*p*-dioxin (hexa-CDD) and 1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin (hepta-CDD) has been examined by various investigators (Schwetz et al.[2]; Stahl et al.[1]). A recent comparative study suggested that the toxicity of these dioxin congeners decreased by approximately a factor of 5 in male Sprague-Dawley rats for each chlorine added to the tetra-CDD molecule (Stahl et al.[1]). Female rats appeared to be almost twice as sensitive to tetra-CDD as male rats (Rozman et al.[3]).

The 90-day multiple dose (subchronic) toxicity of tetra-CDD, penta-CDD, a mixture of two hexa-CDDs and octa-CDD has also been studied by several groups, as compiled by Rozman et al.[3], but not that of hepta-CDD. Rozman et al.[3] examined the relationship between the relative potency of these dioxin congeners after single dose exposure and the relationship between single and multiple dose exposure to tetra-CDD in rats. These authors derived the mathematical formula AUC x time = const. toxicity for this group of compounds. In addition to being a state of the art 90-day subchronic toxicity study for hepta-CDD, this experiment was designed to confirm or refute the validity of this partially substantiated hypothesis by calculating the doses for this experiment using the above formula and well established principles of toxicokinetics.

MATERIALS AND METHODS

This study was conducted in the spirit of GLPs. Hepta-CDD was obtained from Cambridge Isotope Lab. Inc. (Woburn, MA) with a purity > 98.5%. Tetra-CDD was not among the impurities.

Twenty male and 20 female Sprague-Dawley rats each were assigned to seven experimental groups (Table 1) with half of the rats in each group scheduled for sacrifice at the end of the 13-week dosing period and the other half after another 13-week recovery period. Loading and maintenance doses were calculated using half-lifes of 60 days for hepta-CDD (Weber et al.[4]) and 20 days for tetra-CDD (Weber et al.[5]).

The experimental design is depicted in Table 1.

TABLE 1

Experimental Design for the Hepta-CDD Study

Groups			Doses		
Group	Treatment	Sex	Total Dose (μg/kg)	Loading Dose (μg/kg)	Maintenance Dose (μg/kg)
1	Control	Females Males	0 0	4 x 0 4 x 0	6 x 0 6 x 0
2	Hepta-CDD	Females Males	18.5 30.9	4 x 2.44 4 x 4.07	6 x 1.46 6 x 2.43
3	Hepta-CDD	Females Males	222 370	4 x 29.3 4 x 48.8	6 x 17.5 6 x 29.2
4	Hepta-CDD	Females Males	1333 2222	4 x 176 4 x 293	6 x 105 6 x 175
5	Hepta-CDD	Females Males	4000 6667	4 x 527 4 x 879	6 x 315 6 x 525
6	Hepta-CDD	Females Males	6000 10000	4 x 791 4 x 1319	6 x 473 6 x 788
7	Tetra-CDD	Females Males	41.9 70.0	4 x 3.17 4 x 5.29	6 x 4.87 6 x 8.14

RESULTS AND DISCUSSION

Body weight development after 12 weeks of dosing is depicted in Fig. 1, indicating that the two highest doses of hepta-CDD and that of tetra-CDD were overtly toxic in both male and female rats (Table 2). In addition to the wasting syndrome, another cause of mortality was hemorrhage without wasting away in both male and female rats. This effect was observed only infrequently after single dose exposure to dioxins.

The preliminary conclusion that can be derived from the 90-day multiple dose hepta-CDD (subchronic) study is that there are only minor, if any, differences in the toxicity of hepta-CDD after single (acute) and multiple (subchronic) exposures. Results seem to confirm the suggestion of Stahl et al.[1]) that single dose 30-day (acute) exposure to dioxins predicts reasonably well the TEF (relative potency) for multiple dose 90-day (subchronic) exposures.

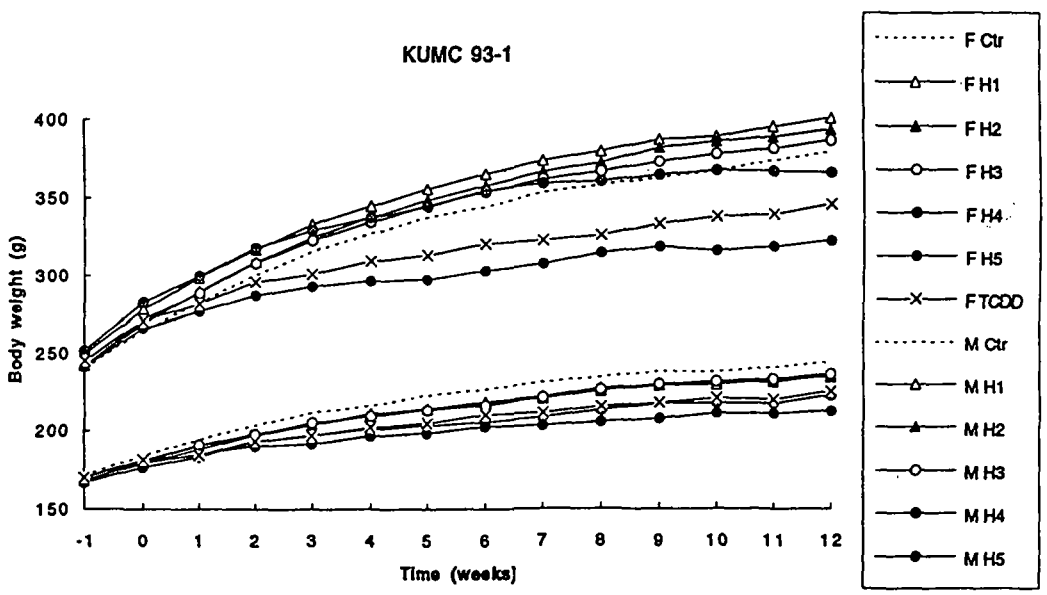

Fig. 1 shows the body weight development of rats in the multiple dose hepta-CDD study.

TABLE 2

Mortality After 12 Weeks of Treatment with Hepta- or Tetra-CDD

Compound	Total Dose (μg/kg)	Wasting (%)	Hemorrhage (%)
	Males		
Hepta-CDD	10,000	30	15
Hepta-CDD	6,667	5	10
Tetra-CDD	70	5	0
	Females		
Hepta-CDD	6,000	5	10

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