ABSENCE OF AN EFFECT OF A NONTOXIC PCDF ON THE TOXICITY OF 23478-PeCDF

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ABSTRACT

Groups of 6 female rats were maintained for 13 weeks on diets containing both, 12348-PeCDF (5500 ppb) and 23478-PeCDF (2 or 20 ppb). Each compound was also administered singly, at the same dose levels. Animals fed the 20 ppb 23478-PeCDF diet (with or without 12348-PeCDF) gained significantly less weight than controls. Thymus and liver weights were affected significantly also only in these two groups with the effect tending to be more pronounced in the group receiving both compounds. Other toxic endpoints investigated (histopathology, hematology) did not hint at any additional effect of the nontoxic isomer. Kinetics of the two isomers, as expected, differed substantially: About 50 to 57 % (of the total dose) of 23478-PeCDF, but only 0.0001-0.0005 % of the 12348-PeCDF was retained in the livers of the rats. Liver retention of the toxic isomer was not affected by coadministration of the comparably large doses of 12348-PeCDF. Adipose tissue levels of 23478-PeCDF were insignificantly higher in animals receiving both compounds. On the other hand, concentration of 12348-PeCDF was decreased to about 1/10 upon coadministration of 23478-PeCDF, most likely the result of an enzyme induction by the 23478-PeCDF. These findings indicate that the toxicity of the toxic 23478-PeCDF is not likely to be modulated by even large amounts of the nontoxic congener. The ability of the liver to metabolize such congeners seems to be changed by 23478-PeCDF.

INTRODUCTION

Additive toxicity of the single constituents of a mixture of PCDDs/Fs is a prerequisite for the currently applied TEF-concept. Some limited evidence for this has been provided by the study of Pluess et al. [1], who fed a mixture of toxic congeners to rats. However, partial antagonism of some compounds, e.g. 6-substituted-1,3,8-trichlorodibenzofurans [2] or Aroclor 1254 [3] towards 2378-TCDD-mediated effects, such as enzyme induction, porphyria or immunosuppression has been reported and thus such effects might have to be considered in the current exposure situation.

In the present study we investigated possible effects of 12348-PeCDF, an isomer that is comparatively nontoxic [1], on the toxic action of 23478-PeCDF. In order to be able to detect such effects, the nontoxic isomer was administered in large excess (275:1 and 2750:1) for 3 months to rats (Iva:SIV 50 (SD), 6 ♀/ group).

RESULTS

Fig. 1: Average feed consumption/rat.

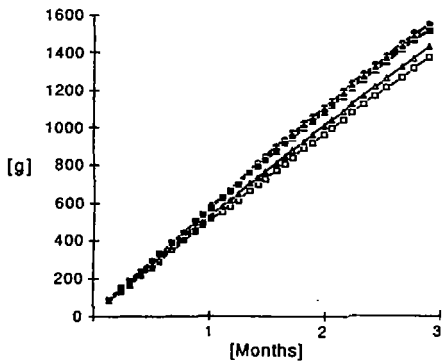

Fig. 2: Weight development of rat maintained on diets as indicated.

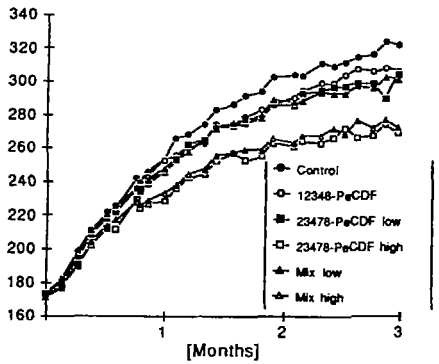

Table 1: Terminal body and organ weights

Dose group		Body	Thymus	Liver	Spleen	Kidney	Heart
Control		322±12	0.47±0.10	10.5±1.1	0.49±0.05	2.1±0.2	0.91±0.08
12348-PeCDF	5500 µg/kg Feed	306±16	0.43±0.08	10.2±0.7	0.45±0.05	1.9±0.1 (b	0.84±0.09
23478-PeCDF low	2 µg/kg Feed	304±19	0.43±0.07	10.8±0.6	0.46±0.07	1.9±0.1 (a	0.82±0.04 (b
23478-PeCDF high	20 µg/kg Feed	270±21 (a	0.22±0.04 (a	11.3±0.7	0.51±0.07	1.9±0.1 (b	0.77±0.06 (a
Mix low	12348-PeCDF 5500 µg/kg Feed 23478-PeCDF 2 µg/kg Feed	301±24	0.40±0.08	10.9±0.8	0.47±0.07	1.9±0.2 (b	0.84±0.04
Mix high	12348-PeCDF 5500 µg/kg Feed 23478-PeCDF 20 µg/kg Feed	272±10 (a	0.18±0.04 (a	11.7±0.8	0.54±0.07	1.9±0.1	0.81±0.1

(b : Significantly different from Control, U-Test, $2\alpha \leq 0.05$
(a : Significantly different from Control, U-Test, $2\alpha \leq 0.01$

Tissue residues:

Table 2: Average concentration of 12348- and 23478-PeCDF in liver and adipose tissue (ng/g wt weight), liver retention (% of total dose/liver), and liver to adipose tissue concentration ratios.

Dose group			Total Dose [µg]	Concentration Liver [ng/g]	Concentration Fat [ng/g]	Retention in Liver [ng]	Retention in Liver [% of Dose]	Liver/Fat - Conc.-Ratio
12348-PeCDF		5500 µg/kg Feed	8390	1.27±0.42	10.38±5.85	12.9±4.0	0.00015	0.08±0.04
23478-PeCDF	low	2 µg/kg Feed	3.02	162.3±22.6	3.77±0.18	1741±222	57.6±8.8	43.2±6.5
23478-PeCDF	high	20 µg/kg Feed	27.39	1213±313	19.85±1.48	13585±3265	49.9±13.3	61.5±17.6
Mix low	12348-PeCDF	5500 µg/kg Feed	9570	4.3±1.1 (b	9.10±1.05 (b	46.8±12.0 (b	0.0005 (b	0.48±0.13 (b
	23478-PeCDF	2 µg/kg Feed	3.10	161.8±20.9	4.19±0.28 (a	1757±201	56.7±6.1	38.8±5.7
Mix high	12348-PeCDF	5500 µg/kg Feed	7890	1±0.5	1.9±1.5 (b	10±5	0.0001	0.5 (*
	23478-PeCDF	20 µg/kg Feed	28.55	1257±266	21.3±1.5	14705±3180	51.5±10.8	59.3±14.2

(a : Significantly different from 23478-PeCDF low, U-Test, $2\alpha \leq 0.05$
(b : Significantly different from 12348-PeCDF, U-Test, $2\alpha \leq 0.01$

(*: approximate value

Histopathological examination (Conducted by Dr. P. Schneider, Thomae GmbH, Biberach, FRG):
Alterations usually seen in the liver (vacuolisation, lipid droplets, glycogen storage), as well as reduction of the width of the cortical region of the thymus became apparent in the 23478-PeCDF high and the mix high groups. No additional effect of the 12348-PeCDF was noted in the mix high group, nor was there any such alteration seen in the 12348-PeCDF group.
Hematology:
Terminal blood samples were somewhat lower in hemoglobin and thrombocyte count in both 23478-PeCDF high and mix high groups.

SUMMARY

12348-PeCDF did not influence the toxic action of 23478-PeCDF upon coadministration in 275-or 2750-fold excess, for effects like feed consumption, body weight increase, terminal body and organ weights, histopathological and hematological alterations.
Liver retention of 23478-PeCDF was quite high and in agreement with previous findings after subchronic or single dose administration [5,6], whereas that of 12348-PeCDF was extremely low. The absence of any toxic effect might be due to the rapid elimination of this congener which does not enable a buildup of effective organ levels.

An interesting kinetic interaction was observed: Fat levels of 12348-PeCDF were decreased upon coadministration of 23478-PeCDF in a dose dependent manner to about 1/10, most likely a result of enzyme induction by the toxic congener (in liver data were inconsistent). This likely was also the cause for the lower retention of 23478-PeCDF itself at the high dose level in both tissues.

Our results give no evidence for an effect of nontoxic congeners on the toxicity of 2,3,7,8-substituted congeners.

References

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