EXCRETION KINETICS OF A COMBINED DOSE OF 3,4,3'4'-TETRACHLOROBIPHENYL AND 2,4,5,2',4',5'-HEXACHLOROBIPHENYL IN FEMALE RATS

D.C. Morse[1*], A.Th.H.J. De Bie[2], P.J. Van Bladeren[2], and A. Brouwer[1]

1) Department of Toxicology, Agricultural University, Bomenweg 2, 6703 HD Wageningen, The Netherlands

2) Department of Biological Toxicology, TNO-CIVO Toxicology and Nutrition Institute, P.O. Box 360, 3700 AJ Zeist, The Netherlands

Abstract:

The excretion and tissue distribution of radioactivity derived from ^{14}C-3,4,-3',4'-tetrachlorobiphenyl (TCB) was determined in female Wistar rats after separate or combined oral dosage with 2,4,5,2',4',5'-hexachlorobiphenyl (HCB). Neither the excretion nor the distribution of radioactivity of the labelled TCB were affected by the presence of HCB.

Introduction:

The general population, especially the human infant, is exposed to polychlorobiphenyls (PCBs) as a mixture of coplanar and nonplanar congeners. Highly toxic coplanar PCBs represent only a minor percentage of PCBs present in mothers' milk, while nonplanar congeners with a relatively lower toxicity are the most abundant (1,2). Knowledge about possible interactive effects between coplanar and nonplanar PCBs is essential for risk assessment of exposure of the infant to PCBs in the diet. Recent studies on the induction of arylhydrocarbon hydroxylase (AHH) and ethoxyresorufin O-deethylase (EROD) indicated that the pretreatment of rats with 2,4,5,2',4',5'-hexachlorobiphenyl (HCB) had a synergistic effect on AHH and EROD induction by the coplanar 3,4,5,3',4'-pentachlorobiphenyl and 3,4,5,3',4',5'-hexachlorobiphenyl (3) as well as with 2,3,7,8-tetrachlorodibenzodioxin (4). To investigate the influence of a nonplanar PCB on the distribution and excretion of a coplanar congener, the toxicokinetics of the coplanar 3,4,3',4'-tetrachlorobiphenyl (TCB) were studied in the rat with and without the presence of nonplanar 2,4,5,2',4',5'-HCB. Changes in the kinetics of TCB due to the presence of HCB could affect the toxicity of the coplanar congener.

Materials and Methods:

Animals: Four groups of 3 female virgin Wistar rats (10-12 wk old) were housed individually in metabolic cages. The rats were dosed by gavage according to the following regime: 4 groups with ^{14}C-TCB, 0.75 KBq/kg, 1 µmol/kg, combined with 0, 1, 10 and 100 µmol unlabelled HCB/kg, dissolved in corn oil (2 ml/kg). The excretion of radioactivity in the urine and feces was followed daily for 7 days for all groups, after which the animals were bled via the aorta and sacrificed. The concentration of TCB-derived radioactivity was determined in various organs of the animals who received only ^{14}C-TCB and those who received the combined dose of 1 µmol ^{14}C-TCB/kg with 100 µmol HCB/kg. Radioactivity in the plasma was measured for all groups.

Determination of Radioactivity: ^{14}C radioactivity in the organs was determined by burning the samples in a Packard sample oxidizer, Model 307, to produce $^{14}CO_2$. Plasma, urine and Soluene digested feces homogenates were directly added to the scintillation liquid. The samples were analysed with a Wallac Model 1410 scintillation counter.

Results:

After 7 days, approximately 82 percent of the TCB-derived radioactivity was excreted in the feces and 3 percent in the urine from the rats in all 4 dose groups.

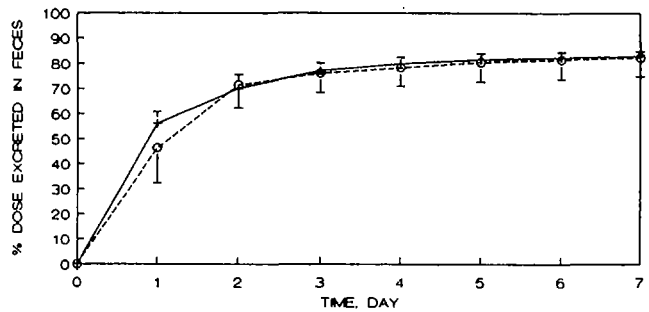

Figure 1. Cumulative fecal excretion of ^{14}C-TCB derived radioactivity from female Wistar rats (n=3) after an oral dose of 1 µmol ^{14}C-TCB/kg (——) and 1 µmol ^{14}C-TCB/kg combined with 100 umol HCB/kg (——).

The excretion of radioactivity from ^{14}C-TCB was similar when the compound was dosed individually or in combination with HCB (figure 1). The tissue distribution of radioactivity on day 7 for each compound was not significantly affected by combined dosage (table 1). There was a slight but consistent increase in ^{14}C-TCB derived radioactivity in the plasma which correlated well with the logarithm of the increasing simultaneous dose of HCB (R>0.99).

Table 1

Tissue Distribution of TCB-Derived Radioactivity in Female Wistar Rats 7 Days After an Oral Dose of 1 μmol ^{14}C-TCB/kg

	Percentage of Dose in Tissue	
Dose Group	14C-TCB (1 μmol/kg)	14C-TCB (1μmol/kg) + HCB (100 μmol/kg)
Tissue		
plasma	0.223 ± 0.105[b]	0.290 ± 0.088
uterus	0.013 ± 0.003	0.014 ± 0.003
liver	0.205 ± 0.018	0.189 ± 0.040
kidneys	0.023 ± 0.007	0.020 ± 0.006
thymus	0.006 ± 0.005	0.003 ± 0.001
brain	0.005 ± 0.002	0.003 ± 0.001
thyroid	0.001	0.001
skin	0.882 ± 0.514	0.367 ± 0.081
muscle, skeletal	0.791 ± 0.749	0.546 ± 0.324
abdominal fat	1.042 ± 0.370	0.752 ± 0.393
carcass	2.729 ± 0.924	1.805 ± 0.741

Note: Data are expressed as means ± SD (n=3). The following assumptions were made: plasma as 4% of body weight, skin as 10% of body weight and skeletal muscle as 40% of body weight.

Discussion:

It appears that HCB has little effect on the excretion and tissue distribution of TCB derived radioactivity at the dose levels used in this study. In studies with the industrial PCB mixture Kanechlor, the whole body half-lives of the congeners in the mixture were similar to those reported in studies in which individual PCB congeners were used (6). However, since TCB is readily metabolized in rats (7), total radioactivity measurements do not reflect changes in the relative amount or nature of metabolites formed. The increase of ^{14}C-TCB derived radioactivity in the plasma with an increasing simultaneous dose of HCB could be due to enhanced induction of the microsomal monooxygenase system responsible for the metabolism of TCB by the presence of HCB, since the pretreatment of rats with HCB leads to enhanced induction of EROD and AHH activity by coplanar PCBs (3). EROD activity is strongly correlated with TCB metabolism in hepatic microsomes prepared from male Sprague-Dawley rats (5). An alternative explanation for the increase in radioactivity in the plasma is that TCB and its

metabolites are displaced from binding sites in other tissues by HCB and thus redistributed into the plasma. A metabolite of TCB, 4-OH-3,5,3',4'-tetrachlorobiphenyl, is in part responsible for the reduction of thyroid hormone (T_4) in rat plasma by the direct displacement of T_4 from the binding site on its transport protein (8,9). Therefore an interactive effect of combined exposure of TCB with other PCB congeners, especially on metabolite-related toxicity, e.g. plasma thyroid hormone reduction, can not be excluded. An examination of plasma TCB metabolite patterns and the levels of thyroid hormone at earlier time points may reveal an effect of combined dosage.

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