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Toxic Potential of Non-*ortho* and Mono-*ortho* Coplanar PCBs in Commercial PCB Preparations: "2,3,7,8-T_4 CDD Toxicity Equivalence Factors Approach"

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Identification of highly toxic polychlorinated dibenzofurans (PCDFs) in commercial PCBs has contributed to the belief that they play a major role in the PCB toxicity (Bowes et al.1975). However, Quanatitative Structure Activity Relationship (QSAR) studies have indicated that PCB congeners with chlorine substitution at both *para* and two or more *meta* positions resemble 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (T_4CDD) in their biologic and toxic effects due to their coplanarity and particularly 3,3',4,4'-tetra (T_4CB), 3,3',4,4',5-penta (P_5CB) and 3,3',4,4',5,5' - hexachlorobiphenyl (H_6CB) were identified as the most toxic congeners of PCBs (Safe 1984). Follow-up studies indicated that mono- and di- *ortho* analogs of these coplanar PCBs also possess comparable toxic potential because of their ability to induce 3-methylcholanthrene (3-MC)- type hepatic drug metabolizing enzymes (Parkinson et al. 1983). The relative toxic potential of these PCB isomers in wild animals such as Forster's tern, marine mammals and Snapping turtle has been emphasized (Harris et al. 1985; Bryan et al. 1987; Tanabe 1988; Kannan et al. 1988a). Some members of these toxic congeners were also identified and quantitated in commercial PCBs (Huckins et al. 1980; Kannan et al. 1987a, 1987b). However, there is no serious effort to evaluate the toxic potential of these PCB congeners in commercial PCB mixtures. Hence an isomer-specific toxic evaluation was attempted in those mixtures to understand the chemical factors behind their toxicity.

MATERIALS AND METHODS

The following isomers of PCBs and PCDFs were selected for evaluating their toxic potential in Kanechlor and Aroclor mixtures because of their proven potency for inducing 3-MC-type enzymes : PCB isomers (IUPAC numbers in parenthesis): Mono-*ortho* coplanar PCBs - 2,3',4,4',5-P_5CB (118), 2,3,3',4,4'-(P_5CB) (105), 2,3,3',4,4',5-

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H_6CB (156); Non-*ortho* coplanar PCBs - 3,3',4,4'-T_4CB (77), 3,3',4,4',5-P_5CB (126), 3,3',4,4',5,5'-H_6CB (169) PCDFs - 2,3,4,7-T_4CDF, 2,3,7,8-T_4CDF, 1,2,3,7-T_4CDF, 2,3,4,7,8-P_5CDF, 1,2,3,7,8-P_5CDF, 1,2,3,7,9-P_5CDF, 1,2,4,7,8-P_5CDF, 1,2,4,6,8-P_5CDF, 2,3,4,6,7,8-H_6CDF, 1,2,3,4,7,8-H_6CDF and 1,2,3,6,7,8-H_6CDF.

The non-*ortho* chlorine substituted coplanar PCBs were separated from other PCB isomers using carbon chromatography followed by high-resolution gas chromatography (HR/GC/ECD) and gas chromatography/mass spectrometry (GCMS) analyses (column: 0.25 mm id x 25 m chemically bonded OV-1701; Gas chromatograph: Shimadzu GC-9A equipped with ^{63}Ni ECD; Mass spectrometer : Shimadzu GC-MS-QP 1000, EI mode, MID scan for M^+ and $[M+2]^+$ ions). This method and quantitation procedures are described in detail elsewhere (Tanabe et al. 1987b; Kannan et al. 1987a, 1987b). The mono-*ortho* coplanar PCBs were quantitated using GC/MS as a part of the PCB analysis after Tanabe et al. (1987c). PCDF isomers were determined following clean-up in silica gel, alumina, HPLC and mass specific detection of M^+ and $[M+2]^+$ ions using Shimadzu GC-MS-QP 1000. The isomer-specific determination of PCDFs in commercial PCBs was detailed in Wakimoto et al. (1988). Kanechlors 300, 400, 500, 600 and Aroclor 1242,1248,1254,1260 were investigated for the present study.

RESULTS AND DISCUSSION

It is increasingly evident that the biologic and toxic activities of PCBs depend on the structure. The lateral substitution of chlorine in vicinal *meta* and *para* positions of the biphenyl rings creates structures with coplanarity which can lie within a rectangle of 3x10 Å so as to bind, as does 2,3,7,8-T_4CDD, to a cytosolic protein , the *Ah* receptor and evoke a toxic response at the target site. Considerable evidence suggest that such isostereomers of 2,3,7,8-T_4CDD elicit toxic and biologic responses typical of 2,3,7,8-T_4CDD including body weight loss, thymic atrophy, reproductive toxicity teratogenicity, immunotoxicity (Safe 1984, 1986).

Thus, it has been encouraged in recent years that the relative toxicity of this group of chemicals can be understood by expressing their toxic potential in terms of 2,3,7,8-T_4CDD toxic equivalents (Safe 1987). Subsequently, 2,3,7,8-T_4CDD Toxicity Equivalence Factors (TEFs) have been developed for several PCDFs and PCDDs based on human carcinogenicity, long-term animal studies, reproductive effects, *in vitro* bioassay etc. (Bellin and Barnes 1987). However, no such comparable acute or chronic toxicity studies are available for mono- and non-*ortho* coplanar PCBs. Fortunately most of these stereoisomers had been tested in a common experi-

mental system and excellent correlations were obtained between toxicity-AHH induction and *in vitro-in vivo* effects (Safe 1987). Based on such studies 2,3,7,8-T_4CDD toxic equivalents can be calculated for those PCB isomers also. Logically, the concentrations of such metabolically stable, biologically accumulative PCB congeners are taken into consideration in such calculations (Tanabe et al 1987a; Kannan et al 1988b). Thus, the toxic equivalents are calculated as 2,3,7,8-T_4CDD toxic equivalents = relative potency of induction for AHH and EROD x concentrations in commercial PCB preparations.

Table 1. Relative potency of induction for aryl hydrocarbon hydroxylase (AHH) and ethoxy resorufin *O*-deethylase (EROD) in rat hepatoma E-4-IIE cell lines by PCDFs, Mono- and Non-*ortho* coplanar PCBs.

Chemicals	Relative potency of induction*	
	AHH	EROD
PCDFs		
2,3,4,7	4.0×10^{-3}	1.3×10^{-2}
2,3,7,8	1.8×10^{-1}	9.5×10^{-1}
1,2,3,7	2.6×10^{-6}	3.0×10^{-6}
2,3,4,7,8	2.8×10^{-1}	1.5
1,2,3,7,8	2.9×10^{-2}	6.1×10^{-3}
1,2,3,7,9	8.4×10^{-4}	2.2×10^{-3}
1,2,4,7,8	6.5×10^{-4}	1.3×10^{-3}
1,2,4,6,8	7.2×10^{-6}	1.6×10^{-5}
2,3,4,6,7,8	1.0×10^{-1}	3.3×10^{-1}
1,2,3,4,7,8	2.0×10^{-1}	5.0×10^{-1}
1,2,3,6,7,8	4.8×10^{-2}	1.6×10^{-1}
Non-*ortho* coplanar PCBs		
3,3',4,4'	2.1×10^{-3}	2.1×10^{-3}
3,3',4,4',5	3.0×10^{-1}	7.6×10^{-1}
3,3',4,4',5,5'	1.2×10^{-3}	7.9×10^{-3}
Mono-*ortho* coplanar PCBs		
2,3',4,4',5	6.0×10^{-6}	2.1×10^{-5}
2,3,3',4,4'	8.2×10^{-4}	1.6×10^{-3}
2,3,3',4,4',5	3.4×10^{-5}	2.1×10^{-4}

$$\text{Relative potency of induction} = \frac{EC_{50}\ (T_4CDD)}{EC_{50}\ (\text{selected isomer})}$$

* Values derived from Safe (1986, 1987).

As in Table 1 the relative potency of induction for AHH and EROD can be calculated from the available EC_{50} data for those enzymes. Subsequently, 2,3,7,8-T_4CDD toxic equivalents can be calculated for any specific toxic

Table 2. 2,3,7,8-T_4CDD toxicity equivalents (μg/g) for PCDFs, Non-*ortho* and Mono-*ortho* coplanar PCBs in Kanechlor mixtures.

Chemicals	KC-300			KC-400			KC-500			KC-600		
	Conc μg/g	T_4CDD eq AHH	T_4CDD eq EROD	Conc μg/g	T_4CDD eq AHH	T_4CDD eq EROD	Conc μg/g	T_4CDD eq AHH	T_4CDD eq EROD	Conc μg/g	T_4CDD eq AHH	T_4CDD eq EROD
PCDFs												
2347	0.72	2.9×10^{-3}	9.4×10^{-3}	2.3	9.2×10^{-3}	2.9×10^{-2}	0.19	7.6×10^{-4}	2.5×10^{-3}	0.044	1.8×10^{-4}	5.7×10^{-4}
2378	0.50	9.0×10^{-2}	4.8×10^{-1}	1.7	3.1×10^{-1}	1.6	0.28	5.0×10^{-2}	2.7×10^{-1}	0.12	2.2×10^{-2}	1.1×10^{-1}
1237	0.56	1.5×10^{-6}	1.7×10^{-6}	1.8	4.7×10^{-6}	5.4×10^{-6}	0.16	4.2×10^{-7}	4.8×10^{-7}	0.042	1.1×10^{-7}	1.3×10^{-7}
23478	0.29	8.1×10^{-2}	4.4×10^{-1}	0.68	1.9×10^{-1}	1.0	0.43	1.2×10^{-1}	6.5×10^{-1}	0.17	4.8×10^{-2}	2.6×10^{-1}
12378	0.068	1.9×10^{-3}	4.1×10^{-4}	0.23	6.7×10^{-3}	1.4×10^{-3}	0.069	2.0×10^{-3}	4.2×10^{-4}	0.024	6.9×10^{-4}	1.4×10^{-4}
12379	0.039	3.3×10^{-5}	8.6×10^{-5}	0.088	7.4×10^{-5}	1.9×10^{-4}	0.056	4.7×10^{-5}	1.2×10^{-4}	0.022	1.8×10^{-5}	4.8×10^{-5}
12478	0.32	2.1×10^{-4}	4.2×10^{-4}	1.2	7.8×10^{-4}	1.6×10^{-3}	0.59	3.8×10^{-4}	7.7×10^{-4}	0.12	7.8×10^{-5}	1.6×10^{-4}
12468	0.049	3.5×10^{-7}	7.8×10^{-7}	0.12	8.6×10^{-7}	1.9×10^{-6}	0.12	8.6×10^{-7}	1.9×10^{-6}	0.075	5.4×10^{-7}	1.2×10^{-6}
234678	0.035	3.5×10^{-3}	1.2×10^{-2}	0.033	3.3×10^{-3}	1.1×10^{-2}	0.05	5.0×10^{-3}	1.7x10-2	0.041	4.1×10^{-3}	1.4×10^{-2}
123478	0.28	5.6×10^{-2}	1.4×10^{-1}	0.37	7.4×10^{-2}	1.9×10^{-1}	0.55	1.1×10^{-1}	2.8×10^{-1}	0.22	4.4×10^{-2}	1.1×10^{-1}
123678	0.12	5.8×10^{-3}	1.9×10^{-2}	0.16	7.7×10^{-3}	2.6×10^{-2}	0.22	1.1×10^{-2}	3.5×10^{-2}	0.091	4.4×10^{-3}	1.5×10^{-2}
Non-*ortho* coplanar PCBs												
33'44'	4400	9.2	9.2	8500	18	18	1500	3.2	3.2	740	1.6	1.6
33'44'5	19	5.7	14	89	27	68	50	15	38	8.6	2.6	6.5
33'44'55'	0.09	1.1×10^{-4}	7.1×10^{-4}	0.57	6.8×10^{-4}	4.5×10^{-3}	1.2	1.4×10^{-3}	9.5×10^{-3}	0.08	9.6×10^{-5}	6.3×10^{-4}
Mono-*ortho* coplanar PCBs												
23'44'5	7700	4.6×10^{-2}	1.6×10^{-1}	27000	1.6×10^{-1}	5.7×10^{-1}	64000	3.8×10^{-1}	1.3	7900	4.7×10^{-2}	1.7×10^{-1}
233'44'	5500	4.5	8.8	16000	13	26	25000	21	40	4500	3.7	7.2
233'44'5	640	2.2×10^{-2}	1.3×10^{-1}	1200	4.1×10^{-2}	2.5×10^{-1}	9900	3.4×10^{-1}	2.0	5000	1.7×10^{-1}	1.1
Total TEFs		20	33		59	116		40	86		8.2	17

Concentrations of PCDFs and Non-*ortho* coplanar PCBs are cited from Wakimoto et al. (1988) and Kannan et al.(1987b) respectively.
TEFs = Toxicity Equivalent Factors.

Table 3. 2,3,7,8-T_4CDD toxicity equivalents (μg/g) for PCDFs and Non-*ortho* coplanar PCBs in Aroclor mixtures

Chemicals	AR-1242			AR-1248			AR-1254			AR-1260		
	Conc μg/g	T_4CDD eq		Conc μg/g	T_4CDD eq		Conc μg/g	T_4CDD eq		Conc μg/g	T_4CDD eq	
		AHH	EROD		AHH	EROD		AHH	EROD		AHH	EROD
PCDFs												
2347	0.085	$3.4x10^{-4}$	$1.1x10^{-3}$	0.39	$1.6x10^{-3}$	$5.1x10^{-3}$	0.026	$1.0x10^{-4}$	$3.4x10^{-4}$	0.052	$2.1x10^{-4}$	$6.8x10^{-4}$
2378	0.093	$1.7x10^{-3}$	$8.8x10^{-2}$	0.31	$5.6x10^{-2}$	$2.9x10^{-1}$	0.17	$3.1x10^{-2}$	$1.6x10^{-1}$	0.13	$2.3x10^{-2}$	$1.2x10^{-1}$
1237	0.039	$1.0x10^{-7}$	$1.2x10^{-7}$	0.17	$4.4x10^{-7}$	$5.1x10^{-7}$	0.10	$2.6x10^{-7}$	$3.0x10^{-7}$	0.043	$1.1x10^{-7}$	$1.3x10^{-7}$
23478	0.019	$5.3x10^{-3}$	$2.9x10^{-2}$	0.12	$3.4x10^{-2}$	$1.8x10^{-1}$	0.26	$7.3x10^{-2}$	$3.9x10^{-1}$	0.17	$4.8x10^{-2}$	$2.6x10^{-1}$
12378	0.003	$8.7x10^{-5}$	$1.8x10^{-5}$	0.058	$1.5x10^{-3}$	$3.2x10^{-4}$	0.13	$3.8x10^{-3}$	$7.9x10^{-4}$	0.14	$4.1x10^{-3}$	$8.5x10^{-4}$
12379	0.004	$3.4x10^{-6}$	$8.8x10^{-6}$	0.052	$4.4x10^{-5}$	$1.1x10^{-4}$	0.002	$1.7x10^{-6}$	$2.0x10^{-3}$	0.001	$8.4x10^{-7}$	$2.2x10^{-6}$
12478	0.006	$3.9x10^{-6}$	$7.8x10^{-6}$	0.23	$1.5x10^{-4}$	$2.9x10^{-4}$	0.54	$3.5x10^{-4}$	$7.0x10^{-4}$	0.21	$1.4x10^{-4}$	$2.7x10^{-4}$
12468	0.001	$7.0x10^{-9}$	$1.6x10^{-8}$	0.046	$3.3x10^{-7}$	$7.4x10^{-7}$	0.23	$1.6x10^{-6}$	$3.7x10^{-6}$	0.16	$1.1x10^{-6}$	$2.6x10^{-6}$
234678	0.001	$1.0x10^{-4}$	$3.3x10^{-4}$	0.001	$1.0x10^{-4}$	$3.3x10^{-4}$	0.024	$2.4x10^{-3}$	$7.9x10^{-3}$	0.027	$2.7x10^{-3}$	$8.9x10^{-3}$
123478	0.001	$2.0x10^{-4}$	$5.0x10^{-4}$	0.018	$3.6x10^{-3}$	$9.0x10^{-3}$	0.39	$7.8x10^{-2}$	$1.9x10^{-1}$	0.57	$1.1x10^{-1}$	$2.9x10^{-1}$
123678	0.001	$4.8x10^{-5}$	$1.6x10^{-4}$	0.011	$5.3x10^{-4}$	$1.8x10^{-3}$	0.16	$7.7x10^{-3}$	$2.6x10^{-2}$	0.21	$1.0x10^{-2}$	$3.4x10^{-2}$
Non-*ortho* coplanar PCBs												
33'44'	5200	11	11	6100	13	13	600	1.3	1.3	260	5.5x10-1	5.5x10-1
33'44'5	17	5.1	13	62	17	47	46	14	35	8.3	2.5	6.3
33'44'55'	0.05	$6.0x10^{-5}$	$3.9x10^{-4}$	0.05	$6.0x10^{-5}$	$3.9x10^{-4}$	0.51	$6.1x10^{-4}$	$4.0x10^{-3}$	0.05	$6.0x10^{-5}$	$3.9x10^{-4}$
Total TEFs		16	24		30	60		15	37		3.2	7.6

Concentrations of PCDFs and Non-*ortho* coplanar PCBs are cited from Wakimoto et al. (1988) and Kannan et al.(1987b) respectively.
Concentrations of mono-*ortho* coplanar PCBs are not available.
TEFs = Toxicity Equivalent Factors.

isomer with a potential for inducing those enzymes as in Table 2 and 3. Isomer-specific determination of Kanechlors and Aroclors has enabled us to calculate toxic equivalents for individual toxic isomers in those mixtures. It is obvious from these tables that inspite of the presence of highly toxic PCDF impurities such as 2,3,7,8-substituted PCDFs in commercial PCBs coplanar PCBs as a group dominate the "toxic equivalents". This is because of the large difference in the concentrations of PCDF isomers and mono- and non-*ortho* coplanar PCBs in PCB mixtures. From the total sum of the TEFs, the percentage of individual toxic contribution of coplanar PCBs can be expressed in comparison to total PCDFs. Coplanar 3,3',4,4',5-P_5CB, 2,3,3',4,4'-P_5CB and 3,3',4,4'-T_4CB emerge as important PCB isomers with high toxic potential (Table 4). Their toxic potential is greatly higher than the potential of all PCDFs together.

Additionally, we have compared the T_4CDD equivalents of three Aroclors obtained through our approach with similar equivalents obtained through a direct measurement of those PCB mixtures in *in vitro* bioassay (Sawyer et al. 1984). The results are shown in Table 5. It is interesting to note that not only the values are comparable (with due consideration given to experimental variations encounter in bioassay systems) but the noted induction of AHH and EROD by those Aroclor mixtures arise exclusively from coplanar PCBs. The toxic contribution by PCDF inpurities seems to be relatively minimal. Sawyer et al. (1984) have observed in their *in vitro* bioassay that AHH/EROD induction potencies of KC-400 and AR-1248 and KC-500 and AR-1254 were comparable while AR-1242 and AR-1016 were not in spite of their similarity in chlorine contents. This difference in activity was interpreted on the difference in the distribution of individual PCBs in those mixtures (Albro and Parker 1979). Indeed, high concentrations of coplanar PCBs in Aroclor 1242 might be a major factor behind this induction (Table 3). On a similar line but in a different study Vos et al. (1980) had concluded after finding depressing effect of 3,3',4,4',5,5'-H_6CB on cell-mediated immunity in young rats and in adult guinea pigs after perinatal maternal exposure that the mixture of stereoisomers of T_4CDD were responsible for commercial PCB toxicity.

Thus, it appears that the toxicity of commercial PCBs arise mostly out of the presence of 3,3',4,4'5-P_5CB, 2,3,3',4,4'-P_5CB, 3,3',4,4'-T_4CB and not much due to PCDF impurities. However, it is not clear whether any additive or antogonistic interactions are involved among these toxic isomers in their toxic manifestation. While the study of Bradlaw and Casterline (1979) is suggestive of additive effects, a recent study

Table 4. Percentage of relative contribution of T_4CDD equivalent toxicity by toxic isomers of PCBs and PCDF impurities in commercial PCB mixtures (Kanechlors).

Chemicals	KC-300		KC-400		KC-500		KC-600	
	T_4CDD eq		T_4CDD eq		T_4CDD eq		T_4CDD eq	
	AHH	EROD	AHH	EROD	AHH	EROD	AHH	EROD
Coplanar PCBs								
33'44'5	29	42	46	59	38	44	32	38
233'44'	23	27	22	22	53	47	45	42
33'44'	46	28	31	16	8	3.7	20	9.4
23'44'5	0.23	0.48	0.27	0.49	0.95	1.5	0.57	1.0
233'44'5	0.11	0.39	0.069	0.22	0.85	2.3	2.07	6.5
33'44'55'	0.00055	0.0022	0.0012	0.0039	0.0035	0.011	0.0012	0.0037
Total PCDFs	1.2	3.3	1.0	2.5	0.73	1.5	1.46	3.0

Table 5. Calculated T_4CDD toxic equivalent factors for ΣPCDFs and ΣNon-*ortho* coplanar PCBs in Aroclor mixtures in comparison to their (Aroclors) direct measurement in *in vitro* bioassay.

	AR-1242		AR-1248		AR-1254	
	T_4CDD eq (M)		T_4CDD eq (M)		T_4DD eq (M)	
	AHH	EROD	AHH	EROD	AHH	EROD
ΣPCDFs	7.3×10^{-8}	3.8×10^{-7}	3.0×10^{-7}	1.5×10^{-6}	5.7×10^{-7}	2.2×10^{-6}
ΣNon-*ortho* coplanar PCBs	1.5×10^{-5}	3.9×10^{-5}	5.7×10^{-5}	1.4×10^{-4}	4.6×10^{-5}	1.1×10^{-4}
In vitro bioassay*	1.0×10^{-5}	4.2×10^{-5}	1.3×10^{-5}	3.7×10^{-5}	7.5×10^{-6}	3.0×10^{-5}

ΣPCDFs and ΣNon-*ortho* coplanar PCBs include all the isomers listed in Table 3, and their T_4CDD equivalents presented here in molar (M) units are individually derived and summed up.

*Values derived from *in vitro* bioassay of Sawyer et al. (1984).

(Haake et al. 1987) points to the other direction.

We have recently demonstrated that indeed mono- and non-*ortho* coplanar PCBs persist in the environment and accumulate to such levels in environmental animals to cause possible interference in their reproductive physiology. It was also shown that the principal source of coplanar PCB contamination to those forms are from commercial PCBs (Tanabe 1987a, 1988; Kannan et al. 1988a). Our recent analysis of 'Yusho samples' also suggest that coplanar PCBs could have been one of the causative factors behind that PCB poisoning.

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