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REP ESTIMATES OF DL ACTIVITY FOR DIOXINS, FURANS, AND DL-PCBS IN ADULTS BASED ON TWO THYROID OUTCOMES AND CYP1A1AND 1B1 GENE EXPRESSION IN BLOOD ASSESSED 12 YEARS APART

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Introduction

Toxic equivalency factors (TEFs) are an important component in the risk assessment of dioxin-like human exposures1. At present, this concept is based mainly on in vitro toxicity data or in vivo animal experiments using oral dosage2 expressed as relative effect potencies (REPs). Previously we suggested REPs for systemic human concentrations of dioxin-like mixture components as basis for assignment of TEFs using thyroid volume or serum free thyroxine (FT4) concentration as the outcomes of interest3. Currently we extended these endpoints by assessment of cytochrome P450 1A1 and 1B1 gene expression in blood. We have examined our volunteering subjects two times 12 years apart. The objective of our study was to examine whether the REPs obtained in the original group of subjects and its subgroup more than a decade apart, agree between themselves and how they comply with the WHO-TEFs.

Materials and methods

The first assessment of thyroid parameters and cytochrome P450 1A1 and 1B1 gene expression in blood took place in year 2000 and the second in year 2012. In year 2000 we examined 315 subjects (195 males, mean age 47±9.4 years and 120 females, mean age 45±11.5 years) and 90 subjects in year 2012 (57 males, mean age 58±11.4 years and 33 females, mean age 62±10.9 years) residing in an organochlorine-polluted area of eastern Slovakia4. Determination of thyroid volume and serum FT43 and quantification of CYP1A1 and CYP1B1 mRNA levels in human PBMCs5 was described earlier. For the values below limits of detection (LOD), we imputed by taking the LOD value divided by the square root of 2 if congeners had fewer than 20% of samples below the LOD; otherwise the LOD values were divided by 2. For the calculation of REPs we used a regression-based approach comparing the strength of association between each dioxin-like compound and the thyroid and CYP1A1and 1B1 gene expression end points3. We calculated the REPs only for congeners have a similar mode of action6. Thus, congeners associated with an opposite outcome as the index chemical were not analyzed further. Finally we compared the obtained REPs between themselves and with WHO TEF values1.

Results and discussion

The REPs obtained by evaluating the 4 different endpoints and at intervals spaced 12 years are shown in Table 1. A high variability of the REP data can be seen. However it has to be noted that a variability of several orders of magnitude can also be seen in REPs that served as the basis for assignment of TEF values2. From Table 2 and Figure 1it can be seen that the REPs obtained in this study with thyroid outcomes for both time intervals agree well with WHO-TEF data. Moreover the thyroid volume derived REPs for year 2000 are at the margin of statistical significance. Agreement was also found for CYP 1A1 data for year 2000. There was no relationship with CYP 1B1 data and the 2012 CYP 1A1 data. Surprisingly good agreement was found between the thyroid derived REPs at 2000 and 2012. On the other hand the CYP 1A1 and 1B1 data spaced 12 years apart did not agree between themselves.

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Table 1. Values of REPs calculated from data obtained by examination of thyroid volume and serum FT4 and quantification of *CYP1A1* and *CYP1B1* mRNA levels in PBMCs. The first study was done in year 2000 and its follow-up in year 2012.

	Thyroid volume			me	FT4				CYP 1A1				CYP 1B1			
	2012		2000		2012		2000		2012		2000		2012		2000	
	Ν	REP	n	REP	n	REP	n	REP	n	REP	n	REP	n	REP	n	REP
PCDDs																
2378-TCDD	87	1.00	312	1.00	90	1.00	316	1.00	69	1.00	277	1.00	69	1.00	277	1.00
12378-PeCDD	87		313	0.69	90	6.47	317	0.34	69	0.97	278		69	2.30	278	21.12
123478-HxCDD	87	0.85	313		90	10.61	317	0.65	69	0.83	278		69	0.33	278	23.70
123678-HxCDD	87		313	0.23	90	5.35	317	0.17	69	0.20	278	0.25	69	0.23	278	5.23
123789-HxCDD	87	0.22	313		90	31.15	317	0.38	69	0.86	278	0.90	69	0.00	278	33.07
1234678-HpCDD	87	0.05	313	0.04	90	0.20	317	0.05	69		278	0.09	69	0.03	278	1.45
OCDD	87	0.01	313	0.01	90	0.04	317		69		278	0.02	69	0.00	278	0.24
PCDFs																
2378-TCDF	87		308	0.58	90		312	0.60	69		274	1.20	69	1.61	274	
12378-PeCDF		1.41	313		90	22.58	317				278	1.04	69		278	
23478-PeCDF	87	0.03	313	0.00	90	0.18	317		69	0.02	278	0.07	69		278	
123478-HxCDF	87	0.05	313	0.13	90	1.53	317		69		278	0.54	69		278	
123678-HxCDF	87	0.48	313	0.54	90	2.16	317		69		278	1.05	69	0.46	278	
123789-HxCDF		3.61	313		90	58.87	317				278		69	4.78	278	
234678-HxCDF	87	1.01	313		90		317		69		278		69	0.43	278	24.27
1234678-HpCDF	87	0.42	313	0.19	90	0.85	317	0.10	69		278	0.98	69		278	
1234789-HpCDF	87	0.42	313	0.02	90	36.09	317	0.05	69		278	0.15	69	1.95	278	
OCDF	87	1.35	313		90	29.98	317	0.21	69	5.77	278		69	1.34	278	8.98
DL-PCBs																
PCB-77	49*	0.02		0.00	49				34	0.24			34			
PCB-81	74	0.02	313	0.02	76		317		56		278	0.01	56		278	
PCB-126	87	0.00	313		90		317		69	0.01	278		69		278	
PCB-169	87	0.00	313		90		317		69	0.00	278	0.00	69		278	
NDL-PCBs																
PCB-105	86	0.00	276		89	0.06	276	0.00	68	0.01	276		68		276	
PCB-114	83	0.01	315		86	0.21	315		67	0.06	315	0.00	65		315	
PCB-118	86	0.00	301		89	0.01	301		69	0.00	301		69		301	
PCB-123	86	0.03	276		88	0.66	276		67	0.21	276		67		276	
PCB-156	86	0.00	315		90	0.02	315		69	0.01	315		69		315	
PCB-157	51*	0.07	315		51	1.39	315		35	0.06	315		35		315	
PCB-167	86	0.00	315		90	0.05	315		69	0.02	315	0.00	69		315	
PCB-189	85	0.00	315		88	0.07	315		68	0.02	315		68		315	

* males only

Table 2. The parameters of regression between log REPs derived from various endpoints and the log WHO-TEFs¹ and the 2012 and 2000 log REPs data.

	Beta	Р	\mathbf{R}^2
Regression of RE	Ps with W	HO-TEF	data
Thyroid volume 2012	0.489	<0,001	0.406
Thyroid volume 2000	0.363	0.097	0.251
FT4 2012	0.404	0.002	0.374
FT4 2000	0.868	0.004	0.612
CYP 1A1 2012	0.158	0.271	0.075
CYP 1A1 2000	0.959	<0,001	0.669
CYP 1B1 2012	0.375	0.182	0.156
CYP 1B1 2000	0.243	0.254	0.181
Regression of RE	Ps from 2	012 and 2	000
Thy 2012/2000	0.643	0.026	0.531
FT4 2012/2000	0.387	0.047	0.407
CYP 1A1 2012/2000	0.286	0.224	0.278
CYP 1B1 2012/2000	0.579	0.294	0.155

Figure 1. Linear regressions with 95 % CI between log REPs derived from various endpoints and the log WHO-TEFs¹ and the 2012 and 2000 log REPs data. A- Thyroid volume, 2012. B- FT4, 2012. C- FT4, 2000. D- *CYP 1A1*, 2000. E- Thyroid volume- 2000/2012. F- FT4, 2000/2012.





