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Impact of Fermented Brown Rice with *Aspergillus oryzae* Intake and Concentrations of Organochlorine Pesticides in Blood of Humans from Japan

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Organochlorine Pesticides (OCPs) were produced in large quantities from 1930's and their global production increased year by year. Because of toxic effects by OCPs, they were banned for usage from late 1960's and early 1970's in developed countries. Japan is one of the developed nations used large quantities of OCPs during 1950's and 1960's. Furthermore, this country has a history of serious environmental problems due to indiscriminate use of toxic chemicals during the post-war period, followed by sudden curtailment in their production due to strict enforcement of the regulations by the Government (Loganathan and Kannan 1991, 1994; Loganathan et al. 1990, 1993). Most of OCPs have persistent properties and long-term health effects in humans. Regular monitoring of these chemicals in humans is essential for understanding their behavior and to prevent health hazards. Among the OCPs, DDTs (o,p'- and p,p'-compounds of DDT, DDE and DDD), HCHs (α,β,γ,δ-hexachlorocyclohexane isomers), chlordane compounds (cis/trans-chlordane, cis/trans-nonachlor, oxychlordane) and HCB (hexachlorobenzene) are of significant importance (Tanabe et al. 1983). This group of compounds has been identified as priority environmental contaminants posing serious chronic toxic effects to humans.

In order to overcome toxic effects by OCPs and to provide healthy environment, biological elimination by efficient OCPs eliminating agent should be identified. In rodents, dietary fiber and chlorophyll was shown to activate fecal excretion of organochlorine chemicals such as dioxins/furans (PCDD/DFs) probably due to inhibition of their absorption in the digestive tract and consequent decrease in liver (Rozman, 1986; Morita et al. 1995). For instance, fermented brown rice with *Aspergillus oryzae* (FEBRA), a rich dietary fiber seems to play a major role for the efficient removal of organic contaminants in humans (Iida et al. 1994). Based on the above-mentioned facts, it should be worth studying impact of FEBRA on the elimination of DDTs, HCHs, chlordanes and HCB in humans. Blood is the most common medium to determine levels of OCPs in human and the levels found here are considered to reflect the body burdens of OCPs. Moreover, blood sampling is comparably easier than other tissue samples. Based on these advantages, we studied the concentrations of DDTs, HCHs, chlordanes and HCB in husband and wife of 9 Japanese couples by classifying them as FEBRA-intake and non FEBRA-intake groups over a 2-year study period. Particularly, our protocol included collection of blood from two groups during 0-year (1-day before study commences), 1-week, 0.5-year, 1-year, 1.5-year and 2-year. Based on the protocol, the exposure and elimination of chemicals for

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the period of 0.5-year, 1-year, 1.5-year and 2-year can be computer normalized from the average concentration of 0-year and 1-week collected blood samples.

MATERIALS AND METHODS

Regarding sampling information and detailed study design has been reported elsewhere (Nagayama et al. 2001, 2002; Takasuga et al. 2004a,b).

$^{13}C_{12}$-labeled standards of OCPs, were purchased from Wellington Laboratories and Cambridge Isotope Laboratories in which their purity were >99%. After spiking $^{13}C_{12}$-o,p/p,p'-DDD, DDE and DDT compounds, $^{13}C_6$-α,β,γ,δ-HCH isomers, $^{13}C_{10}$-cis/trans-nonachlor, cis/trans-chlordane, oxychlordane and $^{13}C_6$-HCB as internal standards in the blood, the samples was extracted (Patterson et al. 1989; Takasuga et al. 2004a,b) described briefly as follows: Extracts were reduced to 20-mL using rotary evaporator. The fat content was determined from the aliquot of the extract by gravimetric method. The remaining extracts were subjected to a cleanup and column chromatographic fractionation procedure. Briefly, fat were removed through dimethyl sulfoxide (DMSO)-hexane partitioning and fractionated using florisil into two fractions. The fraction-1 eluted with 150-mL of hexane contained non-polar OCPs (α,β,γ,δ-HCH isomers, HCB, p,p'-DDE and trans-nonachlor) while fraction-2 eluted with 20%-dichloromethane in hexane contained all polar OCPs (o,p/p,p'-DDD, DDE, DDT, cis-nonachlor, cis/trans-chlordane and oxychlordane).

Identification and quantification of OCPs were performed using Hewlett Packard 6890 Series high-resolution gas chromatography interfaced with a Micromass Autospec - Ultima high-resolution mass spectrometer. The HRGC-HRMS conditions for quantifying OCPs are described elsewhere (Takasuga et al. 2004a,b; Senthilkumar et al. 2005a). The syringe spike recovery labeled standards (o,p'-DDT, γ-HCH and cis-nonachlor) were included prior to the HRGC-HRMS analysis. The recoveries for the OCPs in whole analytical procedure were 91±11 for DDTs, 79±17 for HCHs, 95±9.7 for chlordanes and 80±12 for HCB. The detection limits for DDTs, HCHs, chlordanes and HCB were 11-89, 15-93, 13-160 and 9.3-31 fg (femtogram), respectively. The concentrations in this study were expressed as ng/g fat basis.

RESULTS AND DISCUSSION

Dichloro 2,2'-bis(*p*-chlorophenyl)-1,1,1-trichloroethane (DDTs) and its metabolites were predominant contaminants in human blood (Table 1) with a contribution range from 40% to 91% to the total OCPs load. The maximum DDT concentration was noticed in a male who consume FEBRA for 1.5-year (1600 ng/g fat), while minimum concentration was noticed in 0-year FEBRA intake female (86 ng/g fat). In general, FEBRA-intake individuals contained greater DDTs (423±334) than the non-intake individual (289±202) on ng/g fat. Two samples collected during 1-year and 2-year from all volunteers was analyzed separately in order to see any impact on meal, but results were not significantly different (<10%) and therefore average data of these samples were used for further

discussions. Husbands from six among nine families had higher DDT levels than wife (Table 1). Reduced levels of DDTs in females can be explained as due to gestation and lactation transfer. However, food volume intake between individuals, food composition, metabolism, excretion and other habits should also be considered. Contamination pattern was different in between families and these trends were reflective of different food habit/composition and geographical variations in between families. Although DDTs in some cases show comparable sums of OCPs, the contribution of the different pesticides differ significantly ($p>0.005$).

In order to investigate the contaminant accumulation or elimination rates of DDTs, we computer normalized 0.5-year, 1-year, 1.5-year and 2-year concentrations from the average concentration of 1-day prior to study and 1-week study samples (Table 2) which was normalized as 1.0 (Nagayama et al. 2001, 2002). The overall normalized data obtained in 2-year blood exhibited slightly increased levels of DDTs in FEBRA-intake groups (0.76, 1.18, 1.01, 1.15, 0.82, 1.77, 1.63, 1.44, and 1.20 with average of 1.22) followed by non-intake individual (0.69, 0.84, 1.24, 1.17, 1.07, 2.50, 1.52, 1.30, and 0.65 with average of 1.22). Results obtained from the couples from family-8 showed greater increment of DDTs than the rest of families (Table 2). Normally DDTs:DDE ratio (DDTs/DDE) of >1 suggest recent technical DDTs exposure in the environment. However, there is no higher DDTs/DDE ratio found in this family. However, consumption of DDTs contaminated food in some hot spots regions needed to be considered (Senthilkumar et al. 2005b). Our recent studies showed that brown rat lives in rural and urban part of Japan showed greater DDT concentrations and therefore DDT remains in soil (Senthilkumar et al. 2005b) tend to enter in human food chain such as tubers, vegetables and plant matter may play a predominant role in the fluctuation of DDT concentrations in humans.

Although total DDTs concentrations were reported, the percentage composition of DDTs and its metabolites detected in this study are shown in Figure 1. The *p,p'*-DDE was the predominant (> 95%) accumulant in most of the samples followed by *p,p'*-DDT, *p,p'*-DDD and *o,p'*-DDT. Higher proportion of *p,p'*-DDE in biological samples suggests ability of the individuals to transform *p,p'*-DDT into *p,p'*-DDE.

HCHs were the second predominant contaminants contributing 3.2% to 60% to total OCPs load (Table 1). Maximum concentration (710 ng/g fat) was noticed in a 0.5-year FEBRA intake male whereas, minimum concentration (16 ng/g fat) was observed in 1.5-year non-FEBRA intake female. Consistent to DDTs, FEBRA intake groups had double the HCH level (188±204) than non-FEBRA intake individual (94±111). Unlike DDTs, HCHs were predominant in females than in males. In contrast to DDT accumulation pattern, HCH accumulation in most of the individuals analyzed in this study showed slightly different trend.

The computer-normalized data of HCH suggested similar trend with those to DDTs with increased concentrations by FEBRA-intake and non-intake groups after 2 year (Table 2). For example, slightly elevated exposure of HCHs was noticed in FEBRA intake groups (0.65, 2.41, 1.16, 1.40, 0.83, 1.66, 1.54, 0.98, and 0.85 with

Table 1. Sample details & concentrations (ng-whole blood lipid) of organochlorine pesticides in blood of FEBRA intake and non-intake group.

Family		Husband					Wife				
	Fat (%)	0-yr	0.5-yr	1-yr	1.5-yr	2-yr	0-yr	0.5-yr	1-yr	1.5-yr	2-yr
	OCPs	n=2	n=1	n=2	n=1	n=2	n=2	n=1	n=2	n=1	n=2
	Fat (%)	**0.21**	**0.40**	**0.27**	**0.33**	**0.46**	0.32	0.41	0.33	0.38	0.44
	DDTs	**280**	**170**	**210**	**200**	**210**	330	250	290	240	230
1	HCHs	**55**	**39**	**39**	**33**	**36**	160	180	170	120	140
	CHLs	**56**	**33**	**35**	**39**	**33**	34	24	23	22	18
	HCB	**23**	**10**	**17**	**22**	**18**	17	7.8	11	12	8.1
	Fat (%)	0.30	0.36	0.30	0.38	0.32	**0.27**	**0.46**	**0.34**	**0.39**	**0.36**
	DDTs	160	100	160	130	130	**410**	**350**	**550**	**500**	**490**
2	HCHs	19	27	29	23	22	**200**	**430**	**560**	**470**	**480**
	CHLs	43	44	48	35	32	**53**	**60**	**50**	**73**	**63**
	HCB	12	5.2	8.7	8.8	7.2	**17**	**8.2**	**19**	**21**	**16**
	Fat (%)	**0.76**	**0.73**	**0.72**	**0.69**	**0.87**	0.40	0.53	0.30	0.40	0.42
	DDTs	**710**	**520**	**710**	**730**	**720**	210	140	230	260	260
3	HCHs	**480**	**710**	**620**	**670**	**550**	42	46	56	70	61
	CHLs	**140**	**150**	**83**	**150**	**130**	29	22	22	28	31
	HCB	**33**	**29**	**45**	**49**	**29**	14	7.4	16	22	16
	Fat (%)	0.76	0.46	0.51	0.69	0.65	**0.36**	**0.46**	**0.30**	**0.47**	**0.36**
	DDTs	180	190	300	250	210	**270**	**150**	**340**	**280**	**310**
4	HCHs	41	66	91	73	57	**220**	**190**	**420**	**310**	**300**
	CHLs	51	49	71	49	47	**9.2**	**10**	**13**	**11**	**13**
	HCB	13	14	22	16	10	**16**	**7.6**	**22**	**15**	**11**
	Fat (%)	**0.40**	**0.28**	**0.57**	**0.38**	**0.32**	0.42	0.46	0.30	0.39	0.28
	DDTs	**1100**	**1000**	**1100**	**1600**	**860**	220	160	230	440	240
7	HCHs	**97**	**120**	**120**	**72**	**80**	380	240	460	340	450
	CHLs	**110**	**120**	**130**	**75**	**84**	45	30	53	45	46
	HCB	**75**	**31**	**34**	**72**	**21**	26	17	33	66	23
	Fat (%)	0.60	0.57	0.40	0.40	0.37	**0.36**	**0.44**	**0.31**	**0.38**	**0.32**
	DDTs	240	310	480	920	600	**91**	**110**	**160**	**300**	**160**
8	HCHs	30	37	50	47	61	**48**	**57**	**92**	**71**	**79**
	CHLs	39	42	84	55	88	**20**	**24**	**37**	**21**	**29**
	HCB	12	13	26	77	23	**11**	**12**	**16**	**34**	**11**
	Fat (%)	**0.35**	**0.23**	**0.32**	**0.41**	**0.28**	0.35	0.15	0.35	0.46	0.32
	DDTs	**310**	**450**	**390**	**1000**	**510**	65	110	93	180	99
9	HCHs	**51**	**78**	**86**	**75**	**79**	17	23	22	16	22
	CHLs	**28**	**32**	**37**	**26**	**32**	10	9.1	13	11	10
	HCB	**12**	**16**	**16**	**27**	**19**	5.4	10	10	23	7.4
	Fat (%)	**0.29**	**0.28**	**0.35**	**0.33**	**0.31**	0.41	0.23	0.49	0.55	0.36
	DDTs	**180**	**200**	**210**	**550**	**160**	100	210	130	270	130
10	HCHs	**21**	**20**	**20**	**20**	**20**	43	67	43	36	30
	CHLs	**25**	**23**	**22**	**35**	**31**	28	38	24	23	29
	HCB	**6.2**	**8.2**	**12**	**22**	**10**	7.5	15	11	24	7.8
	Fat (%)	0.21	0.34	0.37	0.27	0.51	**0.35**	**0.37**	**0.53**	**0.39**	**0.51**
	DDTs	540	520	1000	530	350	**86**	**120**	**250**	**98**	**100**
11	HCHs	**88**	65	70	56	42	**59**	**43**	**76**	**52**	**50**
	CHLs	63	51	38	42	28	**14**	**17**	**12**	**15**	**16**
	HCB	19	19	34	15	11	**9.4**	**13**	**24**	**10**	**9.3**

The figures in bold indicate FEBRA-intake subjects
OCPs indicates sum of all analyzed organochlorine pesticides; the values rounded

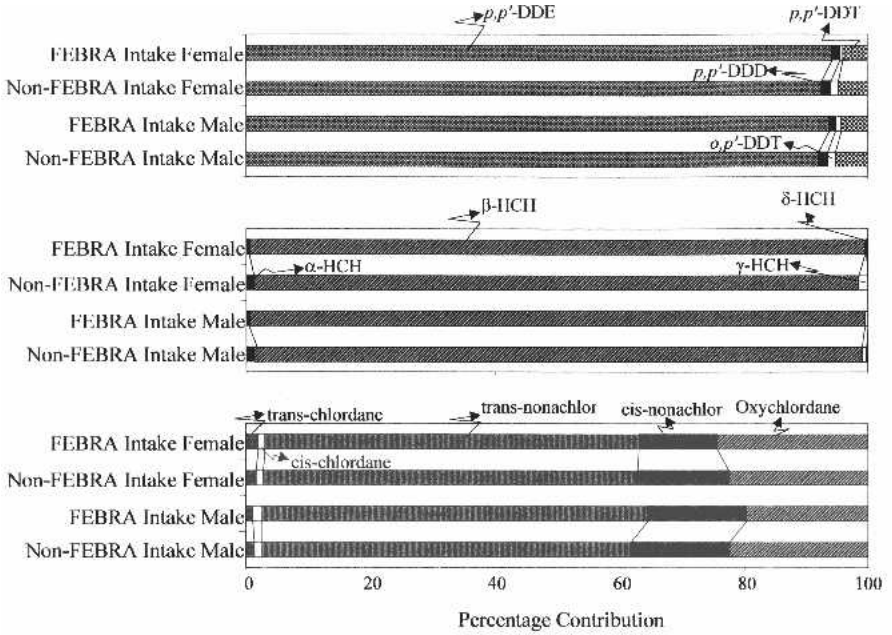

Figure 1. Compositions of DDT compounds, HCH isomers and chlordane compounds in FEBRA intake and non-intake men and women from Japan.

an average of 1.27) than the non-intake groups (0.84, 1.13, 1.45, 1.41, 1.19, 2.03, 1.30, 0.69, and 0.48 with an average of 1.17). FEBRA intake individuals from 4 families tended to decrease HCHs at 0.5-year of sampling but overall results showed increase of concentrations after 2-year. Intake of FEBRA did not reduce HCHs as they were found to be slightly higher in intake group than non-intake group. Overall, in females, HCH levels gradually increased irrespective to FEBRA consumption, geographical and temporal variation. Although total HCHs concentrations were reported for discussion, the percentage composition of HCH isomers detected in this study was shown in Figure 1. The β-HCH was the prevalent isomer (> 95%) in all the samples followed by α-HCH, γ-HCH and δ-HCHs. The predominance of β-HCH is due to its stable nature to enzymatic degradation in human body. In the technical HCH mixtures, the proportion of isomers were in the following order; 70%-α, 15%-γ, 6%-β and 9%-δ and have presence of α-HCH in some samples may also indicate recent exposure by atmospheric transport from places where HCHs still being used (e.g., India, China, etc.,).

Concentrations of chlordane compounds in human blood were 1.3% to 24% to the total OCPs load (Table 1). Chlordane contamination pattern found similar with those of DDTs. A non-FEBRA intake female in 0.5-year had lowest concentrations (9.1 ng/g fat) while a 0.5-year and 1.5-year FEBRA intake male contained maximum concentration (150 ng/g fat). Consistent with DDTs and HCHs,

Table 2. Computer normalized concentrations of organochlorine pesticides in human blood of FEBRA in take and non-intake groups.

Family	OCPs	Husband					Wife				
		0-yr	0.5-yr	1-yr	1.5-yr	2.0-yr	0-yr	0.5-yr	1-yr	1.5-yr	2.0-yr
1	DDTs	**1.0**	**0.62**	**0.75**	**0.73**	**0.76**	1.0	0.77	0.89	0.74	0.69
	HCHs	**1.0**	**0.71**	**0.71**	**0.60**	**0.65**	1.0	1.13	1.03	0.75	0.84
	CHLs	**1.0**	**0.59**	**0.63**	**0.70**	**0.59**	1.0	0.72	0.76	0.66	0.54
	HCB	**1.0**	**0.43**	**0.74**	**0.96**	**0.76**	1.0	0.47	0.67	0.73	0.49
2	DDTs	1.0	0.65	1.03	0.84	0.84	**1.0**	**0.85**	**1.34**	**1.22**	**1.18**
	HCHs	1.0	1.42	1.50	1.21	1.13	**1.0**	**2.18**	**2.84**	**2.38**	**2.41**
	CHLs	1.0	1.02	1.12	0.81	0.73	**1.0**	**1.14**	**0.94**	**1.39**	**1.20**
	HCB	1.0	0.43	0.72	0.73	0.60	**1.0**	**0.48**	**1.12**	**1.24**	**0.91**
3	DDTs	**1.0**	**0.74**	**1.00**	**1.04**	**1.01**	1.0	0.68	1.10	1.27	1.24
	HCHs	**1.0**	**1.49**	**1.31**	**1.41**	**1.16**	1.0	1.10	1.33	1.67	1.45
	CHLs	**1.0**	**1.11**	**0.61**	**1.11**	**0.96**	1.0	0.76	0.77	0.97	1.07
	HCB	**1.0**	**0.89**	**1.38**	**1.51**	**0.89**	1.0	0.53	1.11	1.57	1.14
5	DDTs	1.0	1.06	1.67	1.39	1.17	**1.0**	**0.56**	**1.26**	**1.04**	**1.15**
	HCHs	1.0	1.63	2.23	1.80	1.41	**1.0**	**0.88**	**1.93**	**1.44**	**1.40**
	CHLs	1.0	0.97	1.41	0.97	0.93	**1.0**	**1.09**	**1.36**	**1.20**	**1.36**
	HCB	1.0	1.08	1.69	1.15	0.77	**1.0**	**0.48**	**1.38**	**0.94**	**0.66**
7	DDTs	**1.0**	**0.95**	**1.05**	**1.52**	**0.82**	1.0	0.73	1.02	2.00	1.07
	HCHs	**1.0**	**1.24**	**1.19**	**0.75**	**0.83**	1.0	0.64	1.21	0.91	1.19
	CHLs	**1.0**	**1.09**	**1.14**	**0.68**	**0.76**	1.0	0.67	1.19	1.01	1.03
	HCB	**1.0**	**0.41**	**0.45**	**0.96**	**0.27**	1.0	0.67	1.27	2.59	0.88
8	DDTs	1.0	1.29	2.00	3.83	2.50	**1.0**	**1.22**	**1.77**	**3.31**	**1.77**
	HCHs	1.0	1.23	1.65	1.57	2.03	**1.0**	**1.20**	**1.93**	**1.49**	**1.66**
	CHLs	1.0	1.09	2.18	1.43	2.27	**1.0**	**1.23**	**1.90**	**1.08**	**1.49**
	HCB	1.0	1.08	2.13	6.42	1.88	**1.0**	**1.09**	**1.36**	**3.09**	**1.00**
9	DDTs	**1.0**	**1.45**	**1.24**	**3.23**	**1.63**	1.0	1.69	1.42	2.77	1.52
	HCHs	**1.0**	**1.53**	**1.66**	**1.47**	**1.54**	1.0	1.39	1.30	0.97	1.30
	CHLs	**1.0**	**1.14**	**1.30**	**0.93**	**1.14**	1.0	0.88	1.26	1.07	0.92
	HCB	**1.0**	**1.25**	**1.33**	**2.25**	**1.58**	1.0	1.85	1.83	4.26	1.37
10	DDTs	**1.0**	**1.11**	**1.14**	**3.06**	**1.44**	1.0	2.10	1.30	2.70	1.30
	HCHs	**1.0**	**0.98**	**0.98**	**0.98**	**0.98**	1.0	1.58	1.01	0.85	0.69
	CHLs	**1.0**	**0.94**	**0.90**	**1.43**	**1.24**	1.0	1.36	0.86	0.82	1.02
	HCB	**1.0**	**1.32**	**1.85**	**3.55**	**1.56**	1.0	2.00	1.47	3.20	1.04
11	DDTs	1.0	0.96	1.90	0.98	0.65	**1.0**	**1.40**	**2.92**	**1.15**	**1.20**
	HCHs	1.0	0.74	0.80	0.64	0.48	**1.0**	**0.74**	**1.30**	**0.89**	**0.85**
	CHLs	1.0	0.82	0.60	0.67	0.44	**1.0**	**1.26**	**0.89**	**1.11**	**1.19**
	HCB	1.0	1.03	1.84	0.81	0.57	**1.0**	**1.38**	**2.55**	**1.03**	**0.98**

The letters in bold indicate FEBRA-intake subjects

chlordanes were greater in FEBRA-intake group (49±41) than the non-intake (37±18) group. Collectively, the 1-year blood samples showed slight reductions of chlordanes however, the results were not statistically significant (p=0.001%). Seven among nine males had higher concentrations of chlordanes while; two females had slightly higher concentrations. Similar to HCHs, the male from family-3 had elevated concentrations.

The computer normalized results reveals slight reductions of chlordanes in 0.5-year and 1-year blood samples. Further slight increase was noticed in 1.5-year and 2-year blood (Table 2). Nevertheless, it is apparent that intake of FEBRA had no effect in reducing overall accumulation of chlordanes due to slightly higher levels in FEBRA-intake group (0.59, 1.20, 0.96, 1.36, 0.76, 1.49, 1.14, 1.24, and 1.19 with average of 1.10) than non-intake group (0.54, 0.73, 1.07, 0.93, 1.03, 2.27, 0.92, 1.02, and 0.44 with average of 0.99). Based on these results, it is apparent that FEBRA do not seem to have positive impact on eliminating chlordanes from humans. The *trans*-nonachlor was the prevalent contaminant (40-50%) followed by oxychlordane (20-23%), *cis*-nonachlor (less than 15%), *trans*-chlordane and *cis*-chlordane (Figure 1).

The concentrations of HCB were lower with ranges from 5.2 (0.5-year non-FEBRA intake male) to 77 (1.5-year non-FEBRA intake male) on ng/g fat (Table 1). The observed contribution of HCB was in the range of 1% to 8.6% to total OCPs load. Slightly greater HCB concentrations were noticed in FEBRA-intake (21±15) group when compare to non-intake (17±14) group. Six among nine males had greater concentrations of HCB and the results resembled with those of DDTs for which the male member of family-7 showed elevated levels, the male from family-3 had greater HCHs and chlordane concentrations. The variation of HCB in between males are also well pronounced, while, females however showed similar concentrations. Irrespective to the FEBRA intake and temporal trend, the HCB contamination pattern is similar in husband and wife of all families.

The computer-normalized results showed a fluctuation of a decreasing-increasing-decreasing trend in 0.5-year, 1-year and 2-year respectively (Table 2). On the whole, the computer-normalized data elucidated similar HCB elimination levels in FEBRA intake group (0.76, 0.91, 0.89, 0.66, 0.27, 1.00, 1.58, 1.56, and 0.98 with an average of 0.96) and non-intake group (0.49, 0.60, 1.14, 0.77, 0.88, 1.88, 1.37, 1.04, and 0.57 with an average of 0.97). When compare to other organochlorine pesticides, HCB levels decreased slightly after 2-year. These trends were similar to the results of polybrominated diphenyl ethers and PCDD/DFs (Takasuga et al. 2004a,b).

On the whole, FEBRA intake by humans in Japan seems to not eliminate DDTs, HCHs and chlordanes. However, HCB seems to be eliminated by FEBRA-intake groups nevertheless, it is not considerable and data should be interpreted with great caution. These trends are contrast to dioxins and PBDEs they tend to eliminate in FEBRA-intake group (Takasuga et al. 2004a,b).

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