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Hazards of Organic Chlorine Compounds to the Health of Children

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Abstract. As a group of the study on acute accidental poisoning of PCB, the authors studied the influence of PCB and organic chlorine agricultural poison on liver enzymes. Outlines of the influences and clinical features of these compounds are discussed in the view of pediatrics and environmental pharmacology.

Various organic chlorine compounds are taken up by the human body directly or indirectly via food. Among organic chlorine compounds, polychlorbiphenyl (PCB), BHC, DDT, aldrin, dieldren, endorin, and heptachlor present problems in Japan. Among these, PCB and β-BHC are especially dominating environment-polluting agents. Alarm for PCB intoxication in man was already made by *Schwarz* (7) in 1936 and by *Meigs and Kartin* (6) in 1954. Despite this, so-called 'Kanemi Yusho' (poisoning with edible oil) broke out around the Fukuoka area in Japan in 1968.

Detailed animal experiments have been conducted on the toxicity of these organic chlorine compounds. These organic chlorine compounds are chemically stable, fat soluble and resistant to metabolic degradation, and are stored in high concentrations in body fat, liver and cerebral white matter, influencing lipid and other metabolisms *in vivo*. No report on organic chlorine compound intoxication other than PCB is yet available in Japan.

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Acute Accidental Poisoning by Rice Bran Oil (Kanemi Yusho) in Japan

The cause of rice bran oil intoxication around the Fukuoka area is contamination by PCB. Reports up to the end of August 1971, revealed 17 dead and more than 1,000 poisoned. The actual number of patients probably reached 5,000. The main symptoms of Yusho consist of acne-like eruptions and atheroma in the skin of the face, neck and chest, along with colorful symptoms such as swelling and pigmentation of gingiva, nail pigmentation, darkening corresponding to hair follicle, visual disturbance, hyperemia of conjunctival mucosa, tendency to respiratory infection such as bronchitis, and carious teeth. Besides, many patients complain of headache, abdominal pain, paresthesia of extremities, edema in face and extremities, decrease in body weight and libido, menstrual abnormality and easy fatigability. In the laboratory tests, anemia, hypoalbuminemia, with increase in α-globulin, hypoferremia and hypercupremia, marked rise in triglycerides, aminoaciduria, and increase in urinary excretion of 17-OHCS and 17-KS.

In patients in childhood, repeated respiratory infections predominated among these symptoms, along with abnormalities in the dental and skeletal system such as weak teeth and growth retardation. Mothers with Yusho gave birth to so-called 'black babies', with dark brown pigmentation of the skin and mucous membrane, abnormal hypertrophy of gingiva, and rocker bottom heel. Most of these were small-for-date babies. *Funatsu et al.* (3) called these newborns as chlorobiphenyls-induced fetopathy.

The characteristics of the chlorobiphenyls-induced fetopathy consist of: (1) Mother had taken rice bran oil containing chlorobiphenyls. Mother's symptoms need not always be definite, but chlorobiphenyls are found in the placenta and skin and subcutaneous tissue of the stillborn infant. Animal experiment demonstrated transfer of chlorobiphenyls from mother to the fetus. (2) Symptoms and signs are summarized in a clinical entity: (a) body weight at birth is smaller than expected based on the duration of pregnancy (small-for-date baby: SFD); (b) dark brown pigmentation and desquamation of the skin and mucous membrane; (c) gingival hypertrophy and presence of teeth from immediately after birth; (d) calcification in skull X-ray picture. (3) Unlike embryopathy, malformation does not occur.

In the induced fetopathy, PCB taken by the mother inhibits the growth of the fetus. However, no remarkable pathological change of placenta was reported. Subsequent development of four children reported by Funatsu was described as approximately parallel to the standard curve; on the side of somewhat short

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stature with uneventful mental development. In the laboratory tests, no hypertriglyceridemia was found as in adults or older children. Rise in serum GOT and alkaline phosphatase and abnormal β-lipoprotein represent the main findings, suggesting high sensitivity of the liver to organic chlorine compounds.

Pathogenesis of the PCB-induced fetopathy has been studied by various methods. These symptoms might be secondary to metabolic and endocrine disturbance due to induction of drug-metabolizing enzymes.

From the rice bran oil responsible for 'Kanemi Yusho', about 2,000 3,000 ppm PCB was detected. According to the calculation based on oil intake, patients with Yusho have probably taken a total of 2 g PCB on average. The minimum dose for the manifestation is said to be 0.5 g. An adult with 50 kg body weight who took this amount over a period of 5 months had a daily intake of 67 μg/kg/day. The mother who gave birth to babies with PCB-induced fetopathy took rice bran oil between the 1st and 7th months of pregnancy, taking at least 0.6 g PCB. During the 10 months intrauterine life, the mother with 50 kg body weight took 40 μg/kg/day of PCB.

Food Contamination, Uptake and Storage of PCB or BHC by the Human Body

Food Chain

Organic chlorine compounds such as PCB and BHC contaminate soil and water, and are taken up by man as the last step in the food chain. As to food of animal origin, the food chain rotates quickly and the substance is stored rapidly in fish and shellfish, birds or mammals in high concentrations. We eventually take these foods with high concentration of organic chlorine compounds. These organic chlorine compounds ingested by man are chemically quite stable, fat soluble, and the excretion is said to be difficult. Especially PCB is not excreted in urine at all, and only a small amount is excreted in feces. Most of PCB ingested is stored in fat tissue, and organs rich in fat such as the liver and kidney. As a special pathway of excretion, transfer to the fetus via the placenta was demonstrated. The transfer to baby through mother's milk might also represent a serious risk for the child's health.

Organic Chlorine Compound in Food

Influence of organic chlorine compounds in the health of children should be considered from the time of fertilization throughout the growth period up to

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Table I. Intake of PCB per day calculated from PCB concentration in foods

Foods	PCB, ppm	Food intake, g			PCB intake, μg		
		min	max	average	min	max	average
Cow's milk	0.02	32.2	108.4	65.2	0.664	2.168	1.304
Milk product	0.06	2.7	12.1	10.4	0.162	0.726	0.624
Meat	0.04	17.5	62.2	37.9	0.700	2.488	1.516
Egg	0.03	26.5	51.7	37.9	0.795	1.551	1.137
Fish	0.5	75.9	120.9	86.3	37.95	65.45	43.15
Total		154.8	365.3	237.7	40.27	72.38	47.73

adulthood. The degree of food contamination in Japan at present, and the amount of ingestion of organic chlorine compound should be clarified.

Only PCB and BHC present problems in Japan among organic chlorine compounds. Since the production of both of these compounds was stopped and the use was restricted, a decline is expected in the future. The influence of organic chlorine compounds already contaminating the environment probably lasts a few more years.

PCB. The current status of contamination by PCB, according to the result of a nation-wide survey by the Ministry of Health and Welfare in 1972, shows that the average PCB intake by adult is 72.4 μg daily. Fish and shellfish are responsible for 90.4% or 65.5 μg of this. The daily PCB intake in each food calculated from an average intake of 86.3 g/day of fish and shellfish containing 0.5 ppm PCB, amounts to 43.15 μg/day (4).

The average concentration of PCB in milk is 0.02 ppm, the amount of milk ingestion per capita 65.2 g and the PCB intake 1,304 μg/day (10) (table I).

The Ministry of Health and Welfare in June 1972, prohibited the production of PCB and confined its use, announcing the tentative allowances of PCB ingestion per capita. According to this, 5 μg/kg/day intake of PCB is allowed for man. Values of tentative regulation of PCB content in each food were 0.5 ppm for fish and shellfish in the ocean and 3 ppm for those in the inland sea and gulf, less than 1 ppm for the entire fish and shellfish. The limited PCB content in cow's milk is 0.1 ppm, milk product 1 ppm, dried milk for baby 0.2 ppm, meat 0.5 ppm, eggs 0.2 ppm, and vessels and packages 5 ppm. Since the minimum

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intake in patients with Yusho was 67 μg/kg/day, these figures are presented as the safe limit. Since Yusho is a manifestation of acute poisoning, however, the safe limit for long-term intake should be investigated in the future.

BHC. The contamination by β-BHC with the highest rate of accumulation is most important. No report on the occurrence of intoxication in man is yet available. As to the intoxication by BHC, the influence on the human body is feared to be the same as that of PCB. Like PCB, β-BHC is found widely in foods of animal origin such as meat, especially beef, fatty food, and cow's milk.

In Japan, among BHC isomers, β-BHC with mild pesticidal action and stability is frequently used and accumulated as the characteristic feature. An adult with 50 kg body weight, ingests 29.3 μg γ-BHC and 54 μg β-BHC on average in Japan. Intake of γ-BHC is reported to be about 5% of the WHO permissible level, and β-BHC 22% of the mean value for chronic toxicity, being below the permissible level (2). In Japan, however, β-BHC content of cow's milk decreased to about $^1/_{10}$ of the previous level since the production of BHC was stopped and its use restricted since 1971.

DDT. Only $^1/_{10}$ of the amount of that of BHC is used in Japan. Daily intake is 0.46 μg/kg/day, or $^1/_2$ the intake in Britain and USA, and $^1/_2$ of ADT by FAO/WHO. The intake of dieldrin is 0.1 μg/kg/day and approximately equal to ADT of FAO/WHO.

Contamination of Mother's Milk by PCB and BHC (1)

PCB

According to the report of the Ministry of Health and Welfare survey in December 1972 (10), the maximum PCB concentration in mother's milk was 0.2 ppm and averaged 0.035 ppm, and higher values were seen in those of fishing and city districts. When the average intake of mother's milk by an infant is assumed to be 150 ml/kg/day, the daily PCB intake is maximally 30 μg/kg/day. This reaches a level 6 times as high as that of the temporary regulated value. Since the susceptibility of the liver of young children to PCB was pointed out, the influence on the drug-metabolizing enzyme is anticipated (table II).

BHC

In Tokyo, 0.101 ppm of BHC was found in mother's milk 1 month after birth according to the report by the Tokyo Metropolitan Hygiene Institute in 1971. In Osaka in 1970, a maximum level of 0.293 ppm and an average value of

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Table II. Concentration of PCB in mother's milk

Concentration, ppm	Number of mothers	Sum, %	Urban	Farm	Fishing	Near factories	Mines
0.01	48	7.2	23	19	3	2	1
0.01	84	19.7	30	36	8	6	4
0.02	164	44.1	62	70	20	11	1
0.03	126	62.9	52	47	15	12	
0.04	74	73.9	33	22	16	3	
0.05	68	84.1	34	19	9	6	
0.06	32	88.8	18	7	3	4	
0.07	15	91.1	10	2	1	2	
0.08	20	94.0	11	4	5	-	
0.09	9	95.4	5	–	4	–	
0.1	23	98.8	9	5	5	4	
0.2	8	100.0	4	–	3	–	
Total	671	–	291	231	92	51	6
Average	0.035	–	0.038	0.028	0.045	0.040	–

Table III. Residual organic chlorine pesticides in fat of mother's milk (ppm)

Time after delivery	Number of specimens		BHC	DDT	Dieldrin
1 week	30	average	2.58	1.98	0.132
		range	0.57–8.39	0.74–5.01	0–0.367
		SE	1.72	1.08	0.085
2 weeks	30	average	2.58	1.81	0.125
		range	0.36–8.54	0.62–5.37	Tr–0.370
		SE	1.83	1.10	0.085
1 month	29	average	2.70	1.96	0.133
		range	0.40–8.22	0.58–4.02	Tr–0.585
		SE	1.92	0.92	0.117
2 months	25	average	2.22	2.30	0.209
		range	0.72–8.88	0.12–5.25	0.059–0.820
		SE	1.75	1.36	0.193

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0.195 ppm were revealed. In Kochi Prefecture, a maximum value of 0.255 ppm and an average value of 0.122 ppm were encountered. Lower values are expected at present after the restrictions on use (table III, IV).

Influence of PCB and BHC on Animals, an Experimental Study

In the animal study on the chronic toxicity of PCB, the enzyme induction in the drug-metabolizing system is known to be the most sensitive index. In mice, liver damage lowers the rate of conception and weaning, average body weight of the young, and number of live animals. The possibility of cancerogenicity was also reported, suggesting that intake of a small amount since childhood might participate to carcinogenesis. No tetratogenicity is said to be present, however.

In the animal experiment on BHC, like PCB, the influence on fat metabolism was pointed out (5). The synergistic action with other organic chlorine agricultural drugs is also feared.

Influence of PCB and BHC on Liver Enzyme Activities

Organic chlorine compounds such as PCB have the action of enzyme induction in the drug-metabolizing system of the liver.

The occurrence of enzyme induction of the liver in the mouse is reported above 5 mg/kg of PCB (total dose). In our experiment, liver glucuronyltransferase activity rose about 30% 7 days after feeding with 10 ppm of PCB, and about 150% higher after feeding with 100 ppm of PCB (table V).

In the report by the Yusho study group, by the intraperitoneal pretreatment of PCB, hexobarbital sleeping time in the albino rat was shortened. This is due to the rapid degradation and detoxication of hexobarbital by PCB-induced enzyme induction (8, 9).

The induction of enzymes in the drug-metabolizing system is the increase in detoxication of toxic substances as the defense reaction favorable for the animals, and on the other hand, time means the stimulation of liver cells, with a high probability of causing liver damage. Increased enzyme activity results in an increase of degradation of hormones, leading to a disturbance of the hormone balance and various metabolisms such as decrease in libido and menstrual abnormality. The administration of 3 mg/kg/day of tetrachlorobiphenyl in rats for 90 days caused a slight increase in liver weight.

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Table IV Residual pesticides in mother's milk and blood (ppm)

Time after birth	Number of specimens		Fat, %	BHC				DDT			Dieldrin
				α	β	γ	total	DDE	DDT	total	
Mother's milk											
1 week	30	average	3.2	0.002	0.081	0.002	0.085	0.042	0.020	0.062	0.004
		min	1.1		0.013		0.018			0.023	0.001
		max	4.8		0.271		0.277			0.165	0.013
2 weeks	30	average	4.0	0.002	0.099	0.002	0.103	0.044	0.021	0.065	0.005
		min	2.5		0.007		0.011			0.024	0.001
		max	6.1		0.309		0.313			0.153	0.014
1 month	29	average	3.6	0.002	0.096	0.003	0.101	0.045	0.022	0.067	0.005
		min	2.0		0.022		0.019			0.027	Tr
		max	5.2		0.289		0.306			0.189	0.026
2 months	25	average	2.9	0.002	0.063	0.001	0.066	0.039	0.018	0.057	0.005
		min	0.9		0.009		0.012			0.011	0.001
		max	4.3		0.148		0.151			0.166	0.015
Blood											
1 week	30	average		0.0018	0.0065	0.0007	0.0090	0.0083	0.0007	0.0044	0.0024
		min			0.0003		0.0003			0	0.0003
			max		0.0260		0.0293			0.0117	0.0060

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Table V. Changes (in %) in rat liver enzyme activity after administration of organic chlorines

	β-BHC, 3 months		β-BHC, 1 week		PCB, 1 week	
	10 ppm	50 ppm	10 ppm	100 ppm	10 ppm	100 ppm
GOT	33	−63	N	−34.5	N	N
LDH	−25	+54.4	N	N	N	−18
ALP	−20	N	−20	−57.8	−45	72
LAP	N	+44.8	−9	−23.5	N	−60
Aldolase			−10	−45	−20	−40
Glucuronyl-transferase			N	+114.7	+30	+150.5
Body weight			N	−5	N	−7.1
Liver weight			N	N	N	+17.6
Body weight / Liver weight			N	+15.7	N	+45

N = No change; β-BHC = β-benzene hexachloride; 10, 50, and 100 ppm = contents of organic chlorines in diets.

Administration of 25 mg/kg/day caused fatty degeneration of liver cells and an increase in the smooth-surfaced endoplasmic reticulum in liver cells in the electron microscopic findings. Long-term administration of a small amount in man might give rise to liver damage. Such phenomena is seen remarkably after DDT and β-BHC ingestion. In our experiment with β-BHC (table V), feeding rats with a diet containing 100 ppm β-BHC increased the liver glucuronyltransferase activity by more than twofold after 7 days. Although the increase in liver weight was not pronounced, fatty degeneration of liver cells and an increase in smooth-surfaced endoplasmic reticulum were noted. Some influence was found on GOT, GPT, γ-GTP, alkaline phosphatase and leucine aminopeptidase after PCB or BHC ingestion.

Experiment on Transference of PCB and BHC to Mother's Milk

Also in our experiment, the mother rats were fed with the diet containing 50 ppm PCB or β-BHC and their youngs were raised with mother's milk. In young rats after 7 days, body weight gain became poorer, the liver was swollen, smooth-surfaced endoplasmic reticulum and liver glucuronyltransferase activity were increased.

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Danger of Organic Chlorine Compounds such as PCB and BHC in Infants

Prospective Survey on Disturbance Caused by Organic Chlorine Compounds in Children

No report is yet available on chronic intoxication due to repeated ingestion of small amounts of organic chlorine compounds such as PCB and BHC. Consequently, results in animal experiments and symptoms in patients with accidental acute intoxication such as so-called Kanemi Yusho are used as reference.

The difference of PCB intoxication between adults and children is respiratory infection, and growth retardation, especially dental and skeletal growth in the latter. However, the symptoms due to the long-term intake of a small amount of these organic chlorine compounds are hardly distinguishable from those in general diseases.

The prospective survey on unfavorable effects by the organic chlorine compounds in children is impossible. As to blood chemical tests, no sensitive and specific tests are yet available. Consequently, the screening of disturbances due to organic chlorine compounds is impossible and periodic health examinations for children with possible high intake is the only effective method in the health control.

In the children, contamination takes place from the embryonal and fetal period via the placenta and further contamination continues via mother's milk, cow's milk and food for weaning. The condensation and accumulation of PCB and BHC into fat tissue *in vivo* becomes greater than adults in the future, so that the decrease of PCB and BHC in foods for children is mandatory. Measurement of organic chlorine compounds in blood of mother and mother's milk, and the strict check of food contamination appears to be the most important means for protecting the child's health.

Summary

The outline of the influence of organic chlorine compounds such as PCB and BHC on the human body is reviewed. Daily intake of organic chlorine compounds among the Japanese is reviewed from the literature. Early detection of disturbance due to organic chlorine compound is an extremely difficult problem, and a prospective survey in children should be conducted in the form of periodic health examinations for the detection of the disease. Rather than discussing the early detection of organic chlorine compounds, production of these compounds should be stopped to abolish the source of environmental pollu-

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tion. In Japan, production of PCB and BHC was prohibited and their use restricted in 1971–1972. However, environmental pollution has already been spread, requiring the action of the monitoring system.

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