Approach to Risk Assessment of Chlorinated Dioxins from Yusho PCB Poisoning

Yoshito Masuda
Daiichi College of Pharmaceutical Sciences
22-1 Tamagawa-cho, Minami-ku, Fukuoka 815, JAPAN

Introduction

Polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and polychlorinated biphenyls (PCBs) are all halogenated aromatics and consist of numerous isomers and congeners[1]. PCDDs and PCDFs have originated from the contamination in chlorinated chemicals and the thermal reactions of chlorinated and organic compounds, for example from the incineration of municipal and industrial waste. PCBs have been used in various industrial materials such as transformers, capacitors, heat transfer media and non-carbon copying paper. These groups of chlorinated compounds are now recognized as environmental pollutants as they hardly decompose in the environmental atmosphere after their industrial use and wasting to the environment. They have persistently polluted air, water, soil, plants and terrestrial animals in the global environment. The PCDDs, PCDFs and PCBs can be attributed to human exposure by food intake, drinking water, inhalation of air and dermal contact, and have accumulated in human body because of their lipophilic properties. Some of these congeners are very toxic to animals and the toxicity is variable depending on the animal species. The human health may be affected by the toxic congeners when their accumulation levels attain to certain high concentrations.

Yusho, a mass food poisoning, occurred in Western Japan in 1968 by ingestion of Kanemi rice oil that had been contaminated with PCBs, polychlorinated quaterphenyls (dimers of PCBs), PCDFs, PCDDs and other chlorinated aromatics. As the intakes of these chemicals were estimated in some Yusho patients and the symptoms of the patients were well recorded, toxicities of these chemicals to Yusho patients can be estimated. The toxicity to Yusho patients is helpful to understanding the toxicity of PCDDs, PCDFs and PCBs to the general populations who have polluted with the chemicals.

Environmental pollution of PCDD/PCDFs and PCBs in Japan

Japanese environmental samples have been analyzed for PCDDs, PCDFs and PCBs in recent years. Calculated concentrations of 2,3,7,8-tetra-CDD toxic equivalents (TEQ) in the samples are listed in Table 1. In the case where a person (60 kg body weights) is supposed to inhale 15 m^3 of

Table 1 Concentrations of TEQ from PCDDs, PCDFs and PCBs in Japanese environmental samples

	TEQ level				
	PCDDs	PCDFs	PCBs	Total	Reference
Urban Air	0.04	0.18		0.22 pg/m3	2)
Urban Air, Summer	0.143	0.645	0.098	0.886 pg/m3	3)
Urban Air, Winter	0.350	1.114	0.079	1.543 pg/m3	3)
Indoor Air	0.049	0.148		0.194 pg/m3	4)
Incinerators					
Flue gas	5.5-16	5.0-9.3		11-25 ng/m3*	5)
Flyash	1.3-2.7	0.45-2.6		1.8-5.3 ng/g*	5)
Flue gas	4.9	18	1.46	24.5 ng/m3	6)
Flue gas	26		1.0	27.0 ng/m3	7)
Flyash	5.8		0.16	6.0 ng/g	7)
Drinking water	0.001-0.018		0.003-0.0027	0.021-0.03 fg/ml	8)
Soil	1.1-34	0.6-31	1.2-9.9	2.5-75 pg/g	9)
Sediment	0.0-48		0.0-12.7	0.0-61 pg/g	10)
Fish	0.0-11		0.3-12	0.3-22 pg/g wet	10)
Coastal Fish	0.27	0.60	9.4	10.27 pg/g wet	11)
Marketing Fish	0.10	0.23	0.22	0.55 pg/g wet	11)
Breast Milk	0.36	0.22	0.96	1.54 pg/g wet	12)
Human Adipose	17	11	28	56 pg/g fat	13)

* Geometric Mean-Arithmetic Mean

air every day, personal intakes of TEQ from the air are calculated to be less than 0.4 pg/kg/day. Flue gas from a municipal incinerator is assumed to be dispersed 200,000 times when it reaches to ground surface. TEQ intakes from the flue gas are calculated to be less than 0.04 pg/kg/day in persons living on the ground surface. As a person consumes 1.5 L of water every day, estimated intake of TEQ from the drinking water is less than 0.001 pg/kg/day. Assuming personal daily ingestion of soil is 0.1 g, daily intake of TEQ from the soil is calculated to be less than 0.2 pg/kg/day. As a Japanese consumes 90 g of fish every day, intakes of TEQ from fish are estimated to be 0.45–33 pg/kg/day. It is notable that more than half the TEQ in fish is mostly attributed to PCBs. As a Japanese baby is considered to ingest 150 ml/kg/day of breast milk, intake of TEQ by a baby from breast milk is calculated to be 230 pg/kg/day from the data in Table 1. The TEQ in breast milk is also attributed to PCBs in more than 60%. Intakes of PCDDs, PCDFs and PCBs through food were studied by examining about one hundred kinds of food in Osaka[14,15]. Personal intakes of TEQ from PCDDs, PCDFs and PCBs were estimated to be 40, 135 and 660 pg/day, respectively. In the food

Table 2 Concnetrations of TEQ in Yusho oil, Tissues of Yusho patients and Control serum

	TEQ Factors used	Yusho oil 1 (ppb)	Yusho oil 2 (ppb)	Lipid basis (ppt) Yusho patient Adipose 1977	Yusho patient Blood 1990/91	Control Serum 1991/92
2,3,7,8-Tetra-CDD	1	0	0	0	2.25	3.10
1,2,3,7,8-Penta-CDD	0.5	3.55	3.75	18	3.60	4.58
1,2,3,4,7,8-Hexa-CDD	0.1	1.1	0.57	0	0.29	0.43
1,2,3,6,7,8-Hexa-CDD	0.1	4.2	3.8	32	3.57	3.88
1,2,3,7,8,9-Hexa-CDD	0.1	2.4	2.2	0	0.54	0.83
1,2,3,4,6,7,8-Hepta-CDD	0.01	1.8	1.9	0	0.17	0.46
Octa-CDD	0.001	0.13	0.11	0.46	0.53	1.14
Total PCDDs		13.18	12.33	50.46	10.94	14.41
2,3,7,8-Tetra-CDF	0.1	63	69	8.8	0	0.47
2,3,4,7,8-Penta-CDF	0.5	650	700	1700	120.75	8.70
1,2,3,7,8-Penta-CDF	0.05	14.5	38	2.9	0.08	0.04
1,2,3,4,7,8-Hexa-CDF	0.1	58	120	260	15.25	1.19
1,2,3,6,7,8-Hexa-CDF	0.1	11	23	28	3.44	0.83
2,3,4,6,7,8-Hexa-CDF	0.1	0	0	0	0	0
1,2,3,7,8,9-Hexa-CDF	0.1	17	16	0	0.42	0.34
1,2,3,4,6,7,8-Hepta-CDF	0.01	3.1	2	1.9	0.17	0.09
1,2,3,4,7,8,9-Hepta-CDF	0.01	0.12	0.11	0	0.03	0
Octa-CDF	0.001	0.076	0.076	0	0	0
Total PCDFs		816.80	968.19	2002	140.14	11.64
3,3',4,4'-Tetra-CB	0.0005	5.5	6	0.7	0.01	0.01
3,3',4,4',5-Penta-CB	0.1	53	73	144	4.50	14.15
3,3',4,4',5,5'-Hexa-CB	0.01	0.23	0.31	7.6	1.26	0.92
Total Coplanar PCBs		58.73	79.31	152.30	5.77	15.07
2,3,3',4,4'-Penta-CB	0.0001	2.4	3.2	0.42	0.35	1.00
2,3,4,4',5-Penta-CB	0.0005	0	0	0	1.56	1.38
2,3',4,4',5-Penta-CB	0.0001	2.7	3.7	0.69	1.41	4.23
2',3,4,4',5-Penta-CB	0.0001	0	0	0	0	0.07
2,3,3',4,4',5-Hexa-CB	0.0005	1.35	1.6	24.7	16.69	8.04
2,3,3',4,4',5'-Hexa-CB	0.0005	0	0	0	4.38	1.81
2,3',4,4',5,5'-Hexa-CB	0.00001	0	0	0	0.05	0.08
2,3,3',4,4',5,5'-Hepta-CB	0.0001	0	0	0	0.24	0.09
Total Mono-ortho PCBs		6.45	8.50	25.81	24.68	16.70
2,2',3,3',4,4',5-Hepta-CB	0.0001	0.19	0.21	0	2.49	1.92
2,2',3,4,4',5,5'-Hepta-CB	0.00001	0.018	0.033	0	0.57	0.82
Total Di-ortho PCBs		0.208	0.243	0	3.05	2.74
Total PCBs		65.39	88.05	178.11	33.50	34.51
Total TEQ		895.4	1068.6	2230.2	184.6	60.6

TEQ intake (175 pg/day) from PCDDs and PCDFs, ingestion of fish was responsible for 60% of the exposure from food. Daily TEQ intakes per kg body weight were calculated to be 3 and 11 pg/kg/day from PCDD/PCDFs and PCBs, respectively, body weight being supposed to be 60 kg. Daily TEQ intakes by PCDDs and PCDFs have been estimated in Japan[16], Canada[17], Germany[18] and Netherlands[19], concluding to 1.3, 2, 2 and 1 pg/kg/day, respectively. More than 90% of TEQ intakes were from food and TEQ sources other than food (air, water, soil and others) were accounted for less than 10% as to the total daily intakes. The Japanese TEQ intakes from PCDDs and PCDFs are higher than those in Canada, Germany and Netherlands. TEQ intakes from PCBs were investigated in Netherlands, finding 1.4 pg/kg/day as a median value. The Japanese ingestion of TEQ from PCBs (11 pg/kg/day) is much higher than the intake in Netherlands. The Japanese total TEQ intake (14 pg/kg/day) exceeds the acceptable daily intake or tolerable daily intake (1-10 pg/kg/day) proposed by several national and international organizations[20,21,22].

Yusho incident in relation to PCBs and PCDFs

An epidemic of a strange skin disease similar to chloracne was announced to the public in Fukuoka, Japan in October, 1968. Most common initial symptoms were increased eye discharge and swelling of eyelids, acne-form eruption and follicular accentuation, pigmentation and others. Most of the patients were affected during 1968 and 55% of the patients were concentrated in the 3 months from June to August[23]. All the patients had used Kanemi brand rice oil and the rice oil was produced and shipped by the Kanemi Company on February 5 and 6, 1968 or soon after that. X-ray fluorescence analyses of the rice oil indicated that only the sample produced or shipped in the beginning of February contaminated a large amount of chlorine (maximum 462 ppm) and none of the rice oil shipped in other months was contaminated with more than a trace amount of chlorine. The rice oil samples have been analyzed for PCBs, PCDFs and related compounds as chlorine content, total PCBs, total PCDFs or individual gas chromatographic peaks. Isomer-specific analysis of PCB, PCDFs and PCDDs in the rice oil was carried out by gas chromatography-mass spectrometry in 1989[24]. Obtained concentrations of individual congeners were converted to TEQ concentrations using TEQ factors for PCDD/PCDFs[25] and PCBs[26]. The TEQ values are shown in Table 2. The average concentration of TEQ in the rice oil was found to be 0.98 ppm. A survey of 141 Yusho patients showed that the average consumption of the rice oil was 688 ml in total and 506 ml during the latent period before illness was apparent[27]. Table 3 lists the intakes of rice oil and calculated TEQ amounts. The average daily intake of TEQ was 154 ng/kg/day and the mean latent period was estimated to be 71 days. The smallest daily intake was 28 ng/kg/day during the latent period of 135 days.

Only highly chlorinated congeners of PCBs in the rice oil were retained in the body of Yusho patients. PCB concentrations as high as 76 and 0.2 ppm were measured in the adipose tissue and liver, respectively, in 1968. Only several particular PCDF congeners that have lateral positions (2, 3, 7 and 8) chlorinated retained in the tissues of patients. The highest concentrations observed was 6.9 ppb of 2,3,4,7,8-penta-CDF in the liver in 1969, The highly accumulated PCBs and PCDFs are supposed to decrease the concentrations with biological half-lives of about 4.5 and 2.5 years,

respectively, during the first 10 years after the onset. During the following ten years, decreases of the PCBs and PCDF concentrations were very slowed down with the half-lives of around 10 years. These assumptions were derived from the time course examination of PCB and PCDF levels in the blood of the same Yusho and Yu-cheng patients[28]. Recent TEQ concentrations from PCBs, PCDFs and PCDDs in the blood of Yusho patients are shown in Table 2 with the control levels.

Table 3 Estimated intakes of rice oil and TEQ by Yusho patients

	Rice oil	TEQ
Average total intake per capita	688 ml (195-3375)	0.62 mg (0.18-3.04)
Average intake during latent period	506 ml (121-1934)	0.457 mg (0.11-1.74)
Average daily intake	0.171 ml/kg/day (0.031-0.923)	154 ng/kg/day (28-832)
Smallest intake during latent period	121 ml	0.11 mg
Smallest daily intake during latent period	0.031 ml/kg/day	28 ng/kg/day

TEQs are calculated from 0.98 ppm in the rice oil and 0.92 of oil density.

Clinical features of Yusho patients

The most notable symptoms of Yusho are dermal[29] and ocular[30] lesions such as follicular keratosis, dry skin, comedo formation, acneform eruption, hypersecretion of the meibomian glands and abnormal pigmentation of the conjunctiva. These typical symptoms have diminished gradually during ten years since the onset, while continual subcutaneous cyst formation with secondary infection and squeezing out the cheese-like material from the meibomian glands were still occurring in some of the severe grade patients. Besides the dermal and ocular symptoms, Yusho patients have been suffering from various signs probably caused by the receptor binding and the enzyme induction of retaining PCBs and PCDFs. These signs and changs examined are listed in Table 4 with the time of examination. Most of the signs were observed in early stage of Yusho, while significantly elevated levels of triglyceride, thyroxins and aryl hydrocarbon hydroxylase persisted in Yusho patients for 15-20 years after the exposure to PCBs and PCDFs.

The total number of patients officially registered as Yusho patients was 1862 and deaths among them were 149 by 1990. The number of deaths (120) observed among 1761 patients registered as Yusho by the end of 1983 was compared with the expected number of deaths calculated on the basis of the national death rates[42]. Significant excess mortality was observed for malignant neoplasms at all sites, cancer of the liver and cancer of the lung, trachea and bronchus in male,

while excess mortality for the liver cancer was not significant in female. The excess death from liver cancer was seen in Fukuoka prefecture, while no such excess was seen in Nagasaki prefecture where 550 patients were registered. It seems still too early to draw any firm conclusions from this cancer mortality study.

Table 4 Effects of the Receptor Binding and Enzyme Induction in Yusho

Organ	Sign	Time	Reference
Liver	Smooth surfaced endoplasmic reticulum ↑	1969	31)
Female	Irregular menstural cycle ↑	1970	32)
Teeth	Annomalies in number and shape ↑	1978	33)
Urine	17-Ketosteroids ↑ in male, ↓ in female	1970	34)
Serum	IgA, IgM ↓	1970	35)
Serum	Triglyceride ↑	1973 1988	36) 37)
Serum	Bilirubin ↓	1974	38)
Serum	Ribonuclease ↑	1974	39)
Serum	Thyroxin, Triiodothyronin ↑	1984	40)
Lymphocyte	Aryl hydrocarbon hydroxylase ↑	1985	41)

Risk assessment of dioxins from Yusho

Figure 1 illustrates the intakes of TEQ by Yusho patients and the regulation of TEQ intakes by national and international organizations. The acceptable daily intake (ADI)[20,21] or tolerable daily intake (TDI)[22] for 2,3,7,8-tetra-CDD (1-10 pg/kg/day) were established by the Netherlands, Federal Republic of Germany, Canada, Sweden and World Health Organization, taking 100-1000 times ranges of margin from the no-effect level (NOEL) of 1 ng/kg/day in animal experiments[43]. The evaluating indicator for incinerators in Japan is 100 pg/kg/day[44]. Average intake of TEQ during the latent period of Yusho patients was 154 ng/kg/day and the minimum intake was 28 ng/kg/day. A Yusho limit was estimated to be 0.1 ng/kg/day, because, by the intake of 0.1 ng/kg/day for 60 years of lifetime, the total intake of TEQ eventually attains to the minimum Yusho dose of 0.11 mg.

To compare the regulations and the Yusho intakes, personal intakes of TEQ through various routes are also showing in Figure 1. Direct intakes of TEQ through air, water and soil do not seem to exceed the lowest level of ADI, 1 pg/kg/day, in persons of regular life-style. A general person of the developed countries consumes TEQ through food at the level of 1-3 pg/kg/day, less than the TDI of WHO. However, some Japanese ingested 14 pg/kg day level of TEQ through food, which

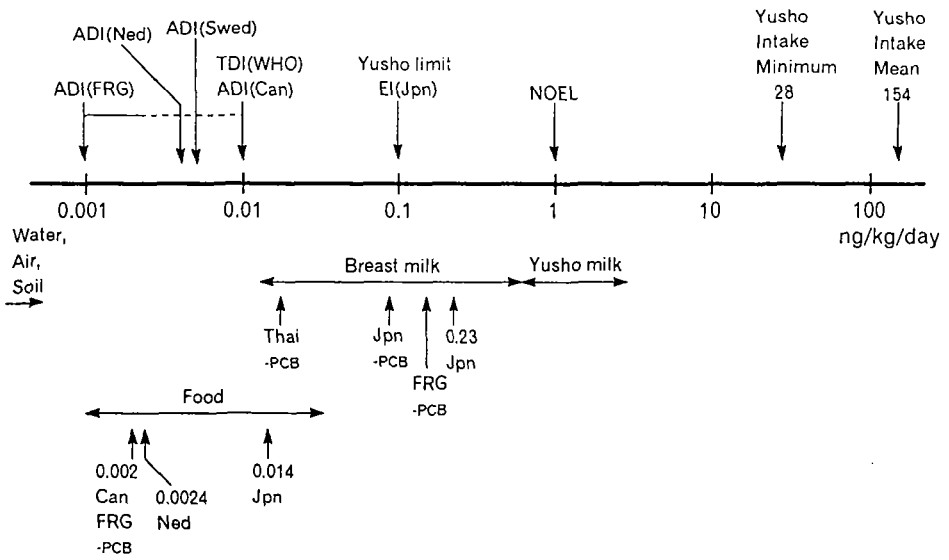

Figure 1 Regulations and Personal Intakes of TEQ

exceeded the highest level of the ADIs. Most parts of the food TEQ were contributed by TEQ of coplanar PCBs. According to the WHO report[45], breast milk-fed babies consumes 18–149 pg/kg/day of TEQ. The values of TEQ, however, were estimated from only the toxicities of PCDDs and PCDFs, not including PCB toxicities. Some Japanese babies ingested high levels of TEQ (100–530 pg/kg/day) through breast milk feeding, more than 60 % being attributed to TEQ of coplanar PCBs. As breast milk from Yusho patients was figured out to contain TEQ up to 22 pg/g wet, a baby would consume high levels of TEQ up to 3.3 ng/kg/day through the breast milk from a Yusho mother, if the baby was nursed with 150 ml/kg/day of the breast milk. In the case where the daily intakes of TEQ by Yusho patients (28 and 154 ng/kg/day) are compared with the daily intakes of general population (1–14 pg/kg/day), there are three or four orders of magnitude differences. However, as the ingestion periods are greatly different between the two groups, 71 and 135 days for Yusho patients and lifelong for general population, the TEQ levels of remaining PCBs, PCDFs and PCDDs in Yusho patients were only 3–100 times higher than those of control persons. When the intakes of nursing babies are compared to those of Yusho patients, the intakes of TEQ by breast milk-fed babies of general population, 530 pg/kg/day at the highest, are only 53 or more times lower than that of Yusho patients, 28 ng/kg/day of the lowest ingestion. Moreover, feeding periods of the toxic chemicals are very close each other in the two groups, several months for babies of general population and from 1 to 5 months for Yusho patients. As the intake of 28 ng/kg/day level was the lowest dose for causing Yusho symptoms in human, the intakes of one or two orders of magnitude lower than this level would originate mild Yusho symptoms, such as the signs mediated by the receptor binding and the enzyme induction, in the baby. In the general population, exposures to high

levels of PCDDs and PCDFs by intra-uterine and via breast milk modulate the hypothalamic-pituitary-thyroid regulation system in human newborns[46].

References

1) Ahlborg, U.G. J. Bellin, B. Birmingham, A.D. Dayan, A. Di Domenico, M. Grenberg, R.D. Kimbrough, R. Koch, C. Rappe, S. Safe, H. Spielmann and J. Vos (1989): Polychlorinated Dibenzo-para-dioxins and Dibenzofurans. Environmental Health Criteria 88, p 1-409. World Health Organization, Geneva.

2) Nakano T., M. Tsuji and T. Okuno (1991): Chlorinated Organic Compounds in the Atmosphere. J. Environ. Chem. 1, 325-332

3) Sugita K., S. Asada, T. Yokochi, M. Ono and T. Okazawa (1993): Polychlorinated Dibenzo-p-dioxins, Dibenzofurans, Co-planar PCBs and Mono-ortho PCBs in Urban Air.Organohalogen Compounds 12, 127-130.

4) Matsueda T., Y. kurokawa, Y. Osaki, H. Hirakawa and T. Iida (1992): Effect of Cigarette Smoking on the Concentration of Polychlorinated Dibenzo-p-dioxins and polychlorinated Dibenzofurans in Indoor Air. J. Environ. Chem. 2, 791-799.

5) Hiraoka M., Y. Takizawa, Y. Masuda, R. Takeshita, M. Tanaka, M. Watanabe, M. Saito and K. Yagome (1991):Overall Report: Studies on Formation Mechanism of Dioxins in Waste Management. Japan Waste Research Foundation 1-312.

6) Miyata, H., O. Aozasa, Y. Mase, S. Ohta, S. Kohno and S. Asada (1993): Real Situation on Emission of PCDDs, PCDFs and Non-ortho Chlorine Substituted Coplanar PCBs via Flue Gas from Urban Waste Incinerators in Japan. Organohalogen Compounds 11, 253-256.

7) Sakai, S., M. Hiraoka. N. Takeda and K. Shiozaki (1993): Coplanar PCBs and PCDDs/PCDFs in Municipal waste Incineration. Chemosphere 27, 233-240.

8) Miyata H., O. Aozasa, S. Ohta, T. Chang and Y. Yasuda (1993): Estimated Daily Intakes of PCDDs, PCDFs and Non-ortho Coplanar PCBs via Drinking water in Japan. Chemosphere 26, 1527-1536.

9) Ohsaki, Y. and T. Matsueda (1994): Levels, Features and a Source of Non-ortho Coplanar Polychlorinated Biphenyl in Soil. Chemosphere 28, 47-56.

10) Environment Agency JAPAN (1993): Chemicals in the Environment. Report on Environmental Survey and Wildlife Monitoring of Chemicals in F.Y. 1990 and 1991. 1-140.

11) Takayama K., H. Miyata, M. Mimura and T. Kashimoto (1991): PCDDs, PCDFs and Coplanar PCBs in Coastal and Marketing Fishes in Japan. Eisei Kagaku 37, 125-131.

12) Matsueda, T., T. Iida, H. Hirakawa, K. Fukamachi and H. Tokiwa (1993): Concentration of PCDDs, PCDFs and Coplanar PCBs in Breast Milk of Yusho patients and Normal Subjects. Fukuoka Acta Med. 84, 263-272.

13) Hirakawa, H., T. Matsueda, T. Iida, K. Fukamachi, K.Takahashi, J. Nagayama and T. Nagata (1991): Coplanar PCBs, PCDFs and PCDDs in the Subcutaneous Adipose Tissue of the Yusho Patients and Normal Control. Fukuoka Acta Med. 82, 275-279.

14) Takayama, K., H. Miyata, O. Aozasa, M.Mimura and T. Kashimoto (1991): Dietary intake of Dioxin-Related Compounds through food in Japan. J. Food Hyg. Soc. Japan 32, 525-532.

15) Miyata, H. (1991): Pollution with Dioxin and Related Compounds of Food and Human Body. J. Environ. Chem. 1, 275-290.

16) Ono, M., Y. Kashima, T. Wakimoto and R. Tatsukawa (1987): Daily intake of PCDDs and PCDFs by Japanese Through Food. Chemosphere 16, 1823-1828.

17) Birmingham, B., A. Gilman, D. Grant, J. Salinen, M. Boddington, B. Thorpe, I. Wile, P. Toft and V. Armstrong (1989): PCDD/PCDF Multimedia Exposure Analysis for the Canadian Population: Detailed Exposure Estimation. Chemosphere 19, 637-642.

18) Beck, H., A. Dross and W. Mather (1992): PCDDs, PCDFs and Related Contaminants in the German Food Supply. Chemosphere 25, 1539-1550.
19) Theelen, R.M.C., A.K.D. Liem, W. Slob and J.H. van Wijnen (1993): Intake of 2,3,7,8 Chlorine Substituted Dioxins, Furans, and Planar PCBs form Food in the Netherlands: Median and Distribution. Chemosphere 27, 1625-1635.
20) Barnes, D.G. (1989): Characterization of the Risks Posed by CDDs and CDFs. Chemosphere 18, 33-39.
21) Ahlborg, U.G. (1992): Risk Assessment of PCDDs and PCDFs in the Nordic Countries. Toxic Substances J. 12, 191-196.
22) Ahlborg, U.G., Kimbrough, R.D. and Yrjänheikki, E.J. (1992): Tolerable Daily Intake of PCDDs and PCDFs. Executive Summary. Toxic Substances J. 12, 101-131.
23) Kuratsune, M. (1989): Yusho, with Reference to Yu-Cheng. In Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Products, R.D. Kimbrough and A.A. Jensen Eds. p 381-400, Elsevier, Amsterdam.
24) Tanabe, S., N. Kannan, T. Wakimoto, R. Tatsukawa, T. Okamoto and Y. Masuda (1989): Isomer-Specific determination and Toxic Evaluation of Potentially Hazardous Coplanar PCBs, Dibenzofurans and Dioxins in the Tissues of "Yusho" PCB Poisoning Victim and in the Causal Oil. Toxicol. Environ. Chem. 24, 215-231.
25) Kutz, F.W., D.P. Bottimore, E.W. Bretthuer and D.N. McNelis (1988): History and Achievements of the NATO/CCMS Pilot Study on International Information Exchange on Dioxins. Chemosphere 17(11), N2-7.
26) Ahlborg, U.G., G.C. Becking, L.S. Birnbaum, A. Brouwer, H.J.G.M. Derks, M. Feeley, G. Golor, A. Hanberg, J.C. Larsen, A.K.D. Liem, S.H. Safe, C. Schlatter, F. Wærn, M. Younes, E. Yrjänheikki (1994): Toxic Equivalency Factors for Dioxin-Like PCBs. Chemosphere 28, 1049-1067.
27) Hayabuchi, H., T. Yoshimura, K. Kuratsune (1979): Consumption of Toxic Rice Oil by 'Yusho' Patients and its Relation to the Clinical Response and Latent Period. Food Cosmet. Toxicol. 17, 455-461.
28) Ryan, J.J., D. Levesque, L.G. Panopio, W.F. Sun, Y. Masuda and H. Kuroki (1993): Elimination of Polychlorinated Dibenzofurans (PCDFs) and Polychlorinated Biphenyls (PCBs) from Human Blood in the Yusho and Yu-cheng Rice Oil Poisonings. Arch. Environ. Contam. Toxicol. 24, 504-512 (1993).
29) Urabe, H. and M. Asahi (1985): Past and Current Dermatological Status of Yusho Patients. Environ. Health Perspect. 59, 11-15.
30) Kohno, T, and Y. Yamana (1979): Ten-year follow-up on ocular manifestations of "Yusho" (Accidental Polychlorinated Biphenyls Poisoning). Fukuoka Acta Med. 70, 181-186.
31) Hirayama, C.,T. Irisa and T. Yamamoto (1969): Fine Structural Change of the Liver in a Patient with Chlorobiphenyls Intoxication. Fukuoka Acta Med. 60, 455-461.
32) Kusuda, M. (1971): Yusho and Female. Studies on Sexual Functions in Female Patients with Rice Oil Poisoning. Sanka to Fujinka (Obstet. Gynecol.) 38, 1063-1072.
33) Fukuyama, H., Y. Anan, A. Akamine and M. Aono (1979): Alteration in Stomatological Findings of Patients with Yusho (PCB Poisoning) in the General Examination. Fukuoka Acta Med. 70, 187-198.
34) Nagai, J., M. Furukawa, A. Tojo and T. Fujimoto (1971): Colorimetric and Gas-Chromatographic Determinations of Urinary 17-Ketosteroids. Survey of Chlorobiphenyls Poisoning Patients by These Methods. Fukuoka Acta Med. 62, 51-65.
35) Shigematsu, N., Y. Norimatsu, T. Ishibashi, M. Yoshida, S. Suetsugu, T. Kawatsu, T. Ikeda, R. Saito, S. Ishimaru, T. Shirakusa, M. Kido, K. Emori and H. Toshimitsu (1971): Clinical and Experimental Studies on Respiratory Involvement in Chlorobiphenyls Poisoning. Fukuoka Acta Med. 62, 150-156.
36) Okumura, M., Y. Masuda and S. Nakamuta (1974): Correlation between Blood PCB and Serum Triglyceride Levels in Patients with PCB Poisoning. Fukuoka Acta Med. 65, 84-87.

37) Hirota, Y., K. Kataoka, S. Tokunaga, T. Hirohata, S. Shinohara and H. Tokiwa (1993): Association between Blood Polychlorinated Biphenyl Concentration and Serum Triglyceride Level in Chronic "Yusho" (Polychlorinated Biphenyl Poisoning) Patients. Occup. Environ. Health 65, 221-225.
38) Hirayama, C., M. Okumura, J. Nagai and Y. Masuda (1974): Hypobilirubinemia in Patients with Polychlorinated Biphenyls Poisoning. Clinica Chimica Acta 55, 97-100.
39) Yamanaka M., K. Akagi, N. Hirao and K. Murai (1975): Abnormality of Serum Enzyme in PCB Poisoning Patients with Special Reference to Ribonuclease. Fukuoka Acta Med. 66, 617-619.
40) Murai , K., K. Okamura, H. Tsuji, E. Kajiwara, H. Watanabe, K. Akagi and M. Fujishima (1987): Thyroid Function in "Yusho" Patients Exposed to Polychlorinated Biphenyls (PCB). Environ. Research 44, 179-187.
41) Nagayama, J., C. Kiyohara, A. Fukuda, Y. Nakamura, T. Hirohata, M. Asahi, T. Yoshimura (1987): A Study of Aryl Hydrocarbon Hydroxylase Activity in Yusho Patients. Fukuoka Acta Med. 78, 301-304.
42) Kuratsune, M., Y. Nakamura, M. Ikeda and T. Hirohata (1987): Analysis of Deaths seen among Patients with Yusho. A Preliminary Report. Chemosphere 16, 2085-2088.
43) Kociba, R.J., D.G. Keyes, J.E. Beyer, R.M. Carreon, C.E. Wade, D. Dittenber, R. Kalnins, I. Frauson, C.N. Park, S. Barnard, R. Hummel and C.G. Humiston (1978): Results of a Two Year Chronic Toxicity and Oncogenicity Study of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TetraCDD) in Rats. Toxicol. Appl. Pharmacol. 46, 279-303.
44) Suzuki, T., T. Goda, R. Takeshita, R. Tatsukawa, T. Okamoto and Y. Masuda (1984): Problems of Dioxins in the Solid Waste Incineration. Report from the Ministry of Health and Welfare, Japan, p 1-16.
45) Yrjänheikki, E. (1989): Levels of PCBs, PCDDs and PCDFs in breast milk. Environmental Health 34, 1-90.
46) Pluim, H.J., J.G. Koppe, K. Olie, J.W. van der Slikke, J.H. Kok, T. Vulsma, D. van Tijin and J.J.M. de Vijlder (1992): Effects of dioxins on thyroid function in newborn babies. Lancet 339, 1303.