The rice oil poisonings: Causal agents and long term effects

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Introduction

Rice oil polychlorinated biphenyl (PCB) poisoning called Yusho occurred in Fukuoka and Nagasaki Prefectures, Japan, in 1968. At that time PCBs were not considered to be very toxic and persistent compounds in Japan and Japanese PCB production was therefore increased until 1970. Yusho was caused by ingestion of rice oil contaminated with Kanechlor-400, a commercial brand of Japanese PCBs. It was later found that the rice oil had been contaminated with not only PCBs but also with polychlorinated dibenzofurans (PCDFs), polychlorinated quaterphenyls (PCQs) and related compounds. Consequently, Yusho was a poisoning by a mixture of PCBs, PCDFs, PCQs and others[1,2]. This paper describes the causal agents of Yusho in the rice oil and their long term health effects to the patients for more than 35 years. The human data will be helpful to understand the real dioxin toxicity to human.

Intake of PCBs and PCDFs

The rice oil was found to contain 5 ppm of PCDFs, about 250 times the concentration (0.02 ppm) expected from the concentration of PCDFs in other unused Kanechlor-400. The marked increase of PCDFs with respect to PCBs in the rice oil could have occurred in the following way. The Kanechlor-400 used as a heat transfer medium for deodorizing rice oil was heated to higher than 200ºC for a long time, and PCBs were gradually converted to PCDFs and PCQs. The PCBs with increased PCDF/PCQ concentrations leaked into the rice oil through a hole of the heating pipe. The contaminated rice oil was further heated at higher than 200ºC under vacuum for purification and degasing. The PCBs and then PCDFs and PCQs, which have higher boiling points, were further concentrated in the rice oil.

A survey of 141 Yusho patients who consumed the rice oil containing 920, 866 and 5 ppm of PCBs, PCQs and PCDFs, respectively, revealed that the average consumption of the rice oil was 688 ml in total and 506 ml during the latent period before illness was apparent. Therefore, the total amounts of PCBs, PCQs and PCDFs ingested by a patient were estimated to be 633, 596 and 3.4 mg, respectively, on average, and the amounts ingested during the latent period were 466, 439 and 2.5 mg, respectively. The smallest amounts ingested by a patient during the latent period were estimated to be 111, 105 and 0.6 mg, respectively. The average concentration of 2,3,7,8-TCDD toxic equivalents (TEQ) in the rice oil was determined to be 0.98 ppm, and the intakes of TEQ by patients were calculated. Table 1 lists the intakes of rice oil and TEQ by a Yusho patient

Table 1 The estimated intakes of rice oil and TEQ by a Yusho patient

Intake	Rice oil	TEQ
Average total intake per capita	688 (195-3375) ml	0.62 (0.18-3.04) mg
Average intake during latent period	506 (121-1,934) ml	0.456 (0.11-1.74) mg
Average daily intake	0.171 (0.031-0.923) ml/kg/day	154 (28-832) ng/kg/day
Smallest intake during the latent period	121 ml	0.11 mg
Smallest daily intake during the latent period	0.031 ml/kg/day	28 ng/kg/day

Mean and range in parentheses of the 141 patients.

The TEQs are calculated by 0.98 ppm in Yusho oil and 0.92 of oil density.

The clinical severity of illness and the blood PCB levels showed a close positive correlation with the total amount of oil consumed but not with the amount of oil consumed per kilogram body weight per day. This might indicate that, during exposure to these highly persistent toxic substances, the level of toxic substances in the patients increased to the level needed for development of the toxic symptoms of Yusho.

The average total intake of TEQ was calculated to be 10 μg/kg, assuming the patient weighed 60 kg. This value was 10 times exceeded the acute LD_{50} of 2,3,7,8-tetraCDD for guinea pigs, 1 μg/kg. The ratios of observed and expected number of deaths were 1.18 for male patients and 0.90 for female patients in 1990.

2,3,4,7,8-PentaCDF significantly induced aromatic hydrocarbon hydroxylase (AHH) and nicotinamide adenine dinucleotide phosphate: quinine oxidoreductase (DT-diaphorase) even at a single dose of 1 μg/kg for rats. Safe and Phil[3] summarized the structure of PCDFs and their toxicity in animals as follows: the AHH-inducing activities of structurally different PCDF congeners were linearly correlated with thymic atrophy, loss in body weight and immunotoxicity induced by the PCDF congeners. Of the PCDF congeners, 2,3,4,7,8-pentaCDF was the most active compounds regarding both enzyme induction and toxicity in animals. Therefore, 2,3,4,7,8-pentaCDF was considered to be the most important etiologic agent for Yusho symptoms. The concentration of 2,3,4,7,8-pentaCDF in the rice oil consumed by the patients was 1350 ppb and the average total intake of the rice oil per person was 688 ml. Thus, the volume of rice oil contained 854 μg of 2,3,4,7,8-pentaCDF. The total intake of this congener was calculated to be 14

μg/kg, assuming the patient weighed 60 kg. This dose exceeded the enzyme-inducing dose of 1 μg/kg body weight in rats by more than 10 times. Of the total TEQ concentrations, 89 and 76 % were considered to be due to the PCDFs in the adipose tissue and blood of Yusho patients, respectively, whereas 76 and 65 %, respectively, of the total toxicity were attributed to a single congener of 2,3,4,7,8-pentaCDF. PCDFs were considered to be the major pathogenic substances in the development of Yusho, because the toxic PCDFs accumulated in the tissues and liver of Yusho patients but not in workers with occupational PCB poisoning[4].
PCQs in the tissue of Yusho patients mainly consisted of hepta, octa and nona chlorinated compounds and showed very broad peaks on their gas chromatograms.. The PCQ concentrations in the tissues and blood of patients were always higher than the corresponding levels in the controls. The levels of PCQs in the blood of control persons were mostly lower than the detection limit of 0.02 ppb. Even though PCQs were actually ingested by the patients with rice oil and retained in their bodies for more than 30 years, the major toxic agents for Yusho have been considered to be PCDFs but not PCQs. PCQs have been found to be much less toxic than PCBs in both rats and monkeys.

Decreases of PCB/PCDF concentrations and health effects

A second rice oil PCB poisoning called Yucheng occurred in Taiwan in 1979, eleven years after the Yusho PCB poisoning. Blood samples of three Yucheng patients and five Yusho patients, who all had been classified into the group with the most severe Yusho symptoms, were continuously examined for PCB and PCDF congeners[5]. Concentration changes of PCB and PCDF congeners in Yusho patients from 1968 to 1999 were estimated from the data of Yusho and Yucheng patients. Estimated levels of total PCBs (75 μg/g lipid) and TEQ (40 ng/g lipid) in Yusho patients just after the incident decreased to 2.3 μg/g lipid and 0.6 ng/g lipid, respectively, 30 years after the onset with half-lives during first fifteen years, 4.2 and 2.5 years, and during the next fifteen years, 9.1 and 7.7 years, respectively (Table 2). At this high level of TEQ exposure, typical Yusho symptoms such as chloracne, pigmentation, cheesy secretion from the meibomian glands of eyes and others were observed in Yusho patients. These Yusho symptoms diminished with time as the level of TEQ gradually decreased down to 0.6 ng/g lipid. Disorder of serum levels of triglyceride, thyroxin and immunoglobulin and higher induction of AHH in lymphocyte chronically persisted in Yusho patients for 20 years and these enzymatic and hormonal disorders are still observed at present time 30 years after the onset. Taiwan Yucheng children prenatally exposed to PCBs and PCDFs had poorer cognitive development at age of 4-7 years. The body height and penis length of Yucheng children were lower than those of controls at age of 11-14 years. These changes might be caused by the estrogenic or antiandrogenic effects of the PCBs/PCDFs in Yucheng children.

Table 2 Changes of PCB and PCDF concentrations in Yusho patients and accompanied symptoms for 30 years

	1968 Outbreak of Yusho	----------→	1999 30 years after
	Concentration	Half-life	Concentration
Total PCBs	**75,000 ppb/lipid**		**2,300 ppb/lipid**
2,2',4,4',5,5'-Hexa-CB	**12,000 ppb/lipid**	4.2 year 9.1 year	**370 ppb/lipid**
2,3,4,7,8-Penta-CDF	**60,000 ppt/lipid**	2.9 year 7.7 year	**800 ppt/lipid**
TEQ	**40,000 ppt/lipid**	(4.5 year)	**600 ppt/lipid**
Acneiform eruption **Dermal pigmentation**	**Gradually recovered with a lapse of several years**		
Increased eye discharge **High serum triglyceride level** **High serum thyroxine level** **Immunoglobulin disorder**	**Persistently maintained for 30 years**		

Blood samples of 83 Yusho patients were examined in 1995 for PCB and TEQ levels, means (ranges) being 0.8 (0.09-5.2) μg/g lipid and 0.16 (0.01-1.02) ng/g lipid, respectively. Blood samples of 152 Fukuoka residents were examined in 1999 for PCBs and TEQ concentrations[6]. Their mean levels and ranges were 0.4, 0.06-1.7 μg/g lipid and 28, 9.2-100 pg/g lipid, respectively. Mean values of PCBs and TEQ in Yusho patients were only 2 and 6 times higher than those in control persons, respectively, in 1999. Concentration ratios of PCBs/TEQ were 5000 in Yusho patients and 14000 in control persons. Yusho patients, still showing elevated levels of the persistent PCDFs and PCBs, continue to suffer from enzyme and/or hormone mediated symptoms after more than 35 years.

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