HUMAN EXPERIENCE; YUSHO AND YUCHENG

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The Yusho/Yucheng session describes and discusses the behavior of very toxic and persistent PCBs/PCDFs in the bodies of Yusho and Yucheng patients for about 30 years, their causative and typical illness like chloracne and pigmentation, the enzyme and/or hormone mediated severe health effects in the patients, and the serious health effects on the offspring of exposed patients.

Two mass-food poisonings called Yusho and Yucheng occurred in Northern Kyushu, Japan in 1968 and Central Taiwan, Republic of China in 1979, respectively, and officially approved patients were counted for more than 1870 and 2000, respectively. Yusho and Yucheng patients steadily consumed the particular rice oil for up to about 210 and 260 days, respectively, and average latent periods before the typical illness became apparent were estimated as 71 and 80 days, respectively. According to the survey on 141 Yusho patients and 98 Yucheng patients, average total intake per capita of PCBs, PCDFs and PCQs were estimated to be 633, 3.4 and 596 mg, respectively for the Yusho patients and 973, 3.84 and 490 mg, respectively, for the Yucheng patients. Average total intakes of TEQ (toxic equivalent quantity for dioxin), calculated from the concentrations of PCDF/PCB congeners, are estimated to be 0.62 mg in a Yusho patient and 0.27 mg in a Yucheng patient. Two groups of patients with Yusho or Yucheng ingested similar levels of dioxin toxicants and showed severe typical symptoms like acneiform eruption, dermal pigmentation, increased eye discharge and others just after the intoxication.

Blood samples from 5 Yusho patients and 3 Yucheng patients were collected several times from 1982 to 1998 and from 1980 to 1995, respectively, and analyzed for PCB and PCDF congeners. Fat base concentration of 2,3,4,7,8-penta-CDF in the Yusho patients, which were responsible for about 70% of the dioxin toxicity, are estimated to be decreased from 60 ppb in 1969 to 0.8 ppb in 1997 with the median half-life of 2.9 years in the first 15 years after the onset and 7.7 years in the next stage of 15 years. TEQ concentration in the Yusho patients just after the onset was calculated to be 40 ppb (fat base) from the concentration of 2,3,4,7,8-penta-CDF. This high TEQ concentration was gradually decreased to 0.6 ppb during 30 years with biological half-life being estimated to be 4.5 years. Fat base concentrations of total PCBs in the blood of Yusho patients are estimated to be decreased from 75 ppm just after the onset to 2.3 ppm after passage of 30 years. Typical Yusho symptoms of acneiform eruption, dermal pigmentation and increased eye discharge were very gradually recovered with lapse of ten years. However, enzyme and/or hormone mediated sign of high serum triglyceride, high serum thyroxin, immunoglobulin disorder and others are persistently maintained for 30 years.

The total number of patients officially registered as suffering from Yusho by March 31, 1990 was 1870. Of these, 1815 patients who registered by March 31, 1983 were investigated, and a total of 292 deaths, 177 males and 115 females was identified during the 28-year follow-up. For deaths from cancer at all sites, a significantly increased mortality was seen in males but not in females.

Neither a significant increased nor decreased mortality was seen for cancer of the esophagus, stomach, rectum and colon, lung, pancreas, breast, and uterus, or for leukemia. The risk of liver cancer in males were five times higher than that of the general population in the first three calendar periods, however, the risk had been decreased down to 2.93 times in the calendar period between 1968 and 1996. The risk of liver cancer in females followed the same trend as that in males, though they are not significant.

Taiwan Yucheng ("oil-disease") cohort includes approximately 2000 Taiwanese people exposed to PCBs and their heat-degradation products (most significantly PCDFs) from the ingestion of contaminated rice oil in 1979. Exposed Yucheng people had initial serum levels estimated to be higher than 20,000 ppb lipid base for PCBs and 40,000 ppt lipid base for PCDFs. Fourteen years after the exposure, the Yucheng female adults had serum levels of PCDF up to two hundred times as high as found in the unexposed, closely matched controls, and serum levels of PCBs up to more than ten times the control subjects. Lactation by breast-feeding reduced the serum levels in the Yucheng mothers, but increased serum levels in their children. This level of exposure was similar to the level in Japan Yusho cohort, except that the levels of toxicants in the contaminated oil were lower in Taiwan, and the duration of exposure was much longer.

The Yucheng cohort exposed as adults was found to have increased mortality secondary to chronic liver diseases and cirrhosis, but similar rate of liver cancer as compared to the national death using standardized mortality ratio 12 year after the exposure. A telephone health survey was conducted 14 years after the exposure, which showed that Yucheng men reported increased prevalence of having skin allergies, chloracne, headache, spine and joint diseases, and goiter. Yucheng women reported increased prevalence of having skin allergies, chloracne, headache, anemia, and goiter. These findings were to some extent similar to those from other exposed populations. Reproductive history of the women was compared with unexposed controls in a retrospective study on Yucheng cohort. Among Yucheng women, 4.2% reported a stillbirth since 1979, as compared to 1.7% in unexposed controls ($P=0.068$). Sex ratio in the offspring of Yucheng mothers was not different from the unexposed population. A recent follow-up study on sex ratio in offspring of Yucheng people confirmed unchanged sex ratio in offspring born to exposed women, but found reduced sex ratio in those born to exposed men. In addition, males exposed before age of 19 years had more significantly affected sex ratio in their offspring.

Children born to Yucheng mothers were affected through intrauterine exposure to PCBs/PCDFs. In a portion of Yucheng children, additional exposure from breast-feeding was noted. More Yucheng women reported that one of their offspring had died during childhood (10.2% vs. 6.1%, $P<0.05$). This is similar to the earlier report that of the 39 Yucheng babies in utero during the time the mothers ingested the contaminated oil, 8 died in the first few years of life, mostly from perinatal conditions and respiratory infections. Children of Yucheng women were born growth retarded, with dysmorphic physical findings, and delayed cognitive development as compared with unexposed children. The dysmorphic features included cola-colored hyperpigmented skin, hyperpigmented oral mucosa, chloracne, Meibomian gland swelling, natal teeth and fragile teeth, and deformed and pigmented nails. Children born to the cohort after the initial exposure have been followed from birth to the present day. From 4 to 11 years of age, Yucheng children had reduced intelligence quotients compared to the unexposed controls. Children born up to 6 years after their mothers were exposed were as affected as children born within the first year, when compared at the same ages. Throughout follow-up, the exposed children scored higher on the

Child Behavior Checklist scales and the Rutter Child Behavior Scale A, indicating that these children had increased problems with behavior. The differences in IQ between exposed children and controls remained stable as the children aged, but the differences in behavioral problems tended to decline once the children reached age 13 years. In a recent reanalysis of tooth findings in Yucheng children, 13% girls and 6% boys had neonatal teeth as reported by parents, and none in the control group. Congenitally missed teeth (29% vs. 3%) and rotated teeth (19% vs. 3%) were significantly increased in the exposed group. The numbers of teeth with developmental defects, such as fusion, microdontia, peg teeth, enamel hypoplasia, and impaction, were also greater in exposed than in control group ($p<0.1$). Yucheng children had fewer deciduous teeth, and more permanent teeth than controls at the age of 9 and 10 years. This might have resulted from earlier eruption and utilization, or weaker structure, of deciduous teeth. In their age 8-14, Yucheng children had increased nail deformities. The main nail findings were transverse coarse grooves and irregularly concaved depression in approximately one quarter of Yucheng children, with predilection for thumbs, followed by big toes and other fingers. Those children born closer to the mothers' intoxication had more nail deformities than those born later. The Yucheng children not only had increased respiratory infections reported by parents, but also increased chronic otitis media compared to the matched controls by examination in 1993. In regards to endocrine disruption in the transplacentally and lactationally exposed subjects, Yucheng adolescent males had decreased capacity to understand spatial relationships as compared to their long-term closely matched males control subjects. Possibility of loss in male advantage in visuospatial capability was suspected. No differences were identified when the exposed and unexposed females were compared. In prenatally exposed young men who had reached sexual maturity, sperm analysis showed increased abnormal morphology, reduced motility, and reduced capability of penetrating hamster oocytes.

In this review, it is clearly shown that exposure to PCBs/PCDFs caused prominent health effects in several outcome measures in both directly exposed and transplacentally exposed people. Those exposed perinatally are probably most susceptible to the toxic effects of these persistent organic pollutants.