REVIEW ARTICLE

Yusho: 43 years later

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Abstract The aim of the present study is to describe recent issues with Yusho disease in Japan, describe the state of dioxin accumulation and the intake of dioxin via food in Japan, and introduce the Japan Environment and Children’s Study. Yusho disease manifested in western Japan in 1968. The causes of Yusho are believed to be dioxin-related compounds, mainly polychlorinated biphenyls (PCBs) and polychlorinated dibenzofurans (PCDFs), via the ingestion of rice oil produced in February 1968. As of March 31, 2011, there were 1961 registered Yusho cases, but of these 539 are deceased. A retrospective cohort study on registered Yusho cases reported that the standardized mortality ratios (SMRs) for the major causes of death were not significantly elevated, with the exception of all-cancer (SMR = 1.26; 95% confidence interval [CI]: 1.03–1.53) and lung cancer mortality (SMR = 1.56; 95% CI: 1.03–2.27) in males. The results of the Yusho mortality study show that the SMR for liver cancer in males tends to decrease over time. In 2011, the Ministry of the Environment of Japan reported that the average concentration of dioxins in the blood (2002–2010) of the Japanese people was 19 pg-TEQ/g-fat, demonstrating a range of 0.10–130 pg-TEQ/g-fat, and that the average dioxin intake from food (2002–2010) was 0.82 pg-TEQ/kg-body weight/day, demonstrating a range of 0.031–6.2 pg-TEQ/kg-body weight/day according to 2006 WHO TEFs. The Japan Environment and Children’s Study Project was launched in 2011 and is supported by the Ministry of the Environment of Japan. In this project, 100,000 mother and child pairs will be recruited over 3 years from designated study areas. Follow-up examinations will be carried out from pregnancy until the children are 13 years of age (a so-called birth-cohort study). This project will be implemented by the National Center at the National Institute for Environmental Studies and is supported by the Medical Support Center at the National Center for Child Health and Development. Field operations will be performed at 15 designated regional centers nationwide.

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Introduction

The aim of the present study is to describe recent issues with Yusho disease in Japan, describe the state of dioxin accumulation and the intake of dioxin via food in Japan, and introduce the Japan Environment and Children’s Study.

History of Yusho

A strange disease was first reported on October 10, 1968 in western Japan, even though several patients with peculiar symptoms had been recognized by alert clinicians several months prior [1–3]. This strange disease—characterized by acne-like eruptions, pigmentation of the skin, and eye discharge—was named Yusho (“oil disease”) [2,4]. At that time, no causal agents were suggested by either the health authorities or other related professionals.

Later, the Yusho Study Group was established to clarify the causal factors of Yusho and establish treatment methods for these patients. The Yusho Study Group was divided into three subgroups: clinical, chemical, and epidemiologic [1,2].

Through intensive effort by the subgroup members (clinicians, epidemiologists, toxicologists, and chemists), the causal agent was determined to be polychlorinated biphenyls (PCBs) within 1 month after the episode [1,2]. The epidemiologic study subgroup concluded that Yusho was caused by the ingestion of a specific rice oil that was produced in early February 1968 [2,3,5]. The rice oil was contaminated with PCBs (commercial name: Kanechlor 400), which were used as a trans-heater in the production of rice oil [2] (Fig. 1).

This conclusion, however, was questioned regarding the following points [2,3]:

1) In 1971, Dr. Risebrough asked Prof. Kuratsune whether Yusho was caused by PCBs alone or in combination with polychlorinated dibenzo-furans (PCDFs) or polychlorinated dibenzodioxins (PCDDs).
2) No dermatological lesions similar to those observed in human beings could be shown to be caused by pure PCBs (Kanechlor 400) in animal experiments.
3) Yusho patients showed severe clinical symptoms even though their blood PCB levels were rather low. In addition, workers exposed to PCBs showed almost no clinical symptoms even though their blood PCB levels were rather high.

In the three year period from 1975–1977, a significant amount of PCDF was detected in the toxic rice oil consumed by Yusho patients, as well as in their tissues. A further investigation revealed that the most important causal agents for Yusho were PCDFs in combination with PCBs [2,3].

In 1990, the Japanese Government classified coplanar PCBs, PCDFs, and PCDDs as a group of dioxin-like compounds (Fig. 2).

The present situation of Yusho

As of March 31, 2011, there were 1961 registered Yusho cases; of these, 539 are deceased.
Mortality of Yusho patients

In order to determine if cancer mortality among Yusho patients has increased or not, a retrospective cohort study was conducted on the 1918 registered Yusho patients in 2007 [9]. By the end of 2007, of these 1918 registered Yusho patients, 1383 alive patients (72.1%) and 502 deceased patients (26.2%) were confirmed by the official residence records. No information could be obtained about 33 cases (1.7%). Record linkage was carried out using the government death registry for the period from 1968–2007, and a file on deceased Yusho patients stating the underlying cause of death of each case was obtained. Standardized mortality ratios (SMRs) were calculated using national mortality data on age, sex, and year of death as reference data. Although SMRs for liver cancer have been elevated for the past 30 years, SMRs for liver cancer were slightly elevated in both males (SMR = 1.67; 95% confidence interval [CI]: 0.99–2.63) and females (SMR = 1.87; 95% CI: 0.81–3.69), but these results were not statistically significant. Among males, the SMRs for all types of cancer (SMR = 1.26; 95% CI: 1.03–1.53) and lung cancer (SMR = 1.56; 95% CI: 1.03–2.27) were increased and statistically significant, but not among females as presented in Table 1. The results of the mortality study on Yusho patients show that the SMR for all liver cancers among males had a tendency to decrease over time. This interpretation, however, is unclear regarding the carcinogenetic effects due to exposure to dioxin-like compounds. The SMR for male lung cancer obtained here might have been influenced by the smoking habits of the Yusho patients. However, the difference between in the smoking rates of the Yusho patients (39.5%; derived from the first fact-finding survey of Yusho patients in 2008) and the general population (36.8%; derived from the National Health and Nutrition Survey in 2008) are not especially large. Therefore, the confounding effects of smoking on the SMRs of male lung cancer would be insignificant; therefore, detailed analysis of the effects of smoking as a confounding factor is needed. The results shown above are almost similar to the published data and are based on the data on 1664 registered Yusho patients as of 2007 [11].

Further issues to be clarified

Many studies have been carried out, and the results of these studies have been published in scientific journals; however, the following issues need to be clarified further.

First, the treatment of Yusho patients should be further examined in order to mitigate the symptoms and signs that patients currently face, such as reducing PCB and PCDF levels in blood. Recently, clinical trials have been planned and conducted in order to examine the effects of using traditional medicine to treat Yusho patients.

Second, it is crucial to investigate the hazardous effects of dioxin-related compounds in the second generation of Yusho patients. Any information obtained regarding the second generation would be calculable, although practical difficulties obtaining, such information, are anticipated due to ethical and privacy problems.

Third, it would be helpful to investigate past findings (e.g., sex ratio at birth among babies born to Yusho mothers, evaluation of the subjective symptoms reported by Yusho patients) by analyzing the available data accumulated by the Yusho Study Group, even though available data are limited. One of the data sources would be the following data set. In 2008, the Ministry of Health, Labor, and Welfare of Japan carried out the first fact-finding survey of all of the registered Yusho patients in order to improve Yusho studies and provide better health care. The targeted participants were all registered Yusho patients as of March 2008. All eligible Yusho patients were reached by local government authorities in order to obtain consent to participate in this survey. The participants were asked to fill out a questionnaire (61 pages) that was prepared by the planning committee and to participate, with informed consent, in a medical examination conducted by the Yusho Study Group. The questionnaire included questions on personal and family demographics, medical history, life style, health and mental status, health status of their children and grandchildren, etc. [12].

Dioxin levels in Japan

The Office of Environmental Risk Assessment at the Ministry of the Environment of Japan carried out a project called “Survey on the Accumulation of Dioxins and Other Chemical Compounds in Humans” from 2002–2010. The objectives of this survey were to obtain an overview of the accumulation of dioxins in the Japanese people and its chronological changes in order to determine the intake

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Standardized mortality ratios (SMRs) according to selected causes of death of Yusho patients.</th>
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</thead>
<tbody>
<tr>
<td><strong>SMRs in Males</strong></td>
<td></td>
</tr>
<tr>
<td>Cause of death</td>
<td>Obs</td>
</tr>
<tr>
<td>All causes</td>
<td>295</td>
</tr>
<tr>
<td>All cancers</td>
<td>106</td>
</tr>
<tr>
<td>Stomach</td>
<td>21</td>
</tr>
<tr>
<td>Liver</td>
<td>18</td>
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<tr>
<td>Lung</td>
<td>27</td>
</tr>
<tr>
<td>HD</td>
<td>41</td>
</tr>
<tr>
<td>CVD</td>
<td>38</td>
</tr>
<tr>
<td>DM</td>
<td>1</td>
</tr>
<tr>
<td><strong>SMRs in Females</strong></td>
<td></td>
</tr>
<tr>
<td>Cause of death</td>
<td>Obs</td>
</tr>
<tr>
<td>All causes</td>
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</tr>
<tr>
<td>All cancers</td>
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</tr>
<tr>
<td>Stomach</td>
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</tr>
<tr>
<td>Liver</td>
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</tr>
<tr>
<td>Lung</td>
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<td>HD</td>
<td>44</td>
</tr>
<tr>
<td>CVD</td>
<td>34</td>
</tr>
<tr>
<td>DM</td>
<td>2</td>
</tr>
</tbody>
</table>

Adapted from Reference 9.
level of dioxins via food and the primary source of dioxins that enter the human body. A summary report appeared on the homepage [13] of the Ministry of the Environment of Japan. For the nationwide survey, the entire country was divided into five survey regions, and one prefecture was selected from each region for a particular year. Three areas (urban, agricultural, and fishery) were selected within each prefecture and designated as the survey areas. Residents aged 15–70 years were recruited, blood samples were collected, the level of dioxins was measured, and a general health check-up and a dietary survey was conducted (a duplicate-portion study for 3 days). A follow-up survey on the same residents was conducted in order to evaluate chronological trends in dioxin accumulation in the residents of designated cities and towns from 2002–2010.

The results show that among 2264 people, the average concentration of dioxins in the blood (over the 9-year survey period) was 19 pg-TEQ/g-fat, demonstrating a range of 0.10–130 pg-TEQ/g-fat according to 2006 WHO TEFs [13]. These results are similar to those obtained by other reported surveys that have been conducted in Japan [13].

The results of the survey further revealed that blood dioxin concentrations were significantly higher at fisheries than urban or agricultural areas, and the blood concentrations in the latter two areas were similar. Some differences were suggested to be present among the five surveyed regions.

Among 625 people, the average dioxin intake from food (over the 9-year survey period) was 0.82 pg-TEQ/kg-body weight/day, demonstrating a range of 0.031–6.2 pg-TEQ/kg-body weight/day, according to 2006 WHO TEFs. Furthermore, 11 people were found to exceed the tolerable daily intake (TDI) of 4 pg-TEQ/kg-body weight/day according to 2006 WHO TEFs.

The follow-up survey conducted from 2002–2007 on the participants who also participated in the previous survey reported that blood dioxin concentrations remained at nearly the same levels.

**Japan Environment and Children’s Study**

Even though a lot of evidence on environmental pollution caused by many chemical substances, such as persistent organic pollutants (POPs), has been accumulated, health effects due to chemical exposure, especially in children, still remain uncertain. That’s why in January 2011 the Ministry of the Environment of Japan launched the Japan Environment and Children’s Study (JECS) to clarify the relationship between chemical exposure during the fetal and infant stages and adverse health effects in children. This study is based on 6-year preparation procedures by the Ministry of the Environment of Japan [14]. Details can be found on the JECS website [14]. One hundred thousand mother-child pairs will be recruited over a period of 3 years from designated study areas. Follow-up examinations will be carried out for 13 years after pregnancy (so-called birth cohort study). This project will be implemented by the National Center at the National Institute for Environmental Studies and supported by the Medical Support Center at the National Center for Child Health and Development. Field operations will be performed at 15 designated regional centers nationwide.

**Comments**

It should be noted that research in the field of food and drug safety assessment/management is performed under the circumstances of limited scientific evidence. Tragic episodes, such as Yusho (occurred in Japan in 1968) and Yucheng (occurred in Taiwan in 1979), should be carefully observed, followed, and analyzed in order to develop a healthy society and provide better healthcare to the victims.

Finally, we should remember the saying by Confucius: “When you know a thing, to hold that you know it; and when you do not know a thing, to allow that you do not know it; this is knowledge.”

**References**