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Review

Yusho and its latest findings—A review in studies conducted by the Yusho Group

Chikage Mitoma [a,*], Hiroshi Uchi [b], Kiyomi Tsukimori [c], Hideyuki Yamada [d], Manabu Akahane [e], Tomoaki Imamura [e], Atsushi Utani [f], Masutaka Furue [a,b]

[a] Research and Clinical Center for Yusho and Dioxin, Kyushu University Hospital, Fukuoka, Japan
[b] Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[c] Department of Obstetrics, Fukuoka Children's Hospital, Fukuoka, Japan
[d] Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka, Japan
[e] Health Management and Policy, Department of Public Health, School of Medicine, Nara Medical University, Nara, Japan
[f] Department of Dermatology, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan

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ABSTRACT

The Yusho incident is an unprecedented mass food poisoning that occurred in Japan in 1968. It was caused by the ingestion of rice bran oil contaminated with polychlorinated biphenyls (PCBs) and various dioxins and dioxin-like compounds, such as polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs). The victims of Yusho have suffered from characteristic skin manifestations associated with systemic, ophthalmological, and mucosal symptoms for a long period of time. The Study Group of Yusho (the Yusho Group) has been conducting annual medical check-ups on Yusho victims for more than 45 years. Since 2002, when concentrations of dioxins in the blood of Yusho patients started to be measured, the pharmacokinetics of dioxins, relationship between blood levels of dioxins and symptoms/signs in patients directly exposed to dioxins, and the adverse effects on the next generation have become dramatically clear. Herein we review recent findings of studies conducted by the Yusho Group to evaluate chronic dioxin-induced toxicity to the next generation as well as Yusho patients in comparison with a similar food mass poisoning, the Yucheng incident. Additionally, we summarized basic studies carried out by the Yusho Group to re-evaluate the mechanisms of dioxin toxicities in experimental models and various functions of the aryl hydrocarbon receptor (AhR), known as the dioxin receptor, pathway.

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* Corresponding author at: Research and Clinical Center for Yusho and Dioxin, Kyushu University Hospital, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan.
E-mail address: mchikage@dermatol.med.kyushu-u.ac.jp (C. Mitoma).

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1. Introduction

In 1968, an unprecedented mass food poisoning involving approximately 1900 individuals occurred in the west of Japan (Kuratsune et al., 1971). This incident is called Yusho, which means oil disease in Japanese, because it was caused by the ingestion of rice bran oil contaminated with Kanechlor-400, a Japanese commercial brand of polychlorinated biphenyls (PCBs) that was used in the process of refining the oil. It was later found that the oil was contaminated not only with PCBs but also with various dioxins and dioxin-like compounds (hereafter simply referred to as dioxins): polychlorinated quarterphenyls (PCQs), polychlorinated dibenzo-*p*-dioxins (PCDDs), and polychlorinated dibenzofurans (PCDFs) generated by heat denaturation of PCBs (Masuda, 1994). Dioxins, in general are extremely lipophilic and biologically stable in the body (Van den Berg et al., 1994); therefore, upon entering the body, they persist in adipose tissue for a long time and can lead to the development of long-term symptoms. After the Yusho incident, in 1979, a similar mass food poisoning event caused by the ingestion of cooking oil contaminated with PCBs and dioxins, Yucheng (oil disease in Chinese), occurred in central Taiwan (Chen et al., 1981).

Since the outbreak of Yusho, the Study Group of Yusho (the Yusho Group) has been conducting annual medical check-ups on Yusho victims. At the time of the incident, characteristic objective symptoms: skin symptoms (comedones, acneiform eruptions, and dark-brownish pigmentation), ophthalmological symptoms (increased cheese-like discharge from the meibomian glands, pigmentation of the conjunctiva, and swelling of the upper eyelids), and oral manifestations (pigmentation of gingiva), were observed in the majority of patients (Goto and Higuchi, 1969). Additionally, the patients suffered from nonspecific symptoms (Kuratsune et al., 1971; Shigematsu et al., 1978), such as general fatigue, headache, numbness in the limbs, cough, and sputa. Some of the babies who were exposed to dioxins in utero exhibited diffuse greyish dark-brown pigmented skin, called foetal Yusho disease (FYD) or foetal PCB syndrome (Kuratsune et al., 1971; Yamashita and Hayashi, 1985).

The initial diagnostic criteria of Yusho published in 1968 were as follows: (1) proven history of ingestion of contaminated rice bran oil, (2) prominent dermatological, ophthalmological, and mucosal signs, and (3) several nonspecific general symptoms and signs (Furue et al., 2005). Later, PCBs were detected in the subcutaneous adipose tissue (Masuda et al., 1974a) and blood of Yusho patients (Masuda et al., 1974b). The gas chromatogram pattern of PCBs in the blood of patients showed a characteristic pattern, A or B pattern, which was quite different than that in the blood of people unaffected with Yusho (Masuda et al., 1974b). In 1972, the levels and patterns of PCBs in blood were added to the diagnostic criteria, and in 1973, blood levels of PCBs started to be measured in annual medical check-ups (Furue et al., 2005). In 1981, the blood concentration of PCQ (dimers of PCBs) was added to the diagnostic criteria (Takamatsu et al., 1984).

From 1975 to 1977, high levels of PCDFs were detected in the tissues of Yusho patients as well as in the contaminated rice oil (Nagayama et al., 1976, 1977). In the 1990s, the relative toxicities of individual halogenated aromatics to TCDD, the most toxic halogenated aromatic, namely, toxic equivalency factors (TEFs), had been determined (Safe, 1990). The toxic equivalent (TEQ), which is calculated by multiplying the levels of individual congeners by TEF (Van den Berg et al., 2006), can be used for hazard and risk assessment of dioxin mixtures in Yusho patients. The relative contribution of PCDF congeners to the total TEQ in the contaminated rice oil was 77% (Yao et al., 2002). The most important compound causing the symptoms of Yusho (Masuda and Yoshimura, 1984), 2,3,4,7,8-penta-chlorodibenzofuran (2,3,4,7,8-PeCDF), the latest TEF of which was estimated to be 0.3 (Van den Berg et al., 2006), was shown to contribute 58% to the total TEQ in the oil (Yao et al., 2002). The concentration of 2,3,4,7,8-PeCDF in blood, however, had not been included in the diagnostic criteria because of the technical difficulty of its measurement. Subsequently, a solvent-cut large-volume injection system with high-resolution gas chromatography/high-resolution mass spectrometry made it possible to determine the concentration of PCDDs, PCDFs, and non-*ortho*-coplanar PCBs using a blood sample of just 5 g with satisfactory accuracy and reproducibility (Iida and Todaka, 2003). In 2004, the blood level of 2,3,4,7,8-PeCDF was adopted for a new criterion for certifying Yusho patients (Table 1). Later, it was

Table 1
Diagnostic criteria for Yusho (2004).

The diagnostic criteria for Yusho have been revised according to some changes in the symptoms and signs, as well as advances in analytical techniques. The diagnostic criteria for Yusho were revised on October 26, 1972. A supplement was added to the diagnostic criteria on June 14, 1976, and the concentration of PCQs in the blood was added to the diagnostic criteria on June 16, 1981. The concentration of 2,3,4,7,8-penta-chlorodibenzofuran (2,3,4,7,8-PeCDF) was added to the diagnostic criteria on September 29, 2004.

Conditions of the incident
- Proof that Kanemi® rice bran oil contaminated with PCBs was ingested.
- There are also some cases in which PCB is transferred from mothers with Yusho to their children.
- Familial occurrence is also seen in many cases.

Important manifestations
1. Acneiform eruptions
Black comedones seen on the face, buttocks, and other intertriginous sites; comedones with inflammatory manifestations; and subcutaneous cysts with atheroma-like contents that tend to suppurate.
2. Pigmentation
Pigmentation of the face, palpebral conjunctivae, and nails of both the fingers and the toes (including babies).
3. Hypersecretion by the meibomian glands.
4. Unusual composition and concentration of PCBs in the blood.
5. Unusual concentration of PCQs in the blood (reference 1).
6. Unusual concentration of 2,3,4,7,8-PeCDF in the blood (reference 2).

Symptoms and signs
1. Subjective symptoms
- A feeling of lassitude
- A feeling of heaviness in the head or headache
- Paresthesia of the limbs (abnormal sensation)
- Increased eye discharge
- Cough and sputum
- Inconstant abdominal pain
- Altered menstruation

2. Objective manifestations
- Manifestations of bronchitis
- Deformation of the nails
- Bursitis
- Increased neutral fat in the serum
- Serum γ-glutamyl transpeptidase (γ-GTP)
- Decrease of serum bilirubin
- Neonatal small-for-date baby
- Growth retardation and dental abnormality (retarded eruption of permanent teeth)

Reference 1.
The following conclusions have been made in regard to the concentration of PCQs in the blood:
1) ≥0.1 ppb: an abnormally high concentration
2) 0.03 to 0.09 ppb: the boundary between high and normal concentrations
3) ≤0.02 ppb (detection limit): normal concentration

Reference 2.
The following conclusions have been made in regard to the concentration of 2,3,4,7,8-PeCDF in the blood:
1) ≥50 pg/g lipids: an abnormally high concentration
2) 30 to 50 pg/g lipids: slightly high concentration
3) ≤30 pg/g lipids: normal concentration

Both age and sex of patients should also be considered.

Notes:
1. With reference to the above conditions of the incident, symptoms, and manifestations, and taking into account the age of the examinees and the temporal progress of their illness, a diagnosis is comprehensively made.
2. These diagnostic criteria are to be used to determine whether a patient is affected by Yusho, but they do not necessarily relate to its severity.
3. In regard to the abnormal properties of PCBs and the concentrations of PCBs and 2,3,4,7,8-PeCDF in the blood, regional differences as well as the patient's occupation should also be considered.
4. Measurements should be performed by inspection agencies recognized by the Study Group of Yusho, at which quality control is carried out.