Excretion of Causative PCDFs Congeners of Yusho by One Year Intake of FBRA in Patients with Yusho

Nagayama, Junya
Laboratory of Environmental Molecular Epidemiology, Graduate School of Medical, Sciences, Kyushu University

Hirakawa, Hironori
Division of Food and Drug Hygiene, Fukuoka Institute of Health and Environmental Sciences

Kajiwara, Junboku
Division of Food and Drug Hygiene, Fukuoka Institute of Health and Environmental Sciences

Iida, Takao
Division of Food and Drug Hygiene, Fukuoka Institute of Health and Environmental Sciences

https://doi.org/10.15017/6143
Excretion of Causative PCDFs Congeners of Yusho by One Year Intake of FBRA in Patients with Yusho

Junya Nagayama1, Hironori Hirakawa2, Junboku Kajiwara2, Takao Iida2, Takashi Todaka3, Takeshi Uenotsuchi3, Satoko Shibata3, Hiroshi Tsuj4 and Teruaki Iwasaki5

1) Laboratory of Environmental Molecular Epidemiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812–8582
2) Division of Food and Drug Hygiene, Fukuoka Institute of Health and Environmental Sciences, Fukuoka 818–0135
3) Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812–8582
4) Division of Internal Medicine, Kitakyushu–Tsuyazaki Hospital, Fukuoka 811–3307
5) Genmaikousou Corp., Sapporo 001–0012

Abstract Thirty-eight years have passed since the outbreak of Kanemi rice oil poisoning, namely, Yusho in the western Japan. However, even now the patients with Yusho have been still suffering from several objective and subjective symptoms. In order to improve or, if possible, to cure the such symptoms, the most important therapeutic treatment is considered to actively excrete the causative agents, that is, polychlorinated dibenzoferans (PCDFs) and polychlorinated dibenzo-p-dioxins (PCDDs) from the bodies of the patients and to reduce their body burdens. In rats, dietary fiber and chlorophyll have been shown to promote the fecal excretion of dioxins and to reduce their levels in rat liver. In this study, we examined whether such kinds of effect were also observed by FBRA, which was the health food and relatively rich with dietary fiber and chlorophyll, in eighteen patients with Yusho, which were divided into two groups, namely group A, ten patients (Male : 3 and Female : 7) with the mean age of 67.7 years old and group B, eight patients (Male : 4 and Female : 4) with the mean age of 64.1 years. Respective mean concentrations of the three PCDF congeners, that is, 2,3,4,7,8–PenCDF, 1,2,3,4,7,8–HxCDF and 1,2,3,6,7,8–HxCDF in the blood on whole weight basis just before initiating this study were as follows ; group A : 1.36, 0.491 and 0.150 pg/g, and group B : 0.571, 0.159 and 0.064 pg/g. Contamination levels of these PCDF congeners in group A were 2 to 3 times higher than those in group B. Group A took 7.0 to 10.5g of FBRA after each meal and tree times a day for the first one year and for second one year, they did not take FBRA any more. Group B took FBRA with the same manner as the group A only for the second one year. The concentrations of these PCDFs congeners in the blood of groups A and B were also measured at the end of first and second year, respectively. Assuming that the lipid content of the blood is 0.3% in order to convert their concentrations on whole weight basis to those on lipid weight basis and also that the body fat is contaminated with these PCDF congeners at their concentrations on lipid weight basis and the content of body fat is 20% of the body weight (60 kg), we computed the average amounts in the net excretion of these PCDF congeners from the body of the patients due to the intake of FBRA in groups A and B. As a result, in group A, 120, 372 and 96 ng/patient of 2,3,4,7,8–PenCDF, 1,2,3,4,7,8–HxCDF and 1,2,3,6,7,8–HxCDF, respectively, were excreted from the body of the patients. In group B, however, 36 ng/patient of 2,3,4,7,8–PenCDF only was excreted, but

Address for Correspondence: Junya Nagayama, D.M.Sc.
Laboratory of Environmental Molecular Epidemiology, Graduate School of Medical Sciences, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812–8582, JAPAN
Fax • Tel: +81-92-642-6735
E-mail: jun@shs.kyushu-u.ac.jp

(89)
other two PCDF congeners were not. Accordingly, promotive excretion of theses PCDF congeners from the patients with Yusho seemed much effective in group A, of which their concentrations in the blood were much higher than those of group B.

**Introduction**

Our environments including foods have been polluted with extremely toxic dioxins such as polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzo-p-dioxins (PCDFs) not only in Japan but also other countries. Consequently, human beings also have already been contaminated with these dioxins. We already have investigated the effects of this kind of compounds on the foetus and sucklings which are considered the most sensitive stages of human beings as well as animals, and observed their unfavorable effects on thyroid hormone and immune response systems in Japanese infants perinatally and lactationally exposed to them. Their adverse effects on developmental condition have also been found in 10-month-old breast-fed Japanese infants.

PCDFs have been the most important etiological agents of Yusho, a mass food poisoning that occurred in western Japan in 1968 and even now. At present, namely, more than 38 years after the outbreak, many patients with Yusho are still suffering from several objective and subjective symptoms. In order to improve or to cure various symptoms of patients with Yusho, their promotive excretion from the body of the patients is considered very useful. In rats, dietary fiber and chlorophyll have been shown to promote the fecal excretion of dioxins, probably due to the restriction or some inhibition of their absorption and re-absorption in the digestive tract and therefore to reduce their levels in rat liver.

In this study, we examined whether such kinds of effect were observed by FBRA, which was the brown rice fermented with *Aspergillus oryzae* and rich with dietary fiber, or not in patients with Yusho.

**Materials and Methods**

FBRA has been manufactured for over 35 years with Genmaikousou Corp., Sapporo, Japan, and taken by more than 100,000 people as one of the health foods. Ingredients of FBRA have already been reported in our previous study.

Eighteen patients with Yusho were voluntarily participated in this study, and divided into two groups in compliance with their wishes, namely, groups A and B. Group A consisted of 3 males and 7 females with the mean age of 67.7 years old and group B 4 males and 4 females with that of 64.1 years old. In group A, they took 7.0 to 10.5g of FBRA after each meal and three times a day for the first one year and didn’t for the second one year. In group B, they took FBRA in the same way as group A in the second one year, but not in the first one year.

Just before starting this study, 20 ml of the peripheral blood was individually taken by venipuncture in both groups A and B, twice at one week intervals. These blood samples were analyzed for 2,3,4,7,8-pentachlorodibenzofuran (2,3,4,7,8-PenCDF), 1,2,3,4, 7,8-hexachlorodibenzofuran (1,2,3,4,7,8-HxCDF) and 1,2,3,6,7,8-HxCDF, which were the most important causative compounds for Yusho disease, by HRGC–HRMS technique using a Micromass Autospec Ultima NT mass spectrometer directly interfaced
with an Agilent Technologies HP-6890A gas chromatography\(^{22}\).

The average concentrations of these three PCDF congeners in the two blood samples of the same patient were expressed as the individual original ones in both groups A and B. In order to evaluate the effect of FBRA on their excretion from the patients, their blood concentrations were determined again exactly with the same manner as those measured just before beginning this study at the end of first and second year in both groups. Their concentrations measured at different times in each group were statistically examined by student’s t-test.

**Results and Discussion**

Changes in concentrations on wet weight basis of three PCDF congeners in the blood of patients with Yusho during the period of this study were shown in Table 1. Just before starting this study, concentrations of 2,3,4,7,8-PenCDF, 1,2,3,4,7,8-HxCDF and 1,2,3,6,7,8-HxCDF in group A were 1.36 ± 1.71, 0.491 ± 0.734 and 0.150 ± 0.195 pg/g wet weight, respectively, and those in group B 0.571 ± 0.465, 0.159 ± 0.113 and 0.064 ± 0.037 pg/g wet weight. Although their concentrations were 2.3 to 3.1 times higher in group A than in group B, even in group B these were 3 to 10 times greater than those in healthy Japanese people, and the concentrations of 2,3,4,7,8-PenCDF, the main causative congener of Yusho, were the highest and 10 times over those of healthy persons\(^{23}\). These results clearly indicate that patients with Yusho are still contaminated with high levels of PCDFs and in order to improve their objective and subjective symptoms, promotive excretion of these

---

**Table 1** Changes in concentrations on wet weight basis of three PCDFs congeners in the blood of patients with Yusho

<table>
<thead>
<tr>
<th>Congener</th>
<th>Concentration, pg / g wet weight*</th>
<th>Initial</th>
<th>After 1st year</th>
<th>After 2nd year</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,3,4,7,8-PenCDF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group / A</td>
<td>1.36 ± 1.71</td>
<td>1.32 ± 1.68</td>
<td>1.31 ± 1.67</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.571 ± 0.465</td>
<td>0.570 ± 0.476</td>
<td>0.561 ± 0.473</td>
</tr>
<tr>
<td>1,2,3,4,7,8-HxCDF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group / A</td>
<td>0.491 ± 0.734</td>
<td>0.410 ± 0.609(^*)</td>
<td>0.423 ± 0.648(^*)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.159 ± 0.113</td>
<td>0.148 ± 0.107</td>
<td>0.144 ± 0.113</td>
</tr>
<tr>
<td>1,2,3,6,7,8-HxCDF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group / A</td>
<td>0.150 ± 0.195</td>
<td>0.128 ± 0.159(^*)</td>
<td>0.133 ± 0.174(^*)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.064 ± 0.037</td>
<td>0.061 ± 0.037</td>
<td>0.060 ± 0.040</td>
</tr>
</tbody>
</table>

\(^*\) : Mean ± S.D.
\(^*\) : Significantly different from the initial concentration in group A, p<0.05

---

**Table 2** Changes in mean concentrations on lipid weight basis of three PCDF congeners in the blood of patients with Yusho

<table>
<thead>
<tr>
<th>Congener</th>
<th>Mean Concentration, pg/g lipid weight*</th>
<th>Initial</th>
<th>After 1st year</th>
<th>After 2nd year</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,3,4,7,8-PenCDF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group / A</td>
<td>453</td>
<td>440</td>
<td>437</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>190</td>
<td>190</td>
<td>187</td>
</tr>
<tr>
<td>1,2,3,4,7,8-HxCDF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group / A</td>
<td>164</td>
<td>137</td>
<td>141</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>53</td>
<td>49</td>
<td>48</td>
</tr>
<tr>
<td>1,2,3,6,7,8-HxCDF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group / A</td>
<td>50</td>
<td>43</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>21</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

\(^*\) : Lipid content of the blood was supposed 0.3%
PCDFs congeners seems quite useful.

As indicated in Table 1, mean concentrations of 2,3,4,7,8-PenCDF, 1,2,3,4,7,8-HxCDF and 1,2,3,6,7,8-HxCDF gradually decreased from the beginning to the end of this study, except those of 1,2,3,4,7,8- and 1,2,3,6,7,8-HxCDFs in group A, in which their concentrations increased from the end of first year to the end of second year and in this period they did not take FBRA.

In order to convert the mean concentrations in Table 1 to those on lipid weight basis, we presumed the lipid content of blood was 0.3%, and the results are shown in Table 2. Again, on the assumption that the body fat was contaminated with these three PCDF congeners at their blood concentrations on the lipid weight basis and the content of body fat was 20% of body weight (60kg), we calculated their total body burdens and the results are indicated in Table 3.

As a result, effects of the intake of FBRA for one year on the excretion of the three PCDF congeners from the body of patients with Yusho in groups A and B are demonstrated in Figs. 1, 2 and 3.

Net reduction of 2,3,4,7,8-PenCDF in the body of patients with Yusho were 120 and 36 ng / patient in groups A and B, respectively, as shown in Fig. 1. Net reduction of 1,2,3,4, 7,8- and 1,2,3,6,7,8-HxCDFs were 372 and 96

<table>
<thead>
<tr>
<th>Congener</th>
<th>Average Body Burden, ng/patient*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
</tr>
<tr>
<td>2,3,4,7,8-PenCDF</td>
<td></td>
</tr>
<tr>
<td>Group / A</td>
<td>5,436</td>
</tr>
<tr>
<td>B</td>
<td>2,280</td>
</tr>
<tr>
<td>1,2,3,4,7,8-HxCDF</td>
<td></td>
</tr>
<tr>
<td>Group / A</td>
<td>1,968</td>
</tr>
<tr>
<td>B</td>
<td>636</td>
</tr>
<tr>
<td>1,2,3,6,7,8-HxCDF</td>
<td></td>
</tr>
<tr>
<td>Group / A</td>
<td>600</td>
</tr>
<tr>
<td>B</td>
<td>252</td>
</tr>
</tbody>
</table>

*: Content of body fat was considered 20% of body weight (60kg)
ng / patient, respectively, only in group A, as indicated in Figs 2 and 3. However, we could not find any significant reduction of these two HxCDFs congeners in group B.

We have already reported the promotive excretion of PCDFs and PCDDs from healthy Japanese people by one year intake of FBRA. Results of this study also confirmed the reduction of PCDFs congeners from the patients with Yusho by the intake of FBRA, and showed that this reduction seemed more effective in the patients with higher concentrations of PCDFs, namely, in group A.

References

1) Ohta S, Nakano T, Nishimura H, Okumura T, Aozasa O and Miyata H: Contamination levels of PBDEs, TBBPA, PCDDs / DFs, PBDDs / DFs and PXDDs / DFs in the environment of Japan. Organohal. Comp. 57 : 57-60, 2002.


7) Wu Y, Li J, Zhao Y, Chen Z, Li W and Chen J: Dietary intake of polychlorinated dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs) in populations from China. Ibid. 57 : 221-224, 2002.

8) Furst P and Papke O: PCDDs, PCDFs and dioxin-like PCBs in human milk and blood from Germany. Ibid. 55 : 251-254, 2002.


油症患者における FBRA 摂取による
油症原因 PCDFs 同族体の体外排泄促進

1) 九州大学医学系医学研究部 環境情報科学部
2) 福岡県保健環境研究所 生活化学科
3) 九州大学医学系医学研究部 皮膚科学分野
4) 北九州津屋崎病院 内科
5) 株式会社 玄米酵素

長山 浩哉1), 平川 博之2), 楢原 浩明3), 飯田 薫4), 戸高 尊5),
上ノ土 武3), 柴田 智子3), 辻 博4), 岩崎 輝明5)

カネミ油症中毒事件が発生してから 38 年が経過したが、今でも油症患者は種々様々な自覚および臨床症状で苦しんでいる。このような症状を改善し治療するには、その主要な原因物質であるポリ塩化ダイベンゾフラン (PCDFs) を積極的に体外へ排泄し、汚染レベルを低下させることが第一である。この研究では動物実験によりダイオキシン類の体外排泄促進作用が認められている食物繊維を比較的多量に含む栄養補助食品 FBRA (発酵玄米栄養補助食品ハイ・ゲンキ, 徳玄米酵素, 本社：北海道札幌市) によるカネミ油症原因物質、中でも特に重要な 2,3,4,7,8-五塩化ダイベンゾフラン (2,3,4,7,8-PenCDF), 1,2,3,4,7,8-六塩化ダイベンゾフラン (1,2,3,4,7,8-HxCDF) および 1,2,3,6,7,8-六塩化ダイベンゾフラン (1,2,3,6,7,8-HxCDF) の体外排泄促進を 18 名の油症患者の協力により調査した。

研究期間は 2 年間で、患者の希望により A、B 二群に分け、A 群は最初の 1 年間、B 群は 2 年目の 1 年間、毎食後 7.0〜10.5g の FBRA を摂取した。A 群は 10 名 (男性 3 名、女性 7 名) で、平均年齢が 67.7 歳、B 群は 8 名 (男性 4 名、女性 4 名) で、平均年齢が 64.1 歳であった。

研究を開始前の血中 PCDFs 同族体の平均濃度は A 群が 2,3,4,7,8-PenCDF；1.36pg/g, 1,2,3,4,7,8-HxCDF；0.491pg/g, 1,2,3,6,7,8-HxCDF；0.150pg/g で、B 群が、それぞれ 0.571, 0.159, 0.064 pg/g であった。A 群のほうが、2 〜 3 倍高かった。研究開始 1 年後と 2 年後にも両群の血中 PCDFs 同族体濃度を測定した。

これらの測定結果より、血液の脂肪含有率を 0.3%として、脂肪重量当りの濃度を算出した。この濃度で患者体内の脂肪組織が汚染されており、体重 60kg の患者について、体脂肪率を 20% 仮定して、これらの PCDFs 同族体の体内蓄積量を算出する。そして、この体内蓄積量が FBRA 摂取と非摂取の期間でどのように変化するかを、両群で比較検討した。

A 群の場合、すべての PCDFs 同族体で FBRA 摂取期間のほうが非摂取期間よりも減少量が多く、平均値減少率は患者一人当たり 2,3,4,7,8-PenCDF が 120ng, 1,2,3,4,7,8-HxCDF が 372ng, 1,2,3,6,7,8-HxCDF が 96ng であった。B 群では 2,3,4,7,8-PenCDF のみ 36ng 減少し、他の二種の同族体では体外への排泄促進は認められなかった。

以上の結果より、FBRA には油症の原因となった PCDFs 同族体の体外排泄促進作用が認められ、その効果は污染レベルの高い患者をより有効と考えられた。