Individuals' half-lives for 2,3,4,7,8-penta-chlorodibenzofuran (PeCDF) in blood: correlation with clinical manifestations and laboratory results in subjects with Yusho

Shinya Matsumoto[12§], Manabu Akahane[2], Yoshiyuki Kanagawa[1], Junboku Kajiwara[3], Takashi Todaka[4], Fumiko Yasukawa[4], Hiroshi Uchi[4], Masutaka Furue,[4] and Tomoaki Imamura[2]

[1]Division of Social Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

[2]Department of Public Health, Health Management and Policy, Nara Medical University School of Medicine, Kashihara, Japan

[3]Fukuoka Institute of Health and Environmental Sciences, Fukuoka, Japan

[4]Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Email addresses:

SM: shinyamatsumoto-tky@umin.ac.jp

MA: makahane@naramed-u.ac.jp

YK: kanagawa-tky@umin.ac.jp

JK: kajiwara@fihes.pref.fukuoka.jp

TT: todaka@fihes.pref.fukuoka.jp

FY: yasukaf@med.kyushu-u.ac.jp

HU: uchihir@dermatol.med.kyushu-u.ac.jp

MF: furue@dermatol.med.kyushu-u.ac.jp

TI: imamura-t@umin.ac.jp

[§]Corresponding author

Division of Social Medicine, Graduate School of Medicine, The University of Tokyo,

7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

Phone: +81-3-5800-8716; Fax: +81-3-5800-8765

E-mail: shinyamatsumoto-tky@umin.ac.jp

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Correlations between half-life of 2,3,4,7,8-PeCDF and symptoms were evaluated.

Symptoms that accelerate excretion of lipids may lead to a shorter half-life.

Red blood cells are related to the half-life of 2,3,4,7,8-PeCDF.

Further studies are required to investigate the excretory mechanism of 2,3,4,7,8-PeCDF.

Abstract

Background

In 1968, many people developed dioxin poisoning (Yusho) in Japan. Ingestion of 2,3,4,7,8-pentachlorodibenzofuran (2,3,4,7,8-PeCDF) was considered to be the cause of this poisoning. Although some patients had high concentrations of 2,3,4,7,8-PeCDF in their blood, individuals' half-lives of 2,3,4,7,8-PeCDF were long.

Objectives

To evaluate the relationship between clinical and laboratory parameters and the individual half-life of 2,3,4,7,8-PeCDF in blood.

Methods

Clinical and laboratory data were collected during annual check-ups from 2001 to 2008. We enrolled 71 patients, who were measured more than 3 times, and who had 2,3,4,7,8-PeCDF concentrations in blood >50 pg g^{-1} lipid. The half-life of 2,3,4,7,8-PeCDF for each patient was estimated using linear regression. Moreover,

relationships between clinical and laboratory parameters and individual half-life were investigated by linear regression.

Results

A shortened individual half-life for 2,3,4,7,8-PeCDF was significantly correlated with an increased red blood cell count, increased viscous secretions from the meibomian glands, existing black comedones, and severe cedar pollen allergy.

Conclusions

Symptoms that accelerate excretion of lipids from the body, such as viscous secretions from the meibomian glands, may lead to a shorter half-life of 2,3,4,7,8-PeCDF. Red blood cells are related to the half-life of 2,3,4,7,8-PeCDF. However, further studies are required to investigate the excretory mechanism of 2,3,4,7,8-PeCDF.

Keywords

Dibenzofuran, cedar pollen allergy, Yusho, half-life, red blood cell, 2,3,4,7,8-pentachlorodibenzofuran

76

77 Abbreviations

78 PeCDF: pentachlorodibenzofuran

79 PCB: polychlorinated biphenyl

80 RAST: radio allergosorbent test

81 1. Introduction

82 In 1968, an unknown disease was diagnosed in patients in Western Japan who had
83 presented with several devastating symptoms. This disease was named "Yusho".
84 These patients had ingested rice-bran oil contaminated with extremely high
85 concentrations of various polychlorinated biphenyls and dioxin-like compounds
86 (Furue et al. 2005; Yoshimura 2003). At the time, poisoning due to polychlorinated
87 biphenyls was thought to be the cause of Yusho. However, subsequent chemical
88 analyses and medical investigations revealed that the dioxin-like compound 2,3,4,7,8-
89 pentachlorodibenzofuran (2,3,4,7,8-PeCDF) was the main causative agent (Furue et al.
90 2005; Iida et al. 2003; Imamura et al. 1977; Toyoda et al. 1999: Yoshimura 2003).
91 Since 2001, medical examinations have been conducted annually in subjects with
92 Yusho to measure the concentrations of dioxin-like compounds (Kanagawa and
93 Imamura 2005; Todaka et al. 2003). Such dioxin-like compound measurements are
94 used to estimate the half-lives of 2,3,4,7,8-PeCDF in individual patients. In recent
95 years, our research team has published several articles on the association between
96 health outcomes and PCDF exposure, using a wealth of data and *inter alia* data-
97 mining methods. Also, kinetic calculations have been published earlier using the
98 binary logarithmic value of each dioxin concentration as a dependent variable and the

year of measurement as the independent variable. The linear coefficient obtained from this linear regression analysis was the negative reciprocal number of the half-life. We previously estimated individuals' half-lives of 2,3,4,7,8-PeCDF in >100 patients with Yusho and observed that the half-life varied among patients and that there were two peaks. At first sight, the bimodal distribution was unexpected on physiological grounds (Matsumoto et al. 2009). In some of these patients, the concentrations were high and the half-lives appeared to be infinite. Ongoing ingestion of large amounts of 2,3,4,7,8-PeCDF is unlikely because of recent restrictions on dioxins and dioxin-like compounds. The distribution of the reciprocals of half-lives is similar to a normal distribution. It was considered that these deviations were caused by a randomness that obeyed a normal distribution. These deviations were considered to be due to measurement errors and changes in body weight in adulthood, which obeyed a normal distribution. The mode of the distribution of the reciprocal of half-lives indicated an infinite half-life. It was thought that this infinite half-life was the result of removing the randomness. Hence, this infinite half-life was not the apparent half-life shown by Shirai and Kissel (Shirai and Kissel 1996). A clear conceptual distinction between apparent and true half-lives is required to reduce the uncertainty in the elimination half-lives of persistent chemicals (Milbrath et al. 2009, Ritter et al. 2011). However, the infinite half-life reported previously is close to the true half-life, because these half-lives were estimated for patients with high concentrations. This discrepancy of "the true half-life is less than 10–15 years", as stated by Ritter et al. (Ritter et al. 2011). It is considered that the term "true half-life" has two meanings: one is the "true half-life" for each individual, and the other is a representative value of the "true half-lives" of a group. Ritter et al. used "true half-life" as a representative value of true

123 half-lives. To investigate the half-life and underlying mechanisms, a physiologically
124 based pharmacokinetic (PBPK) model was used. Kreuzer et al. described the lifetime
125 body burden of 2,3,7,8-tetrachlorodibenzodioxin (Kreutzer et al. 1997). Milbrath et al.
126 presented another model. However, these models could not show a bimodal
127 distribution. A model involving discrete parameters to show the bimodal distribution
128 is needed.
129 In early studies of half-lives of dioxins, the status of patients was disregarded, and
130 individuals' apparent half-lives were determined to calculate the representative value
131 (Masuda et al. 1995). Flesch-Janys et al. determined individuals' half-lives to examine
132 the relationship between the individual half-life and patient status (Flesch-Janys et al.
133 1996). Ritter et al. determined the representative value of true half-lives from
134 measurements in healthy individuals by assuming that true half-lives did not vary
135 between individuals (Ritter et al. 2011). However, there are no reports on whether
136 individuals' true half-lives are equal among individuals.
137 We aimed to evaluate the relationship between the individual true half-life of
138 2,3,4,7,8-PeCDF in blood and the status of individuals with Yusho. Items strongly
139 correlated with half-lives are good candidates to enhance the PBPK model.

140 # 2.Methods

141 ## 2.1.Subjects

142 Of 267 patients whose 2,3,4,7,8-PeCDF concentrations in blood were measured four
143 times or more between 2001 and 2008, we selected 72 patients whose concentrations
144 of 2,3,4,7,8-PeCDF in blood were >50 pg g^{-1} lipid. Blood concentrations of 2,3,4,7,8-
145 PeCDF were 52.9–1230.3 pg g^{-1} lipid (mean ± SD, 283.4 ± 226.9 pg g^{-1} lipid). Table

146 1 shows the sex and age distributions among the selected patients. Normal blood
147 concentraions of 2,3,4,7,8-PeCDF in the general population are 3.5–41.7 pg g^{-1} lipid
148 (15.2 ± 8.9 pg g^{-1} lipid). For healthy individuals, current concentrations were caused
149 by ongoing exposure. For individuals with high concentrations in Yusho, the effects
150 of ongoing exposure were small. Therefore, subjects with mean blood concentrations
151 of 2,3,4,7,8-PeCDF >50 pg g^{-1} lipid were included. We initially recorded the age and
152 sex of patients. Using a general medical questionnaire, we then recorded body weight,
153 body mass index (BMI), changes in BMI, consumption of alcohol and tobacco,
154 nutritional state, and the prevalence of headache, general fatigue, arthralgia, diarrhea,
155 and cough. Dermatological manifestations (history of acneform eruptions, black
156 comedones, pigmentation and recent recurrence of cystic lesions) and
157 ophthalmological manifestations (abnormal discharge from the eyes and viscous
158 secretions from meibomian glands) were also documented. Laboratory examinations
159 included counts of white blood cells (WBCs), red blood cells (RBCs), platelets,
160 neutrophils, and basophils, cedar pollen allergy class based on IgE radioallergosorbent
161 (RAST) scores, and the bone mineral density (BMD) test. BMD test results are
162 expressed as the percentage of the young adult mean level (Wu et al. 2004). Each
163 clinical and laboratory parameter value for each patient was calculated as the mean if
164 multiple values were available for each patient. Changes in the amount of body fat
165 affect the half-life of 2,3,4,7,8-PeCDF (Milbrath et al. 2009). Therefore, changes in
166 weight and BMI were calculated for each patient using linear regression analysis.

2.2. Statistical Methods

First, the rate of change in concentration for each patient was estimated by univariate linear regression. The binary logarithm of 2,3,4,7,8-PeCDF concentrations was the dependent variable, and measurement years were independent variables.

$$log_2 C_{ij} = a_i \cdot t_{ij} + b_i \qquad \text{Eq. 1}$$

The rate of change in concentration is a negative reciprocal of half-life (years). It was considered that measurement errors were distributed as normal distribution. Linear regression was calculated based on the assumption that residuals of dependent variables were distributed as normal distribution. The estimated coefficient was distributed as normal distribution because of the principle of linear regression. We used the rates of change in concentration instead of half-lives. In the final step, half-life was calculated from the rate of change in concentration and evaluated.

The relationship between the rate of change in concentration and clinical and laboratory parameters was then investigated by comparing t-values of univariate linear regressions, which were determined by the rate of change in concentration as the dependent variable, and each clinical and laboratory parameter were independent variables.

We estimated an equation which estimates the rate of change in concentration using clinical and laboratory parameters. This method started involving clinical and laboratory parameters of which p values were less than 0.15 in previous evaluations of relationships between the rate of change in concentration and clinical and laboratory parameters. The backward stepwise method initially involved all listed variables. One variable was then removed, which had the highest p value in each step. These steps

were repeated until p values of all variables were < 0.05. The stepwise method can estimate the most suitable equation.

Some researchers have reported that half-life is related to age and sex (Flesch-Janys et al. 1995, Milbrath 2009). We estimated an equation to estimate rates of change by sex and age.

3.Results

3.1.Half-lives for all patients

Half-lives for all patients were estimated more than or equal to four times for each patient from their 2,3,4,7,8-PeCDF concentrations. Figure 1 shows the distributions of the half-lives of 2,3,4,7,8-PeCDF in patients. As we reported previously (Matsumoto et al. 2009), there were two peaks, one was infinite and the other was approximately 10 years.

One patient was an outlier among the 72 patients. This patient's data were removed, and 71 patients were included for analysis.

3.2.Relationships between half-lives and individual clinical manifestations

Table 2 shows clinical and laboratory parameters, which had p values less than 0.15. Usually, 0.05 is the criterion for p values. The equation that is represented by multiple parameters shows higher p values if the equation has fewer parameters than an appropriate number of parameters, i.e., the variables were evaluated as worse p values. There were four items that had a p value less than 0.05. Increased red blood cell count was the most strongly related to shorter half-lives of 2,3,4,7,8-PeCDF, followed by increased black comedones. Positive results for viscous secretions from the

meibomian glands and cedar pollen allergy were related to a shorter half-life of 2,3,4,7,8-PeCDF. Items that had p values between 0.05 and 0.15 were BMD, sex, smoking status, general fatigue, and past pigmentation.

Standard RBC counts for both sex and age, as reported by Ota (2008), were substituted for RBCs in an equation (Table 2), which estimates rates of change. This resulted in the following half-life values for 2,3,4,7,8-PeCDF: 13.89 years in men aged 30–39 years (RBC count, 4,995,000 cells mm^{-3}); 25.26 years in women aged 30–39 years (4,290,000 cells mm^{-3}); 25.11 years in men aged 80–89 years (4,295,000 cells mm^{-3}); and 32.90 years in women aged 80–89 years (4,090,000 cells mm^{-3}).

3.3. Most suitable equation for estimating the true half-life of 2,3,4,7,8-PeCDF

The most suitable equation for estimating the rate of change in concentration was Eq. 2 (Table 3). This equation was obtained by selecting variables using the backward stepwise method with the criterion of 5%, starting with all items with p values less than 0.15. Similar clinical/laboratory items were removed using the stepwise method, and dissimilar items were used to create an equation for estimating the rate of change in concentration.

$$\begin{aligned}\text{Rate of change in concentration} = {} & -0.089861 \\ & -0.038591 \times \text{Black comedones} \\ & -0.018018 \times \text{Cedar pollen allergy} \\ & +0.023333 \times \text{General fatigue} \\ & +0.041891 \times \text{Past pigmentation}\end{aligned} \quad \text{Eq. 2}$$

We found that a higher severity of black comedones and higher cedar pollen allergy levels led to a shorter individual half-life of 2,3,4,7,8-PeCDF in patients. Higher

231 general fatigue and higher past pigmentation were correlated with a longer individual
232 half-life.

233 **3.4.Equation for estimating the half-life of 2,3,4,7,8-PeCDF according to sex and**
234 **age**

235 We created an equation to estimate the individual true half-life of 2,3,4,7,8-PeCDF on
236 the basis of sex and age.

$$\text{Rate of change in concentration} = -0.1726165 + 0.0011512 \times \text{Age} + 0.0302986 \times \text{Sex} \quad \text{Eq. 3}$$

237

238 There was not a strong relationship between half-life and sex and age ($p>0.05$). Figure
239 2 shows the half-lives which were calculated by Eq.3 (Table 4) for ages between 30
240 years and 80 years. This age range was wider than the range that Eq. 3 was estimated.
241 Interpretation of the results for both ends of the age range is needed. The half-life
242 values for 2,3,4,7,8-PeCDF calculated using Eq. 3 were longer in women than those
243 in men, and generally increased with age.

244 # 4.Discussion

245 Several accidental instances of dioxin intoxication, such as Yusho in Japan, Yu-
246 Cheng in Taiwan, and the Seveso disaster in Italy, have been reported (Bertazzi et al.
247 1998; Hsu et al. 1985). Dioxin-like compounds are lipophilic substances that are not
248 readily excreted by the human body. Kerger et al. (Kerger et al. 2006) surveyed
249 children involved in the Seveso disaster and reported that the half-lives of dioxins and
250 dioxin-like compounds are dependent upon patient age and dioxin concentrations.
251 Among patients with PeCDF blood levels of ≥ 50 pg g^{-1}, there were two groups: one
252 showing a half-life of approximately 7 years and the other showing no reduction in

253 PeCDF levels over time. These results suggest that there is a group of patients whose
254 PeCDF levels are maintained at a high level. Our previous study suggested that a
255 more complicated model is required to explain PeCDF excretion in humans
256 (Matsumoto et al. 2009). We studied, by association analysis, combinations of
257 symptoms which were strongly associated with high concentrations of PeCDF
258 (Imamura et al. 2007). Principal component analyses have revealed that the
259 concentrations of PeCDF is strongly associated with the concentrations of PCB and
260 polychlorinated quarter phenyl (PCQ). It is also associated with levels of blood
261 glucose, arthralgia, total cholesterol, urinary sugar, 2-h erythrocyte sedimentation rate,
262 thymol, and sodium, as well as conventionally dermatological symptoms such as
263 acneform eruptions and black comedones (Kanagawa et al. 2008). In one of our
264 previous studies, the incidence and severity of most of the dermatological and
265 ophthalmological symptoms decreased from 1988 to 2001–2003 (Matsumoto et al.
266 2010).
267 Leung et al. (Leung et al. 2007) reached a similar conclusion after estimating dioxin-
268 like compounds half-lives in five subjects with Yusho and three with Yu-Cheng. Half-
269 life values of 1.1 years in patients with high concentrations of dioxin-like compounds
270 in blood and 7.2 years in patients with low concentrations of dioxin-like compounds
271 in blood were determined. Other estimates of dioxin-like compound half-lives include
272 8.9 years by Masuda et al. (Masuda et al. 1995), 9.6 years by Ryan et al. (Ryan et al.
273 1993), and 9.1 years by Iida et al. (Iida et al. 1995). Even though half-life values of
274 <10 years have been reported (Ritter et al. 2011), we previously observed that some
275 subjects with Yusho showed considerably longer 2,3,4,7,8-PeCDF half-life values
276 than expected (Matsumoto et al. 2009).

277 The four clinical/laboratory items examined in the present study showed a strong
278 correlation with a short half-life for 2,3,4,7,8-PeCDF (Table 2). "Increased viscous
279 secretions from the meibomian glands" and "increased severity of black comedones",
280 which are symptoms specific to Yusho, were correlated with a shorter half-life for
281 2,3,4,7,8-PeCDF. These symptoms cause lipid excretion from the body. Such
282 excretion of lipids in combination with 2,3,4,7,8-PeCDF may explain the shorter half-
283 life.
284 Some researchers have reported that the half-life of dioxins is related to sex and age
285 (Kerger et al. 2006; Leung et al. 2005; Milbrath et al. 2009). We estimated an
286 equation, which estimates the rate of change in concentration with age and sex (Eq. 3).
287 However, we found that the half-life of 2,3,4,7,8-PeCDF was not strongly related to
288 sex and age (p value for age was >0.2). The estimated half-lives with sex and age in
289 our study are similar to results of Flesch-Janys et al. (Flesch-Janys et al. 1996). It is
290 possible that a large variation in the characteristics of subjects might cause large p
291 values for these relationships.
292 The present study identified previously unreported clinical/laboratory items related to
293 the half-life of 2,3,4,7,8-PeCDF. A higher RBC count was correlated with a shorter
294 half-life for 2,3,4,7,8-PeCDF. In subjects with severe Yusho, anemia developed in the
295 stage of early exposure (Furue et al. 2005). Dioxin binds to RBCs and induces their
296 lysis (Bukowska 2004). There are big differences in concentration between Yusho
297 patients and those in the study of Bukowska, and *in vivo* and *in vitro*. Taking into
298 account the high turnover rate of RBCs, the scavenger function of RBCs against blood
299 dioxin may be an important excretory pathway, particularly during the chronic phase
300 of intoxication. The number of RBCs is also associated with differences in age and

sex (Ota 2008). Metabolism and genetic differences resulting in different capacities, excretion differences related to nutrition, and change in body weight could explain these observations. A more biophysiologic approach is warranted when mechanisms are speculated upon; for example, looking as well at the number of erythrocytes and reticulocytes might give further clues. Patients aged >70 years and women are anemic compared with younger individuals and men. These confounding factors appear to affect the excretion rate of 2,3,4,7,8-PeCDF. In the current study, the number of RBCs was removed in the process of the stepwise method for estimating a suitable equation. When RBCs were removed from the calculation, the t-value of black comedones was improved. Therefore, RBCs might be related to dermatological activity.

The current study found that the presence of cedar pollen allergy (high scores for the radioallergosorbent test:RAST) was correlated with a shorter half-life for 2,3,4,7,8-PeCDF. Once ingested, dioxins are thought to be excreted via the feces, urine, sebum, and sputum (Furue et al. 2005; Weber et al. 1993). Diarrhea, severe seborrhea, and excessive production of sputum are apparent acute and chronic features in subjects with Yusho (Furue et al. 2005; Kanagawa et al. 2008). Cedar pollen allergy causes seasonal rhinitis in patients, and such patients may develop severe rhinorrhea that may aid in the excretion of 2,3,4,7,8-PeCDF. However, dioxin concentrations in rhinorrhea patients have not been measured. In our study, the variable of viscous secretions from the meibomian glands was removed in the process of backward stepwise. When this item was removed, the t-value of cedar pollen allergy was improved. The severity of cedar pollen allergy may be related to acceleration of various body fluids, such as sputum, phlegm and eye mucus. Among Yusho patients, past pigmentations are

stronger for patients with high 2,3,4,7,8-PeCDF concentrations (Kanagawa et al. 2008). Past pigmentation (which is a non-discharge symptom without excretion of body fluids) is correlated with longer half-lives.

Equation 2 included the variables of black comedones, cedar pollen allergy class, general fatigue, and past pigmentation. Equation 2 was determined using a stepwise method and most accurately estimates the individual half-life of 2,3,4,7,8-PeCDF. This equation yields a better estimation of the 2,3,4,7,8-PeCDF individual half-life than an equation that uses sex and age parameters, which have been previously reported to correlate with apparent half-life (Flesch-Janys 1996, Milbrath 2009). Shirai and Kissel (1996) showed that estimated half-lives based on observations are affected, not only by excretion, but also by ongoing exposure and physiological changes, such as changes in body weight. However, most of the half-lives reviewed by Shirai and Kissel (1996) were estimated from two measurements in each patient: the first and last measurements. Therefore, errors could not be evaluated at the time of measurement. Consequently, alterations could not be distinguished (i.e., they may be temporary or long-term changes or caused by measurement errors). Our study included patients who were measured at least four times. Therefore, effects of measurement errors and temporal changes were reduced by linear regression.

Ongoing exposure affects apparent half-lives. The present study involved subjects with >50 pg g^{-1} lipid, which is a higher concentration than that of healthy individuals. Therefore, ongoing exposure has fewer effects in such patients with high concentrations. Apparent half-lives are affected by continuous dilution by a gain in body weight during the growth phase (Clewell et al. 2004). In the present study, a gain or loss in body weight was determined for each patient, and we evaluated the

correlation with the rate of change in body weight and the rate of change in concentration of 2,3,4,7,8-PeCDF. We found that the rate of change in weight was not strongly correlated to the rate of change in concentration. It was considered a contingency that concentration would continuously decrease or increase when body weight gain or loss occurred throughout the measurement period. In adults, it is difficult to assume that long-term continuous gain or loss in body weight occurs. Therefore, continuous condensation and dilution due to changes in body weight are not considered as important factors. It has been reported that changes in body weight affect apparent half-lives, possibly reflecting temporary intra-individual variations. There are no reports on long-term continuous condensation caused by physiological status (not changes in physiological status) in adults. Long-term continuous changes in concentration reflect an excretion pathway if 2,3,4,7,8-PeCDF is metabolized into a different compound. Long-term continuous changes in concentration are dependent upon excretion if there is neither ongoing exposure nor *in-vivo* synthesis.

Some studies have reported that the representative true half-life of dioxins is shorter than 10 or 15 years (Ritter et al. 2011; Shirai and Kissel 1996). However, no study has found that the individual true half-life is limited.

Ongoing exposure is negligible if the true half-life is 10–15 years for patients with high 2,3,4,7,8-PeCDF concentrations, as in the subjects in the present study. The present study showed that half-lives varied among individuals. For patients with high 2,3,4,7,8-PeCDF concentrations and long half-lives, ongoing exposure was not negligible. If patients have 25-fold high concentrations and 25-fold long true half-lives compared with those of the general public, they are in a steady-state (i.e., their apparent half-lives are infinite), similar to the general public. Apparent half-lives,

373 which are affected by a temporary change in body weight and measurement errors,
374 have a normal distribution. In figure 2, females are distributed similar to normal
375 distribution around infinite as described above.
376 Apparent half-lives have been reported to be correlated with physiological status and
377 changes in physiological status (Milbrath et al. 2009). Some types of physiological
378 status do not change in the long-term. Long-term continuous changes in concentration
379 not related to ongoing exposure are caused by excretion, metabolism, and synthesis. It
380 is possible that previously reported body status (not a change in body status) was
381 correlated with apparent half-lives, but was also correlated with individual true half-
382 lives.
383

384 5.Conclusions

385 In the present study, the relationship between symptoms and half-life of 2,3,4,7,8-
386 PeCDF was evaluated in 71 Yusho patients with 2,3,4,7,8-PeCDF concentrations as
387 high as 50 pg g^{-1} lipid. The shortened half-life (high excretion rate) of 2,3,4,7,8-
388 PeCDF in subjects with Yusho was significantly correlated with increased RBC count,
389 positive results for black comedones, positive results for viscous secretions from the
390 meibomian glands, and increased cedar pollen allergy. Individuals' half-lives of
391 2,3,4,7,8-PeCDF varied with the patients' status. Notably, the individual half-life of
392 2,3,4,7,8-PeCDF was long in older women. Symptoms that lead to excretion of lipids
393 outside of the body may lead to a shorter half-life of 2,3,4,7,8-PeCDF. Further studies
394 are required to determine the role of RBCs in 2,3,4,7,8-PeCDF.
395

Competing interests

The authors declare that they have no competing interests.

Author contributions

SM designed the project, developed the analytical method, and drafted the manuscript. MA interpreted the results of the BMD test. YK interpreted the results. JK examined the data quality for analyses. TT, FY, HU, and MF interpreted the results (particularly in relation to dermatology). TM directed and coordinated the project. All authors approved the final manuscript.

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506

Figure legends

Figure 1. Distribution of half-life values

Half-life values for each patient were estimated using univariate linear regression for each patient.

Figure 2. Estimated half-life values on the basis of sex and age

Half-life values were estimated based on the sex and age of the patients.

Table legends

Table 1. Sex and age of the study subjects

Table 2. Estimation of the rate of change of 2,3,4,7,8-PeCDF on the basis of individual parameters and goodness-of-fit

Table 3. β coefficients and evaluation of best-fit estimation of the equation for the half-life of 2,3,4,7,8-PeCDF

Table 4. β coefficients and evaluation of estimation of the equation for the half-life of 2,3,4,7,8-PeCDF by sex and age

Table 1. Sex and age of the study subjects

Age (years)	Males	Females
40–50	1	2
50–60	3	8
60–70	7	22
70–80	12	14
80–90	3	0

Figure 1. Distribution of half-life values

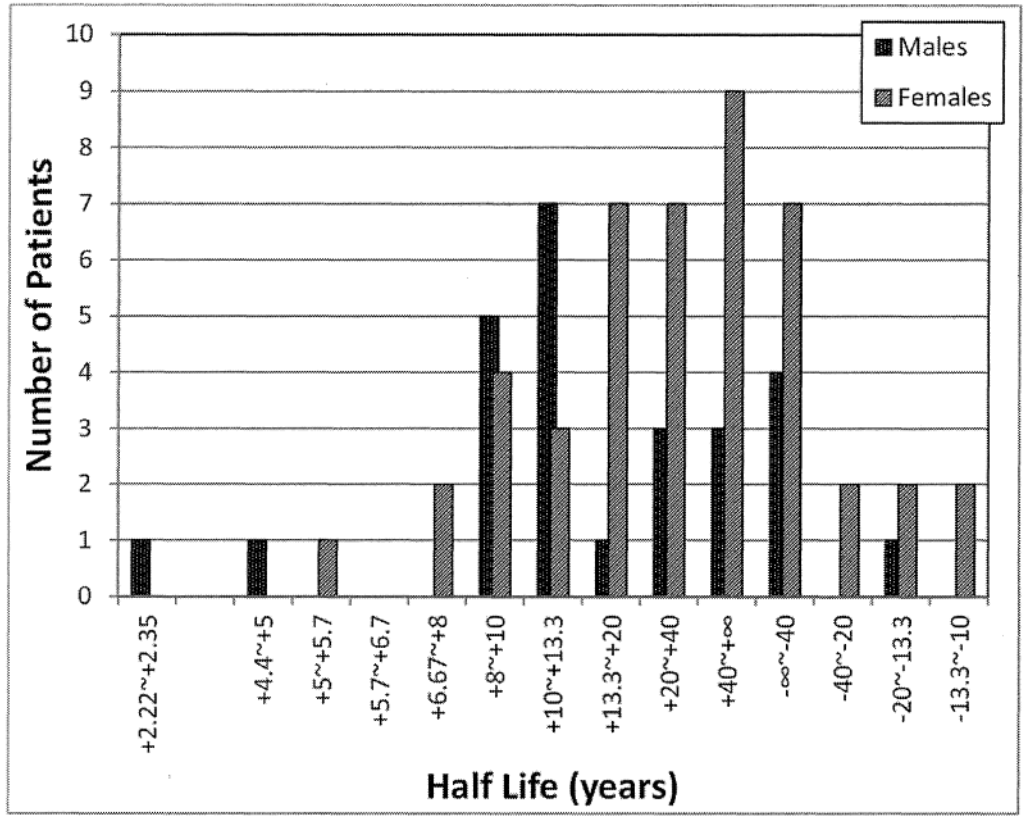

Table 2. Estimation of the rate of change of 2,3,4,7,8-PeCDF on the basis of individual parameters and goodness-of-fit

	Items correlated with a high excretion rate (shortened PeCDF half-life)	F-value	Equation to estimate the rate of change (x indicates an item)	p value	R squared
1	Increased red blood cell count	6.607	0.1577034 - 0.0004599 · x	0.01232	0.08738
2	Black comedones	5.243	-0.001301 - 0.026198 · x	0.02510	0.07061
3	Positive results for viscous secretions from the meibomian glands	4.701	-0.006176 - 0.027205 · x	0.03359	0.06379
4	Cedar pollen allergy	4.421	-0.036677 - 0.015482 · x	0.03914	0.06022
5	Increased bone mineral density	3.960	0.0129792 - 0.0007208 · x	0.05056	0.05428
6	Male sex	2.791	- 0.08383 + 0.02491 · x	0.09931	0.03888
7	Smoking status	2.741	- 0.01588 - 0.02062 · x	0.10230	0.03821
8	General fatigue	2.500	-0.05342 - 0.01971 · x	0.11840	0.03497
9	Past pigmentation	2.159	-0.08726 + 0.02774 · x	0.14630	0.03034

Table 3. β coefficients and evaluation of best-fit estimation of the equation for the half-life of 2,3,4,7,8-PeCDF (R squared = 0.2613)			
	β coefficient	t-value	p value
Constant value	-0.089861	-2.621	0.01086
Black comedones	-0.038591	-3.439	0.00102
Cedar pollen allergy	-0.018018	-2.643	0.01025
General fatigue	0.023333	2.027	0.04667
Past pigmentation	0.041891	2.279	0.02590

Table 4. β coefficients and evaluation of estimation of the equation for the half-life of 2,3,4,7,8-PeCDF by sex and age (R squared = 0.06121)

	β coefficient	t-value	p value
Constant value	-0.1726165	-2.323	0.0232
Age	0.0011512	1.272	0.2078
Sex	0.0302986	1.963	0.0538

Figure 2 Estimated half-life values on the basis of sex and age