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Human Body Burden of Polychlorinated Dibenzofurans Associated with Toxicity Based on the Yusho and Yucheng Incidents[1]

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Human Body Burden of Polychlorinated Dibenzofurans Associated with Toxicity Based on the Yusho and Yucheng Incidents. RYAN, J. J., GASIEWICZ, T. A., AND BROWN, J. F., JR. (1990). *Fundam. Appl. Toxicol.* **15,** 722–731. The polychlorinated dibenzofurans (PCDFs) are one group of man-made toxicants for which reasonably extensive data exist relevant to dose–response relationships in humans. Examination of contaminated food oil consumption from the yusho (Japan) poisoning incident indicates the mean uptake or body burden of 2,3,4,7,8-pentachlorodibenzofuran (PnCDF) equivalents (PEQ) associated with nausea and anorexia to be 4.4 μg/kg body wt and that associated with chloracne to be 5.9 μg/kg. For the yucheng (Taiwan) poisoning incident, blood measurements for chloracne show a similar body burden of 4.0 μg/kg. The latter value is toxicologically equivalent to a 2,3,7,8-tetrachlorodibenzo-*p*-dioxin equivalent (TEQ) body burden of 2.0 μg/kg body wt or about 150 μg for an adult person. This corresponds to an adipose tissue level of about 10 μg/kg fat, and is comparable to that known to cause chloracne in rhesus monkeys. These body burdens on a TEQ basis are more than 200 times higher than the average current levels of PCDDs/PCDFs found in North American populations and are the first to relate human body burdens of PCDFs with a known effect and to compare them to animal data. Since the effects reported may not be the most sensitive indicator of human toxicity, lower body burdens could be associated with more subtle toxicological events.

Polychlorinated dibenzofurans (PCDFs) and polychlorinated dibenzo-*p*-dioxins (PCDDs) are two classes of man-made chemicals which occur as contaminants in certain industrial chemicals and which are produced in thermal processes, including the incineration of municipal wastes (OME, 1985; US EPA, 1985). Due to their potent acute and long-term toxicities in experimental animals (Poland and Knutson, 1982), their effect on the health of humans has been the subject of much concern, particularly since the demonstration of their presence at low to high parts per trillion (ppt; ng/kg) levels in adipose tissue from general populations of industrialized countries (Ryan *et al.*, 1985; Stanley *et al.*, 1986; Rappe, 1984; Graham *et al.*, 1985; Patterson *et al.*, 1986; Ono *et al.*, 1986). Generally, the human health significance of such a body burden would be assessed by extrapolation from studies in experimental animals in which relatively high exposures were used.

Nevertheless, there have been a number of incidents in which individuals have been exposed to relatively high levels of PCDFs and PCDDs. In particular, a substantial amount of information on adverse effects and tissue

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evels exists for two human populations that were exposed to PCDFs. These are the rice oil poisonings in Japan in 1968 (yusho) (Kuratsune, 1980) and in Taiwan in 1979 (yucheng) Hsu *et al.*, 1984). In both cases, exposure was by repeated oral ingestion of a toxic mixture of PCDFs, polychlorinated biphenyls (PCBs), and polychlorinated quaterphenyls (PCQs) which inadvertently contaminated a food-grade rice oil. Even though the concentrations of PCBs and PCQs in the rice oil were from 100- to 500-fold greater than the PCDFs, the main causal agent in these poisonings is believed to be the PCDFs (Miyata *et al.*, 1985; Kunita *et al.*, 1985; Takamatsu *et al.*, 1985; Tanabe *et al.*, 1989). Comparison of symptoms and total PCB levels in yusho victims to those in Japanese workers in a PCB using industry showed higher levels of total PCBs in the occupational workers with few or none of the symptoms present in the rice oil poisonings. In the same vein, a study of Tanabe *et al.* (1989) has shown that the toxic coplanar PCBs accumulated in yusho subjects only 2- to 4-fold over controls while the two toxic PCDFs had concentrated 150 to 200 times over control tissues. On the basis of persistence and clinical symptoms, the PCDFs are more important than the PCBs in the etiology of yusho.

Chloracne, characterized by hyperplasia and hyperkeratosis of the epidermis, hyperkeratosis of the hair follicles, and squamous metaplasia of the sebaceous glands, has long been recognized as the hallmark of human exposure to chlorinated multicyclic aromatics, including PCDFs and PCDDs (Taylor, 1979; Crow, 1981; Suskind, 1985). However, it must be recognized that chloroaromatics do not cause specific effects but a complex of symptoms which are a function of species and even individuals. Moreover, chloracne may not be the most sensitive indicator of human exposure to these compounds, but the one that is most distinct and easily observed. In the yusho rice oil poisoning, the earliest symptoms were complaints of "feeling sick" (fatigue, headache, nausea, numbness), followed by increased eye discharge and swelling of the upper eyelids, with dermal effects not appearing until some time later (Kuratsune *et al.*, 1972; Goto and Higuchi, 1969; Toshitani and Kitamura, 1971). Classification of the patients according to severity of the disease led to the following grading system (Goto and Higuchi, 1969; Hayabuchi *et al.*, 1979):

Grade 0, no apparent clinical symptoms, but physical complaints

Grade 1, grade 0 plus increased eye discharge; pigmentation of nails

Grade 2, grade 1 plus comedones

Grade 3, grade 2 plus limited acneform eruptions and cysts

Grade 4, grade 3 plus extensive acneform eruptions and follicular openings

Many of the children of these poisoning victims who were exposed to the oil contaminants both transplacentally and through breast milk have recently been shown to have similar abnormalities as their mothers as well as developmental effects (Rogan *et al.*, 1988). In this report we use data from the yusho and yucheng poisonings to estimate the total uptake or body burdens of specific PCDFs associated with either Grade 3 (chloracne) or Grade 0 (physical complaints) symptoms. The calculations for the yusho patients used previously reported data for the amounts of contaminated rice oil consumed (Hayabuchi *et al.*, 1979) and more recent determinations of toxic PCDF congener levels in the oil and their toxicological equivalents. Calculations for the yucheng patients begin with the previously reported blood PCDF levels (Kashimoto *et al.*, 1983) and calculate back to the body burden and the original amount consumed, using data on blood–lipid partitioning and uptake efficiency. A flow sheet diagram of the sequences in both calculations is shown in Fig. 1.

METHODS

The systemic toxic response to PCDFs in humans has been shown by Hayabuchi *et al.* (1979) to be closely re-

Yusho	Yucheng
1. PCDF content of rice oil (mg/kg), Feb. 1968	1. Whole blood PCDFs value for Grade 3 response in Nov. 1979
2. PnCDF eq (PEQ) (PnCDF plus HxCDF) of rice oil (mg/liter)	2. Whole blood PEQ values (PnCDF plus HxCDF)
3. Oil consumption per kilogram body weight for Grade 0 and 3 responses	3. Serum PEQ values
4. PEQ consumption per kilogram body weight	4. Serum lipid PEQ values
5. PEQ uptake per kilogram body weight or total	5. Body burden PEQ (total or per kilogram body weight)
6. TEQ uptake total or per kilogram body weight	6. TEQ body burden (total or per kilogram body weight)

FIG. 1. Summary of calculation sequences for estimation of body burden of PEQ and TEQ for the yusho and yucheng incidents. PCDF, polychlorinated dibenzofuran; HxCDF, hexachlorodibenzofuran; PEQ, PnCDF toxic equivalents; TEQ, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin toxic equivalents.

lated to the total amount consumed of the contaminated rice oil containing the toxic PCDFs but not to the amount taken per day or to the dosing rate. This characteristic of PCDFs, and also PCDDs, is likely related to the slow metabolism and long half-lives of certain persistent congeners containing 2,3,7,8-chlorine substitution (Birnbaum, 1985). The importance of a critical body burden rather than a dosing rate in the expression of a toxic effect has also been noted for PCDFs in experimental animals (Decad *et al.*, 1981; McNulty *et al.*, 1981; Ioannou *et al.*, 1983) and for the related chemical, hexachlorobenzene, in humans (Cam and Nigogosyan, 1963).

I. Yusho

The concentration of total PCDFs in the yusho oil has been variously reported at between 1.9 and 7.4 ppm (mg/kg) depending on its date of manufacture and the laboratory carrying out the analysis (Kuratsune, 1980; Miyata *et al.*, 1985; Kunita *et al.*, 1984, 1985; Hayabuchi *et al.*, 1979; Masuda *et al.*, 1982). The value most quoted is 5.0 mg/kg.

Of the more than 40 PCDF congeners present in the yusho and yucheng oils, the two major PCDFs that accumulate in humans are 2,3,4,7,8-PnCDF and 1,2,3,4,7,8-HxCDF. The amounts of 2,3,4,7,8-PnCDF and 1,2,3,4,7,8-HxCDF in the rice oil have been reported by Kashimoto *et al.* (1983) and Hori *et al.* (1986) as 8.0 and 8.5%, respectively, of the total PCDFs. However, there is some uncertainty in these results due to the recent finding (Ryan *et al.*, 1989) that saponification of fatty samples such as oils and adipose tissue under the hot alkali conditions sometimes used for sample preparation results in both a decrease of their total PCDF content and formation of small amounts of partially dechlorinated congeners. Thus, the percentage values of 8.0 and 8.5% in the rice oil quoted above for the two toxic congeners may be somewhat lower than the actual values, particularly for 1,2,3,4,7,8-HxCDF. The contributions of the other 2,3,7,8-chlorine substituted PCDFs (i.e., 1,2,3,7,8-PnCDF; 1,2,3,6,7,8-, 1,2,3,7,8,9-, and 2,3,4,6,7,8-HxCDFs; and 1,2,3,4,6,7,8-HpCDF) to the toxic effects are not considered to be substantial since these congeners were not present in significant amounts in the oil, were not accumulated to any extent in human tissues, or, in the case of the latter congener, were of lower toxic potency.

A number of recent publications (Yoshihara *et al.*, 1981; Mason *et al.*, 1985; Nagayama *et al.*, 1985; Safe, 1987; Birnbaum *et al.*, 1987; NATO, 1988) have appeared on the relative toxicities of the various isomers and congeners of PCDFs. Comparisons have been made *in vivo* and *in vitro* in experimental animals and *in vitro* with human cells monitoring responses such as enzyme induction, binding to the Ah receptor that mediates these responses, atrophy of the thymus, inhibition of body weight gain, and teratogenic effects. The ratio of the response of 2,3,4,7,8-PnCDF to that of 1,2,3,4,7,8-HxCDF, i.e., their toxic equivalency factor (TEF), varies between 1 and 0.75 depending on what end point is chosen and whether exposure is repeated or simultaneous. However, for simplicity in this report we use the ratio of 5 as suggested by an international group (NATO, 1988).

Bringing together the factors of (i) the density of 0.91 of the oil, (ii) the total PnCDF content of 5.0 mg per liter oil, (iii) 8% of the penta-congener and 8.5% of the hexa-congener, and (iv) their relative toxicity of 5:1, 1 ml of toxic rice oil is equivalent to 0.44 μg 2,3,4,7,8-PnCDF equivalents (PEQ).

A thorough study by Hayabuchi *et al.* (1979) estimated the quantities of contaminated oil ingested by 141 patients diagnosed as having the signs and symptoms of yusho disease. The study was carried out by retrospective interview to determine the total amount of oil purchased per household and the amount consumed by each individual. The latter estimate was less accurately determinable than the former since it was based on the number of meals eaten at home, national statistics on relative di-

etary intakes according to age and sex, and the patients' recollections as to just when they began to feel sick. For the population as a whole, there was a mean latent period of 71 days before a Grade 0 response appeared. During this period, an average of 506 ml (estimated range 121–1934) of oil was consumed. The mean total consumption was 688 ml (estimated range 195–3375) of oil, and the average of the graded skin responses was 2.6.

No difference between the sexes was noted in the response, but an age dependency was noted, with patients between 0 and 11 years showing milder effects as classified above (Goto and Higuchi, 1969) than did those aged 12–19 years or older. Hayabuchi *et al.* (1979) reported, for each of the four age groups, the average latent period, the oil consumption both total and during the latent period, and the daily intake rate (μl/kg/day). From these data, we calculated the mean body weights for each group and the total intakes of oil on a milliliter per kilogram body weight basis.

II Yucheng

A second estimate of a body burden in humans associated with chloracne can be made using the blood PCDF levels of the yucheng patients as reported by Kashimoto *et al.* (1983). In this poisoning incident, symptoms were first noticed in May 1979 and the causal agent was discovered in October 1979. The PCDF content of the cooking oil was much lower than in the yusho case (0.29 versus 5.0 ppm), but exposures to the PCDFs did not differ markedly as a much higher average amount of oil was believed to be consumed in the yucheng incident. The blood of some 67 patients in a school for the blind in Taichung County, Taipei, was assayed for total PCDFs, PCBs, and PCQs over several time periods. Dermatological symptoms from each patient correlated strongly with the blood PCDF level. In order to have a more direct comparison with the body burden calculated from the yusho cases, we have selected those 12 individuals, out of 30 measured in November 1979, who had been diagnosed as having Grade 3 symptoms (moderate chloracne) 1 month after the last ingestion of the toxic oil. The total PCDF content of the blood of this group of 12 averaged 118 ng/kg of whole blood with a standard deviation of 42 ng/kg. For comparison, the 2 individuals having Grade 0 symptoms, which was defined in the yucheng case as having an "abnormal" blood PCB level without clinical manifestations (Hsu *et al.*, 1984), had an average blood value of 46 ng PCDF/kg. In the publication of Kashimoto *et al.* (1983), greater than 90% of the PCDF in blood from the yucheng patients was identified as 2,3,4,7,8-PnCDF and 1,2,3,4,7,8-HxCDF. Another peak, 1,2,4,7,8-PnCDF, is now known to be an artifact of the sample preparation (Ryan *et al.*, 1989).

Previous information on the distribution of PCBs (Brown and Lawton, 1984) and PCDDs/PCDFs (Patterson *et al.*, 1988, 1989) between either serum or plasma and red blood cells has shown that little or no chlorinated material is present in the polar lipid fractions of membranes of intact cells and that adipose tissue lipid and serum have shown a partitioning ratio of about 200. Hence the partitioning ratio between whole blood (as used in the yucheng case) and lipid may be calculated by dividing the partitioning ratio for serum by the serum content of whole blood. The latter was taken as one minus the mean hematocrit number, i.e., 0.44 (International Commission on Radiological Protection, 1975), giving a partitioning ratio of 200 × 0.56 or 355.

RESULTS AND DISCUSSION

Using the mean body weight of each age group in the yusho case, the milliliters of oil consumed per kilogram of body weight can be assessed from the data of Hayabuchi *et al.* (1979). This value is multiplied by 0.44 μg PEQ/ml of oil and by a factor of 0.85 to account for incomplete absorption to determine the presymptomatic (Grade 0) and total (Grade 3) uptakes of PEQ. In addition, a small adjustment has been made for clearance of the PEQ from the body during the latent period (71 days) and the total ingested period (96 days). Assuming a half-life of 1.5 years for the two toxic PCDFs (Ryan and Masuda, 1989), these adjustments, averaged over the two time periods, amounted to factors of 0.97 and 0.96, respectively. As shown in detail in Table 1, the average body burden that was associated with chloracne in the yusho patients was calculated to be 5.9 μg PEQ/kg and that producing the first signs of illness was 4.4 PEQ/kg.

In the yucheng case, the mean blood value of 118 ng total PCDF/kg whole blood converts to 71 ng PEQ/kg blood assuming a 1:1 ratio of the two toxic congeners and a 5:1 ratio in relative toxicity. As 1 kg of whole blood corresponds to 2.82 g of plasma lipid, the blood value corresponded to 25.1 μg PEQ/kg of lipid. As most of the patients in the study of Kashimoto *et al.* (1983) were less than 20 years old, we assume an average body weight of 45 kg containing 7.2 kg lipid (16%). Thus the mean body burden causing chloracne in the yucheng case is 4.0 ± 1.4 μg PEQ/kg body wt.

TABLE 1

ESTIMATED MEAN BODY BURDENS OF 2,3,4,7,8-PENTACHLORODIBENZOFURAN EQUIVALENTS (PEQ) PRESENT IN YUSHO PATIENTS AND MEAN GRADE OF SKIN RESPONSE[a]

Age group	N	Latent period[b] Body burden (range) μg PEQ/kg	Latent period[b] Mean skin response	Final outcome[c] Body burden (range) μg PEQ/kg	Final outcome[c] Mean skin response
0–11	26	7.5 (3.2–19.4)	0	9.2 (4.2–36.6)	1.9
12–19	27	4.7 (2.4–14.8)	0	5.8 (2.3–14.7)	3.1
20–44	60	4.0 (0.82–11.9)	0	5.6 (1.5–22.5)	2.8
45+	28	3.0 (1.2–9.2)	0	4.3 (1.6–14.9)	2.6
All ages	141	4.4 (1.1–16.8)	0	5.9 (1.7–28.8)	2.6

Note. Range values are based on the average weights for each group calculated: 0–11 years, 16.4 kg; 12–19 years, 46.9 kg; 20–44 years, 53.3 kg; 45+ years, 51.5 kg.

[a] As calculated from data presented by Hayabuchi *et al.* (1979).

[b] Time between first ingestion of toxic rice oil and appearance of clinical effect.

[c] Final reported clinical effects of patients.

We have derived two independent values for a human body burden or uptake of PCDFs causing moderate chloracne. Using data on total oil consumption from the yusho poisoning, an average value of 5.9 μg PEQ/kg body wt has been derived. Alternatively, using blood values in the yucheng poisoning, an average value of 4.0 ± 1.4 μg PEQ/kg body weight has been estimated. These mean values differ by little, even though a number of assumptions and uncertainties are involved. However, there is likely greater uncertainty in the calculations based on the yusho incident than those obtained using data from the yucheng patients. In the former case, some error may be due to the estimate of (i) analysis of the specific isomers in oil due to the methods of extraction employed, (ii) the estimation of the TEF of 2,3,4,7,8-PnCDF relative to 1,2,3,4,7,8-HxCDF (< twofold), (iii) the total PCDFs in the oil (< twofold), (iv) an assumption of 85% absorption of the contaminants contained in the ingested oils, and (v) the actual quantity of oil consumed. In the yucheng case, since actual blood values were determined, no assumptions have been made regarding estimates (iii), (iv), and (v) above. Here, errors in the estimated body burden are largely due to the variation in blood levels (standard deviation within 36% of the mean value), the relative amounts of the two PCDFs in blood, the assumptions for the distribution coefficient of PCDFs among blood, serum, and adipose tissue, and average body weight.

The above calculations are directed toward estimating the mean human PEQ accumulation associated with specific toxic responses. One would also like to know the minimum dose producing a recognizable effect in the most sensitive individual in the study population. Hayabuchi *et al.* (1979) do list the cumulative oil consumption for the two adults showing the lowest estimated oil consumption (121 and 170 ml vs 506 ml for the population average) during their recollected (30 day) latent periods and also for the six adults showing the lowest ingestion rates (cumulative intakes 220, 235, 309, 314, and 353 ml vs 506 ml population average) during their recollected (120–135 day) latent periods. In our opinion, the available data do not permit a precise estimate of a minimum uptake in the most sensitive individual. However, the data do suggest that the range of values for producing either Grade 0 or 3 symptoms

must be quite narrow and may be within a factor of two of the mean values.

Wilson (1987) has made a less precise study of a dose–response curve for the yusho case by using data only for the total PnCDFs. He used the earlier oil PCDF concentration data (Kuratsune *et al.*, 1972) combined with a probit analysis to estimate an ED50 dose for the production of Grade 3 symptoms in this same population. He found a value of 68 μg of total PCDFs consumed per kilogram body weight (range 45–104 μg/kg). Using our estimates for the percentages of 2,3,4,7,8-PnCDF and 1,2,3,4,7,8-HxCDF in the rice oil (8.0 and 8.5%, respectively), absorption of 85%, and a TEF of 5 for relative toxicity of the two congeners, the ED50 by Wilson equates to about 5.6 μg PEQ/kg body wt. This value is quite close to our calculated value of 5.9 μg PEQ/kg body wt (Table 1) for the entire group.

TCDD Equivalents

In recent years, an attempt has been made to simplify the assessment of the toxic response to a whole series of PCDDs/PCDFs of varying substitution and chlorination. To this end a response factor of 1.0 has been allocated to 2,3,7,8-TCDD, and the other PCDDs and PCDFs, particularly those with 2,3,7,8-substitution, are assigned a toxic equivalent factor (TEF) between 0 and 1.0 depending on their relative potency in animal experiments. While the concept of TCDD equivalents (TEQ) with its assumption of additivity but not synergism or antagonism of effects has been accepted by many scientists, the actual TEFs can vary widely depending on the authority, country involved, or toxic end point chosen. The TEF for 2,3,4,7,8-PnCDF (relative to 2,3,7,8-TCDD) has been assigned 0.5 by an International Group (NATO, 1988). Using their numbers, our mean value of 4.4 μg PEQ/kg body wt for the toxic dose causing overt illness in yusho would correspond to 2.2 μg TEQ/kg, and the mean body burden for yucheng and yusho patients who developed Grade 3 chloracne (4.0 and 5.9 μg PEQ/kg) would correspond to 2.0 and 3.0 μg TEQ/kg. The corresponding total body burdens for an adult person would be between 150 and 200 μg TEQ and the adipose tissue level would be 9 to 13 μg TEQ/kg adipose.

Background Levels in General Population

The most comprehensive data available on background levels of PCDFs and PCDDs in general populations of the United States and Canada are those of Stanley *et al.* (1986) and Ryan *et al.* (1985), respectively. In the former study, analysis of 46 composite samples of adipose tissue taken from about 900 individuals from across the United States in 1982 showed average concentrations for 2,3,4,7,8-PnCDF and total HxCDFs of 35 ± 21 and 23 ± 11 ng/kg, respectively, on a lipid basis. In the latter study, 46 samples of adipose tissue from across Canada in 1976 showed concentrations of the same analytes on the same basis of 17 ± 8 and 18 ± 11 ng/kg. These adipose tissue levels of the two "yusho" congeners along with all the other 2,3,7,8-substituted PCDDs/PCDFs when converted into TEQ using the NATO TEFs correspond to accumulations or body burdens of 6.4 and 11 ng TEQ/kg body wt for Canada and the United States, respectively, or, based on a 70-kg person of 19% fat, 450 to 780 ng total. These background levels are more than 200 times lower than the body burden we calculate to have caused Grade 0 symptoms in the yusho incident and indicate that current mean body burdens are, on the average, much lower than those liable to cause overt toxic effects. If one considers, however, the upper limits of these adipose tissue concentrations, the difference would be only 100-fold.

Daily Uptake to Maintain Levels

Using the steady state relationship

$$\text{Dosing rate} = \frac{A \ln 2}{t_{\frac{1}{2}}},$$

where A is the mean accumulation (for the

TABLE 2

ESTIMATED BODY BURDENS OF 2,3,7,8-TCDD/2,3,7,8-TCDD EQUIVALENTS (TEQ) ASSOCIATED WITH BIOCHEMICAL/BIOLOGICAL EFFECTS IN EXPERIMENTAL ANIMALS AND HUMANS

Effect	Species	Dose and duration[a]	Estimated body burden[b]
Acute lethality	Guinea pig	2.0 μg/kg, single dose	2000 ng/kg
Aryl hydrocarbon hydroxylase (AHH) induction	Rat	2.0 ng/kg, single dose	2.0 ng/kg
Suppression of serum complement	B6C3F$_1$ mouse	10 ng/kg/day, 14 days (ip)	96 (140) ng/kg[c]
Altered T cell subsets	Rhesus monkey	0.12 ng/kg/day, 1 year	32 (44) ng/kg
Chloracne	HRS/J hairless mouse	0.1 μg/day, 3 days/week, 6 weeks (dermal)	22,500 (90,000) ng/kg[d]
	Rabbit	4 ng/day, 5 days/week, 4 weeks (dermal)	25 (32) ng/kg
	Rhesus monkey	34 μg 2,3,4,7,8-PnCDF/kg (iv)	17000 ng TEQ/kg[e]
	Rhesus monkey	1 μg/kg, single dose	1000 ng/kg[f]
Nausea, anorexia	Human	PCDFs, several months	2200 ng TEQ/kg
Chloracne	Human	PCDFs, several months	2000 to 3000 ng TEQ/kg
Reproductive effects, impaired conception, spontaneous abortion	Rat	10 ng/kg/day, 1 year	434 (3650) ng/kg
	Rhesus monkey	50 pg/kg/day (NOEL) 5.3 months (steady state)	50 ng/kg body fat[g] 11 ng/kg body wt
Cancer	Rat	10 ng/kg/day, 2 years	435 (7300) ng/kg

Note. Table modified from Universities Associated for Research and Education in Pathology (1988).

[a] All doses are for 2,3,7,8-TCDD and are oral or dietary unless otherwise indicated.

[b] Values were calculated based on determined and estimated first-order elimination.

[c] Values in parentheses indicate the body burden if there were no metabolism and/or elimination of 2,3,7,8-TCDD.

[d] On the basis of data of Puhvel *et al.* (1982) and assuming the body weight of the mice to be 20 g and the first-order elimination half-life to be 11 days, i.e., the same as the C57Bl/6 mouse.

[e] On the basis of data of Brewster *et al.* (1988); 90% of the dose was eliminated from the blood within 6 min of dosing and the whole-body half-life was approximately 49 days. Since two out of three animals died 40 and 48 days after treatment, the value of 17,000 ng TEQ/kg may be high relative to a lower dose that causes chloracne in the absence of lethality.

[f] On the basis of data of McNulty (1985).

[g] On the basis of the calculated steady state no-observable-effect level of 50 pg/kg/day determined by Bowman *et al.* (1989) and assuming 5.6 kg body wt and 14% fat per animal.

yusho patients with Grade 0 symptoms taken as 4.4 μg PEQ/kg), and $t_{\frac{1}{2}}$ is the clearance half-life taken as equal to 1.5 × 365 days (Ryan and Masuda, 1989), the daily ingested dosing rate that may produce physical complaints in an individual (assuming 85% uptake efficiency) would be 6.6 ng PEQ/kg/day or approximately 460 ng PEQ total per day for a 70-kg individual. In terms of TEQ, these values would be 3.3 ng TEQ/kg/day and 230 ng TEQ/day, respectively. Using this same relationship and assuming a $t_{\frac{1}{2}}$ for 2,3,7,8-TCDD of 5.8 years (Poiger and Schlatter, 1986), the corresponding daily ingested doses (6.4 and 11 ng TEQ/kg body wt) for the general populations of Canada and the United States which would give rise to current adipose tissue average levels would average about 3.4 pg TEQ/kg/day or 240 pg total TEQ/day, respectively.

Comparison to Animal Data

Table 2 offers a comparison of the doses of 2,3,7,8-TCDD equivalents we have estimated to cause chloracne in the yusho and yucheng poisonings with the doses of 2,3,7,8-TCDD or 2,3,4,7,8-PnCDF known and/or calculated to cause chloracne or other toxic effects in a variety of experimental animals. The body burdens were calculated by the panel of the Universities Associated for Research and Education in Pathology (1988) for the time immediately following the last dose using the methods described by Rose *et al.* (1976), published values for elimination half-lives of 2,3,7,8-TCDD, and assuming 100% absorption for oral dosing. Table 2 shows that the 2,3,7,8-TCDD and 2,3,4,7,8-PnCDF doses found to elicit chloracne in some experimental animals, particularly the rhesus monkey, are similar to those presently estimated to cause this skin disease in some exposed humans. Other effects, including AHH enzyme induction, altered immune system parameters, and reproductive impairment, generally occur in experimental animals at 2,3,7,8-TCDD doses that are lower than those that cause chloracne in these species. The relative sensitivity of humans to these other effects is only partially defined by the available data. The extreme sensitivity of the rhesus monkey to spontaneous abortion has not been observed in humans (Rogan *et al.*, 1988). Elevations in human AHH enzyme levels are now known (Brown *et al.*, 1989) to be manifested by the long known alterations in the PCB clearance pattern exhibited by yusho (Kuratsune, 1980) and yucheng (Chen *et al.*, 1982) patients. These alterations were found to correlate with manifestations of chloracne (Kuratsune, 1980), suggesting similar dose–response relationships for AHH enzyme elevation and chloracne development. However, nausea and anorexia do occur in humans at lower PCDF accumulations than those causing chloracne. At present, there are no data to indicate whether other types of subtle physiological or biochemical effects may occur at levels lower than those that produce these physical complaints.

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