Half-Lives and Body Burdens for Dioxin and Dioxin-Like Compounds in Humans Estimated from an Occupational Cohort in Germany.

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Introduction

Polychlorinated dibenzodioxins (PCDDs) and dibenzofurans (PCDFs) are synthetic chemicals which form or were formed during the production of a number of chlorinated chemicals and as a byproduct to chlorinated bleaching and waste incineration. Environmental contamination by the PCDD/Fs has been documented worldwide and is ubiquitous. Recent improvements in the analytical techniques used to measure PCDD/Fs allow for the concentration of these compounds to be assessed in reasonable amounts of human tissue, most notably plasma.

A number of symptoms and diseases have been associated with dioxin exposure[1]. Acute symptoms include smarting of eyes, nose or throat, vertigo, nausea and vomiting, itching, flushing and/or swelling of the face followed by skin symptoms characterizing chloracne. Longer term symptoms include fatigue, irritability, muscle pain and porphyria cutanea tarda. Chronic symptoms include highly nonspecific liver function disorder, hyperlipidemia, neurasthenic and depressive syndromes and poly-neuropathy. Also reported are impairments of sensory systems, carbohydrate metabolism, respiratory tract, heart and circulatory system, and the urinary tract. In most studies individual exposure was defined and classified, not by measurement of dioxin concentration in the human tissue, but by working history assessment or by acute symptoms which occurred early after exposure (e.g. chloracne). Those studies performed since the late sixties have associated many diseases to dioxin exposure, but they were also affected by the obvious methodological weaknesses of a retrospective epidemiological approach.

When PCDD/F concentration measurements in humans became possible, retrospective studies could be performed which related the disease outcomes to the currently measured PCDD/F concentration in the human, at first determined in human adipose tissue and later in human serum lipids[2-13]. Only a few of these studies exhibited evidence of an association of increased PCDD/F concentrations measured in the individual with an increased health risk. One possible reason for this failure is that the actual PCDD/F levels determined a long time after the exposure might not be adequate to describe the exposure level which would be causative for an outbreak of a disease. Better explanations would seem to relate the occurrence of diseases to PCDD/F levels experienced during the exposure before disease onset and disease diagnosis. In the case of a retrospective study, which is the most common type of PCDD/F studies, previous levels have to be estimated from present ones.

Retrospective determination of PCDD/F levels in humans and their subsequent use in risk assessment are strongly connected to their pharmacology. Chronic environmental exposure, route of exposure, fat storage, and mechanism of elimination are important determinants of the level of PCDD/Fs in serum 1 or 2 decades following high occupational exposure.

In what follows, a simple pharmacokinetic model will be used to estimate the half-lives for certain PCDD/Fs using tissue samples from a cohort of men occupationally exposed to PCDD/Fs. This simple model follows along classical pharmacological compartmental analysis and uses as much of the available evidence on PCDD/F distribution and metabolism as possible in making the reverse calculation of the half-life. Evaluation of the toxicokinetics of PCDD/Fs can substantially improve any risk assessments performed on these agents by providing a means of understanding historical exposures and studying tissue concentrations during key etiological periods for the diseases of interest.

Materials and Methods

Boehringer Cohort

The participants in this study came from two plants operated by the C.H. Boehringer Sohn Chemical Company, one in Ingelheim and the other in Hamburg. The Boehringer-Ingelheim plant produced 2, 4, 5-trichlorophenol (TCP) from 1950 to 1954. Irregularities in the production (excesses in the allowed reaction temperature, over-foaming of the distillant) caused contamination of TCP with PCDD/Fs. The Boehringer-Hamburg plant used TCP from the Ingelheim plant from 1951 to 1954. In 1954, chloracne cases occurred in Hamburg eventually causing a halt to the production of TCP at the Ingelheim plant; this resulted in closure of this production area at the Hamburg facility. Beginning in 1957, TCP production was restarted in Hamburg using a different process. From 1957 to 1983, lesser contamination with PCDD/Fs occurred. The production in the Hamburg plant was stopped in April 1983 and the plant was finally closed in October 1984 (for a better description of the process and the cohort, see 13).

At that time, an investigation program independent of the C. H. Boehringer Sohn company was initiated and performed by the Institute of Occupational, Social and Environmental Medicine of the University of Mainz[31]. During 1984, a total of 339 persons were identified as potential members of this cohort; 196 of these people joined the program and 186 were examined according to an investigation protocol. This cohort was further investigated in a follow-up study using dioxin concentration measurements for 88 persons of the 186 cases of both Boehringer plants. In 1992 a second medical investigation program was initiated. A total of 192 people (out of 375 invited) were evaluated for health effects. The description of analytical methods used to obtain tissue concentrations is given elsewhere[14-16] and a full description of the individuals measured is given in an earlier manuscript[12].

Blood and fat concentrations of PCDD/Fs were obtained from these medical screenings. In total, blood tissue concentrations were measured in 187 individuals with multiple samples (over time) for some individuals leading to a total of 382 tissue samples for analysis. The contaminant concentrations are expressed in pg/g (ppt) based on the lipid content. This quantity is denoted ppt, lipid adjusted and is equivalent to ng/kg of body fat. In the present analysis, contaminant level

measurements from both adipose tissue (n=48) and blood lipids (n=334) are used. This is justified by results[18] showing excellent correlations of dioxin levels determined in adipose tissue and in blood serum lipids. Note, that a large fraction of the former employees of the C. H. Boehringer Sohn Company of the Hamburg plant are also part of several separate investigations[13,17].

The Hamburg plant was subdivided into 16 areas corresponding to different production processes which would logically result in different exposures to dioxins between 1953 and 1984. The Ingelheim plant which lead to PCDD/F exposures only between 1952 and 1954 was not further subdivided but considered as one area. One additional category was introduced which summarized all other occupational activities which could not be classified into one of the other categories, including a few persons working for a clean-up service which worked at the plant after 1984.

Occupational histories of workers at the Boehringer plants in Hamburg and Ingelheim were documented using a recall questionnaire. Information obtained included, start of employment, end of employment, sojourn times in a maximum of 3 working areas in any one period, start of work in that area and end of work in that area. In the few cases where more than three areas were reported for one time period, the areas with the highest expected exposures were used. In cases were multiple work areas were described for one time interval, exposure was weighted uniformly amongst the work areas in these cases.

From the working history data, a computer file was created describing the sequence of life history intervals where $I_i = [t_i, t_{i+1}]$ represents the i^{th} history interval starting at time t_i and ending at time t_{i+1} for i=1 to m. I_0 is the interval from birth to the start of employment and I_{m+1} is the interval from the end of employment to the time of tissue sampling for the contaminants.

It was assumed that, over the entire period covered by this analysis, exposures in each area were possibly different from one another and were constant. The overall goal of this analysis is to create an exposure matrix for these work areas by estimating a daily dose (d_k) of contaminant (pg/g body fat/day) for each area (k=1,2,… 19) which provided the best explanation of the observed blood concentrations. As part of this analysis, it was also possible to estimate a background exposure (b_0 in units of pg/g body fat/day) and a half-life (in days) for each contaminant. The individual contributions from each area will be described in a different report.

A Simple Kinetic Model For Estimating Half-Lives

An individual's contaminant concentration at any time t, was modeled by a first order kinetic of constant input and linear outflow. The general form of this model can be expressed using the ordinary differential equation:

$$\frac{dC(t)}{dt} = d - k_e C(t) \qquad (1)$$

where *C(t)* is the concentration in lipid (pg/g body fat) at time t, *d* is the inflow of contaminant into the lipid compartment (pg/g body fat/day) and k_e is the rate of elimination of the contaminant (1/day). Assuming constant inflow of contaminant in a given area, the concentration of contaminant in blood at the end of the $(i-1)^{th}$ exposure period (t_i) can be simplified to the equation:

$$C_i = \left[\frac{e_i + b_0}{k_e} \left(1 - \left\{ 1 - \frac{C_{i-1} k_e}{e_{i-1} + b_0} \right\} e^{-k_e (t_i - t_{i-1})} \right) \right] \quad (2)$$

where C_i (pg/g body fat) denotes concentration at the end of the (i-1)th interval, e_{i-1} (pg/g body fat/day) denotes the contribution during the ith interval from the work area the individual is employed in and b_0 (pg/g body fat/day) denotes the constant input from non-occupational environmental exposures. The contribution from the individual work areas (d_k), the background exposure (b_0) and the elimination half-life (k_e) were estimated from the observed tissue concentrations using the least-squares algorithm. Due to some degree of non-symmetry in the error around the data, the natural log of the concentrations (both predicted and observed) were used in the least squares algorithm. In addition, the algorithm converged better if estimates for the log exposures were obtained rather than the arithmetic estimates. The half-life (λ_h) can be estimated from the elimination rate by using the simple formula:

$$\lambda_h = \frac{\ln(2)}{k_e} . \quad (3)$$

Model parameters (b_0, k_e, d_i) were estimated using a nonlinear least-squares algorithm in SAS[19]. Standard errors were estimated using the asymptotic standard errors provided by the NLIN algorithm in SAS. In the model, no specific route is assumed and intake is expressed as picograms of PCDD/F into the blood per kilogram body weight per day (pg/kg/day). The analysis was performed separately for each PCDD/F which had sufficient exposure data above the limit of detection (which varied for each agent).

Results

A simple pharmacokinetic model assuming a first order elimination from one compartment was used to analyze measured tissue levels in humans occupationally exposed to PCDD/Fs. The most basic parameter of this model is the elimination constant which is proportional to the reciprocal of the half life for each PCDD/F. Based on this simple model, numerous studies have tried to characterize the elimination of PCDD/Fs and like compounds. Table 1 gives estimates for the half-life and background exposure to TCDD, 1,2,3,7,8-pentachlorodibenzo-dioxin (PCDD), 1,2,3,4,7,8-hexachlorodibenzo-dioxin (HxCDD), 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8-heptachlorodibenzo-dioxin (HpCDD), octachlorodibenzo-dioxin (OCDD), 2,3,4,7,8-pentachlorodibenzo-furan (PCDF), 1,2,3,4,7,8-hexachlorodibenzo-furan (HxCDF), 1,2,3,6,7,8-HxCDF, 2,3,4,6,7,8-HxCDF and 1,2,3,4,6,7,8-heptachlorodibenzo-furan (HPCDF).

In general, as the number of chlorines increase, the half-life for the individual agent decreases. TCDD has the longest half-life of all of the dioxins studied at 9.52 years. The one PCDD studied (1,2,3,7,8-PCDD) had a half-life one-third smaller than TCDD at 6.52 years. The three HxCDDs had close half-lives with 1,2,3,4,7,8-HxCDD and 1,2,3,7,8,9-HxCDD having half-lives of about 4.6 years and 1,2,3,6,7,8-HxCDD with a half-life of 7.45 years but with a larger standard error. The one HpCDD studied (1,2,3,4,6,7,8-HpCDD) had the smallest half-life of all the dioxins at

3.38 years. OCDD reversed the trend observed of increasing half-lives with decreasing occupation of chlorines with a larger half-life than two of the HxCDDs and the HpCDD at 5.06 years.

The dibenzofurans studied displayed a less consistent pattern of decreasing half-lives with increasing occupation of chlorines and, for the penta and hexa's, had generally longer half-lives than the dibenzo-dioxins. The one penta studied (2,3,4,7,8-PCDF) had the longest estimated half-life at 19 years but was also the most unstable estimate with a standard error of 4.8 years. Two of the hexa's (1,2,3,4,7,8-HxCDF and 1,2,3,6,7,8-HxCDF) had rather long half-lives (6.4 and 7.9 years respectively) and the remaining (2,3,4,6,7,8-HxCDF) had the shortest estimated half-life of all of the congeners examined (2.7 years). Finally, the one hepta studied (1,2,3,4,6,7,8-HPCDF) closely matched the half-life (3.2 years) of the similarly chlorinated dibenzodioxin.

Table 1: Half-lives and background exposure to TCDD and similar compounds estimated from human tissue samples measured in occupational workers in Germany (Manz et al, 1991)

Congener	*Half-Life in Years (Standard Error)*	*Background Exposure in pg/kg/day (log standard error)*	*Calculated Steady-State Body Burden (ppt)*
2,3,7,8-TCDD	9.52 (1.59)	0.29 (0.73)	3.40
1,2,3,7,8-PCDD	6.52 (0.86)	0.67 (0.51)	5.32
1,2,3,4,7,8-HxCDD	4.62 (0.50)	1.14 (0.52)	6.41
1,2,3,6,7,8-HxCDD	7.45 (0.93)	3.66 (0.50)	33.13
1,2,3,7,8,9-HxCDD	4.63 (0.56)	0.59 (0.57)	3.31
1,2,3,4,6,7,8-HpCDD	3.38 (0.37)	6.12 (0.51)	25.04
OCDD	5.06 (0.63)	36.66 (0.50)	225.10
2,3,4,7,8-PCDF	19.09 (4.82)	0.60 (0.55)	13.87
1,2,3,4,7,8-HxCDF	6.36 (0.70)	0.74 (0.50)	5.70
1,2,3,6,7,8-HxCDF	7.90 (1.03)	0.48 (0.48)	4.63
2,3,4,6,7,8-HxCDF	2.69 (0.38)	0.17 (0.61)	0.56
1,2,3,4,6,7,8-HpCDF	3.24 (0.28)	1.49 (0.39)	5.87

Discussion

Other reports have given estimates of the half-lives for these dioxins and dibenzofurans. The estimates presented generally fall within the range of existing estimates with some deviations. The half-lives in the literature for 2,3,7,8-TCDD range over numerous values such as 6.1 years[20], 7.1 years[21], 8.7 years[22], 11.3 years[23], with most of the remaining estimates falling on the lower end. Half-lives for the 1,2,3,7,8-PCDD in humans are generally based upon a calculated half-life of 5 years in serum[24] which is slightly shorter and almost significantly different from the value presented here. The HxCDDs have been studied by several groups. In adipose tissue, the half-life for 1,2,3,6,7,8-HxCDD was estimated to be 3.5 years[25] and the half-life for 1,2,3,4,7,8-HxCDD was calculated to be 15 years[24]. Both numbers differ substantially from the estimate presented here; these values suffer from either small sample sizes[25] or from extrapolation using animal data[24] and the values given in Table 1 should provide more accurate estimates. The same two references provide estimated half-lives for 1,2,3,4,6,7,8-HpCDD with values of 3.2 years[25] and 25 years[24];

again, the value above is more likely to be accurate. Similarly, disparate estimates exist for the half-life of the OCDD, with a range of 5.7 years[25] to 50 years[24] as compared to 5.06 years presented in Table 1.

Half-lives for the dibenzofurans cover similar ranges in the literature to those discussed above for the dioxins. Estimated half-lives for 2,3,4,7,8-PCDF range from 1.3 years[26] to 7.2 years[27] with other values falling in this range[24,26]. The value presented in Table 1 is considerably larger and, given the large standard error, unreliable; it is difficult to ascertain from these data if this value is too large. The half-lives presented for the HxCDFs are larger than existing literature values with the exception of 2,3,4,6,7,8-HxCDF for which no estimate could be found. For 1,2,3,4,7,8-HxCDF, estimates of 4.5 years[27] and 2.4 years[26] exist and for 1,2,3,6,7,8-HxCDF, a single literature estimates of 4.9 years[27] exists. Finally, the estimate for the half-life of 1,2,3,4,6,7,8-HpCDF falls in the range of existing literature estimates ranging from 2.4 years[26] to 6.8 years[27].

In general, the half-lives presented in Table 1, with the exception of 2,3,4,7,8-PCDF, represent fairly accurate estimates of long-term (greater than 15 years) elimination kinetics of these agents. It is unclear why the estimate for 2,3,4,7,8-PCDF is unstable and has a large standard error; however, given the other, much lower estimates in the literature, it is unlikely this estimate is correct.

One article[17] deserves special attention when evaluating the current study. This analysis focused on a subgroup of 48 individuals from the current analysis for which 2 or 3 separate blood measurements had been done. Their estimates for these PCDDs/Fs are as follows: 2,3,7,8-TCDD, 6.9 years; 1,2,3,7,8-PCDD, 15.7 years; 1,2,3,4,7,8-HxCDD, 8.4 years; 1,2,3,6,7,8-HxCDD , 13.1 years; 1,2,3,7,8,9-HxCDD, 4.9 years; 1,2,3,4,6,7,8-HpCDD, 3.7 years; OCDD, 6.7 years; 2,3,4,7,8-PCDF, 19.6 years; 1,2,3,4,7,8-HxCDF, 6.4 years; 1,2,3,6,7,8-HxCDF, 6.0 years; 2,3,4,6,7,8-HxCDF, 5.8 years; and 1,2,3,4,6,7,8-HpCDF, 3.0 years. The most marked disagreements are for 2,3,7,8-TCDD (-2.5 years), 1,2,3,7,8-PCDD (+9 years), 1,2,3,7,8,9-HxCDD (+3.8 years), 1,2,3,6,7,8-HxCDD (+5.6 years) and 2,3,4,6,7,8-HxCDF (+3.1 years); the remaining values are very similar. Part of this difference may be due to the effect of covariates such as age and percentage body fat which was not controlled for in this analysis but was included in the analysis with the sub-sample[17]; these factors contribute considerably to their baseline half-life. Also, the sub-sample analysis did not focus on the occupational history as contributing to the half-life determination but instead used a direct analysis from the multiple samples.

The half-lives of the dioxins and dibenzofurans studied in this paper do not parallel the binding affinity of the agents to the Ah-receptor[28]. While there is some agreement, it is clear that compounds like 1,2,3,6,7,8-HxCDF and 2,3,4,6,7,8-HxCDF with equivalent binding affinities have very different half-lives. Hence, the half-lives of these agents are not wholly governed by the proteins they induce via the Ah-Receptor or their residency times with this receptor. Because of this, toxic equivalency factors (closely aligned to receptor binding) developed for chronic exposure to these agents may not be appropriate for short-term exposures or exposures which have variable patterns over time.

The half-lives and background exposures in Table 1 can be used to estimate steady-state, lipid-adjusted body burdens in humans using a simple formula[29]; these values are given in the last

column of Table 1. Estimates of lipid-adjusted blood concentrations in the general population exist for Germany[30]. All of the steady-state levels presented in Table 1 are smaller than the mean estimated blood levels[30]. In some cases, the difference is very small (e.g. 3.6 ppt versus 3.4 ppt for 2,3,7,8-TCDD) but in others, as much as a 4-fold difference exists (e.g. 828 ppt versus 225 ppt for OCDD); the explanation for this difference is unclear. It is possible that the analysis above using the occupational cohort is inappropriately assigning too much of each agent to the occupational setting. This could result through simple statistical variation or may be a result of temporal changes in background exposure occurring at the same time as the majority of the occupational exposures (the environment might have been dirtier in the past or these individuals may have seen greater background due to their proximity to other sources). It is also possible that the means estimates[30] do not represent the central tendency of the exposure distribution (as would occur for means from log-normally distributed data) whereas the estimates presented in this analysis would (having adjusted for assymetry in the distributions for the parameter estimates); a comparison based upon medians may have been closer.

References

1. Webster, T. and Commoner, B. (1994) Overview: The Dioxin Debate. In: Schecter, A. (ed.) Dioxins and Health, Plenum Press, New York, 1-50.
2. Calvert GM, Sweeney MH, Morris JA, Fingerhut MA, Hornung RW, Halperin WE (1991) Evaluation of chronic bronchitis, chronic obstructive pulmonary disease, and ventilatory function among workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Am Rev Respir Dis 144(6):1302-6
3. Calvert GM, Hornung RW, Sweeney MH, Fingerhut MA, Halperin WE (1992) Hepatic and gastrointestinal effects in an occupational cohort exposed to 2,3,7,8-tetrachlorodibenzo-para-dioxin. JAMA 267(16):2209-14
4. Calvert GM, Wall DK, Sweeney MH, Fingerhut MA (1998) Evaluation of cardiovascular outcomes among U.S. workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Environ Health Perspect Suppl 2:635-43
5. Mocarelli P, Brambilla P, Gerthoux PM, Patterson DG Jr, Needham LL (1996) Change in sex ratio with exposure to dioxin. Lancet 348(9024):409
6. Ott MG, Messerer P, Zober AOtt et al, (1993). Assessment of past occupational exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin using blood lipid analyses. Int Arch Occup Environ Health 65(1):1-8
7. Ott MG, Zober APatterson et al, (1989). Cause specific mortality and cancer incidence among employees exposed to 2,3,7,8-TCDD after a 1953 reactor accident. Occup Environ Med 53(9):606-12
8. Pesatori AC, Zocchetti C, Guercilena S, Consonni D, Turrini D, Bertazzi PA (1988) Dioxin exposure and non-malignant health effects: a mortality study. Occup Environ Med. 55(2):126-31.
9. Patterson DG Jr, Fingerhut MA, Roberts DW, Needham LL, Sweeney MH, Marlow DA, Andrews JS Jr, Halperin WE (1989) Levels of polychlorinated dibenzo-p-dioxins and dibenzofurans in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Am J Ind Med. 16(2):135-46.
10. Sweeney MH, Fingerhut MA, Arezzo JC, Hornung RW, Connally LB (1993) Peripheral neuropathy after occupational exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Am J Ind Med. 23(6):845-58.

11. Wolfe WH, Michalek JE, Miner JC, Rahe A, Silva J, Thomas WF, Grubbs WD, Lustik MB, Karrison TG, Roegner RH (1990) Health status of Air Force veterans occupationally exposed to herbicides in Vietnam. I. Physical health. JAMA. 264(14):1824-31.
12. Jung D, Berg PA, Edler L, Ehrenthal W, Fenner D, Flesch-Janys D, Huber C, Klein R, Koitka C, Lucier G, Manz A, Muttray A, Needham L, Papke O, Pietsch M, Portier C, Patterson D, Prellwitz W, Rose DM, Thews A, Konietzko J (1998) Immunologic findings in workers formerly exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin and its congeners. Environ Health Perspect. 106 Suppl 2:689-95.
13. Manz A, Berger J, Dwyer JH, Flesch-Janys D, Nagel S, Waltsgott H (1991) Cancer mortality among workers in chemical plant contaminated with dioxin. Lancet. 338(8773):959-64.
14. Patterson DG Jr, Hampton L, Lapeza CR Jr, Belser WT, Green V, Alexander L, Needham LL (1987) High-resolution gas chromatographic/high-resolution mass spectrometric analysis of human serum on a whole-weight and lipid basis for 2,3,7,8-tetrachlorodibenzo-p-dioxin. Anal Chem. 59(15):2000-5.
15. Beck H, Eckart K, Mathar W, Ruhl CS, Wittkowski R (1988) Isomer-specific determination of 2,3,7,8-tetrachlorodibenzo-p-dioxin and related compounds in human fat and food. Biomed Environ Mass Spectrom. 16(1-12):161-5.
16. Papke O, Ball M, Lis Za, Scheunert K (1990) Determination of pcdd/pcdf in whole-blood from persons involved in fire incidents Chemosphere 20: (7-9) 959-966
17. Flesch-Janys D, Becher H, Gurn P, Jung D, Konietzko J, Manz A, Päpke O. (1996) Elimination of polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/F) in occupationally exposed persons. J Toxicol Environ Health 47:363-378.
18. Patterson DG Jr, Needham LL, Pirkle JL, Roberts DW, Bagby J, Garrett WA, Andrews JS Jr, Falk H, Bernert JT, Sampson EJ (1988) Correlation between serum and adipose tissue levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin in 50 persons from Missouri. Arch Environ Contam Toxicol. 17(2):139-43.
19. The Statistical Analysis System (1999), Version 6.12, SAS Institute Inc., Cary, NC, USA
20. Patterson DG, Holler JS, Smith SJ, Liddle JA, Sampson EJ, Needham LL. (1986) Human adipose data for 2,3,7,8-tetrachlorodibenzo-p-dioxin in certain U.S. samples. Chemosphere 15:2055-2060.
21. Poiger H, Schlatter C, (1986) Pharmacokinetics of 2,3,7,8-TCDD in man. Chemosphere 15:1489-1494.
22. Michalek JE, Pirkle JL, Caudill SP, Tripathi RC, Patterson G, Needham LL. (1995) Pharmacokinetics of TCDD in veterans of Operation Ranch Hand: 10-year follow-up. J Toxicol Environ Health 47:209-220.
23. Wolfe WH, Michalek JE, Miner JC, Pirkle JL, Caudill SP, Patterson DG Jr, Needham LL (1994) Determinants of TCDD half-life in veterans of operation ranch hand. J Toxicol Environ Health. 41(4):481-8
24. Schlatter C. (1991) Data on kinetics of PCDDs and PCDFs as a prerequisite for human risk assessment. In: Biological Basis for Risk Assessment of Dioxins and Related Compounds (Gallo MA, Scheuplein RJ, van der Heijden KA, eds). Banbury Rpt 35. Plainview, NY:Cold Spring Harbor Laboratory Press, 215-227.
25. Gorski, T., Konopka, L. and Brodzki, M. (1984) Persistence of some polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans of pentachlorophenol in human adipose tissue. Roczn. Pzh. T. 35(4), 297-301.

26. Ryan, J. and Matsuda, Y. (1991) Elimination of polychlorinated dibenzofurans (PCDFs) in humans from the Usho and Ucheng rice oil poisonings. Proc. 11th Int. Symp. On Chlorinated Dioxins and Related Compounds, Dioxin '91, September 23-27, Research Triangle Park, NC p. 70.
27. Schecter A, Ryan JJ, Kostyniak PJ (1990) Decrease Over A 6 Year Period Of Dioxin And Dibenzofuran Tissue-Levels In A Single Patient Following Exposure. Chemosphere 20: (7-9) 911-917
28. Safe, S. (1990) Polychlorinated biphenyls (PCBs), dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs) and related compounds: environmental and mechanistic considerations which support the development of toxic equivalency factors (TEFs). Crit. Rev. Toxicol 21: 51-88.
29. Portier, C. (1998) Risk ranges for various endpoints following exposure to 2,3,7,8-TCDD. In WHO-ECEH / IPCS Consultation On Assessment Of The Health Risk Of Dioxins; Re-Evaluation Of The Tolerable Daily Intake, Worl Health Organization ICP EHH 019 Vd98.2/10, Geneva
30. Schecter, A. (1994) Exposure Assessment: Measurement of dioxins and related chemicals in human tissue. In: Schecter, A. (ed.) Dioxins and Health, Plenum Press, New York, 1-50.
31. Benner, A., Edler, L., Mayer, K. and Zober, A. (1990) Plychlorinated dibenzodioxin (PCDD) and dibenzofuran (PCDF) levels and morbidity data of employees occupationally exposed in the chemical industry. In Untersuchungsprogramm "Dioxin", BG Chemie, ISBN 3-88383-3D2-9