# First results of an investigation of the elimination of polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/F) in occupationally exposed persons

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## 1. Introduction

To assess health risks of PCDD/Fs to humans, especially with regard to their carcinogenic potential, knowledge about dose-response-relationships from epidemiological data would provide important information. For the estimation of dose-response-relationships a quantitative dose parameter is needed. Currently available data indicate that PCDD/Fs in general accumulate in human fat tissue and are eliminated only slowly so that past exposure can be assessed many years after termination by measurements of PCDD/F-levels in human adipose tissue or blood. However, to determine the magnitude of exposure to PCDD/Fs retrospectively more exact knowledge about the elimination rate of these substances in humans is of basic importance.

With regard to 2,3,7,8-TCDD, a recent study[1] found a median half-life of 11.3 years (95%CI 10.0, 14.1) in n=337 veterans of the Operation Ranch Hand using serum levels from two time points with a distance of 5 years assuming a first-order-kinetic. This study also included n=36 persons for whom a median half-life of 7.1 year was reported earlier [2]. In a consecutive paper[3] an effect of percent body fat (PBF) on the half-life could be demonstrated. Schlatter[4] reported a half-life of 9.7 years in one person for whom the time course of elimination could be determined by 6 measurements over 6 years. The data were compatible with the assumption of a first order kinetic.

Little is known about the time course of elimination for the other 2,3,7,8-substituted dioxins and furans in humans. RYAN et al.[5] reported mean half-lives between 2 and 5 years in highly exposed persons from the Yucheng (n=4) and Yusho (n=9) accidents, again under the assumption of a first order kinetic. They speculated that the differences observed between these two groups could be due to deviations from a first order kinetic. SCHECTER[6,7] described the elimination of 4 PCDFs. The estimated half-lives were in the range of 4 to 6.8 years. Finally, GORSKI et al.[8] reported half-lives between 3.2 and 5.7 for one Hexa-, Hepta- and Octa-dioxin and less than 1.8 year for one Hepta- and Octa-furan in one person with two measurements 2.5 years lagged.

This paper describes the first results of an investigation of the elimination for most of the 2,3,7,8-substituted dioxins and furans in occupationally highly exposed persons.

## 2. Materials and methods

*Description of the study group*

The study group consists of a subgroup of a cohort of workers from a herbicide producing plant in Germany for which the cancer mortality was studied earlier[9]. In 1992-1994, n=188 workers from a former herbicide producing plant in Hamburg, FRG, with high exposure to PCDD/Fs participated in a health investigation program by the Institute for Occupational and Social Medicine, University of Mainz. Blood samples were ascertained and constantly frozen at -20$^0$C. For all participants it was checked whether an older frozen blood sample was available from two occasions: First, a health investigation program by the same Institute in 1985/1986, second, from the ERGO-laboratory, which in the past had provided dioxin-measurements for some workers for claims for compensation for occupational disease. For n=37 persons an earlier blood sample from the health investigation program 1985/86 was identified. In addition, for 5 persons out of these a third blood sample between 1985/86 and 1992/94 was identified at the ERGO laboratory. For n=14 no sample was available from the investigation 1985/86, but samples at the ERGO-laboratory for the time period 1989/91. For one person, whose blood sample in 1992 was missing, a sample from the 1985/86-program and a second from the ERGO-laboratory from 1989 could be identified. In total, n=47 persons with two samples and n=5 with three samples were eligible for investigation.

Earlier PCDD/F-levels were available for n=43, either in adipose tissue from the 1985/86 investigation (n=15; these data are part of those described by BECK et al.[10]) or in whole blood (n=28; ERGO-laboratory). For 3 persons neither the TCDD-concentration nor the TEQ-concentration (Federal Health Office, Germany) exceeded the upper limit of German background values[11] (see table 2). They were excluded from the study. The TCDD-level for one person (21 ng/kg) was above background, but the time period between the two samples was only 1.5 year. Thus, it was excluded, too. For n=9 persons no information on their PCDD/F-concentration was available. In summary, n=43 persons with two samples and n=5 with 3 samples entered the measurement phase of the elimination study.

Table 1 shows some demographic and occupation related variables for the study group.

**Table 1 Sex, age at first blood sample, year of entry, duration of employment, time between end of employment and first blood sample and time between first and last blood sample for n=48 persons**

| Variable | |
|---|---|
| Sex | Males n=45 Females n=3 |
| Age at first blood sample | AM*48.7 yr, MD** 48, Min 32, Max 79 |
| Year of entry | AM 1968, MD 1969, Min 1952, Max 1980 |
| Duration of employment | AM 13.10 yr, MD 12.5 Min 2.3, Max 32.9 |
| Time between end of employment and first blood sample | AM 5.4 yr, MD 2, Min 0, Max 37 |
| Time between first and last sample | AM 5.6 yr, MD 6.3, Min 1, Max 9 |

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The study group consists of n= 45 males and n=3 females. Mean year of entry was 1968 and mean duration of employment was 13.1 years. Mean time between end of employment and first blood sample was 5.4 years (Median 2 years), and mean time between first and last blood sample was 5.6 years (Median 6.3).

For all persons complete health inventories from the investigations 1985/86 and 1992/94 were available, including height and weight, unintentional weight change in the study period, major diseases, and basic clinical laboratory parameters to check for potential influential factors.

*PCDD/F-measurements*

The frozen whole blood samples were transported to the ERGO-laboratory and kept frozen until analysed for the PCDD/F. The analytical method used for the blood samples was nearly identical to that used for the successfull participation in WHO interlaboratory validation studies (round II and III) on human blood and will not be described here[12-14]. The "old", the "new" and - if available - the "middle" sample were analyzed parallel at the same time. All HRGC/HRMS measurements have been performed in duplicate.

*Statistical Analysis*

In the present analysis for all persons the first and the last sample were used. Individual half-lives were calculated under the assumption of a one compartment-, first-order-kinetic- model using the equation

$$t_{1/2} = \frac{t * ln2}{\ln(\frac{C_0}{C_1})}$$

where $t_{1/2}$ is the half-life, t the time between the samples, $C_0$ and $C_1$ the PCDD/F-concentration at the first and the last time point.

Only persons, whose blood levels in all samples exceeded the 95%-upper confidence intervall of the German background concentration[10] were included in the analysis. In addition, for each congener an estimate of the half-life was obtained only for those persons, whose blood concentration of the first sample exeeded that of the last. For the characterization of the distribution of individual half-lives median, minimum, maximum and interquartile range were calculated. In the determination of these parameters persons whose last blood level exceeded the first and consequently no half-life estimate could be calculated were treated as if their half-life would be greater than the maximum estimate.

**3. Results**

Table 2 presents the results for the half-lives for each congener together with the distribution parameters for the first and last sample. Median of TCDD-levels in the first sample was 84.1 ng/kg (Min 15.6, Max 300.2), decreasing in the last sample to 48.9 ng/kg (7.7, 277.9). Substantially elevated levels, especially for the higher chlorinated dioxins, but also for some furans, were observed. Expressed as toxic equivalencies, the median concentration at the first time point was 191.9 ng/kg TEQ (43.1,767.2), decreasing to 115.3 ng/kg (29.4,500.4).

**Table 2 Concentration of PCDD/F in the first and last sample (ng/kg blood fat) and median half-lives (years)**

| | | First blood sample | | | Last blood sample | | | Indiv. half-life based on first and last sample | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | N[a] | Median | Minimum | Maximum | Median | Minimum | Maximum | Median | Minimum | Maxim.[b] | $q_{75}$-$q_{25}$[c] |
| 2,3,7,8-TCDD | 48 | 84.1 | 15.6 | 300.2 | 48.9 | 7.7 | 277.9 | 6.9 | 2.5 | - (1) | 5.1 |
| 1,2,3,7,8-PCDD | 40 | 51.1 | 27.2 | 251.2 | 35.9 | 13.2 | 190.3 | 15.7 | 3.6 | -(11) | -[d] |
| 1,2,3,4,7,8-HCDD | 41 | 83.2 | 25.6 | 746.9 | 51.3 | 18.7 | 559.7 | 8.4 | 1.3 | -(4) | 10.6 |
| 1,2,3,6,7,8-HCDD | 40 | 354.7 | 127.7 | 2939 | 255.8 | 101.6 | 2493 | 13.1 | 2.9 | -(9) | 52.9 |
| 1,2,3,7,8,9-HCDD | 39 | 88.2 | 29.3 | 680.8 | 39.5 | 17.6 | 288.3 | 4.9 | 2.0 | -(1) | 4.5 |
| 1,2,3,4,6,7,8-HPCDD | 26 | 641.2 | 310.5 | 5152 | 234.5 | 94.2 | 1526 | 3.7 | 1.7 | 16.3 | 4.4 |
| OCDD | 32 | 2526 | 1356 | 17566 | 1288.5 | 842 | 10395 | 6.7 | 1.8 | -(1) | 7.6 |
| 2,3,7,8-TCDF | . | . | . | . | . | . | . | . | . | . | . |
| 1,2,3,7,8-PCDF | . | . | . | . | . | . | . | . | . | . | . |
| 2,3,4,7,8-PCDF | 5 | 105.9 | 76.4 | 406.7 | 71.3 | 47.9 | 108 | 19.6 | 2.3 | 31.8 | 9.3 |
| 1,2,3,4,7,8-HCDF | 42 | 116.7 | 37.5 | 1035 | 61.6 | 21.9 | 498.4 | 6.4 | 1.9 | -(3) | 5.3 |
| 1,2,3,6,7,8-HCDF | 31 | 50.4 | 28.5 | 374 | 30.2 | 13.6 | 205.9 | 6.0 | 2.2 | -(3) | 11.6 |
| 2,3,4,6,7,8-HCDF | 6 | 16.3 | 10.1 | 38 | 8.8 | 6.1 | 14.8 | 5.8 | 3.1 | 19.7 | 4.8 |
| 1,2,3,4,6,7,8-HPCDF | 22 | 123.1 | 47.3 | 1028 | 45.8 | 24.7 | 243 | 3.0 | 2.1 | -(1) | 1.4 |
| 1,2,3,4,7,8,9-HPCDF | 6 | 14.8 | 3.6 | 26 | 3 | 1.6 | 5.4 | 3.2 | 2.1 | -(1) | 1.0 |
| OCDF | . | . | . | . | . | . | . | . | . | . | . |
| TEQ (FHO) | 45 | 191.9 | 43.1 | 767.2 | 115.3 | 29.4 | 500.4 | . | . | . | . |

[a]Number of persons whose levels exceed upper background concentrations at all points in time

[b]If no maximal half-life is announced there is at least one person (exact number in parantheses) showing an increase of levels over time.

[c]Range of quartiles

[d]Range of quartiles is not calculated because more than 25% of the persons show an increase of levels over time.

The median of individual half-lives for TCDD was 6.9 years. For the other dioxins, median half-lives ranged from 3.7 years (1,2,3,4,6,7,8-HpCDD) to 15.7 years (1,2,3,7,8-PCDD). With the exception of 2,3,4,7,8-PCDF, for which the analysis yielded a median half-life of 19.6 (Min 2.3, Max 31.8), based on only n=5 persons with blood levels exceeding 95%-upper background values at both points in time, median half-lives for the furans appeared to be a little bit shorter. They ranged from about 3 years for the Hepta-furans to about six years for 2,3,4,6,7,8-HCDF. For 2,3,7,8-TCDF, 1,2,3,7,8-PCDF and OCDF no half-life was estimated because no person in the study exceeded the background levels at all time points for these congeners.

An examination of minimum, maximum and quartile range of the half lives revealed considerable interindividual variation. In addition, while there was only one person showing no decrease for TCDD, especially for 1,2,3,7,8-PCDD and 1,2,3,6,7,8-HCDD no decrease in blood levels was observed for about 25% of the workers. Simultanously, for these congeners the variation was extremely large.

## 4. Discussion

We investigated the half-lives of polychlorinated dibenzo-p-dioxins and furans in a group of workers with substantial exposure. We made every effort to reduce laboratory variations by measuring each pair of sample parallel at the same time.

The median half-life of 6.9 years obtained for TCDD was close to that reported by PIRKLE et al.[2], but less than the estimate of WOLFE et al.[1] published recently. In the present study, the median of TCDD-levels in the first sample is about twice as large as in the latter study, but comparable to the median in the study by PIRKLE.

Except for 1,2,3,7,8-PCDD and 1,2,3,6,7,8-HCDD the median half-lives for the different dioxin congeners all range in the same order of magnitude. However, the estimates for these two congeners appear to be very unstable due to a large variation indicated by the quartile range and the fact that about 25% of the persons showed no decrease. The half-life given by GORSKI et al.[8] for 1,2,3,6,7,8-HCDD (3.5 years) is substantially shorter, but was determined in only one person. For Hepta-dioxin (GORSKI 3.2 vs. 3.7 in the present study) and OCDD (5.7 vs. 6.7) the results are in good agreement.

For the furans we obtained median half-lives slightly shorter than those for the dioxins. An exception is 2,3,4,7,8,-PCDF, which showed the largest estimate (19.6 years), but this estimate is based on only 5 paired samples. SCHECTER et al.[7] gave an estimate of 4.5 years for this congener, but again the estimate is based on only one person at 7 time points. The half-lives for the other furans are comparable to those reported by RYAN et al.[5] for the 9 persons from the Yusho-study, but shorter than those reported by these authors for 2-4 persons from the Yucheng-study. The furan-levels in the present study are considerably lower compared to those in the Yucheng-study. Together with the above mentioned differences in the half-life-estimate for TCDD in the present study in relation to the WOLFE-study corresponding to a twofold difference in the median TCDD-levels this finding may be interpreted as additional hint of a concentration-dependent elimination rate as speculated by RYAN et al[5]. However, to definitely answer this question more data are needed. The results for the five persons with 3 samples in our study will be reported seperately.

For the furans the data indicate a trend to shorter half-lives with increasing degree of chlorination, while for the dioxins no consistent trend was observed. Considerable interindividual variations in half-lives for all congeners was found. The potential impact of other factors, namely percent body fat, change in percent body fat and disease anamnesis is currently investigated.

## 5. Literature


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