Effects of Dioxins and Furans on Liver Enzymes, Lipid Parameters, and Thyroid Hormones in Former Thermal Metal Recycling Workers

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A cross-sectional study was performed to examine the internal exposure of polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans (PCDF) in former workers in a nonferrous metal recycling facility. Liver enzymes, lipid parameters, and thyroid hormones were measured to check possible biologic effects. Compared to background levels, the international toxicity equivalent levels of exposed workers were slightly elevated (median 42 ppt, range 13–281 ppt). The workers had also higher total PCDF concentrations (median 128 ppt, range 30–1338 ppt). Correlation analyses demonstrate significant associations with only one liver enzyme, alanine aminotransferase. There were no such associations with serum cholesterol levels or with serum thyroid hormones. Because of the cross-sectional design of the study, firm conclusions cannot be drawn. For further evaluation, a follow-up examination appears necessary. — Environ Health Perspect 106(Suppl 2):697–700 (1998). http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-2/697-700/triebig/abstract.html

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Introduction and Aim of the Study

In 1985 high concentrations of dioxins and furans in soil and dust were found close to a nonferrous metal recycling plant located in Rastatt, a small town in southwestern Germany (1,2). Recovery of copper was the main objective of the recycling plant. Dust generated during thermal metal recycling processes of scrap material such as cables and electronic equipment and other equipment was identified as the main source of polychlorinated dibenzo-p-dioxins (PCDD) and polychlorinated dibenzofurans (PCDF).

Because no data were available on the extent of PCDD/PCDF exposure of former workers—the plant closed in 1986—the legal accident insurance organization (Edel- und Unedelmetall-Berufsgenossenschaft, Stuttgart, Germany) decided to offer all employees a comprehensive medical examination. A steering group was established to coordinate and organize the activities, and especially to identify and recruit the subjects under study.

The aims of this study were 2-fold. First, the body burden of PCDD/PCDF was measured by blood fat analysis in a representative sample of the workforce. Second, health status of each worker was determined in comprehensive medical examinations carried out between 1992 and 1995. Details of the study group and methods are described elsewhere (3). In light of the well-known or suspected adverse effects of PCDD/PCDF exposure, liver function, lipid metabolism, and thyroid function were chosen target organs and the mechanisms to be investigated (4,5).

Materials and Methods

The workforce studied consisted of a total of 679 persons employed between 1961 to 1986 (Table 1). Duration of employment ranged from a few months up to almost 40 years. Despite intensive efforts only 250 persons could be completely examined. The main reasons for nonparticipation in the study were lack of interest (167 workers), emigration abroad, and unknown residence (194 workers).

PCDD/PCDF blood analyses were carried out on 76 subjects (70 men and 6 women). Relevant variables such as age, duration of employment, and time between end of employment and examination were not significantly different among the subgroups and the whole cohort (Table 2). A comparison of work functions was not possible because of lack of data.

Table 1. Profile of the study cohort of German workers exposed to PCDD and PCDF in a German recycling plant, 1961 to 1986.

| Category                                      | Workers, no. |
|-----------------------------------------------|---------------|
| All identified employees                      | 675           |
| Unknown residence, i.e., not located for study | 142           |
| Deceased                                      | 68            |
| Not participating                             | 167           |
| Employees undergoing complete examination     | 250           |
| With PCDD/PCDF analysis                      | 76            |
| Without PCDD/PCDF analysis                   | 174           |

Table 2. Description of the cohort.

| Characteristic | Whole cohort, n=250 | Subcohort, n=76 |
|----------------|---------------------|-----------------|
| Male           | 228 (9%)            | 70 (92%)        |
| Female         | 22 (9%)             | 6 (8%)          |
| Age, years (range) | 53 (25–72)  | 50 (25–72)    |
| Duration of employment, years (range) | 26 (14–41)   | 9 (0.2–41)    |
| Time between end of employment and examination, years (range) | 9 (6–28)  | 12 (6–34)    |

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Abbreviations used: ALC, alcohol intake; ALT, alanine aminotransferase (GPT); AST, aspartate aminotransferase (GOT); CDF, chlorodibenzo-furans; CHOL, total cholesterol level; GGT, y-glutamyltranspeptidase; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic-pyruvic transaminase; I-TEQ, international toxicity equivalent; PCDD, polychlorinated dibenzo-p-dioxins; PCDF, polychlorinated dibenzofurans; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin.
In Table 3 job activities and workplaces of the employees are shown according to the degree of PCDD/PCDF exposure, which was estimated by an overall evaluation of PCDD/PCDF concentrations in dust samples, the production process, and geographic and meteorologic aspects of the process. The relatively high exposures in office workers was explained by the fact that the predominant wind direction appears to have led to increased dust pollution in this area of the plant. PCDD and PCDF levels were analyzed in worker blood samples by gas chromatography/mass spectrometry after separation of the blood lipids. The analytical procedure is described in detail elsewhere (6).

To examine the target organs or functions, the following parameters were determined: γ-glutamyltranspeptidase (GGT), alanine aminotransferase ([ALT] or glutamic pyruvic transaminase [GPT]), and aspartate aminotransferase ([AST]) or glutamic-oxaloacetic transaminase ([GOT]), alkaline phosphatase, total cholesterol level (CHOL), high density lipoprotein cholesterol, serum triiodothyronine, serum thyroxine, and thyroid-stimulating hormone.

Parametric and nonparametric tests were applied to analyze the results. Correlations were tested by linear regression as well as multivariate analysis. A level of significance, $p < 0.05$, was chosen for all statistical tests.

### Results and Discussion

Blood lipid concentrations of total PCDD and PCDF, sum of total PCDD and PCDF and of toxic equivalency factors (North Atlantic Treaty Organization Committee on the Challenges of Modern Society) are shown in Table 4 (9). For a comparison with background levels, the results of Päpke et al. (7) were chosen; these results were calculated from analyses of 102 nonoccupationally exposed individuals from Germany. Because all blood samples were measured in the same laboratory using identical methods, systematic analytical errors were unlikely.

PCDD concentrations appear to be within the background range. PCDF levels, on the other hand, are elevated compared...

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Table 3. Job activities and workplaces of German recycling plant employees with PCDD/PCDF exposure.

| Workers, n=76 | Type of worker | PCDF exposure |
|---------------|----------------|---------------|
| 4             | Sludge transportation | High |
| 3             | Bricklayers        |               |
| 8             | Electrolysis workers|               |
| 7             | Office workers     |               |
| 25            | Furnace operators  |               |
| 15            | Mechanics          |               |
| 5             | Electricians       |               |
| 3             | Laboratory workers | Low |
| 6             | Workers in other areas |            |

Table 4. Internal exposure of German recycling plant workers expressed as PCDD/PCDF levels in lipid content of blood, ppt.

| Chemical tested | Exposed workers, n=76, median and range | Background, n=102, median and range |
|-----------------|----------------------------------------|-----------------------------------|
| Total PCDD      | 586 (155–1484)                         | 703 (221–1983)                    |
| Total PCDF      | 128 (30–1138)                          | 91 (27–192)                       |
| Total PCDD/PCDF | 758 (200–2477)                         | 836 (269–2134)                   |
| TEQ (NATO-CCMS) | 42 (13–281)                            | 38 (12–94)                       |

NATO-CCMS, North Atlantic Treaty Organization Committee on the Challenges of Modern Society. #Data from Päpke et al. (7).

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**Figure 1.** Distribution of median PCDD/PCDF concentrations in blood lipids in the study group compared to background levels. Data on background levels adapted from Päpke et al. (7). CDD, chlorodibenzo(oxins).
to those of the normal population. The highest concentration was 1138 ppt, about 6-fold above the maximum background level. It must be mentioned, however, that the average age of control subjects is about 10 years below that of the study group (median 39 [22–69] years of age). Because of age dependent increases in body burden of PCDD/PCDF, the differences are more pronounced (8).

Further analyses showed that penta-, hexa-, and hepta-chlorodibenzo-p-dioxins (CDF) contributed most to the elevated internal exposure (Figure 1). This pattern is partly in accordance with the distribution of PCDD/PCDF in dust samples (2). It can be used as an indicator of PCDD/PCDF exposure during nonferrous metal recycling processes.

With respect to the biochemical parameters and the fact that an adequate control group was not examined, the subjects were dichotomized into low- and high-exposure subgroups (Table 5). Low exposure was defined as having an international toxicity equivalent (I-TEQ) below 38 ppt, the median of the background level in nonoccupationally exposed persons (7). Highly exposed workers had increased total PCDF concentrations caused by the congeners penta-, hexa-, and octa furans. Results of examination of the biochemical parameters of both high- and low-exposed workers are given in Table 6. The only significant difference found was an increased serum cholesterol level in high exposure subgroup. Triglyceride serum levels were also measured. They were not further analyzed, however, because not all workers fasted before their blood samples were collected.

To evaluate possible relationships between internal exposure and biochemical parameters, correlation analyses were performed (Table 7). For total PCDF concentrations as well as for I-TEQ, positive and significant correlation coefficients were observed for ALT (GPT) and AST (GOT) as well as for CHOL. Because of the well known associations between liver enzyme activity, serum cholesterol level, and alcohol intake, a multiple regression analysis was performed (Table 8). I-TEQ correlated significantly only with serum ALT (GPT) activity (p<0.05). The correlation between I-TEQ and serum cholesterol is not significant (p = 0.063). These results may indicate an exposure–response relationship. However, statistically significant results do not necessarily reflect causality.

Our results must be discussed in the context of other publications. Note that PCDD/PCDF can cause liver damage in humans in high doses [reviewed by the World Health Organization (5)]. However, in the case of low PCDD/PCDF exposure, relevant effects on liver function are questionable. To our knowledge there are no data on liver toxicity of PCDF in humans. According to the tissue- as well as enzyme-specific relative potency, 2,3,4,7,8-penta-CDF has the highest hepatotoxic potency of the furans (9). PCDF, however, were not increased in our study subjects (Figure 1).

In several studies hepatotoxicity in PCDF/PCDD-exposed workers was addressed with different results. Only a few studies found statistically significant associations between 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) exposure and liver parameters (GGT, ALT, AST), but to our knowledge a consistent pattern has not been reported (10–12). In other studies no such relationships were reported (13–15). In a group of 138 former chemical workers with high TCDD exposure, none of the liver function indicators (AST, ALT, GGT) were significantly correlated with current and backcalculated TCDD concentration (13,15). In a total of 281 former workers of a trichlorophenol production plant, a significantly elevated risk of an out-of-range GGT was found only for persons with a history of significant alcohol consumption (14).

In conclusion, workers in nonferrous metal recycling plants may be exposed to dust contaminated with PCDF and to a lesser degree with PCDD. To prevent increased exposure, technical and personal preventive measures should be applied to reduce inhalation of dust and fumes originating from thermal processes. Statistical associations found between internal PCDF/PCDD exposure indicators and some liver parameters as well as cholesterol in serum should be reevaluated in a follow-up study.

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### Tables

#### Table 5. Characteristics of subgroups of German recycling plant workers with low and high PCDF/PCDF exposures (median values).

| Characteristic | Low exposurea | High exposureb |
|---------------|-------------|--------------|
| Age, years*   | 46          | 55           |
| Exposure, years* | 4.7          | 17.3         |
| Latency, years* | 4           | 9            |
| I-TEQ, ppt*   | 24          | 88           |
| Total PCDD, ppt* | 486         | 626          |
| Total PCDF, ppt* | 65          | 306          |
| Total PCDD/F, ppt* | 551         | 932          |

Abbreviations: a, female; m, male; I-TEQ<38 ppt; f = 4, m = 26. I-TEQ≥38 ppt; f = 2, m = 44. *Latency means time between end of employment and examination. **Significant difference (p<0.05).

#### Table 6. Comparison of liver, lipid, and thyroid parameters in German recycling plant workers with low and high PCDF/PCDF exposure.

| Parameter | Low exposure, I-TEQ<38 ppt | High exposure, I-TEQ≥38 ppt |
|-----------|-----------------------------|----------------------------|
| GGT, U/liter | 20±13                      | 17±9                      |
| ALT, U/liter | 10±3                       | 10±3                      |
| AST, U/liter | 17±7                       | 15±5                      |
| AP, U/liter | 106±27                     | 115±30                    |
| CHOL, mg/dl | 184±39                     | 216±45*                   |
| LDL, mg/dl | 47±10                      | 46±18                     |
| T3, µg/liter | 1.3±0.3                    | 1.2±0.3                   |
| T4, µg/liter | 75±18                      | 76±14                     |
| TSH, mU/liter | 1.4±0.9                    | 1.2±0.9                   |

Alcohol intake, 14±25 to 22±31 g/day (range) (0–118) to (0–130).

#### Table 7. Result of correlation analyses between I-TEQ and biologic parameters.

| Parameter | Pearson correlation | p<0.05 |
|-----------|---------------------|--------|
| GGT       | 0.129               | No     |
| ALT       | 0.383               | Yes    |
| AST       | 0.299               | Yes    |
| AP        | 0.074               | No     |
| CHOL      | 0.384               | Yes    |
| HDL       | 0.104               | No     |
| T3        | 0.010               | No     |
| T4        | 0.038               | No     |
| TSH       | 0.126               | No     |

#### Table 8. Results of multiple regression analyses. Levels of probability of error are given.

| ALT | AST | CHOL | ALC | I-TEQ |
|-----|-----|------|-----|------|
| GGT | 0.281 | 0.227 | 0.069 | 0.087 | 0.362 |
| ALT | 0.001 | 0.295 | 0.312 | 0.031 |
| AST | 0.694 | 0.086 | 0.741 |
| CHOL | -       | 0.583 | 0.063|
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