Exposure to polychlorinated dibenzo-p-dioxins and -furans and breast cancer mortality in a cohort of female workers of a herbicide producing plant in Hamburg, FRG

Flesch-Janys D[A], Berger J[B], Manz A[A], Nagel S[B], Ollroge I[C]

[A] Centre for Chemical Workers Health, Fuhlsbüttler Str. 401, 2000 Hamburg 61

[B] Institute for Mathematics and Computer Science in Medicine, Martinistr. 52, 2000 Hamburg 20, FRG

[C] State Department of Health, Tesdorpfstr. 8, 2000 Hamburg 13

Introduction

We report here on the exposure to polychlorinated dibenzo-p-dioxins and -furans (PCDD/Fs), especially 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), and breast cancer mortality in a cohort of female workers of a plant in Hamburg, FRG, which had produced 2,4,5-Trichlorphenol, 2,4,5-Trichlorophenoxyacetic acid, Lindane and some other herbicides and insecticides. The mortality of the male cohort was described earlier[1].

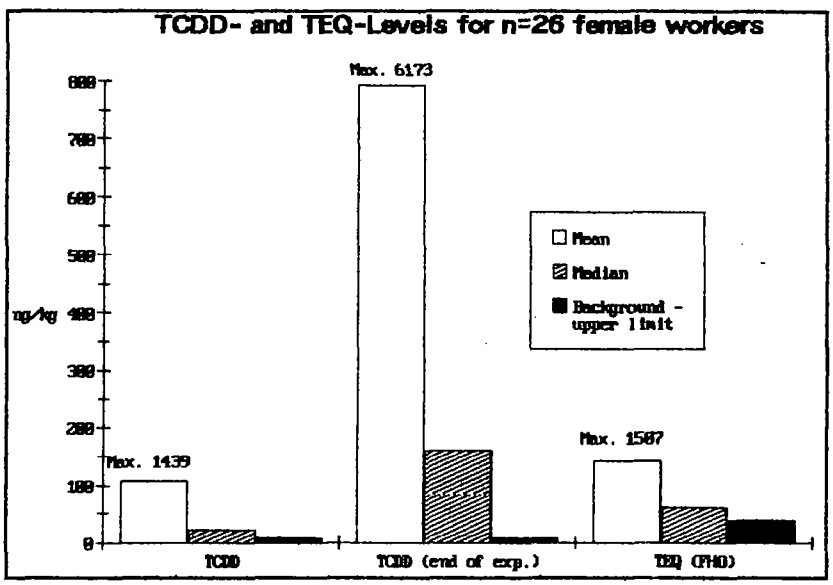
Materials and methods

The basic methods are reported elsewhere[1]. In brief, the cohort consists of n=399 women employed at the plant for at least 3 months in the years 1952-1984, when the plant was closed. Follow-up started in 1952 and ended in 1989. Causes of death were derived from medical records and coded (ICD-9th revision) by an experienced nosologist. Measurements of the PCDD/F-concentrations were available for a total of n=26 women (n=22 blood/-ERGO; n=4 adipose tissue/Prof. Beck-FHO/FRG). Working times in different production departments served as exposure variables[2]. PCDD/F-concentrations were analysed by multiple regression using the logarithm of the concentrations as dependent and the working times as independent variables using SPSSPC+ (4.0). Standardized mortality ratios were calculated using the person-year method and FRG-mortality data as reference. 90%- confidence intervals were computed assuming the Poisson distribution. In addition, year-of-birth-stratified COX-regression were performed using an unexposed cohort of n=532 female workers of a gas supply company as external reference group, observed for the same time period. For these calculations EGRET was used.

Results

Fig. 1 shows the concentrations of TCDD and higher chlorinated PCDD/Fs, measured as TEQs (FHO/FRG) together with upper bounds of current background concentrations of unexposed persons in FRG (PÄPKE et al. 1991). The median for TCDD was 23 ng/kg while the arithmetic mean (AM) was 109.7 ng/kg (range 7-1439). For TEQs the respective values were 62.1 and 143.7 ng/kg (Range 13.4-1507.6). The estimated concentration at the end of exposure using a half life of 7.1 years[3] (PIRKLE et al. 1989) was 163 ng/kg (median) and 794 ng/kg (AM). For n=20 women TCDD-concentrations exceeded 10 ng/kg, while the TEQs were higher than 40 ng/kg for n=14 women.

Fig. 1



The highest TCDD-levels were observed in three women with working times in the 2,4,5-T/2,4,5-TCP-laboratory (1439 ng/kg-17.6 years, 591 ng/kg-4.6 years and 177 ng/kg-1 year). A total of n=29 women had working times in these departments. Elevated TCDD-concentrations were found for the Formulation (n=210 women) and the Central Laboratory (n=40), ranging up to 84 ng/kg for a women with more than 30 year of work in the Formulation. In a multiple regression analysis including only women with working times in the analytical laboratory and Formulation both showed a significant effect on TCDD-levels (multiple $R=0.72$, $p<0.05$). From the coefficients a yearly intake of about 2 ng/kg TCDD could be estimated. Two women with short working times in the Formulation (1.7y resp. 1.8 y) showed unexpected high TCDD-levels of 78 ng/kg and 37 ng/kg more than thirty years after the end of exposure in 1953 were not included in this analysis.

Total mortality showed a SMR of 0.83, based on n=57 observed cases (Tab. 1). For all cancer combined (n=21) a SMR of 0.98 was obtained. The confidence interval included 1. A total of n=10 cases of breast cancer of different histology were observed, yielding a SMR of 2.37 (1.29,4.04). For women who ever had worked in the Formulation department (n=6 cases) the SMR was 2.38 (1.04,4.69). The other n=11 cases were cancer of the colon (2), gall bladder (1), lung (1), uterus (2), ovary (1) and kidney (1), Hodgkin (1), unspecified (2).

Tab. 1 Standardized Mortality Ratios (FRG-mortality as reference)

	Observed	SMR	90%CI
All causes	57	0.83	0.66,1.04
All cancer (ICD 140-208)	21	0.98	0.66,1.41
Breast cancer (ICD 174)	10	2.37	1.29,4.04
Breast cancer (only Form.)	6	2.38	1.04,4.69

Model 1 of the Cox-regression analysis (Tab. 2) yielded a relative risk for breast cancer for the whole cohort of 2.08. The confidence intervall included 1. An increase in risk with total duration of employment (RR=1.95 per 10 years) was observed. In model 3 working times in the Formulation was included as continous variable, while the 2,4,5-TCP-department and Central Laboratory were included as factors. Relative risk per ten year duration of work in the Formulation yielded was 2.84 (1.49,5.46), while for the two departments mentioned above it was 2.09 and 4.19. However, for the latter the number of cases were small and the confidence intervals large.

Tab. 2 Estimated relative risks from year-of-birth-stratified Cox-regression

	No. of cases	Rel. Risk	90%CI
Model 1: Cohort/control group	10	2.08	0.94,4.60
Model 2: Total duration of employment per 10 year	10	1.95	1.26,3.02
Model 3:			
Duration Formulation per 10 year	6	2.84	1.49,5.46
Ever had worked in the 2,4,5-TCP-laboratory	1	2.09	0.35,12.62
Ever had worked in the Central Laboratory	2	4.19	1.12,15.66

We know of 4 prevalent cases of breast cancer. For three women PCDD/F-concentrations are known (TCDD 71 ng/kg, TEQ 90.8 ng/kg, 31 year Central Laboratory; 31 ng/kg, TEQ 62.9 ng/kg, 15 year Formulation; 8 ng/kg, TEQ 19.8 ng/kg, 0.5 years store and transport). For one deceased case TCDD-concentration in adipose tissue was 84 ng/kg (TEQ 172 ng/kg; 30 years Formulation).

Discussion and Conclusions

An elevated risk of breast cancer mortality compared to FRG mortality was observed. The Cox regression showed that risk increased with duration of work in the plant, especially for the working time in the Formulation. The blood- and fat-levels indicate that substantial exposure, especially to TCDD, had occured in the cohort. From the known risk factors for breast cancer late age of menopause could not explain the excess risk because 8 cases had died before age 55, 5 before age 50. Social status was low, so a decreased risk would be expected. Other risk factors could not be assessed on an individual base. Some authors discuss whether these factors are correlated to the status of being occupationally active. We used an additional comparison with another cohort of working women, so the same correlation should have occured in the control group. The empirical data are contradictory. While some authors find elevated breast cancer risk in occupational cohorts of women[4] others do not. In the only other occupational female cohort in the context of herbicide- and PCDD/F-exposure the authors[5] did not see an increase. Exposure was predominantly to MCPA which is supposed not to be contaminated with TCDD. Finally, exposure to other carcinogens or suspected carcinogens may have contributed to the elevated risk. There are data from a small case-control-study[6] showing elevated beta-HCH-levels in breast tissue from breast cancer cases. From the male cohort substantial beta-HCH-exposure in the thermic decomposition, HCH- and Lindane-department is known[7]. For three women beta-HCH concentrations were 2.6 mg/kg, 1.2 mg/kg and 0.7 mg/kg fat exceeding current background levels of about 60-320 μg/kg[8].

In summary, an elevated risk of breast cancer mortality was found in a cohort of female workers with exposure to PCDD/Fs, especially TCDD. It seems unlikely that the increase could be fully explained by known risk factors, though this could not totally be ruled out. Exposure to beta-HCH may have contributed to the excess risk, but more data are needed.

Literature

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