EXPOSURE TO POLYCHLORINATED DIOXINS AND FURANS (PCDD/F) AND CARDIOVASCULAR DISEASE MORTALITY IN A COHORT OF OCCUPATIONALLY EXPOSED WORKERS

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1. Introduction

Within the spectrum of potential health effects of 2,3,7,8-tetrachlorodibenzop-dioxin (TCDD) and the other polychlorinated dibenzo-dioxins and furans (PCDD/F) the impact of these substances on the cardiovascular system has not received as much attention as, for example, cancer, so the experimental and epidemiologic evidence in this field is less compelling. There are, however, a number of reports suggesting that TCDD may influence a number of risk factors for ischemic heart diseases (IHD). This possible link was addressed in several epidemiological studies investigating outcomes related to IHD: prevalence of IHD [1-4], hypertension[2,3,5], blood lipid disturbances[2,3,5-9] and diabetes[10,11]. However, no definite conclusion can be drawn from these studies due to potential selection bias, uncertainties about exposure, and inconsistencies in findings. Several animal studies also investigated effects of TCDD exposure on cardiovascular outcomes. The reported effects include morphologic changes in peripheral vessels[12,13], functional disturbances[14-16] and disturbances in lipometabolism[17-20].

Mortality studies in the context of PCDD/F exposure have shown no consistent pattern. However, these studies have not included detailed exposure-response analyses. Zober et al.[21] observed a slight elevation of deaths due to all cardiovascular diseases (CVD;ICD 390-459). Based upon only 24 deaths, they found a SMR of 1.21 (90%CI:0.83,1.7) in relation to the mortality of the German population. In a study with much more power Fingerhut et al.[22] reported a SMR of 0.96 (95%CI:0.87,1.06) based on 393 cases. No detailed exposure-related analysis for IHD was reported. A study from the Netherlands[23] found 8 deaths due to myocardial infarction in a group of 141 workers exposed in a TCDD accident in 1963. Seven of these workers suffered from severe chloracne. Other occupational mortality studies have shown slight non-significant elevated risks for arteriosclerotic heart diseases[24] or no effect[25,26]. In the Seveso mortality study[27] an elevated SMR was observed for all cardiovascular diseases (1.75;95%CI:1.0,3.2) and for ischemic heart disease (2.22; 95%CI:0.8-5.9) in the population of the most contaminated zone A. However, the authors attribute this observation to stress induced by the accident.

This paper reports findings on the quantitative relations between CVD and IHD and estimated blood levels at the end of exposure in a cohort of occupationally exposed workers from a former herbicide

producing plant in Hamburg, Germany. The authors reported previously on cancer mortality in this cohort[28] for the follow up period 1952-1989.

2. Methods

The cohort consisted of all regular employees of a chemical plant in Hamburg, Germany, employed for at least 3 months between 1952 and 1984 when the plant was closed. Workers were identified by company personnel and union election records and by information obtained from employees. The mortality follow-up reported here covered the years 1952-1992. A quantitative estimate of PCDD/F-exposure, expressed as toxic equivalencies (TEQ) relative to TCDD for the whole cohort derived from an analysis of blood and adipose tissue levels and working histories in a subgroup (n=190) was constructed. The construction process is described elsewhere[29]. Quintiles and deciles of these estimates served as dose parameter in the estimation of relative risks using year-of-birth stratified Cox-regression. An unexposed cohort of gas workers served as external reference group. Vital status was assessed by direct contact or through community registries. Causes of death were derived from records obtained from a hospital or family doctor by a pathologist. The quality of determinations of underlying cause of death was assessed for ICD 390-579 by an independent pathologist.

3. Results

Table 1 summarizes the mortality of the cohorts. Vital status was ascertained for 99.0% of male chemical workers and 99.6% of the gas workers. A total of 414 deaths were observed in the chemical workers. No information on the causes of death was available for five deceased workers. Thirty per cent of deaths were attributed to cancer and 18.4% to IHD. Corresponding percentages in the reference group were 30% and 21.7%.

Reliability of study determinations of cause of death was assessed by a second pathologist. The confirmation rate for cancer deaths among chemical workers was 96.5% as reported earlier[28], comparable to that for the referent group (99%). The IHD and CVD diagnoses among the chemical workers were confirmed in 77.8% and 85.1% of the cases, respectively. In the referent group of gas workers, the corresponding confirmation rates were 92.9% and 94.1%.

Relative risks (RR) from Cox-regression are shown in table 2. Total mortality was elevated across all exposure categories. The highest relative risk was observed in the 10th decile (RR=2.28;95%CI 1.67,3.12). A pattern of increasing risk of all CVD and IHD mortality across exposure categories emerged. The relative risk of IHD mortality was essentially one for the three lowest quintiles. In the fourth quintile (range 99.0-278.5 ng/kg TEQ above background) it was 1.13 (95%CI 0.64,2.00) and increased in the 9th decile (RR=1.73; 95%CI 0.92,3.27) to RR=2.72 (95%CI 1.49,4.98) in the 10th decile. For all CVD the relative risk was significantly elevated in the third quintile (RR=1.48;1.01,2.17) and increased to 2.06 (1.23,3.45) in the 10th decile. The test for trend was significant for both mortality outcomes ($p < 0.01$). For the non-IHD mortality within all CVD risk increased up to the fourth quintile, but decreased in the two highest exposure categories. Consequently, the trend test was not significant for this group of causes of death (p=0.299).

4. Discussion

We observed a nearly monotonic increase in risk for CVD and IHD mortality with increasing levels of TEQ. For IHD the relative risk was not numerically elevated until an estimated dose in the range 99.0-278.5 ng/kg TEQ above background, while for all CVD a significant elevated risk was observed already in the range 39.6-98.9 ng/kg. The dose-response curve is clearly sublinear. Thus, the data appear to be consistent with a threshold model for these outcomes.

Other established risk factors (serum lipoproteins, blood pressure, diabetes and body mass index) could be confounders of the observed association, if any of these factors was strongly associated with assignment to jobs with higher PCDD/F exposure. While such a job assignment process seems unlikely, there is evidence from epidemiologic findings and animal models suggesting that some of these IHD risk factors may be impacted by PCDD/F exposure. Such effects would constitute a causal pathway by which an impact of PCDD/F exposure on IHD mortality might operate.

Though - as outlined above - the epidemiologic evidence is inconsistent there are several lines of evidence of a link between TCDD and atherosclerotic disease from animal models. The first vein was concerned with TCDD induced hyperlipidemia and subsequent preatherosclerotic lesions in a rabbit model[17]. The authors have found a reduction in hepatic LDL binding. This presumed down regulation of LDL receptors by TCDD is analogous to the lack of LDL receptors in familial hypercholesterolemia and is part of the general pattern of TCDD induced transition from a lipogenic to a lipolytic mode. The second vein has focused on the lipid peroxidation effects of TCDD in animal models[16]. These studies are suggestive that lipid peroxidation effects of TCDD could lead to modification of LDL particles and unregulated uptake via "scavenger" receptors in macrophages and endothelial cells.

The data presented here suggest a link between CVD and IHD mortality and exposure to PCDD/F in a dose related way where risks increases at comparably higher doses. The mechanism remains to be clarified.

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Table 1 Number of workers, vital status and causes of death

	Chemical Workers		Gas Workers	
	n	%	n	%
Cohort size	1189		2528	
Vital status known	1177	99.0	2518	99.6
unknown	12	1.0	10	0.4
Vital status known	1177	=100	2518	=100
alive	763	64.2	1575	62.7
deceased	414	34.8	943	37.3
Cancer (ICD 140-208)	124	30.0	283	30.0
All CVD (390-459)	157	38.0	459	48.6
IHD (410-414)	76	18.4	205	21.7
Other CVD	81	19.6	254	26.9
Other Causes	133	32.1	201	21.3

Table 2 Total - , CVD-, IHD-, and Other CVD (without IHD) mortality in relation to quintiles (upper quintile divided in deciles) of estimated TEQ-levels (ng/kg blood fat) at the end of exposure above German median background levels using the cohort of Gas Workers as reference

TEQ Conc.	Total Mortality			CVD			IHD			Other CVD		
	RR	CIlo	CIup	RR	CIlo	CIup	RR	CIlo	CIup	RR	CIlo	CIup
0	1.0			1.0			1.0			1.0		
1.0-12.2	1.46	1.11	1.93	0.93	0.57	1.50	1.02	0.54	1.95	0.84	0.40	1.74
12.3-39.5	1.39	1.07	1.81	0.92	0.59	1.46	0.96	0.51	1.82	0.91	0.48	1.75
39.6-98.9	1.54	1.20	1.97	1.48	1.01	2.17	0.97	0.52	1.81	2.05	1.26	3.36
99.0-278.5	1.34	1.04	1.74	1.55	1.07	2.24	1.13	0.64	2.00	2.07	1.27	3.38
278.6-545.0	1.65	1.20	2.25	1.63	1.01	2.64	1.73	0.92	3.27	1.53	0.73	3.20
545.1-4361.9	2.28	1.67	3.12	2.06	1.23	3.45	2.72	1.49	4.98	1.19	0.44	3.26
p for trend	0.01			<0.01			<0.01			0.30		

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