Laboratory results for selected target organs in 138 individuals occupationally exposed to TCDD

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I. Introduction

In 1953, an uncontrolled decomposition reaction occurred during production of 2,4,5-trichlorophenol at a BASF facility in Ludwigshafen, Germany. Details regarding the accident, the conditions of exposure and health investigations carried out have been described in various publications, most recently by Zober et al. 1990[1]. TCDD analyses in blood lipids have now been completed for 138 members of the accident cohort. At the same time clinical laboratory data were also obtained. The relationship between TCDD concentrations and targeted laboratory parameters are reported here.

II. Methods

The dioxin determinations were carried out at ERGO-Forschungsgesellschaft, Hamburg, between October 1988 and February 1992. Details regarding the methods of collection and epidemiological analysis have been previously reported by Ott et al. 1993[2]. Two measures of TCDD exposure are utilized in this study, the current TCDD concentration at the time of examination and the log of the back-calculated TCDD concentration at the time of exposure assuming a seven-year half life for TCDD. This latter calculation was model based. A total of 34 laboratory parameters, seven liver function indicators, four lipid parameters, serum glucose, four hematological outcomes, four parameters of thyroid function, and the immunoglobulins as well as eleven other immunological parameters were examined. For all parameters except complements C3 and C4, data are available for more than 90 percent of study participants. Group means and standard deviations were compared with reference data obtained through routine occupational medical examinations of company employees between 50 and 60 years of age. For most of these reference parameters, more than 1,000 observations were available. For the immunological parameters comparison data were available only for a group of 42 referents previously described[3]. In addition, linear regression analysis was carried out for each laboratory parameter separately for the two TCDD measures incorporating age, body mass index (BMI) and smoking history as potential confounding variables. A log transfor-

mation was utilized for those parameters not fitting a normal distribution. Tabulated results are based on the final model in which the TCDD factor was included as well as potential confounding factors utilizing a .15 significance level for inclusion. Additionally scatterplots were computed for all parameters to further evaluate the relationship between TCDD and log TCDD respectively and the laboratory outcomes.

III. Results and discussion

The mean age of the TCDD exposed individuals is 60.7 ± 8.4 years; approximately 80 percent ranged in age between 50 and 70 years. The mean BMI in the exposed group was 27.4 ± 3.2. BMI was marginally associated with current TCDD concentration (p = .066+) but not with back-calculated TCDD. Thirty-four percent of the study group members were current smokers. The geometric mean current TCDD concentration of the study group is 15.4 ppt with a range of less than 1 to 553 ppt. The geometric mean back-calculated TCDD concentration was 94 ppt with a range of 3.3 to 12,200 ppt. All results are summarized in Table 1. The regression analysis findings for potential confounders are shown, but are not discussed. Regarding the liver function indicators, there are no remarkable differences in the means between the two groups. Cholinesterase (ChE) levels are somewhat lower in the study group. None of these parameters was associated with current TCDD concentration. Alkaline phosphatase was positively correlated with back-calculated TCDD. Nevertheless there appears to be no consistent laboratory pattern indicating chronic liver injury due to TCDD in this population. There was one individual with a diagnosis of liver cancer in this cohort as previously described[1] . For serum glucose the group means did not differ remarkably. A marginal increase in serum glucose level was seen with current but not back-calculated TCDD concentration. This result is not inconsistent with those from the NIOSH and Ranch Hand studies[4,5]. With respect to lipid metabolism there was no indication of any TCDD related effects. Regarding hematologic parameters there is a trend towards higher erythrocyte sedimentation rate (ESR) in the study group. ESR is significantly associated with current TCDD. The correlation is driven by the 43 mm-value of the liver cancer case. Without this observation, the p-value is .07. Mean white blood cells (WBC) appear to be decreased by 19 percent in the study group. However, there is a weak increasing trend in WBC with cumulative back-calculated TCDD. There are no differences between the groups regarding platelet counts. There is a significant decrease in platelets with higher current TCDD. The lowest value of 71 platelets/nl was observed in a person with liver cirrhosis. The p-value is .24 when this case is deleted. There is no apparent trend with regard to hemoglobin. With respect to parameters of thyroid function no notable differences in mean values are seen. Both TCDD measures were positively correlated with thyroxine-binding globulin (TBG) which is synthesized in the liver (see Fig. 1). With few exceptions all TBG values are within the normal range of 9.3 to 18.0 mg/l. The increase of TBG with TCDD is unexplainable to date. Given the liver parameter findings, leakage from damaged hepatocytes seems an implausible explanation. Increased synthesis by enzyme induction remains speculative. 'Yusho' patients did not show elevated TBG compared with controls[6] . With respect to parameters of humoral immunity there are slightly higher mean values in the study group. In addition, there are indications of increased IgA, IgG and complement C4

values relative to current TCDD levels and for IgA and IgG in relation to back-calculated TCDD. These findings indicate no more than very slight if any influence of TCDD exposure on parameters of humoral immunity. Furthermore the positive relationships between IgA and IgG respectively and TCDD again are driven by a single case of cirrhosis of the liver (IgA = 822 mg/dl) and the liver carcinoma (IgG = 1,883 mg/dl). Regarding the distribution of immunocompetent cells the mean lymphocyte count is 13 percent lower in the study group although there is no relationship with either TCDD measures. The percent distribution of cells appears to be similar in both groups. None of the cell types is significantly related to TCDD at the .05 level. These laboratory data pertain to a survivorship cohort with varying TCDD exposure. Only chronic and/or latent health effects of TCDD could have been detected with this study design. Although the observed associations do not fit a pattern suggesting specific health effects, these laboratory findings should provide added perspective in interpreting results from other clinical studies regarding TCDD exposed populations.

References:

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Laboratory parameter		Study Group Mean	Study Group SD	Referent Groups Mean	Referent Groups SD	Summary regression analyses findings (p-values) [a] TCDD	log TCDD back-calculated	Confounding factors [b]
GOT (AST)	U/l	11.0	4.4	11.3	6.4	-	-	BMI.048+
GPT (ALT)	U/l	14.8	8.4	15.1	10.0	-	-	BMI.000+
GGT	U/l	30.5	58.4	29.9	43.5	-	-	BMI.014+
Cholinesterase (ChE)	U/l	5827.0	1345.0	6020.5	1173.3	-	-	AGE.036-
Alkaline Phosphatase	U/l	105.5	27.6	99.3	28.1	-	0.025+	
Bilirubin	mg/dl	0.69	0.31	0.68	0.33	-	-	
GLDH	U/l	3.05	4.45	3.1	3.89	-	-	
Glucose	mg/dl	115.8	34.7	111.2	32.5	0.062+	-	AGE.061+. BMI.095+
Cholesterol	mg/dl	237.7	38.9	246.4	45.3	-	-	
Triglycerides	mg/dl	169.3	105.6	174.5	146.0	-	-	BMI.000+. SMK.009+
High-density lipoprotein (HDL)	mg/dl	50.3	12.8	51.2	13.4	-	-	BMI.005+. SMK.094+
Low-density lipoprotein (LDL)	mg/dl	163.5	39.8	178.2	37.9	-	-	
Erythrocyte sedimentation rate (ESR)	mm	6.53	8.4	4.95	5.79	0.002+	-	AGE.071+
White blood cells (WBC)	/micl	6034.0	2034.0	7410.0	2210.0	-	0.073+	SMK.000+
Platelets	/nl	254.0	73.8	253.5	57.9	0.003-	-	SMK.006+. AGE.101-
Hemoglobin	g/dl	15.2	1.2	15.2	1.0	-	-	SMK.003+. AGE.043-
T4	micg/dl	7.8	1.9	8.3	1.5	-	-	AGE.039+. SMK.138+
Thyroxine-binding-globulin (TBG)	mg/l	12.7	3.2	12.7	2.9	0.000+	0.000+	
T4/TBG	mU/l	6.33	1.26	6.58	1.55	-	0.122-	
Thyroidea-stimulating hormone (TSH)	myE/ml	1.19	0.90	n.a.	-	-	-	AGE.103+
IGA	mg/dl	305.1	112.6	288.5	116.1	0.034+	0.021+	
IGG	mg/dl	1199.0	226.0	1182.6	310.0	0.012+	0.003+	SMK.107-
IGM	mg/dl	139.6	65.1	134.7	70.0	-	-	
Complement C4	mg/dl	29.3	8.6	28.5	8.9	*) 0.015+	-	AGE.144+
Complement C3	mg/dl	78.2	13.0	77.8	11.2	*) 0.116+	-	BMI.010+
Lymphocytes	/ul	1978.3	805.1	2267.6	837.5	*) -	-	SMK.000+
Lymphocytes	%	33.4	9.4	36.0	12.4	*) -	0.053-	AGE.023-
Natural killer cells	%	13.8	8.2	11.9	7.1	*) -	-	AGE.045+.SMK.103-
B-cells	%	10.4	6.0	12.3	5.1	*) -	-	AGE.036-. SMK.102+
T-cells	%	69.1	10.4	73.3	7.7	*) 0.067-	0.067-	
T-helper -cells	%	42.5	10.4	45.1	8.9	*) 0.133-	0.145-	
T-suppressor-cells	%	31.9	10.4	32.0	7.1	*) -	-	AGE.092+. SMK.102+
CD4/CD8 ratio		1.6	0.94	1.5	0.6	*) -	-	AGE.099-
T-helper inducer cells	%	26.0	7.7	23.2	7.1	*) -	-	SMK.016+

a) p-values shown when less than 0.15
b) BMI=body mass index. SMK=level of cigarette smoking
+ = positive association
- = inverse association
*) data available for N=42 referents only

Table 1: Summary of laboratory results and regression analyses findings in 138 individuals occupationally exposed to TCDD vs referent groups.

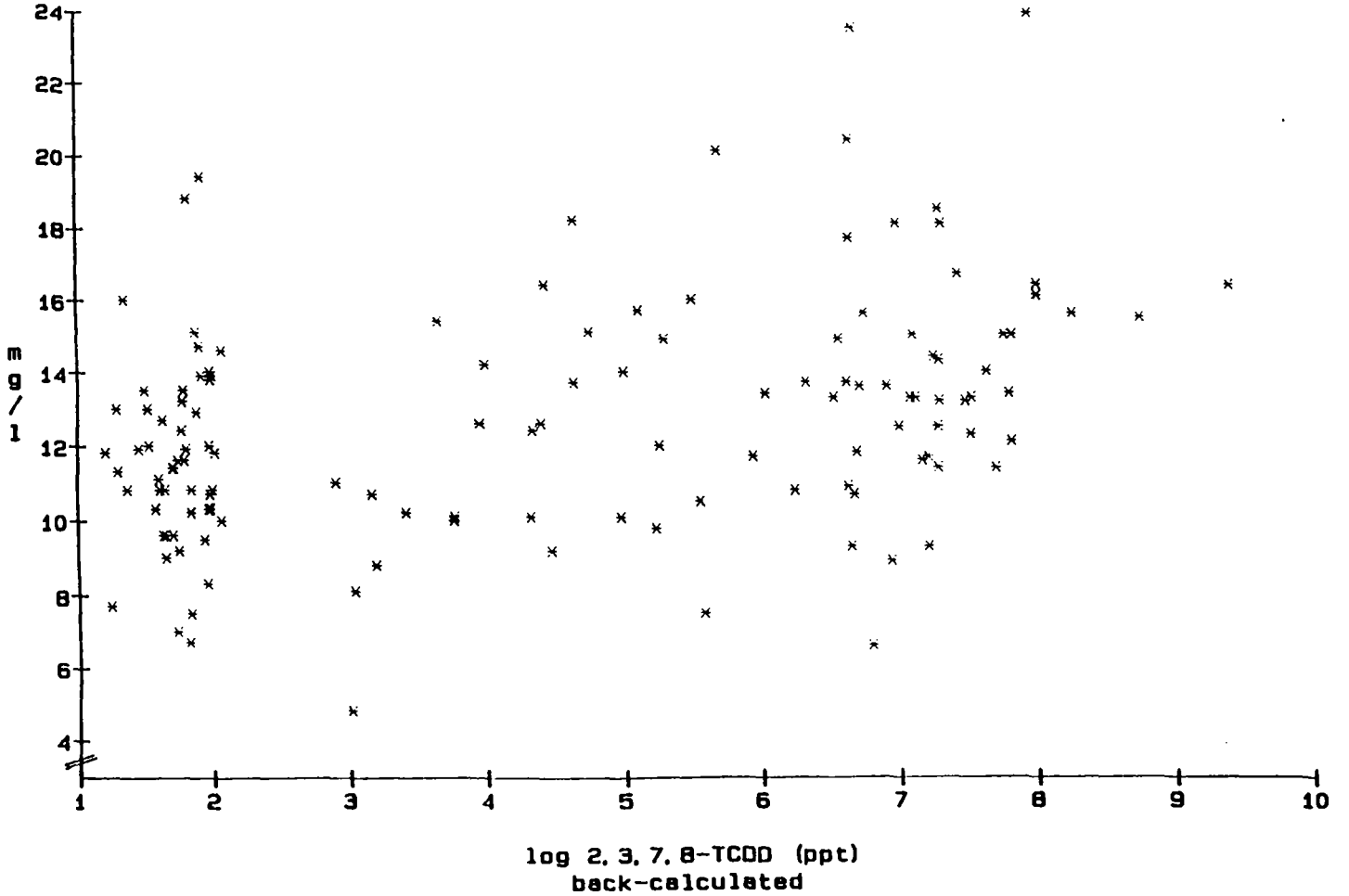

Figure 1: TBB (mg/l) vs log 2, 3, 7, 8-TCDD (ppt) back-calculated based on the lipid content of blood of 138 exposed persons.