Morbidity study of extruder personnel with potential exposure to brominated dioxins and furans
II Results of clinical laboratory studies

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Abstract

***Objectives*—To test whether dioxins affect liver and thyroid function, lipid metabolism and glucose or immunological variables, in workers exposed to brominated dioxins and furans.**

***Methods*—34 male production employees (29 were extruder operators) and eight technical support personnel were studied, all of whom were potentially exposed to polybrominated dibenzo-*p*-dioxins (PBDDs) and furans (PBDFs) during production of resins containing polybrominated diphenyl ethers (PBDEs). Controls were from a similar resin producing plant that did not use PBDEs. Blood samples were analysed for tetra, penta, and hexabrominated congeners, but 2,3,7,8-TBDD was the only exposure measure used in the regression analyses. Seven liver function indicators, five measures of blood lipids and glucose, four haematology and blood coagulation measures, and three measures of thyroid function were examined.**

***Results*—None of the variables was statistically related to concentration of 2,3,7,8-TBDD in the regression analyses. Cigarette smoking was related to several outcomes at the 0·05 level: aspartate aminotransferase, alanine aminotransferase, glutamate dehydrogenase (GLDH), erythrocyte sedimentation rate, and white blood cell count. Body mass index was also related to alanine aminotransferase, γ-glutamyltranspeptidase, cholinesterase, GLDH, cholesterol, triglycerides, high density lipoprotein, low density lipoprotein, and glucose concentrations. No definitive associations between liver, blood lipid, thyroid, or immunological variables and exposure to brominated dioxins or blood lipid concentration of 2,3,7,8-TBDD were found.**

***Conclusions*—The study population was small and hence the findings must be interpreted with caution. Nevertheless, these results provide a base for interpreting the results of clinical studies in similarly exposed populations.**

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Polyhalogenated dibenzo-*p*-dioxins are thought to exert their toxic effects through interaction with a specific intracellular protein, the Ah receptor.[1] Although far less toxicological and epidemiological information is available on the brominated congeners, existing evidence suggests that these compounds are only slightly less potent in toxicity than the corresponding chlorinated dioxins and that metabolic pathways are similar as well.[1 2]

Previously, we described biomonitoring and immunological findings for 42 employees potentially exposed to polybrominated dibenzo-p-dioxins (PBDDs) and furans (PBDFs) during extrusion blending of resins containing the flame retardant decabromodiphenyl ether.[3] Among production employees measured concentrations of 2,3,7,8-tetrabromodibenzo-p-dioxin (2,3,7,8-TBDD) in blood lipids ranged from non-detectable to 475 parts per trillion (ppt). The median concentration of 2,3,7,8-TBDD among 18 extruder operators first assigned to the unit before 1986 was 91 ppt.

In this report, the results of liver function tests, lipid and glucose measures, thyroid function variables, and haematological and coagulation indicators are presented in relation to exposure status and blood lipid concentration of 2,3,7,8-TBDD. These variables, together with the previously examined immunological measures, were selected for study based on evidence that dioxins exert effects on liver, thyroid, and immunological tissue and may alter lipid metabolism.[1]

Subjects and methods

The study group consisted of 34 production employees (29 were extruder operators) and eight technical support personnel, all of whom were potentially exposed to PBDDs and PBDFs during production of resins containing polybrominated diphenyl ethers (PBDEs). Brominated flame retardants were first used in this production process during 1975; however, octa and decabromodiphenyl ethers were probably not processed before 1977. The control group was recruited from a similar resin producing plant that did not use PBDEs and consisted of an equal number of employees frequency matched to the study group by age, general type of employment, and nationality. There were no women employees in either group. The average age of study group partici-

pants was 36·6 years and that of the controls was 38·3 years at the time of examination. The two groups were comparable for cigarette smoking, with the average number of cigarettes smoked daily being 11·4 and 11·5 in the two groups, respectively.

Blood specimens for measurements of PBDDs and PBDFs were obtained between February and April, 1990. Details of the sample collection and analytical methods have been described previously.[3] Blood samples were analysed for tetra, penta, and hexabrominated dioxin congeners as these were the only congeners for which an existing internal standard was available at the time. Toxicity equivalents were calculated to express the PBDD and PBDF values as a single number with toxicity factors derived for chlorinated dioxins and furans. However, because 2,3,7,8-TBDD is assigned a weighting at least 10 times higher than any other congener in the toxicity equivalent calculations and 2,3,7,8-TBDD measurements were highly correlated with the corresponding toxicity equivalent values, 2,3,7,8-TBDD was the only exposure measure used in the regression analyses.

A comprehensive medical examination programme was also initiated in 1990 after a preliminary biomonitoring study had established the presence of brominated dioxins in blood lipid samples of five employees with long term assignments in the extrusion area. The laboratory measures examined in this report consisted of seven liver function indicators (γ-glutamyltranspeptidase, alanine aminotransferase, aspartate aminotransferase, cholinesterase, alkaline phosphatase, bilirubin, and glutamate dehydrogenase (GLDH), five measures of blood lipids and glucose (cholesterol, triglycerides, high density lipoprotein, low density lipoprotein and fasting glucose), four haematology and blood coagulation measures (erythrocyte sedimentation rate at one hour, white blood cell count, platelet count, and haemoglobin), and three measures of thyroid function (serum thyroxine, thyroxine binding globulin, and thyroid stimulating hormone). The laboratory tests were performed by the clinical laboratory of the Occupational Medical and Health Protection Department of BASF AG. The thyroid function variables were analysed by enzyme immunoassay with an ES 22-system (Boehringer, Mannheim, Germany) and the routine clinical laboratory variables were measured on an autoanalyser (Hitachi 717) with "Optimierte Standard-Methoden" of the Deutsche Gesellschaft für Klinische Chemie at 25°C.[4]

For each laboratory outcome, means (SDs) were calculated for the study group and controls and were compared by analysis of variance (ANOVA). Separate stepwise regression analyses were also performed for each of the 19 laboratory outcomes with 2,3,7,8-TBDD concentration as the exposure measure and age, body mass index (BMI), and smoking as additional explanatory variables at a significance level of 0·15. A log transformation was used for laboratory variables not fitting a normal distribution. Cigarette smoking was recorded as the current number of cigarettes smoked a day.

Results and discussion

The table shows comparisons of laboratory findings in the study group versus controls and the results of regressing each laboratory outcome on 2,3,7,8-TBDD concentration in the combined groups. There were no remarkable differences in group means between the study and control groups for any of the laboratory variables. Variance estimates were statistically higher in the study group for cholesterol and low density lipoprotein cholesterol and higher in the control group for alkaline phosphatase. The variance of log values of triglyceride concentrations did not differ significantly between

Laboratory results in study group and controls in relation to blood lipid concentration of 2,3,7,8-TBDD in selected target organs

Variable	Study group		Controls		Group difference P value	Regression slope TBDD estimate (SD)
	n	mean (SD)	n	mean (SD)		
Liver function indicators:						
AST (GOT)* (U/l)	42	11·1 (4·0)	42	10·5 (4·1)	0·30	0·00020 (0·00046)
ALT (GPT)* (U/l)	42	16·7 (9·7)	42	14·8 (7·6)	0·32	0·00004 (0·00062)
GGT* (U/l)	42	25·2 (22·4)	42	18·8 (14·0)	0·13	0·00117 (0·00093)
Cholinesterase (U/l)	42	6047 (1309)	42	5872 (1182)	0·52	0·27920 (1·72227)
Alkaline phosphatase (U/l)	41	103·9 (22·2)	42	107·7 (32·7)	0·54	−0·00900 (0·04148)
Bilirubin, total* (mg/dl)	42	0·59 (0·27)	41	0·72 (0·43)	0·09	−0·00054 (0·00075)
GLDH* (U/l)	41	2·54 (2·00)	42	2·79 (2·26)	0·71	0·00075 (0·00105)
Lipid metabolism or glucose:						
Glucose* (mg/dl)	41	103·4 (14·0)	42	103·7 (11·6)	0·81	−0·00023 (0·00016)
Cholesterol (mg/dl)	42	227·9 (48·7)	42	227·7 (33·3)	0·99	0·04979 (0·05763)
Triglycerides* (mg/dl)	42	166·5 (173·8)	42	145·0 (76·8)	0·87	0·00092 (0·00082)
HDL* (mg/dl)	42	52·8 (17·1)	42	46·0 (11·2)	0·05	−0·00007 (0·00040)
LDL (mg/dl)	40	150·5 (50·4)	42	160·0 (33·9)	0·32	−0·01275 (0·06059)
Haematology/coagulation:						
ESR* (mm)	42	3·24 (3·41)	40	3·35 (2·89)	0·58	0·00116 (0·00096)
WBC* (n/μl)	42	6252 (2138)	42	6585 (2002)	0·40	0·00020 (0·00041)
Platelets (n/η)	42	253·5 (45·0)	42	258·3 (57·3)	0·67	−0·05047 (0·07685)
Haemoglobin (g/dl)	42	15·6 (0·7)	42	15·6 (0·8)	0·93	−0·00170 (0·00101)
Thyroid variables:						
T4 (μg/dl)	38	7·64 (1·15)	40	7·55 (1·10)	0·70	−0·00061 (0·00172)
TBG (mg/l)	38	12·21 (3·05)	40	11·85 (2·81)	0·60	−0·00394 (0·00436)
TSH (mU/l)	38	1·24 (0·51)	40	1·35 (0·64)	0·43	0·00006 (0·00084)

*Log transformation used in group comparisons and regression analyses.
AST (GOT) = aspartate aminotransferase; ALT (GPT) = alanine aminotransferase; GGT = γ-glutamyltranspeptidase; GLDH = glutamate dehydrogenase; HDL = high density lipoprotein; LDL = low density lipoprotein; ESR = erythrocyte sedimentation rate; WBC = white blood cell count; T4 = serum thyroxine; TBG = thyroxine binding globulin; TSH = thyroid stimulating hormone.

the two groups although the untransformed variance estimate was noticeably higher in the study group. Additionally, none of the variables was statistically related to concentration of 2,3,7,8-TBDD in the regression analyses. Statistical associations were found for several explanatory variables. For example, cigarette smoking was related to several outcomes at the 0·05 level: aspartate aminotransferase, alanine aminotransferase, GLDH, erythrocyte sedimentation rate, and white blood cell count. The BMI was also related to alanine aminotransferase, γ-glutamyltranspeptidase, cholinesterase, GLDH, cholesterol, triglycerides, high density lipoprotein, low density lipoprotein, and glucose concentrations. Additional analyses of 2,3,7,8-TBDD subgroups of < 10 ppt (n = 19), 10–99 ppt (n = 15), and ⩾ 100 ppt (n = 8) showed several weak trends consistent with the regression results. These included a higher log of the concentration of γ-glutamyltranspeptidase in the high dose group compared with controls (3·08 (0·74) *v* 2·74 (0·60) U/l), a lower platelet count in the high dose group compared with controls (238 (46) *v* 258 (57) n/ηl), and higher log values of concentrations of triglycerides in the two highest dose groups compared with controls (control 4·85 (0·52), 10–99 ppt group 5·03 (0·72), and ⩾ 100 ppt group 5·13 (0·88) mg/dl).

We had also examined these same laboratory variables in a study of 138 employees with previous exposure to chlorinated dioxins—namely, 2,3,7,8-TCDD.[5] In both instances biomonitoring data were obtained to support the characterisation of the corresponding dioxin exposures. As the distributions of 2,3,7,8-TBDD and 2,3,7,8-TCDD concentrations measured at the time of the examination were similar within the respective study groups, a comparison of findings across the two studies is of interest. However, it should be noted that the exposure circumstances giving rise to the current dioxin burdens were very different.

In the case of the chlorinated dioxin study group, exposure had occurred after a 1953 autoclave accident and the entire dioxin dose was received in a matter of days for many people in that cohort. Taking into account both the > 30 year interval between exposure and measurement of dioxin concentrations (2,3,7,8-TCDD half life estimates were calculated to be about six years in our study population) and differences in duration of exposure under the respective scenerios, it is likely that dose rates were up to three orders of magnitude higher in the 1953 accident group. This is reflected in the finding that 25% of the participants in the chlorinated dioxin study were diagnosed with severe chloracne after the accident and another 17% with moderate chloracne, whereas with the brominated dioxins no single case of bromacne has been diagnosed.

No laboratory variables were statistically linked to exposure in the dioxin study group. In contrast, within the chlorinated dioxin study group, some thyroid variables—namely, serum thyroxine and thyroxine binding globulin—were associated with current as well as cumulative concentrations of 2,3,7,8-TCDD and chloracne status. Morbidity follow up studies over a > 30 year period have also suggested an increase in sick absenteeism due to thyroid disease in this population.[6] In neither study were liver function variables associated with exposures, other than an association between alkaline phosphatase and both chloracne and cumulative concentration of 2,3,7,8-TCDD and weak non-statistical associations between log values of the concentrations of γ-glutamyltranspeptidase and current dioxins in both studies. In the chlorinated dioxin study group, erythrocyte sedimentation rate was positively and platelet count was negatively associated with current concentration of 2,3,7,8-TCDD. A weak negative trend was found between platelet count and current 2,3,7,8-TBDD concentration. Toxicity and mechanistic studies indicate that the potency of 2,3,7,8-TCDD may be about one order of magnitude higher than that for 2,3,7,8-TBDD.[7] Thus, if the effects found in the chlorinated dioxin group are indeed related to exposure, the differences in findings between the two study groups could be due to a combination of influences that include differences in dose rate and cumulative dose as well as in toxic potential between the chlorinated and brominated dioxin analogues.

To summarise, laboratory studies in 42 employees with past exposure to brominated dioxins (2,3,7,8-TBDD blood lipid concentrations ranging from non-detectable to 475 ppt) and 42 controls have not shown definitive trends in liver, blood lipid, thyroid, or immunological variables in relation to exposure or blood lipid concentration of 2,3,7,8-TBDD. The study population is small and hence the findings must be interpreted with caution. Nevertheless, these results provide a base for interpreting the results of clinical studies in similarly exposed populations.

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