

Lipid abnormalities in workers exposed to dioxin

J V MARTIN

From Oldham and District General Hospital, Oldham OL1 2JH, UK

ABSTRACT Ten years after an incident in which workers were exposed to tetrachlorodibenzodioxin (TCDD) a controlled biochemical study showed statistically significant increases in the serum cholesterol and triglyceride concentrations of workers both with and without chloracne. Urinary excretion of D-glucaric acid was significantly higher for all workers.

Tetrachlorodibenzodioxin (TCDD) is a potent multisystem toxin with high acute toxicity, the LD 50 for several species being of the order of 0.1 mg/kg bodyweight.¹ Other toxic effects include chloracne, impaired liver function, carcinogenesis, lipid abnormalities, porphyria, peripheral neuropathy, and psychiatric disturbances.^{1,2}

It has been suggested that some of the toxic effects of TCDD may be linked to its enzyme inducing action.³⁻⁵ In epidemiological research on subjects exposed to TCDD life style factors such as social class, alcohol intake, dietary and smoking habits, and drug therapy could have a confounding effect⁶ because of differences between subjects and controls in the extent of enzyme induction due to agents other than TCDD. In this study, therefore, the subject and control populations were matched for age, social class, alcohol intake, smoking habits, height/weight ratios, and drug therapy.

Subjects with and without chloracne who had been exposed to TCDD were tested as, although the presence of chloracne is a good indicator of exposure to TCDD, evidence from a study of workers exposed to a different chloracnegen⁷ shows that it does not necessarily follow that its absence in an individual exposed to TCDD precludes the possibility of other toxic manifestations.

Subjects

Three groups of subjects were recruited.

Group A—One hundred and twenty control subjects from an engineering works where there was no exposure to organic chemicals. Most were operatives on shift work but some were management staff.

Group B—Fifty four subjects, mainly shift workers but including some laboratory and management staff, with varying levels of exposure to TCDD, but who had never had chloracne.

Group C—Forty one subjects, mainly shift workers but including some laboratory and management staff, who had been diagnosed as having chloracne.

Methods

Subjects were asked to fast for 10 hours (overnight) and a venepuncture sample of blood was obtained at 9.30 am for the following biochemical tests: alkaline phosphatase, alanine and aspartate aminotransferase, bilirubin, protein corrected calcium, total and HDL cholesterol, triglyceride and gammaglutamyl transferase (GGT). D-glucaric acid/creatinine ratios (DGA) were measured on a sample of urine taken at the same time. All estimates were carried out using standard methodology in two NHS laboratories with some of the analyses being carried out in both laboratories.

Results

The table shows the means and range of values, plus the laboratory's normal range for those of the tests where there were differences between the subjects and controls. Mean cholesterol and triglyceride are significantly higher in groups B and C than in the controls. The parameters of enzyme induction, GGT and DGA, were raised in both groups of subjects but only in respect of DGA were they significantly higher than the controls. Serum bilirubin and protein corrected calcium concentrations were lower in both groups of subjects, although only for the latter did they differ significantly from the controls. The correlation coefficient (*r*) for the relationship between GGT and triglyceride in the subjects exposed to TCDD was +0.44, *p* < 0.001.

Biochemistry: mean values

Test (units)	Laboratory normal range	Controls mean (and range) (n = 126)	Subjects without chloracne mean (and range) (n = 53)	Subjects with chloracne mean (and range) (n = 39)	All subjects mean (and range) (n = 92)
Cholesterol (mmol/l)	3.5-7.8	5.6 (2.8-8.3)	6.14* (4.5-8.6)	6.02** (2.9-8.1)	6.09*** (2.9-8.6)
Triglyceride (mmol/l)	Up to 2.2	1.41 (0.3-3.2)	1.90* (0.4-4.6)	1.97**** (0.4-4.0)	1.93*** (0.4-4.6)
HDL cholesterol (mmol/l)		1.25 (0.8-2.02)	1.23 (0.65-2.12)	1.19 (0.89-1.88)	1.22 (0.65-2.12)
Gamma-glutamyl transferase (U/l at 37°C)	Up to 35	32 (11-90)	36 (10-120)	40 (14-91)	37.4 (10-120)
D-glucuronic acid (ratio)	Up to 3.5	1.59 (0.8-8.3)	2.09 (0.7-7.6)	2.09 (0.7-7.9)	2.09** (0.7-7.9)
Bilirubin (μ mol/l)		10.47 (5-23)	10.1 (5-22)	9.5 (4-23)	9.84 (4-23)
Protein corrected calcium (mmol/l)		2.33 (2.13-2.46)	2.307 (2.14-2.47)	2.282**** (2.10-2.61)	2.285*** (2.10-2.61)

*p < 0.005; **p < 0.05; ***p < 0.001; ****p < 0.01. Level of significance of the difference between the means of subjects and controls.

Discussion

This work confirms previous findings of a relationship between human TCDD exposure and abnormalities of all three lipid fractions estimated.⁸⁻¹³ Lipid abnormalities in experimental animals exposed to TCDD are also well recognised.¹⁴⁻¹⁶

The consensus of opinion is that raised total cholesterol and low HDL cholesterol concentrations probably confer an increased risk of ischaemic vascular disease.¹⁷ A recent study has also shown a convincing relationship between raised triglycerides and coronary atheroma.¹⁸ Consistently, two small human studies^{2,13} and one uncontrolled study (A P Redgrave, personal communication) have suggested a link between exposure to TCDD and ischaemic vascular disease, and there have been two case reports of premature coronary atheroma, diagnosed clinically and by angiography in sprayers of the herbicide 2, 4, 5-T which is contaminated with varying amounts of TCDD.¹⁹ Intravascular thrombosis has also occurred in rats exposed to TCDD.²⁰ The failure to show an increased incidence of ischaemic vascular disease in two studies of workers exposed to TCDD^{6,21} may have been due to failure to include an adequate proportion of all affected employees in the first study (A P Redgrave and J V Martin, personal observations) and failure to include subjects without chloracne in the second.

The significant positive correlation between GGT and triglyceride, the significantly lower serum calcium concentrations, and the significantly higher DGA concentrations support the hypothesis that enzyme induction by the TCDD could be the explanation for the abnormal lipid concentrations. The duration of the abnormalities in years rather than months is not an argument against this as has been

suggested,⁶ because raised DGA concentrations were found up to three years later in the TCDD exposed Seveso population.²² Whatever the mechanism for the lipid abnormalities, they have been found to persist for 10 years in another controlled study of workers exposed to TCDD.²³

This comparison of TCDD exposed workers with a control group matched for social class and known relevant variables confirms other workers' findings by various experimental approaches of TCDD induced lipid abnormalities and their possible clinical consequences.

References

- International Agency for Research on Cancer. *Monographs on the evaluation of the carcinogenic risk of chemicals to man*. Vol 15. Lyon: IARC, 1977.
- Joint National Institute of Environmental Health Sciences/International Agency for Cancer Research Working Group report. *Long-term hazards of polychlorinated dibenzodioxins and polychlorinated dibenzofurans*. Lyon: IARC, 1978.
- Neal RA, Beatty P. Influence of enzyme induction on TCDD toxicity. In: Cattabeni F, Cavallaro A, Galli G, eds. *Dioxin toxicological and chemical aspects*. New York: SP Medical and Scientific Books, 1978.
- Tung TT. Pathologie humaine et animale de la dioxine. *La Revue de Médecine* 1977;14:653-7.
- Poland A, Glover E. An estimate of the maximum in vivo covalent binding of 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin to rat liver protein, ribosomal RNA, and DNA. *Cancer Res* 1979;39:3341-4.
- May G. Tetrachlorodibenzodioxin: a survey of subjects ten years after exposure. *Br J Ind Med* 1982;39:128-35.
- Scarbrick DA, Martin JV. Biochemical changes associated with chloracne in workers exposed to tetrachloroazobenzene and tetrachloroazoxybenzene. *J Soc Occup Med* 1981;31:158-63.
- Dugois P, Colomb L. Remarques sur l'acné chlorique à propos d'une écloison de cas provoqués par la préparation du 2-4-5-trichlorophénol. *Journal de Médecin de Lyon* 1957;38:899-903.

- ⁹ Jirasek L, Kalensky J, Kubeck K, Pazderova J, Lukos E. Acne chlorina, porphyria cutanea tarda and other manifestations of general intoxication during the manufacture of herbicides. *Ceskoslovenska Dermatologie* 1974;**49**:145-57.
- ¹⁰ Poland AP, Smith D, Metter G, Possick P. A health survey of workers in a 2, 4-D and 2, 4, 5-T plant with special attention to chloracne, porphyria cutanea tarda and psychologic parameters. *Arch Environ Health* 1971;**22**:316-27.
- ¹¹ Ashe WF, Suskind RR. Progress report—patients from Monsanto Chemical Company, Nitro, West Virginia, 1959. Quoted by Hay, AWM in: *The chemical scythe: lessons of 2, 4, 5-T and dioxin*. New York and London: Plenum Press, 1982.
- ¹² Oliver RM. Toxic effects of 2, 3, 7, 8-tetrachlorodibenzo 1, 4-dioxin on laboratory workers. *Br J Ind Med* 1975;**32**:49-53.
- ¹³ Walker AE, Martin JV. Lipid profiles in dioxin exposed workers. *Lancet* 1979;i:446-7.
- ¹⁴ Gasiewicz TA, Neal RA. 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin tissue distribution, excretion and effects on clinical chemical parameters in guinea pigs. *Toxicol Appl Pharmacol* 1979;**51**:329-39.
- ¹⁵ Zinkl JG, Vos JG, Moore JA, Gupta BN. Haematologic and clinical chemistry effects of 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin in laboratory animals. *Environ Health Perspect* 1973;**5**:111-8.
- ¹⁶ Cunningham MH, Williams DF. Effect of tetrachlorodibenzo-p-dioxin on growth rate and the synthesis of lipids and proteins in rats. *Bull Environ Contam Toxicol* 1972;**7**:45-51.
- ¹⁷ Lewis B. Dietary prevention of ischaemic heart disease—a policy for the 80s. *Br Med J* 1980;**281**:177-80.
- ¹⁸ Cabin HS, Roberts WC. Relation of serum total cholesterol and triglyceride levels to the amount and extent of coronary arterial narrowing by atherosclerotic plaque in coronary heart disease. *Am J Med* 1982;**73**:227-34.
- ¹⁹ England JF. Herbicides and coronary ectasia. *Med J Aust* 1980;**1**:140.
- ²⁰ Kociba RJ, Kayes DG, Beyer JE, et al. Results of a two year chronic toxicity and oncogenicity study of 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin in rats. *Toxicol Appl Pharmacol* 1978;**46**:279-303.
- ²¹ Zack JA, Suskind RR. The mortality experience of workers exposed to tetrachlorodibenzodioxin in a trichlorophenol accident. *JOM* 1980;**22**:11-4.
- ²² Ideo G, Bellati G, Bellobuono A, Mocarelli P, Marocchi A, Brambilla P. Increased urinary D-glucaric acid excretion by children living in an area polluted by tetrachlorodibenzoparadioxin (TCDD). *Clin Chim Acta* 1982;**120**:273-83.
- ²³ Vejlupkova JP, Nemkova M, Pickova J, Jirasek L. The development and prognosis of chronic intoxication by tetrachlorodibenzo-p-dioxin in men. *Arch Environ Health* 1981;**36**:5-11.