

Reduction of serum testosterone concentration and
perturbation of serum immunoglobulin M and G3 concentrations
in a group of dioxin exposed workers.

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1. Introduction

In April 1968, the 2,4,5-trichlorophenol process at the Coalite Chemicals Ltd plant in Derbyshire, UK, overheated and an explosion occurred. 79 male workers subsequently contracted chloracne. Tests on liver function, urine, and blood counts were carried out at the time on fourteen of the workers involved in the

accident. This research did not find any abnormalities in the men¹⁾ though the sensitivity and appropriateness of the testing regime was questioned²⁾ and other research never published did show adverse effects³⁾.

Despite the discontinuation of the manufacture of 2,4,5-trichlorophenol in 1976, the site has again become the focus of attention in the 1990s as a result of dioxin contamination of the surrounding area^{4,5)}.

In 1994, the UK Health and Safety Executive published a long-term mortality study of the workers at the plant⁶⁾ which was limited by the small population size both in terms of the whole population and those subpopulations likely to have been more highly exposed. Interestingly, they report seven cases of chloracne in persons not employed at the time of the accident in 1968. In the whole population a significant excess of deaths was found only in motor vehicle traffic accidents. Two cases of myeloid leukaemia were recorded as against 0.5 expected, though the authors were not able to draw any conclusions from this. However, in populations with greater latency periods, significant excesses in deaths were observed for cerebrovascular disease and oesophageal cancer. Further, there appeared to be a rise in SMRs for lung cancer and stomach cancer and some other causes of death with longer latency periods, indicating perhaps an effect which will become more apparent with time.

No other studies have been carried out recently and none of the above were able to relate measured dioxin concentrations to medical phenomena. In 1993, 9 workers were found to exhibit elevated concentrations of blood PCDD/Fs⁷⁾. Since sublethal effects such as impairment of the immune system and male reproductive system are thought to occur at doses insufficient to cause

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significant elevations in malignant disease, it was decided to apply some of the more sensitive biochemical tests currently available to investigate of the possible sub-lethal effects on these exposed workers.

2. Experimental

Sampling and analysis of blood for blood fat, coplanar PCBs and PCDD/Fs is described elsewhere⁷⁾. Further samples were taken for the analysis of hormonal and immunological parameters on two subsequent occasions with a two month interval. Samples were analysed for immunoglobulin M (IgM) and G3 (IgG3) once and testosterone, luteinising hormone (LH) and follicle stimulating hormone (FSH) on two occasions, with the exception of one patient (total PCB/PCDD/F TEQ 55ppt) for whom only one testosterone and no immunoglobulin measurements were obtained.

Serum testosterone was measured by radioimmunoassay (RIA) using a commercial kit supplied by the Diagnostic Products Corporation (Llanberis, UK). FSH and LH were measured by RIA using reagents purchased from Chelsea kits and Reagents (Hammersmith Hospital, London, UK). Reference ranges were established from the male population (aged 18-85) of Merseyside, UK, according to International Federation of Clinical Chemists (IFCC) guidelines. Immunoglobulin determination was carried out by commercially available ELIZA under Clinical Pathologists Association accredited laboratory practices.

3. Results

Average testosterone concentrations ranged from 8.35nmol/l to 23.9nmol/l with an overall mean of 13.7nmol/l. The reference range for the general population is 9nmol/l to 40nmol/l. IgM ranged from 0.3g/l to 1.36g/l with a mean of 0.80g/l. The normal range for this parameter is 0.56-3.52g/l. IgG3 ranged from 0.33g/l to 1.66g/l with a mean of 0.93g/l. The normal range is 0.04-1.07g/l. LH and FSH were within acceptable limits in 8 of the 9 men studied. In the subject with the highest measured testosterone concentration, LH and FSH were at the upper limit of the reference range.

Results are plotted against total planar PCB/PCDD/F ITEQ in figures 1-3 below.

4. Discussion

Testosterone and IgM concentrations are generally at the lower end of the reference range for the normal population and correlate negatively with dioxin level whereas IgG3 concentrations are elevated and there is a positive correlation with dioxin concentration.

Because of the poor likelihood of the data being normally distributed, the Spearman rank correlation was used. For immunoglobulin M, the correlation coefficient was 0.707 and significant at the 95% level. For testosterone level the correlation coefficient was -0.48 with a confidence level of 80%. For IgG3 the correlation coefficient was -0.56 with a confidence level of 84%. These two latter confidence concentrations are quite high considering the low

number of data points (9 and 8 respectively). Age is a factor in the serum concentration of testosterone, so study subjects were compared to randomly selected age-matched controls using a Mann-Whitney test. The result approached, but did not achieve, significance.

Few measurements of immunoglobulins in dioxin exposed workers have been made. The depression of serum IgM has previously been observed in animal studies and in human subjects exposed to PCBs, PCDFs and PCQs in Taiwan⁸⁾. IgG was measured both in the Taiwanese Yucheng case⁸⁾ and a study of Missouri residents with known 2,3,7,8-TCDD concentrations⁹⁾. In neither case did IgG appear to be affected but measurement of the whole IgG group may have obscured any alteration in the IgG3 subgroup.

Egeland and coworkers¹⁰⁾ reported decreased testosterone and elevated LH and FSH in a cohort of dioxin exposed workers. In the present study, however, although the concentration of testosterone is lower than expected it has not resulted in the classical feedback at the pituitary which would increase secretion of LH and FSH. Hypogonadism exists in some of these males and the suppression of testosterone correlates with the circulating concentration of dioxin equivalents. This combination of results would suggest that the dioxin molecule may have agonist effects at both the pituitary and peripheral tissue receptors for testosterone, resulting in a down regulation of testosterone secretion and at the same time a mild decrease in pituitary production of FSH and LH. The reason for the difference in the findings between that study and this with regard to LH and FSH is not clear, though it is notable that the previous work¹⁰⁾ did not observe elevated LH and FSH in subjects with decreased testosterone. Moreover, both cohorts were exposed to a variety of chemicals

and some competing influence may be at work. Longitudinal studies would be required to fully explore these possibilities but this cross-sectional data would certainly support a simultaneous effect on male gonadal and pituitary function.

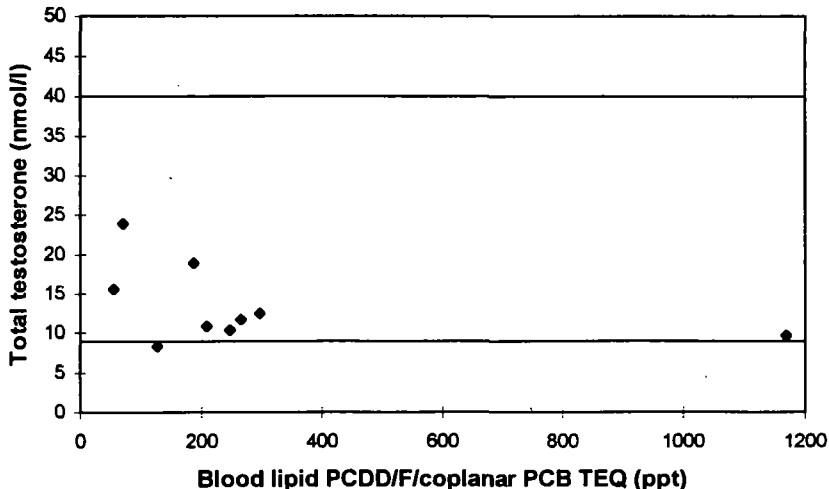


Table 1: Average total serum testosterone versus blood fat dioxin equivalents. The horizontal lines show the normal upper and lower limits.

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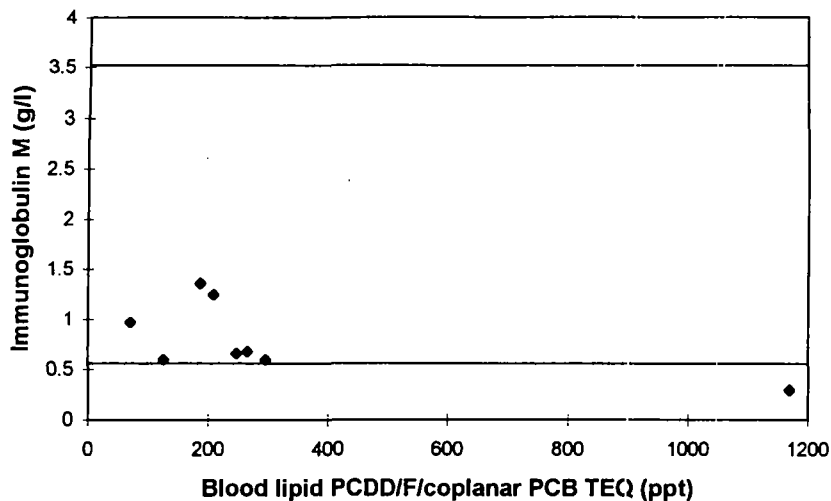


Table 2: Total serum immunoglobulin M versus blood fat dioxin equivalents. The horizontal lines show the normal upper and lower limits.

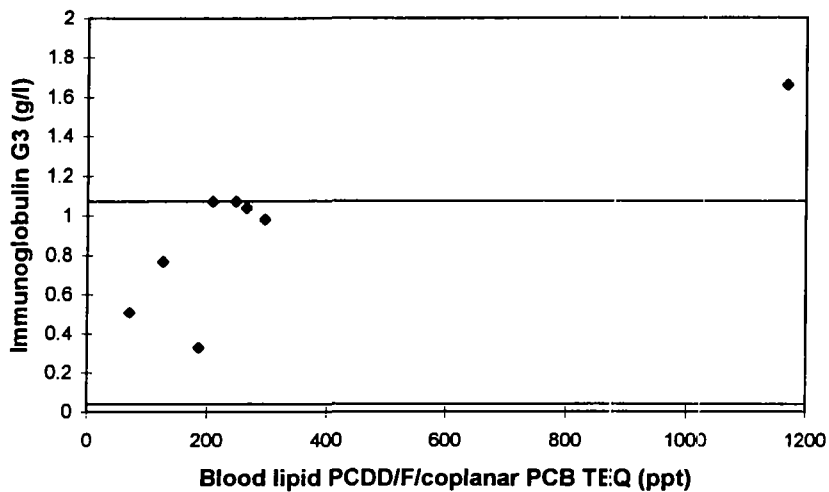


Table 3: Total serum immunoglobulin G3 versus blood fat dioxin equivalents. The horizontal lines show the normal upper and lower limits.

5. References

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