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Tetrachlorodibenzodioxin: a survey of subjects ten years after exposure

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ABSTRACT Ten years after an incident following which 79 workers developed chloracne due to exposure to tetrachlorodibenzodioxin a study was undertaken to establish the current state of health of the affected employees remaining in the company's (Coalite Oils and Chemicals Ltd, a subsidiary company of Coalite Group Ltd) employment. The opportunity was used to examine effects on mortality, morbidity, carcinogenesis, reproduction, teratogenicity, fetotoxicity, biochemistry, immunology, and genetic change. Concurrently, control groups were established with which to make comparison. The control groups selected from within the works matched the study group in respect of sex and age but it was not possible to match them for occupation and social status. Half the affected subjects still have minor chloracne. Other than this there is no evidence that they have been adversely affected in any way.

On 24 April 1968 an accident occurred during the manufacture of 2,4,5 trichlorophenol (TCP) that led to the release of crude TCP containing a higher than normal concentration of the impurity 2,3,7,8 tetrachlorodibenzodioxin (2,3,7,8-TCDD) commonly referred to as dioxin.[1] A total of 79 cases of chloracne was reported, but there was no clinical evidence of other dioxin-related diseases. The great majority of the cases responded favourably to simple treatments, several of the more intractable having good results from steam baths and dermabrasion. At the time of this examination (10 years later), symptoms had disappeared completely from half the cases still under observation while in the remainder they were insignificant.

Before 1968, TCP production was maintained in the fine chemicals unit, an open-plan building consisting of four steel production decks. The unit was manned by 24 shift process operators, three shift chemists, and about 20 general maintenance workers, a total of 47 to 50 men. Eight of the shift process operators worked exclusively on TCP production, the shift chemists did so occasionally as also did the maintenance men, a total of 31 to 34. A maximum of 34 men therefore came into immediate contact with the process by nature of their duties and a further 16 by their presence in the unit building. None had chloracne before the 1968 incident. Three members of the research and development staff had previously contracted a very mild form of chloracne that had gone unrecognised.

After the incident workers, largely maintenance men (fitters, plumbers, electricians and labourers), were drawn from over the whole plant site for cleaning-up and restorative purposes. In the immediate aftermath the risk to this type of operative was not recognised, and development of chloracne among some of these increased the total number of cases to 79 in the course of six months. Exposure was only short-term, and six months denotes the period over which diagnosis was made and reaction time would be governed by factors such as individual dosage and sensitivity.

In 1970 operation was resumed in a newly constructed building devoted to TCP production. The total workforce, all grades, was 32, 11 of whom had had mild chloracne in 1968, which had largely disappeared. In 1973 there were 13 cases of chloracne associated with workers in this building, seven of fresh contraction or recrudescence, and six entirely new cases in men who had had no connection with the previous episode. An unusual contact case arose at this time in an infant, the son of a worker who did not himself have chloracne. This outbreak, which was rapidly controlled, therefore affected seven new subjects. Its source was traced to human factors which, once identified, were relatively easily eliminated.

Production of TCP thereafter continued in a

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controlled environment (with no further medical problems) on a 24-hour day, seven-day week basis until 2 July 1976, when the unit was shut down for annual maintenance. On 10 July, the much publicised Seveso incident occurred and, after much public debate, the company decided first to delay and then to suspend production indefinitely.

In 1971 two contractors working almost exclusively with brand new materials developed severe chloracne.[2] They had worked together for only half a shift during which time they welded a new collar to an old (pronounced dioxin-free) vessel. The wife of one and son of the other also developed the condition. The source of their dioxin exposure was obscure at the time and even now has not been positively identified. These four cases, with the seven from 1973, brought the grand total to 90.

Although all company employees were given a general medical examination every six months, it was decided in 1977 to carry out a much more intensive study of the current state of health of the small group of workers who had suffered from chloracne or who had worked regularly on the TCP plant, together with a control group. An overall total of 50 to 60 was originally envisaged but in practice the survey was greatly extended.

Subjects

Of the 46 individuals remaining in the company's employment who had had chloracne, 41 agreed to take part. While most of these had actually worked on the production unit, several had contracted the condition in the research and pilot-plant stages. A further 54 employees had been in contact with the dioxin-containing stage of the TCP plant. This group, though largely plant workers, also extended into the laboratory and to management.

"Controls" were then recruited from the remaining laboratory staff, all of whom were willing to be included, and some from management.

Three groups of subjects were finally established:

Group A—No dioxin exposure; mainly management and laboratory staff but with some plant workers: 31 employees, average age 42·7.

Group B—Possible dioxin exposure; mainly plant workers but with some laboratory and management staff: 54 employees, average age 41·9.

Group C—Dioxin exposure with chloracne; mainly plant workers with some laboratory staff: 41 employees, average age 38·5.

Method

A comprehensive medical and total employment history was taken from all participants. Particular attention was paid to eliciting any note of persistence of features reported as being possibly associated with dioxin intoxication as immediate sequelae of exposure, including headaches, lassitude, depression, psychological change, joint pains, lack of concentration, disturbances of the digestion and liver, and cardiovascular complaints. Current complaints were carefully recorded as were the details of medication, alcohol consumption, and tobacco smoking. Sexual activity and reproduction were covered in detail. All aspects of contact with TCP and the chemicals and processes concerned in its production with dates and duration were noted and confirmed where necessary in company records.

Blood was taken at Chesterfield Royal Hospital, as were mid-stream urine specimens. Samples of "live" blood were forwarded to the Royal Hallamshire Hospital, Sheffield, for immunological assay and to the Centre for Human Genetics, also in Sheffield, for genetic study. No indication was given to the consultants concerned as to which group the individual belonged and for the purpose of these tests participants were identified by random numbers and not by name.

Biochemical and haematological studies included alkaline phosphatase, bilirubin, uric acid, cholesterol, high density lipoprotein, triglycerides, inorganic phosphate, calcium, albumin, total protein, gamma glutamyl transpeptidase, asparate amino-transferase, alanine aminotransferase, fibrinogen, clotting factor XIII, and total cholesterol/high density lipoprotein level. At the immunology department immunoglobulins G, A, M, D, and E were estimated as were the lymphocytes, T cells, B cells, PHA response, haemoglobin, and white cell and platelet counts. Examination for genetic damage was largely based on chromatid exchange rate. Urine analysis consisted of the usual basic examination, microscopy, tests for urinary porphyrins, and the estimation of D-glucaric acid.

Results

Among men in group C, 22 cases of chloracne (roughly 50%) were still extant but most could be described as mild to minimal. Most were periorbital, but a few still had mild evidence on the trunk. The most obvious of these latter cases was a man with sparse scattered cysts 2-3 mm in diameter. He had been one of the worst sufferers but his facial condition, having earlier been quite severe, had responded well to dermabrasion, though still having a tendency to recur.

REPRODUCTIVE HISTORY

The reproductive histories are shown in table 1.

Table 1 *Reproductive histories after exposure*

	A	B	C
Normal deliveries	8	26	19
Miscarriages	0	1	3
Perinatal deaths	0	0	1
Neonatal deaths	0	0	0
Infant mortality	0	0	0

Table 2 *Biochemistry: mean figures*

Laboratory range	*Group*	*A*	*B*	*C*
3·5-7·8	Cholesterol	6·6	6·03	5·97 mmols/l
Up to 2·0	Triglyceride	1·83	1·93	2·03 mmols/l
Up to 35	Gamma glutamyl transferase	27·7	37	39 IU/l
Up to 3·5	D glucaric acid	1·52	2·14	2·07
Up to 14·5	Alkaline phosphatase	7·7	7·8	8·8 KA units/ 100 ml
Up to 18	Bilirubin	10·6	9·9	9·6 mmols/l

The surviving children of parents in all three groups were all normal and healthy. In group B there was one miscarriage at four months in 1977 to a woman who had had a normal delivery in 1975. In group C there were three miscarriages. One was in 1970 at five months and here the fetus "was said to be incomplete." This pregnancy had been preceded by normal deliveries in 1965 and 1968 and was succeeded by one in 1971, which was terminated at seven months by caesarean section for placental insufficiency and resulted in a live child of 1133 g. The second and third were to one woman in 1972 and 1973. In this instance there had been a miscarriage in 1965, a year before the father joined the company. There were normal pregnancies in 1963 and 67, both girls. One perinatal death occurred in 1969 eight hours after delivery and was said to be due to inhalation of meconium. This woman had had a miscarriage at three months in 1967, and there had been one further normal pregnancy in 1970. Apart from the possible "incomplete" fetus there was no history or evidence of congenital abnormality or teratogenicity.

BIOCHEMICAL RESULTS

The mean results (table 2) show evidence of progressively increased liver enzyme induction and increased serum triglyceride from group A (lowest) to group C (highest). The mean test results were significantly different only in respect of gamma glutamyl transpeptidase, urinary D-glucaric acid excretion, and serum bilirubin, which showed a reverse gradient. Mean serum calcium was significantly greater in groups A and B. Only the mean gamma glutamyl transpeptidase value for group C was outside the normally accepted laboratory ranges. Although, for the purposes of this particular study, only one series of measurements was taken, mean results of liver function and lipid profile

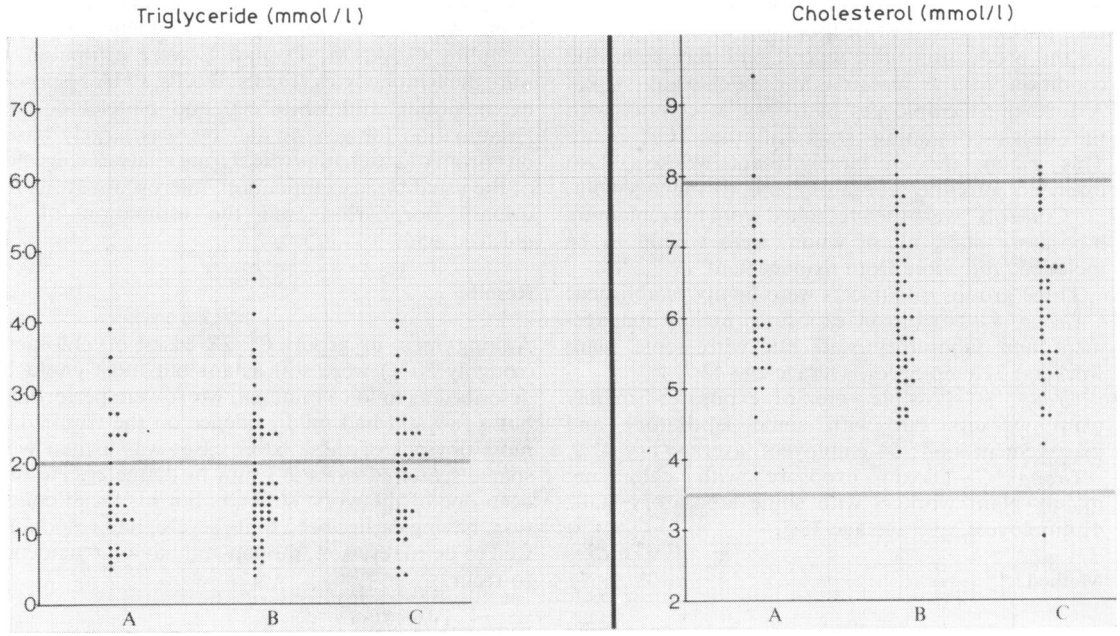

Fig 1 *Scattergrams showing individual readings and group spread.*

both before and since have been fairly consistent for chloracne sufferers. This refers to an average of five blood tests each on the original 79 sufferers in the period 1968-70, a study on all the occupants of the new unit in 1973, a follow-up to this present study in 1980, and another, which is in progress. The summation of these indicates that there has been no progression of average readings to indicate developing damage. While there are differences between groups in this series of tests (other series have concentrated on sufferers from chloracne) these differences, while interesting, are not clinically significant to any individual and are not considered to be related to employment. Individual results

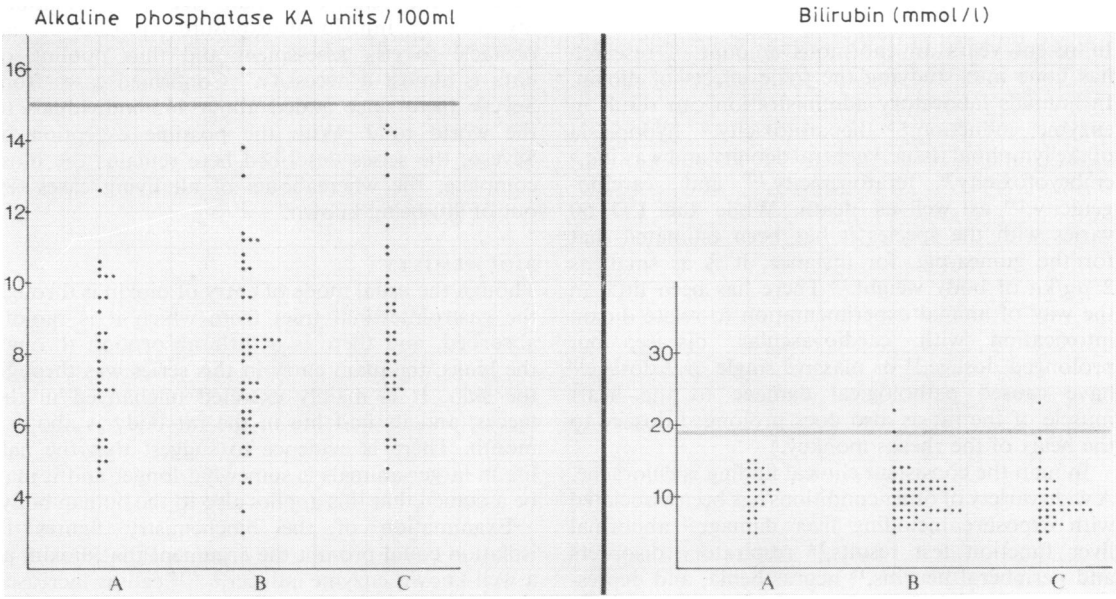

Fig 2 *Scattergrams showing individual readings and group spread.*

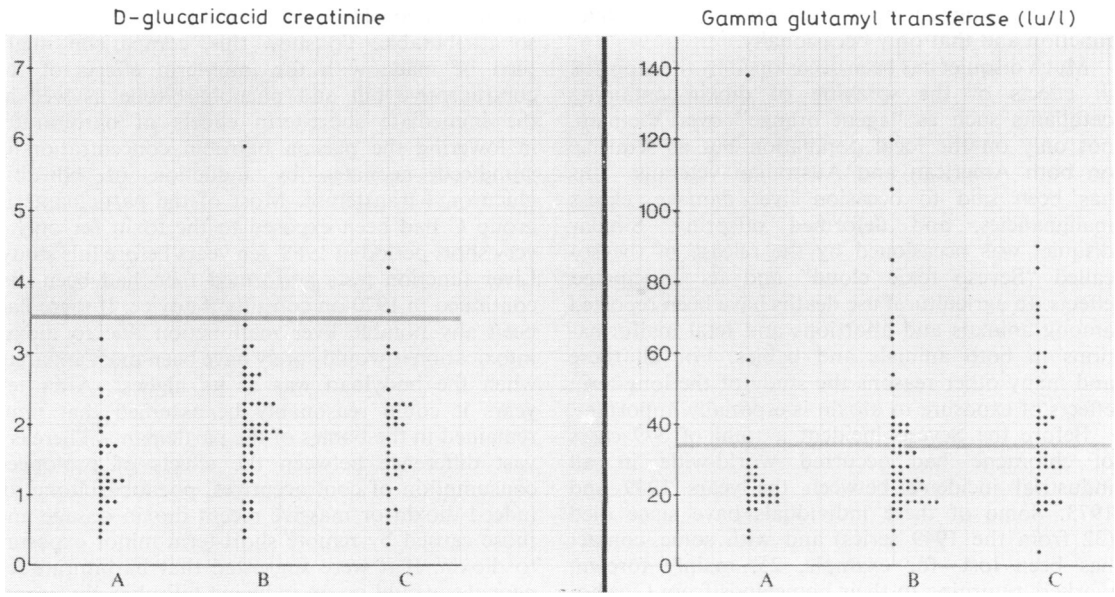

Fig 3 *Scattergrams showing individual readings and group spread.*

show deviations from normal ranges in all three groups. With the exception of two individuals (diabetics), no overt disease state is shown by these tests in any worker in any of the groups.

Scattergrams (figs 1 to 3) and table 2 illustrate individual findings in six of the tests undertaken.

Discussion

In recent years an enormous amount of research has gone into studying the toxic effects of dioxin. In animals laboratory administration can result in enzyme induction,[4 5] hepatotoxicity,[6] hypoplasia of the lymphoid tissue,[7] general debility and wasting,[8] embryotoxicity,[9] teratogenicity,[10] and carcinogenicity,[11] as well as death. While the LD 50 varies with the species it has been estimated that for the guinea-pig, for instance, it is as small as 2 μg/kg of body weight.[12] There has been little in the way of animal experimentation to relate dioxin intoxication with cardiovascular disease, but prolonged dosage,[11] or massive single oral dosage[13] have caused pathological damage to the heart muscle of the rat as also does prolonged dosage to the heart of the rhesus monkey.[8]

In man the consistent clinical finding is chloracne. A wide variety of other conditions has been associated with exposure including liver damage,[3] abnormal liver function test results,[14] respiratory disorders and peripheral neuritis,[15] neurasthenia, and depressive syndromes.[16] Very few indeed have been consistent over several episodes, the most important of these being enlarged liver and impaired liver function and that only occasionally.

Much disquiet has been occasioned by the reported ill effects of the spraying of dioxin-containing defoliants such as "agent orange" over Vietnam, not only on the local population but as sequelae on both American and Australian veterans. This has been said to occasion liver damage, excess malignancies, and deformed offspring. Similar disquiet was occasioned by the release of the so-called "Seveso toxic cloud" and its anticipated effects. In agricultural use deaths have been reported among animals and abortions and fetal malformations in both animals and babies. For all these and many other reasons the study of the long-term effects of exposure to dioxin is especially important.

Before the Seveso incident a total of 579 cases of chloracne had occurred world-wide in all industrial incidents between the years 1949 and 1973. Some of these individuals have since died (32 from the 1949 series) and with some, contact has been lost—for example, 25, mainly foreign, workers returning to their homelands from Czechoslovakia. At a World Health Congress to study the problem (The Joint National Institute of Environmental Health and Safety and the International Agency for Research in Cancer Working Group meeting of January 1978) the following was urged: "Development of an international registry of exposed persons to serve as a basis for long-term follow-up. This was considered especially important because the relatively small size of populations involved in individual exposure episodes is an obstacle to risk assessment and thus pooling of data is almost a necessity." Confirmed cases from Seveso have since added about 175 individuals to the world total. With the possible exception of Seveso, the series described here remains the most complete, the whereabouts of all living cases (89 out of 90) being known.

BIOCHEMISTY

Though the usual mode of entry of dioxin is through the gastrointestinal tract from which it is rapidly absorbed, and there is a little absorption through the lungs, the main entry in this series was through the skin. It is mainly excreted unchanged in the faeces, and its half life in the rat body is about a month. There is evidence to suggest that the half life in larger animals is somewhat longer and it may be assumed that this applies also to the human body.

Examination of the biochemistry figures in isolation could prompt the argument that dioxin, as a well-known enzyme inducer,[4-6 12] causes increased liver enzyme induction and hence increased serum triglyceride. The other apparent differences between the groups considered here could also be held to be so attributable. To show this, comparison might then be made with the long-term effects of the contraceptive pill and phenobarbitone as well as the immediate short-term effects of barbiturates in lowering the plasma bilirubin concentration in jaundiced neonates by induction of bilirubin glucuronyl transferase. Most of the participants in group C had been exposed to the toxin for only a very short period in 1968, ten years before this study. Liver function tests performed then had been discontinued in 1970 on consultant advice. If there had been any notable liver malfunction due to dioxin intoxication it would surely have been most apparent when the bodyload was at its highest. After ten years it could reasonably be assumed that none remained in the bodies of the participants. There is a vast difference between the effects of prolonged consumption of contraceptives, phenobarbitone, or indeed dioxin or massive recent dioxin dosage and those caused by remote short-term minor exposure to dioxin. If it were suggested that barbiturate-fed neonates would go on inducing bilirubin glucuronyl transferase for the rest of their lives, its use would

quickly be abandoned and the author would postulate that there is no reason to assume that minimal dioxin exposure can go on inducing gamma glutamyl transferase a decade after excretion.

If it can be thus accepted that enzyme induction so long after the incident is, to say the least, unlikely, and that in light of the fact that group mean results show progressive increased liver enzyme induction and serum triglyceride from A to C, it then becomes necessary to seek an explanation. Reference has already been made to the difficulties encountered in reconciling the numbers of participants with the practicability of balanced controls. The main factor of imbalance can be shown to be social. Subjects fell into four social categories thus: (I) senior executives and unit managers (10 subjects), (II) middle management, senior laboratory and works staff (40), (III) junior works staff, craftsmen, and process operators (55), and (IV) labourers (21).

The mean social groupings in A, B, and C on this basis are 1·93, 2·79, and 3·12 respectively. It can be quite clearly shown that as the social group score rises so also does the average triglyceride and blood pressure level, with a gain in weight relative to height, accompanied by a fall in height. The other group mean differences probably have similar origins, and there is work to support this belief.[17–19] There is an actual fall in mean cholesterol concentrations from A to C, whereas it has hitherto been accepted that exposure to dioxin gives raised cholesterol concentrations.[20]

Table 2 shows quite clearly that with the exception of triglycerides in group C and gamma glutamyl transferase in B and C the means of all parameters in all groups fall within the laboratory standard ranges. The gamma glutamyl transferase in B and C are so close as to preclude the attachment of any significance to the difference. The marginal mean triglyceride excess in group C, when taken in conjunction with the consumption of alcohol and tobacco, height/weight ratio, social status, and other related factors causes no surprise.

CHLORACNE

Chloracne has been described as the hallmark of dioxin intoxication. Schulz[21] has induced chloracne on himself with a dose of between 50 and 100 μg of dioxin: Kligman has shown (unpublished observation) that the minimal required dose is between 16 and 7500 μg. This ultrasensitive "chloracne response mechanism" had not only, in our subjects, failed to be accompanied by other clinical signs, but there had been a consistent and complete absence of acceptable biochemical indicators of toxicity both before, during, and after the chloracne response. The implication is that there must be a comparatively wide gap in dosage, albeit still in tiny quantities, before the onset of secondary indicators of toxicity.

TERATOGENIC AND EMBRYOTOXIC EFFECTS

Most of the recent interest in dioxin began with the description of teratogenic effects in mice treated with TCP containing about 30 ppm of 2,3,7,8-TCDD,[22] and this has been supported by much subsequent work. Dioxin also has an embryotoxic effect.[23] It still remains, however, that the only teratogenic effects that have been successfully shown in such studies are cleft palate and hydronephrosis.[22] No evidence was given in the histories to suggest that any of the offspring was suffering from either of these conditions or, for that matter, any other congenital deformity.

The miscarriage at four months in group B was in 1977. The father had not been associated with the process since 1973 and there had been a normal delivery in 1976. It would therefore seem reasonable to assume that if fetotoxicity had been the result of exposure to dioxin the first of these pregnancies would have been the one to suffer.

Of the three miscarriages in group C, two occurred four and five years after exposure in a family where there had been a miscarriage in 1965, in which no pregnancy had gone to term, and where the husband had lost two brothers around birth. This history does suggest some form of fetotoxicity, paternal in origin, probably genetic, and possibly associated with the Rhesus factor. Of the third abortion in this group the fetus was said to be incomplete. In the hospital case notes no reference was made to this or, for that matter, to any observed deformity. It has been suggested that confusion may have arisen with the term "incomplete abortion" requiring evacuation of the uterus. It may be recalled that this pregnancy was followed by one having placental insufficiency. All four abortions were spontaneous. There was no record of induced abortion despite specific questioning.

Owing to the fact that many very early abortions go unrecognised, UK figures for abortion rates with which to make comparison are not available as it is the official view that they are unreliable. In 1970, however, the World Health Organisation accepted a rate of 15-20% as being realistic for spontaneous abortion.

CARCINOGENESIS

There has been no death from neoplasm and no evidence of carcinoma of any kind in the relevant population.

CARDIOVASCULAR DISEASE

Eleven individuals had specific complaints related

to or who were under treatment for cardiovascular disease: group A (2), group B (5), and group C (4)—average group ages for these being 53, 52, and 53. Two of these men gave no family history of cardiovascular disease, while the remaining nine gave a maternal history of such disease and in eight of those the fathers or sibling(s) and sometimes both were so affected.

MORBIDITY

A simple analysis was set up to determine whether exposure to dioxin had impaired health and activity to the extent that attendance at work had suffered. Thirty-one of the production and maintenance workers in group C had been with the company continuously during the decade starting 1 April 1968, and their work records over that period were compared with those of the 29 men from groups A and B who most nearly matched them for age and employment experience. Only periods of certified sickness were considered. The men from groups A and B were found to have averaged 100 days each of certified sickness while those from group C averaged 78 days.

Conclusion and summary

Ten years of general clinical monitoring of those members of the work force who had chloracne in 1968 or later and who were still employed by the company had given the firm impression that they showed no significant difference from their colleagues, either those who had been exposed to dioxin without dermatological signs or the greater group who had never had any contact with dioxin. No attempt had hitherto been made, however, to follow up leavers, analyse work records, and record deaths and malignancies, reproductive performance, or social and family histories and backgrounds. Neither, in view of the continuing essential normality of this group had it been thought necessary to record and correlate any persisting symptoms, signs, or biochemical tendencies that they may have had. An enormous amount of detail has been gathered which it is possible to refer to and report only in outline here. It is evidently unwise to draw conclusions based only on laboratory figures from a very limited sample of the employees concerned, and consideration must also be given to clinical, personal, employment, and peer details. This wider and more comprehensive analysis does not confirm findings[24] based on laboratory results for a small sample only of the men covered by this study. Apart from persisting minor chloracne in half the subjects, it has not been possible to show any essential difference in any of the parameters studied between those individuals who evinced clinical evidence of dioxin exposure and their colleagues. Owing to the apparent extreme sensitivity of chloracne response it is suggested that in the absence of this condition the more unusual evidences of dioxin intoxication are unlikely to be found.

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