Toxic effects of 2,3,7,8 tetrachlorodibenzo 1,4 dioxin in laboratory workers

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Oliver, R. M. (1975). *British Journal of Industrial Medicine*, 32, 49-53. Toxic effects of 2,3,7,8 tetrachlorodibenzo 1,4 dioxin in laboratory workers. The toxic effects on three young scientists who had transient minimal exposure to 2,3,7,8 tetrachlorodibenzo 1,4 dioxin (dioxin) are described. Two of them suffered from typical chloracne. Delayed symptoms about two years after initial exposure occurred in two of the scientists. These symptoms included personality changes, other neurological disturbances, and hirsutism. All three scientists were found to have raised serum cholesterol but no other biochemical disturbances, and no porphyria nor liver damage was demonstrated. The question whether the unusually delayed physiological effects were in fact due to the initial dioxin exposure is discussed. Although conclusive evidence is lacking, it seems likely that these delayed effects were in fact due to dioxin intoxication.

2,3,7,8 Tetrachlorodibenzo 1,4 dioxin (dioxin) is known to be a highly toxic chemical and there have been many reports of illness ascribed to it (Poland *et al.*, 1971; Jensen, 1972; Bosshardt, 1973; May, 1973; Poland and Glover, 1973). Most of these toxic reactions have occurred in factory process workers following accidental exposure to dioxin produced as a contaminant of trichlorophenol in the manufacture of the herbicide trichlorophenoxyacetic acid (2,4,5-T) (May, 1973; Goldmann, 1972).

2,4,5-T is an efficient and widely used herbicide in agriculture and forestry and has also been used as a defoliant in jungle warfare. In 1969 and early 1970 there were disturbing reports from the United States of America of possible teratogenic and other ill effects from 2,4,5-T (McCrystal, 1969; Chemical and Engineering News, 1970; Leading article, 1970). Such effects were ascribed to dioxin contamination of 2,4,5-T. Although 2,4,5-T is not used in the United Kingdom on edible crops it is used extensively in forestry and to some extent by professional and amateur gardeners.

Chloracne is perhaps the best known toxic effect of

dioxin but many other ill effects have been reported (Kimmig and Schulz, 1957; Bauer, Schulz, and Spiegelberg, 1960/1961; Bleiberg *et al.*, 1964; Schulz, 1968; Poland *et al.*, 1971; Goldmann, 1972). Symptoms and signs reported have included:

- Various skin lesions such as hyperpigmentation, thickening, and lack of perspiration
- Hair fall or hirsutism
- Porphyria cutanea tarda
- Central and peripheral nervous disorders including loss of hearing, sense of smell or taste
- Liver, kidney, and gastrointestinal disturbances
- Neurasthenia characterized by altered basic frame of mind, lack of drive and vigour, sleep disorders, emotional instability, such as a tendency to anger or irritability, diminished libido or potency
- Respiratory and cardiac disorders
- Hypothyroidism

Although such a wide range of disorders has been reported from various sources it is by no means certain that all the symptoms were attributable to dioxin exposure.

Following the American reports doubts inevitably arose about the safety of 2,4,5-T in the United

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Kingdom but it was considered that if the dioxin content of the herbicide was kept below one part per million and the material was applied in the recommended way, no significant health hazard existed. A need therefore arose to test samples of 2,4,5-T from various sources for dioxin contamination and scientists in two government laboratories independently started experiments in 1970 to prepare a standard concentrated dioxin. The hazardous nature of the chemical was well appreciated by those concerned, and normal laboratory precautions were taken to avoid personal contamination. Nevertheless one scientist in each of the two laboratories later developed severe chloracne and one other scientist developed symptoms highly suggestive of dioxin intoxication but without chloracne. The purpose of this paper is to report these three cases and some of the unusual features they presented.

Patient A

White male scientist, born in 1942. In July 1970 he was attempting to synthesize dioxin by heating trichlorophenol in an alkaline solution in the presence of a catalyst. This was carried out in a chemical fume cupboard with an air-cooled condenser tube passing from the top of the heated vessel through the extract vent of the cupboard. He wore an overall and disposable plastic gloves, taking the utmost care to avoid skin contamination. The dioxin evolved sublimed on the upper part of the condenser tube although undoubtedly much must have also passed into the extract ducting of the fume cupboard.

About eight weeks after this he began to develop chloracne with a typical distribution on the pinnae, behind the ears, and on the forehead and malar regions of the neck. A less extensive eruption appeared on the arms and trunk. The genital area was unaffected. There had been no preceding excessive oiliness of the skin. He had suffered severe acne as an adolescent and there remained a tendency to seborrhoea of the scalp. He had noted no other symptoms related to this attack. The urine had always been normal in colour. There was no hair fall nor hirsutism. He had noticed increasing fatigue and a tendency to headache but these did not seem to be related to his exposure to dioxin. There were no emotional disturbances.

His previous medical history revealed nothing of significance except an attack of jaundice at the age of 13.

He was first seen in November 1970 when apart from chloracne physical examination was unremarkable. Liver function tests were normal and there was no porphyrinuria. The rash was persistent in spite of treatment and gradually subsided over the next 12 to 18 months when the incident was regarded as closed.

In view of the possibility of the development of later symptoms suggested by the history of patient C he was recalled for examination in October 1973. He then showed almost complete clearance of the chloracne with only a few isolated blackheads. There was some scattered pigmentation of the areas affected by the chloracne but this was probably part of a generalized tendency to freckles. There were some slightly depressed pigmented

scars along the hairline of the forehead. The texture of the skin was normal. Nothing else of significance was found on physical examination. He had noticed no abnormality in his general health or wellbeing since his earlier examination.

A full blood biochemical analysis was undertaken and this revealed a surprisingly high blood cholesterol (7.8 mmol/l; 302 mg/100 ml) for a man of his age. No other significant biochemical changes were detected, the liver function tests were again normal, and no porphyrinuria was present.

Patient B

White male scientist, born in 1932. In May 1970 on two separate occasions about one week apart he was engaged in the preparation of a dioxin standard by heating prepared potassium trichlorophenate in a closed system. An overall and plastic gloves were worn and the apparatus was set up in a fume cupboard with rigorous precautions to avoid inhalation or skin contact.

About five to six weeks after the experiments he noticed an excessive oiliness of the skin, first affecting the nose and then spreading to the lower part of the cheeks and downwards onto the neck. He likened the appearance to the skin being smeared with melted butter. Two to three weeks later (about eight weeks after the experiments) typical chloracne started to develop, affecting in sequence the sides of the nose, the lower parts of the cheeks, the ears, the front of the neck, the chin and finally behind the ears and the back of the neck. There was none on the chest or back. In addition, a follicular rash appeared on the hairy parts of the backs of the fingers and hands and to a lesser extent on the forearms. In contrast to the chloracne this follicular rash cleared rapidly. It was also noticeable that the development of the chloracne appeared to come in two waves about one week apart, corresponding to the interval between the two earlier chemical experiments.

He was first seen in November 1970 when the chloracne was well established. At that time he had no other significant symptoms and his previous history was unremarkable apart from a history of skin sensitivity to hydroxylamine some years previously. The skin did not reveal any evidence of increased fragility and the urine was normal in colour although it was not tested for porphyrins. Blood examination at this time showed no evidence of liver damage. The serum cholesterol was not estimated on this occasion.

The skin was treated by gentle expression of the comedones and it was noted that the sebaceous material had a strong rancid odour. The chloracne gradually subsided over the ensuing year and the episode was considered closed.

For the same reasons as patient A he was also recalled for examination in October 1973. It became evident that during the summer of 1972 and the following winter months (two to two and a half years after the original episode) he had in fact been unwell with a number of unusual symptoms. Most noticeable was a marked tendency to colicky abdominal pains with excessive flatulence. This was aggravated by eating breakfast foods containing oats, and this symptom has persisted. He had no loss of appetite but there was an unexplained loss of about 1 stone (6.5 kg) in weight from which he has

gradually recovered. He complained of oppressive headaches and a remarkable and unusual loss of vigour and drive with excessive fatigue. He became easily irritable and was prone to episodes of uncharacteristic anger. His concentration was diminished. There was no loss of libido. Concurrently with these symptoms he started to develop longer and darker hair growth on the shoulders, upper part of the back, the infraclavicular region, and around the nipples. Larger dark hairs developed on the eyebrows, which tended to extend laterally towards the temporal hairline. These hair changes subsequently regressed so that by the time of his examination in October 1973 the hair distribution was nearly back to normal.

He described worrying difficulties with muscular and mental coordination as though he were not fully in control of his limbs. Writing was difficult and laboured, and such tasks as sorting objects into groups resulted in frequent errors. He had some blurring of vision. There was at the time no obvious explanation for these symptoms and no domestic or working stress. The symptoms were nevertheless bad enough for him to consult his general practitioner who treated him symptomatically. All the symptoms, with the exception of the indigestion and flatulence after eating oats, fully subsided over a period of about six months.

Examination in October 1973 revealed a few acneiform spots on the neck and some irregularity of the skin of the face at the site of the earlier chloracne. Physical examination was otherwise unremarkable.

Blood examination showed no evidence of liver damage and no significant biochemical changes with the exception of a raised serum cholesterol (7.9 mmol/l; 305 mg/100 ml). Electrophoretic strip indicated a type 2A hyperlipoproteinaemia. Serum triglycerides were 1.3 mmol/l (114 mg/100 ml). The urine showed no porphyrinuria. Thus as in patient A there was evidence of a mild hypercholesterolaemia.

Patient C

White male scientist, born in 1940. He was a colleague of patient B, working in the same laboratory in 1970 but not actually engaged in the experiments to prepare dioxin. He had, however, been working in the following few months with the diluted dioxin standard prepared by patient B. All his work had been done with the utmost caution and with special care to avoid personal contamination.

He first reported with abnormal symptoms in June 1973. These symptoms had been present over the preceding 12 months and he had become increasingly concerned that they might be related to his work with dioxin. With the exception of skin abnormalities his symptoms had a remarkable similarity to those of patient B, in both character and timing.

He had never had any chloracne or evidence of skin fragility. The urine was always normal in colour. He had however noticed an uncharacteristic and inexplicable loss of energy and drive since about April 1973. He experienced marked loss of concentration to the extent that he felt he was not doing justice to his job. There were no headaches and no loss of libido. He complained of vague indigestion with very marked flatulence, worse after farinaceous foods, and intermittent diarrhoea. He had some loss of appetite, probably related to a marked

diminution in his sense of taste, but his weight remained steady. There were occasional palpitations. He had a peculiar sensation of flickering of vision in the peripheral visual fields and a transient period of difficulty focusing his eyes. He experienced some difficulty in sleeping. There were occasional superficial neuralgic pains with a patchy distribution over the left thigh.

Early in 1973 he had a spell of markedly increased oiliness of the skin, especially on the forehead. About this time he noticed the development of longer, coarser hair growth on the shoulders, infraclavicular region, upper back, and below the scapulae. Longer darker hairs grew in the eyebrows, which tended to extend laterally towards the temporal hairline. A few isolated long dark hairs grew on the backs of the hands. By November 1973, although there had been slight improvement, this hirsutism had not fully regressed. In contrast to the body hirsutism, he had noticed a clearly recognizable thinning of the scalp hair, which has persisted but not progressed.

Examination in June 1973 was unremarkable apart from the hirsutism. A full blood analysis showed normal liver function and the only significant abnormality was, as in the other patients, a hypercholesterolaemia (310 mg/100 ml).

Blood examination was repeated in July 1973 when the liver function tests were normal and hypercholesterolaemia (8.0 mmol/l; 310 mg/100 ml) was confirmed. The electrophoretic strip showed a type 2A hyperlipoproteinaemia. Serum triglycerides were 0.9 mmol/l (80 mg/100 ml). No porphyrinuria was detected.

Discussion

There is no doubt that patients A and B developed chloracne from what must have been the most trivial exposure to dioxin in the course of their experimental preparation of the pure standard. It is clear that the precautions they took, even in the knowledge of the likely hazard, were inadequate. Whether the symptoms experienced by patient C were related to his dioxin exposure must remain uncertain but the presence of hirsutism is highly suggestive that a toxic effect had occurred, and it is reasonable to suppose that his other symptoms were similarly caused.

The general symptoms experienced by patients B and C, who worked in the same laboratory, had much in common, and although it can be argued that some at least may be the result of suggestion, the impression given is that both were reliable critical observers used to conducting scientific enquiry and aware of such pitfalls. They are themselves quite definite that their symptoms were a genuine clearly identifiable departure from their normal states of health over a specific period. Against this must be set the fact that patient A had only chloracne and did not experience any of these general symptoms.

None of the patients had evidence of acquired porphyria, which is a well recognized result of dioxin contamination (Poland *et al.*, 1971; Bleiberg *et al.*, 1964).

A further unusual feature was the presence of hypercholesterolaemia in excess of 7.8 mmol/l; (300 mg/100 ml) in all three patients. Hypercholesterolaemia has previously been reported but does not seem to be a regular feature of dioxin intoxication. In only seven of Poland's (1971) 71 cases was the serum cholesterol raised above 7.6 mmol/l (294 mg/100 ml), the mean of the whole group being 6.1 mmol/l (237 mg/100 ml) (average age 39.3 years). Jensen's (1972) cases showed no abnormality of serum lipid levels. The chemically related polychlorinated biphenyls responsible for the Japanese outbreak of the rice-oil disease 'Yusho' (Report of Study Group for 'Yusho', 1969) are known to disturb metabolism. However, the effect was mainly on the triglycerides whereas the serum cholesterol levels were essentially normal (Uzawa, Ito, and Notomi, 1969 and 1971; Panel on Hazardous Trace Substances, 1972). It is possible that the hypercholesterolaemia in the present enquiry was simply a chance finding but in three young men (aged 31, 41, and 33 years) this would be an unusual coincidence. The presence of hypercholesterolaemia so long after the original event is especially noteworthy. It is unfortunate that there is no record of the pre-exposure or immediately post-exposure serum cholesterol levels which might have provided conclusive evidence of any relationship to dioxin intoxication.

The increased oiliness of the skin preceding the chloracne in patient B does not appear to have been reported in the literature previously. There is a suggestion that this symptom was also present in patient C, who did not subsequently develop chloracne. The significance of this finding is unknown but suggests that chloracne may result from an effect on the sebaceous gland secretion itself rather than (or in addition to) an effect on the sebaceous gland duct.

The way in which dioxin exerts its toxic effect is unknown. Animal experiments by Vinopal and Casida (1973) confirm the metabolic stability of dioxin indicating, so far as liver toxicity is concerned, that it is the unmetabolized chemical rather than a metabolite which is responsible.

One of the most striking features is the extremely long interval of about two years between the original exposure to dioxin and the development of hirsutism and other symptoms in patients B and C. It must be conceded that perhaps these patients had some further unsuspected significant exposure to dioxin in the interval, but from knowledge of the laboratory this is unlikely. It is also possible that some other chemical in the working environment may have been responsible for their later symptoms and, in particular, may independently have caused the hypercholesterolaemia. No other scientists working subsequently in the same laboratory have experienced

abnormal symptoms or signs. Additionally in November 1973 blood was taken from three other male scientists in the laboratory who were exposed to a roughly similar range of laboratory chemicals with the exception of any known dioxin. These samples showed entirely normal biochemical results and no evidence of hypercholesterolaemia (5.2, 6.6, and 4.4 mmol/l; 201, 255, and 171 mg/100 ml). There is thus no evidence that hypercholesterolaemia is caused by the normal chemical exposure in this laboratory.

Conclusion

The history of these three patients emphasizes that dioxin must be regarded as a highly toxic chemical and that even those working with laboratory quantities with normal precautions are at significant risk. Intoxication may occur in the absence of abnormal liver function tests, and urinary porphyrins and even chloracne and more fundamental physiological effects may be apparent after a long interval extending to two years or more after the initial contact. Such profound long-term effects suggest that the dioxin molecule is highly active when absorbed into the body in minute quantities. Why this should be remains uncertain but seems worthy of further study. Could it be, for example, that the effect on the sebaceous glands, the blood cholesterol, oiliness of the skin, and hair growth have a common origin in some hormonal disturbance? Although chloracne is clearly a different clinical entity from adolescent acne, can cases such as these shed any light on the aetiology of adolescent acne?

The evidence presented above, although far from conclusive, suggests that those accidentally exposed to dioxin may be subject to long delayed toxic effects. Clearly these findings need confirmation from larger numbers of cases. Unless specifically looked for, such symptoms could readily be missed, as could their possible relationship to earlier dioxin absorption.

My thanks are due to the scientists concerned who so readily cooperated with this investigation. I am also grateful to Dr. P. Wilding, of the Wolfson Research Laboratory, Queen Elizabeth Medical Centre, Birmingham for his advice and for carrying out most of the biochemical tests. Finally, I thank Dr. Thomson, the Civil Service Medical Adviser, for permission to publish this paper.

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Received for publication 16 May 1974.

Accepted for publication 26 July 1974.