SCIENCE AND SOCIAL CONCERN, A CASE HISTORY FROM PLANT PHYSIOLOGY

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I have long been an admirer of the late Dr A. C. Neish, and I wish to record my feeling of deep pride and honor at having been asked to deliver the Second A. C. Neish Memorial Lecture at Dalhousie University on October 12th 1977.

This paper, subtitled 'The Devilish Dioxins', omits many personal remarks which I made to explain my involvement in the social consequences of scientific research. These details have been published several times previously, and the interested reader can find them in Galston (1972)*.

One of our most widely used herbicides, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), carries within it a trace impurity with the potential to cause mutations, human cancer, and various fetal malformations. Although the impurity is generally present in what appears to be vanishingly small quantities, such as 0.1 part per million in the best preparations, it is still abundant enough to cause trouble. Dr J. R. Allen, of the University of Wisconsin Medical School's Department of Pathology has found that as little as 5 parts per trillion in the diet of a rat over an 18-mo period can cause the appearance of some cancers, and the incidence rises steadily with increasing dosage. Among the cancer types reported are adenocarcinoma of the kidney, angiosarcoma and malignant histiocytomas. In non-human primates, 500 parts per trillion of the impurity in the diet for a period of nine months produced mortality in over 50% of the exposed animals, death generally occurring from a marked diminution in red and white blood cells. Thus, even a million-fold dilution of the original herbicide would still produce toxic effects. Previously, Dr W. T. Jackson of Dartmouth College had found 2,4,5-T and its impurity to cause chromosome breakage in dividing plant cells.

The offending impurity, called TCDD or dioxin for short, is 2,3,7,8 -tetrachloro-para-dibenzodioxin. It is formed almost inevitably as a trace side product when the herbicide 2,4,5-T is synthesized from two simple starting materials, 2,4,5-trichlorophenol and iodoacetic acid (Fig 1). In the normal reaction, the acetic acid hooks on to the oxygen of the phenol, forming the 2,4,5-T in one simple coupling reaction. In the alkaline medium employed for the reaction, that hydriodic acid split out of the two reactants during the coupling is neutralized to sodium iodide.

During the Vietnam war, when large quantities of 2,4,5-T were manufactured for use as a defoliant, synthetic facilities were strained, and attempts were made to speed up production by the simple expedient of raising the temperature of the reaction vessel. Under these conditions, an undesired side reaction occurred, in which two of the phenolic reactants united with each other, giving rise to the dioxin (Fig 2).

*Galston, A. W. 1972. Science and social responsibility: A case history. Ann. N.Y. Acad. Sci. 196: 223-35.

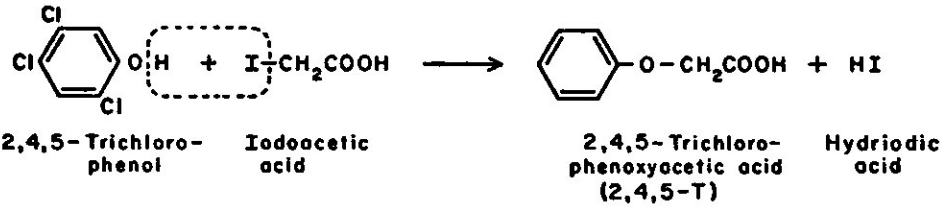

Fig 1. Synthesis of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T).

Some dioxin is also apparently generated during hydrolysis of trichlorobenzene to form the phenol. In some preparations available commercially in the late 1960's, as much as 25 parts per million of the TCDD were present, although the best preparations at the time contained more like 1 part per million. So, inadvertently, a poisonous contaminant was dispensed with the herbicide.

Like all chemical compounds designed for use in large scale agriculture, the phenoxyacetic acids had been tested for toxicity and found to be innocuous. But those tests, conducted in the immediate post-World War II era when the herbicides were first developed, are now regarded as inadequate. The trials were never carried out for long enough periods of time to detect the tumorous transformations, nor were offspring examined, making impossible the detection of genetic aberrations and fetal malformations. The latter, referred to as teratogenic effects, were first picked up in 1969, when the Bionetics Laboratories in Maryland, under federal contract, supplied the Surgeon General of the United States with information that ultimately led the then Presidential Science Advisor, Dr Lee DuBridge, to suggest a temporary ban on the use of 2,4,5-T. The ban has, over the years, been partially lifted, and the United States Forest Service, a branch of the Department of Agriculture, regularly uses the compound as an aerial spray to thin forests. This practice has not gone unchallenged, and there are currently some lawsuits in the courts in which citizens are seeking recompense for alleged damage to their plants, animals and themselves. Since the Forest Service plans to continue using the compound, this kind of litigation is bound to increase. And since recent tests in Sweden and the United States have documented the carcinogenicity and mutagenicity of TCDD, some of these lawsuits may be successful.

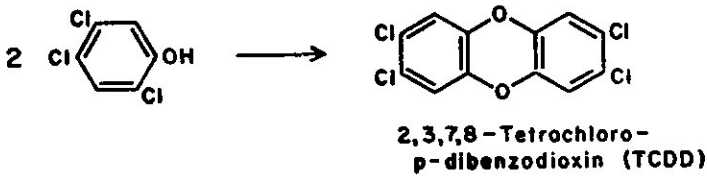

Fig 2. Formation of 2,3,7,8,-tetrachloro-p-dibenzodioxin (TCDD) through a side reaction.

In the spring of 1970, I accompanied then Congressman Richard D. (Max) McCarthy of Buffalo to Globe, Arizona, where an aroused group of citizens was protesting an aerial herbicide spray program that they felt was endangering their health and property. McCarthy, an improbable Democrat from a heavily Republican area, had concerned himself especially with problems of chemical and biological warfare, and had thus focused on herbicides because of their massive use in Vietnam. McCarthy's hearings revealed that the Forest Service aerially sprayed portions of the Tonto National Forest to kill 'unwanted' vegetation. The aim of the operation was really to decrease the amount of water evaporated by those trees in the process of transpiration; killing the trees would thus increase runoff into streams that ultimately fed into the water supply for rapidly growing Phoenix. This is obviously a potentially adversary situation, in which pressures of all kinds might be brought to bear on regulatory agencies. Unhappily, the borders of the National Forest wander into and out of residential areas of Globe, and this, together with some carelessness in operation, led to drift of the droplets of the sprayed herbicide onto private property. Damage of various kinds, to plants, domestic animals and humans was claimed, and the courts will shortly have to evaluate the validity of the allegations. In the meantime, other incidents of the same sort have cropped up, but the Forest Service, undeterred, proposes to continue its spray program into the future.

A few years ago, Robert Baughman and Matthew Meselson at Harvard devised an improved method for the detection of minute traces of TCDD and related dioxins. Based on the use of gas chromatography, their method was able to detect and measure dioxins in materials previously considered dioxin-free. Using this technique, Meselson and his colleague O'Keefe have now found traces of dioxins in samples of human mothers' milk obtained from Texas and Oregon, where previous spray operations had occurred. This finding, if substantiated, would indicate that the dioxins may find their way into the human environment, with possible effects on human health. Whether the dioxins are absorbed by plants, passed on to animals, and accumulated during passage up the biological food chain is unknown, but given the example of DDT, this possibility cannot be overlooked.

The intrusion of dioxins into our lives is not limited to operations involving herbicides. The recent explosion of a chemical plant in Seveso, Italy is a case in point. This factory was employing chlorinated phenols in synthetic operations, but the explosion, causing the release of many products into the atmosphere and ground, alarmed those who knew about the danger of dioxins. Many workers in such factories had previously contracted chloracne, a serious skin irritation, and other troubles were suspected as well. So gravely did the government view the incident that it evacuated the town and sealed off the area. Presented with the evidence on dioxin-caused fetal aberrations, the Catholic hierarchy gave permission for rarely sanctioned abortions. The town remains uninhabited, and given the persistence of dioxins, may remain so for a long time. Given the widespread use of chlorinated phenols in the chemical industry and wood preservation, additional accidents and incidents are sure to occur.

In Vietnam, where an estimated 550 lbs of dioxins were inadvertently deposited along with the herbicidal "Agent Orange" (a mixture of

esters of 2,4-D and 2,4,5-T in a barrel with an Orange stripe), there have been reports of some unusual health problems. Dr Ton That Tung, the distinguished and internationally recognized surgeon who heads the Viet Duc hospital in Hanoi, is struck by the fact that primary cancer of the liver, formerly an unimportant cause of death in Vietnam, has now risen to second place in the list of cancer-related mortalities. Many of the cases he treated in the north of his country involved people who had been in the south, where the bulk of the spray operations had occurred. He also points to the prevailing south-to-north currents off the coast as a possible means of bringing to the populated areas of the north residues washed into the waters from the zone of deposition in the south. Dioxin residues have been detected in fish and shellfish long after the defoliation program ceased and Vietnamese consume such foods as their major source of protein. There is no certain linkage between TCDD and health problems in Vietnam, but Dr Tung points out that the liver is a likely locale for the body to send TCDD for decontamination.

In the light of these facts, it comes as a bit of a surprise to learn that the United States Forest Service, undeterred by the medical findings, proposes to continue its 2,4,5-T spray program in the northwest. Citizens groups of various kinds are banding together to fight this plan, and some scientists are giving their opinions in advance of the start of operations. Certainly, the Environmental Protection Agency as well as other governmental bodies must get into the act before long. It will be interesting to see what policy is eventually adopted; the decision is certain to reflect sharply the division between the environmentalists, for whom preservation of health and ecological balance is paramount, and the technocratic types, who want the facilitation of productive processes to be the decisive issue.

Whatever happens with 2,4,5-T, there is certain to be some concerned reappraisal of that long-time standard herbicide, 2,4-D. Long used to kill dicotyledonous broadleaved weeds in a field of monocotyledonous plants, this herbicide is a component of virtually every spray designed to rid lawns of such 'offensive' weeds as dandelion and plantain. Is there danger from dioxins in 2,4-D preparations as well? After all, they are synthesized from chlorinated phenols, and might, therefore, undergo the same side reactions. The evidence so far appears to give 2,4-D a relatively clean bill of health. The same Bionetics Laboratory test that found 2,4,5-T to be teratogenic did show some slight activity with 2,4-D as well, but the samples used in that test were extraordinarily contaminated by modern standards. Also the tendency to form dioxins seems to be diminished when there are fewer chlorine atoms in the ring, and the resulting dioxins are much less toxic than the 2,3,7,8-tetrachloro-derivative formed during the synthesis of 2,4,5-T. Nonetheless, careful tests for mutagenicity and carcinogenicity must be carried out with this compound as well, for like 2,4,5-T, it came into use at a time when toxicological tests were much less stringent than we now know they should be. A decision to limit or terminate the use of 2,4-D would have widespread consequences, not only for present agricultural practice, but also for the willingness of manufacturers to enter on the risky road to the production of a new herbicide.