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Environmental Contamination and Toxicology

The Epidemiology and Toxicology of TCDD

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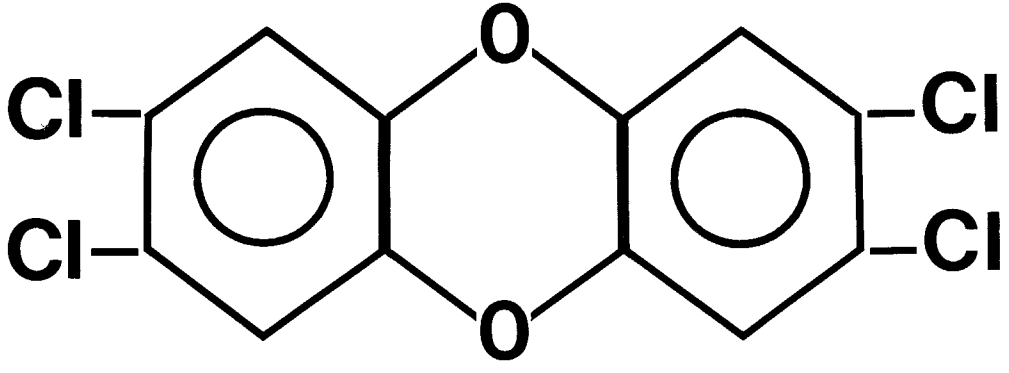
The toxicology and epidemiology of dioxin is a broad subject, so I will very briefly review the animal toxicology, then the early studies we conducted here in Missouri and finally other human aspects of TCDD exposure.

Figure 1 is the chemical structure of 2,3,7,8 tetrachlorodibenzodioxin. There are many other chlorinated dibenzodioxin isomers, and the term dioxin is used very loosely. For some isomers, the chlorines are not in the 2,3,7,8 position, but in other places. Some of those isomers are not nearly as toxic as the TCDD; an important point to remember. For instance, the octochlorodibenzodioxin, which is completely chlorinated, has an LD_{50} of about 2 grams per kilogram body weight.

Table 1. Chlorinated compounds in samples of soil and oil

Sample Origin and type	Date Collected	Concentration TCP	TCDD (ppm)	PBC(ppm)
Arena A soil	8/71	0.56-0.65%	31.8-33.0	1350-1590
	8/74*	Trace	None	None
	8/74	11.5 ppm	0.22-0.44	15
Arena C soil from dump sites	8/74	1.8 ppm	0.49 25	
	8/74	14.8-19.2 ppm	0.63-0.85	20
	8/74	1.5 ppm	0.38	10
Farm road oil	9/74	32.6 ppm	0.61	None
Chemical waste from oil plant	9/74	30.4-34.3%	306-356	None

* Collected after arena had been excavated twice.



2,3,7,8 - tetrachlorodibenzodioxin

The TCDD is formed during the production of 2,4,5 trichlorophenol (2,4,5-T) from tetrachlorobenzene. Thus, 2,4,5-T and all products made from 2,4,5-T may be contaminated with the TCDD, both the commercial products and the waste material. It was the waste material in Missouri that created the problem, however, it was not from the production of 2,4,5-T, but from the production of hexachlorophene that this waste material arose. Hexachlorophene is also made from 2,4,5-trichlorophenol.

What are the effects of this particular compound? It has been studied extensively in animals since the late 1960s. We know a lot less about what it actually does in people. Scientists have been very interested in this compound because of the many effects that it causes, and we really still do not quite understand its mechanism of action. The acute oral LD_{50} in different species is usually in the microgram range except in the hamster, where the oral LD_{50} is between 1 and 5 milligrams per kilogram body weight. In different animal species, the toxicity varies a great deal -- not only the amount that it takes to cause an effect but also the types of tissue reactions that are seen. We do not know, for instance, where people are in this range. Acute toxic doses in all animal species cause severe weight loss. When autopsies are performed on these animals they have no adipose tissue left. Death is usually delayed. Even if doses higher than the oral LD_{50} are given, it still takes one to two weeks or longer for the animals to die. In small laboratory animals it takes two to three weeks and may take as long as 40 days. Another important fact is that lower doses given daily will have, to some extent, a cumulative toxic effect. In other words, it takes a whole lot less to kill an animal or to cause a toxic effect if daily doses are given than it will when a single dose is given. For an extremely toxic compound this is somewhat unique in that most of the other really toxic compounds, like some of the organophosphorous compounds, do not accumulate. They are acutely very toxic but almost as much has to be given every day to cause long-term effects.

In the late 1960s and the early 1970s it was found that TCDD is teratogenic in mice, causing cleft palates. In most other animal species it is fetotoxic in that it causes resorptions in rodents. In subhuman primates, spontaneous miscarriages have been reported. Furthermore, edema and hemorrhage have been reported in rat offspring. Most teratologists do not consider this compound to be a very potent teratogen since mice are the only species where it causes cleft palates.

Hemorrhage can also occur in adult animals because TCDD may produce thrombocytopenia and other effects on the peripheral blood. In the horses in Missouri and also in rats, ulceration of the mucosa of the stomach has been reported as well as hyperplastic changes in the gastric mucosa in subhuman primates. Particularly in the guinea pig, the rat and the mouse, atrophy of the lymphatic system and atrophy of the thymus occur. This is particularly pronounced in the guinea pig. In some animal species severe liver damage may occur,

namely in the rabbit, the rat and to some extent the mouse. I noted toxic effects in the livers of the horses that suffered from TCDD poisoning here in Missouri. On the other hand, the toxic effects are minimal in the liver of the guinea pig and the hamster.

In birds and chickens TCDD seems to cause chickedema disease, which is an accumulation of fluid in the pericardial sac, the peritoneum and the subcutis. Chickedema disease was first observed and reported in the United States in 1957, but it took almost eight years to determine the cause. Other causes include some chlorinated compounds that are related to these types of halogenated aromatics, such as hexachlorodibenzodioxins and polychlorinated biphenyls (Kimbrough 1974).

The skin is affected in some animals but not in all. Hyperkeratosis, or X-disease, has been observed in cattle. A similar effect was noted in the horses in Missouri. Before the identity of TCDD was known in the 1940s and the 1950s, it was recognized that during the production of 2,4,5-T the workers would develop a skin disease called chloracne. A test was developed to determine which of these technical materials would cause the skin lesion by screening rabbit ears (Adams et al. 1941). Rabbit ears were painted with TCDD, a reaction similar to chloracne in workers was produced and, in the rabbit, this was referred to as hyperkeratosis. To determine whether TCDD was present in the soil of the riding arenas where many horses had died, we first conducted this test. In chronic feeding studies in rats, TCDD caused hepatocellular carcinoma and tumors in other organs at the relatively low dosage levels of 0.1, 0.01 and 0.001 micrograms per kilogram body weight per day (Kociba et al. 1978). The dose of 0.001 micrograms/kg would be the same as one nanogram. The incidence of hepatocellular carcinoma in female rats was statistically significant (P 0.05) increased at the 0.1 ug/kg per day dose and, in the female rats, squa mous cell carcinoma of the lungs was also observed at that same dosage level -- seven out of 49 developed this lesion. Since then an additional study has been conducted by the National Cancer Institute (NCI) and hepatocellular carcinomas were again observed. Squamous cell carcinomas of the lung were not found. Kociba's study was a feeding study, where the material was mixed into ground chow. The NCI study was a gavage study where they dosed twice a week. Because in the feeding study, the material was in ground chow, the animals may have inhaled some of the material and the effect of the TCDD on the lungs may have been a local effect rather than a systemic effect. It could, of course, also be a difference in species response, because the strain of rat used by NCI was different. In addition to liver and lung cancer in the Kociba study, cancers also developed in the soft palate and the nasopharynx.

TCDD is stored to some extent in adipose tissue and in other organs. At the end of this two year study by Kociba, 24 micrograms per kilogram of TCDD were present in the liver at the 0.1 microgram/kg dosage and 0.54 at the lowest dose. At the highest concentration,

8.1 micrograms per kilogram was found in adipose tissue. This is contrary to what we know from other halogenated compounds in that the concentrations are usually much higher in adipose tissue. The reason for that may be that this particular compound is somewhat more polar. In the subhuman primate, tissue levels were measured in a few animals. In this species, the concentration in adipose tissue and in skin was actually higher than what was found in the liver. We do not know what the distribution of TCDD is in people.

We also do not really know what the mechanism of action of TCDD is. Poland et al. (Poland and Glover 1975; Poland et al. 1976; Poland and Glover 1979) have determined that TCDD is bound to a receptor cytosol in the cell cytoplasm and the complex translocates to the nucleus (Greenlee and Poland 1979) where it affects the messenger RNA which then, in turn, affects many enzymes within the cell. These studies were only conducted in the liver. It is not known whether the same reactions occur in cells of other organs.

Another argument at the moment is whether TCDD is a promoter or an initiator of cancer or both. Some evidence exists which suggests that it is a promoter in that animals exposed to nitrosamines and then secondarily exposed to TCDD had a higher incidence of liver cancer than those exposed only to the nitrosamine (Pitot et al. 1980). It has been argued that because TCDD has been shown to bind to DNA that it is also an initiator, but I do not think simply binding to DNA can be equated necessarily with initiation. Furthermore, the amount of TCDD bound to DNA is four to six orders of magnitude less than that for other known carcinogens (Poland and Glover 1979). Other evidence that has been brought forth that TCDD is an initiator of cancer is the fact that it causes cell transformation (Hay 1982). To me, cell transformation means the same as metaplasia, which should not be equated with initiation. Further work should be conducted to elucidate the significance of cell transformation. A few papers recently have shown that TCDD causes lipid peroxidation, and thus affects cell membranes (Stohs et al. 1983; Sweeny and Jones 1983). This is an avenue of research which should be pursued since earlier studies (Jones and Butler 1974; Kimbrough et al. 1977) showed that these particular compounds in livers, for instance, result in multinucleated cells which suggests that only the nucleus divides during cell division, and thus, suggests some effect on all membranes. This effect on cell membranes could be caused by lipid peroxidation products.

Usually the acute and chronic toxic effects of chemicals are examined. Rarely is recovery following cessation of exposure studied. This is also true for TCDD. Very little information exists in that regard. The question of recovery following cessation of exposure is a problem for the Public Health Service (PHS) and is unrelated to product safety testing for which most animal studies are done; therefore, that information usually is not available.

Chronic reproduction studies in animals have shown an effect on reproduction at dosage levels which are similar to the dosage levels used in the cancer studies. Finally, in a number of animal species, hepatic porphyria has been produced with TCDD. Uroporphorinogen decarboxylase in the liver is inhibited by TCDD resulting in increased excretion of uroporphyrin and carboxylic porphyrins in urine. Uroporphyrins and the carboxylic porphyrins also accumulate in the liver.

What do we know about human health effects? Most of our information has been obtained in workers who have had occupational exposure. Untoward effects in workers following accidental exposure to TCDD first occurred in the late 1940s and the 1950s. The workers were either exposed because they were producing commercial products which contained the material, and after working in a particular area for several months and sometimes years, they developed a skin disease termed chloracne; or there were accidents where the reaction vessel, in which 2,4,5-T was made, overheated and exploded. In these episodes, exposure was probably to higher concentrations of TCDD and effects occurred more rapidly. Those who had been exposed started developing chloracne about a week or two after the explosion. As far as I am aware, in none of these episodes do we actually know what the dose was that these people received. None of that has been published in the literature. It has been stated that the TCDD in vessels where extothermic reactions occurred may have been as high as 1,000 parts per million.

Hyperpigmentation and hirsutism have been reported in connection with the chloracne. In two plants, one in Czechoslovakia and one in the United States, in New Jersey, where 2,4,5-T was also manufactured, porphyria cutanea tarda was observed. Hirsutism was particularly pronounced in the plant in Czechoslovakia. In both of these plants, the additional exposure to hexachlorobenzene cannot be excluded. In addition, a sensory neuropathy was noted, which has been noted in other plants as well. Usually workers will complain of pains in their joints, particularly early on, after they have very acute severe chloracne; however, there are usually no abnormal physical findings in the joints. In the early studies of the affected workers, I do not think any attempts were made to objectively measure the effects on the sensory nervous system. Tests have now been developed which evaluate sensory nerves and which can be used in field studies. The nerve conduction tests, which primarily have been used thus far, are actually not very useful to measure neuropathy. Differences in nerve conduction were shown among residents from Seveso, Italy who had chloracne and residents who did not (Fillipini et al. 1981). A recent workshop of the World Health Orgnization (WHO) has addressed the subject of standardizing neurological examinations. This workshop will be published with recommendations on how to evaluate the nervous system. Testing nerve conduction velocity would not be very useful in determining whether a sensory neuropathy was present.

Abnormal liver function tests have been associated with exposure to TCDD. The transaminases and the gammaglutamyl transpeptidase were elevated in children with chloracne from Seveso (Favaretti et al. 1982). Of course, gammaglutamil transpeptidase is a very nonspecific enzyme. It has been claimed that it becomes elevated in association with the induction of microsomal enzymes. In animals it has been demonstrated that TCDD is a very potent inducer of microsomal enzymes; both the P_{450} and P_{448} systems are induced in the liver. This induction is extremely persistent after the animals have been removed from exposure.

The excretion of glucaric acid can also be measured in urine. It has been shown to be elevated in the children with chloracne who were exposed in Seveso (Ideo et al. 1982). At the moment we have no good baselines for glucaric acid in humans and, before we can interpret the significance of these findings for human health, more information needs to be colleced. It is presently also not known whether increased excretion of glucaric acid in urine is associated with elevated gammaglutamil transpeptidase. If that were the case, then just one or the other test would suffice for screening populations.

In some workers, elevated serum cholesterols have been reported. However, cholesterol may also be elevated in the unexposed general population. In the exposed workers, cholesterol usually was not measured prior to exposure. It is, therefore, difficult or impossible to determine whether the elevated cholesterol is really an effect of TCDD. On the other hand, elevated cholesterol blood levels have been observed in TCDD-exposed animals.

In 1977, it was initially suggested in a report from Sweden that an association existed between exposure to 2,4,5-T and other phenoxy herbicides and an increased incidence of soft tissue sarcomas. These reports were followed by others where such an association could not be demonstrated. One problem with many of the "negative" studies is that the number of people studied was very small. Soft tissue sarcoma is a very rare cancer. To test the hypothesis of whether or not such an association exists, a very specific type of epidemiology study, a case control study, would have to be conducted. In such a study, the soft tissue sarcomas are identified and compared to a group of controls that do not have soft tissue sarcomas. Of course, soft tissue sarcomas also occur in the general population without any known excessive exposure to phenoxy herbicides. A problem with these types of epidemiology studies is that all sorts of biases can be introduced. For instance, in the Swedish studies a bias may have been introduced because the people were questioned retrospectively about their exposure. It would be possible that people who had a disease might have better recall because they were wondering why they had this disease or they might have read something about it in the newspaper (Coggon and Acheson 1982). In a study done at the National Institute for Occupational Safety and Health (NIOSH) (Fingerhut et al. 1984) it was found that by pooling different worker populations a total of four soft tissue sarcomas

was found among 105 deaths against an expected level of 0.07% among U.S. males aged 20-80. Subequently three additional cases were identified among workers bringing the total cases to seven. Microscopic review of tissue sections from these tumors was recently completed. Two of the four cases with documented evidence of exposure and three additional cases that did not have documented evidence of exposure were confirmed to represent soft tissue sarcoma (Fingerhut MA, et al., unpublished data). The other two tumors turned out to be anaplastic carcinomas. Thus, only two cases were identified with both soft tissue sarcoma and documented exposure. This is still higher than expected and the question of whether or not exposure to phenoxy herbicides is associated with an increase in these types of tumors will still have to be pursued. NIOSH is examining a large registry of workers who have been exposed to phenoxy herbicides. The NCI is conducting a study in users of this product. The final answer is really not out on whether or not there is this association and what it means.

I mentioned explosions previously. In 1976 in the ICMESA plant in Seveso, Italy, an exothermic reaction occurred. Material from the reaction vessel descended as a cloud on the surrounding area, which was populated. Early on, it was not recognized that TCDD was present. It took about two weeks to determine the fact that the vegetation, soil and everything else was contaminated with varying concentrations of TCDD. The highest levels on the vegeta tion were about 15 parts per million (ppm). Only very few samples of vegetation were taken and all were collected in close proximity to the plant.

Fifteen parts per million would be the same as 15,000 parts per billion (ppb). The levels in soil were much lower than those measured in contaminated areas in Missouri. However, the acute exposure of this population might have been at higher levels. We do not know what levels were present in the cloud. Some of the people, particularly children, were outside when the accident occurred in the early evening. The children, at first, developed skin lesions that looked like burns. Possibly that was caused by the chlorophenols and also sodium hydroxide in the cloud. Several weeks later, some of these children and other children developed skin lesions that were consistent with chloracne.

Chloracne consists of skin colored cysts which, in workers, can measure up to 10 mm with a central opening. The other dominant lesion is the comedo. The lesions start in the lateral part of the face, but may affect other parts of the face and body, including the back and legs. In most cases, it is not difficult to distinguish chloracne from juvenile acne but, if juvenile acne is sevre with a lot of scarring, it may present a problem. Sometimes to only way the diagnosis is made is by history. Young children do not usually have juvenile acne and so, in a child population in Seveso, juvenile acne was less of a problem. On the other hand, there were difficulties in that many children were said to have chloracne and, when this was reviewed by dermatologists with experience, many of those cases turned out not to be chloracne.

The 2,3,7,8-tetrachlorodibenzodioxin poisoning episode in Missouri. In 1971, a child was admitted to Children's Hospital in St. Louis because of hemorrhagic cystitis. The Centers for Disease Control (CDC) was contacted. At first, it was suspected that this child had some peculiar infection, since it came from a riding arena where a number of horses had died. A CDC epidemiologist was sent to St. Louis. He visited the hospital and also inspected the riding arena where the horses had died. During his visit there, he learned that all of this had happened after the riding arena had been oiled by a waste oil dealer. The waste oil dealer claimed that he had only picked up waste oil and did not know of any other chemicals that could have caused this outbreak. The epidemiologist collected some soil samples and people from other agencies also went to the arena and collected soil samples. The chemists at CDC were told that a volatile material was suspected to be the culprit because at first all the birds and insects died, and later the horses became ill and there was an odor. The chemists proceeded to look for a highly volatile material but TCDD is only slightly volatile. For this reason, TCDD was not found. In 1973, one of the chemists (Dr. Richard Cline), by accident, had determined that 2,4,5-trichlorophenol was present in the soil. Once the 2,4,5-trichlorophenol was identified, then, because that particular compound could not cause all of the problems in Missouri, we decided we wanted to look for TCDD, except that our laboratory director felt we should not work with TCDD because it was so extremely toxic. So I then suggested that the chemist make an extract of the soil for animal studies. We painted rabbit ears to see whether we could produce the hyperkeratotic skin lesion that I mentioned earlier. The exposed rabbit did develop the hyperkeratosis confirming our suspicions. We subsequently identified it by chemical analysis and quantified TCDD.

We then returned to Missouri in 1974 to determine the extent of the problem. At that time, we found that there were four riding arenas. There was also a farm where some material had been dumped and we learned that most of the other material that had been collected by the waste oil dealer who had sprayed the arenas had been sent to a refinery in Illinois. The waste oil dealer still could not remember where he had gotten the TCDD. We decided that it had to be a waste product that had come from a chemical company. We then contacted the Department of Defense to find out who in this area might have made 2,4,5-T for the spraying of Agent Orange in Vietnam during the 1960s and we came up with a chemical company. When we visited the company we found that, if they actually had ever made the 2,4,5-T, they had gone out of production in 1969 but then had subleased the premesis to another company that was making 2,4,5-trichlorophenol for the production of hexachlorophene. It was from that company that the waste had come. After we had discovered this, the waste oil dealer suddenly remembered that he did indeed pick up some of the material. In going through the records, we were never really able to account for all of the materials that had been picked up; but eventually we decided, after trying to measure TCDD in some different areas where we could not find it, that maybe most of it did go to this refinery

in Illinois. The oil was used for roads there. We collected samples from some oiled roads but were not able to detect TCDD. One problem we had was that the analytical method we were using at that time was only good at parts per million levels rather than very low parts per billion and parts per trillion levels.

The people who had been exposed at the time in the riding arenas included the six year old girl who had a hemorrhagic cystitis and nosebleeds, headache, diarrhea and other complaints. There was also a ten year old child who complained of nosebleeds, headaches, diarrhea. This child had some skin lesions. The problem was that, when we returned in 1974, several years after the exposure, we could not really verify the skin lesions anymore. There were also complaints of joint pains, but we made no attempts to substantiate this. One possibility would be that this really was a sensory neuropathy. There were, in another riding arena, two little boys who had skin lesions which lasted for a few days and then subsided. Again, we did not really see these skin lesions.

The soil from arena A, the first arena we were aware of, was collected in August of 1971. We found 31 to 33 ppm TCDD which is the same as 31,000-33,000 ppb. In addition, there was 2,4,5-trichlorphenol at about ½% and there were polychlorinated biphenyls at around 1,300-1,600 ppm. This arena was excavated twice and the soil dumped at other sites. On reexamination in 1974, additional soil was collected in that particular arena. The analytical method we were using then had a limit of detection in the 100 ppb (ug/kg) range; therefore, we were not really able to detect TCDD at concentrations much below 1 ppm (mg/kg). Some trichlorophenol was also still present in the riding arena. When collecting soil samples at different periods of time, they are usually not collected from exactly the same place. Since areas are not contaminated uniformly, hot spots may be present in some areas, lower levels in other areas, and comparison of measurements made in different years is tenuous unless a very rigid collection system is followed. Also, if the soil is disturbed as in riding arenas, the soil gets moved around.

At the time of the reinvestigation in 1974, it was learned that additional arenas had also been contaminated (Kimbrough et al. 1977). In another area where soil was collected, we still found some trichlorophenol, 0.6-0.85 ppm TCDD, and about 20 ppm of PCB. Some of the soil from that arena had also been removed. At the dump site, we found 1.5 ppm trichlorophenol and 0.38 ppm of TCDD and 10 ppm of PCB. The waste oil dealer picked up the waste from the chemical company (Figure 1) and took it to his holding tanks where he mixed the TCDD into the other chemical wastes with salvage oil. At one point, a driver had overloaded and had received a ticket at a weighing station. He had to pass another weighing station before he reached his destination so he unloaded some of his material from the factory on a farm. We collected soil from that farm three years later and found 2,4,5-T and the TCDD, but no PCB. We then located the tank that had contained the TCDD waste on the premesis of the plant. We took

samples from waste material still present in the tank and found that the concentration of TCDD in this waste was 306-356 ppm.

The horses exposed to the contaminated riding arenas had severe weight loss. Unfortunately, autopsies were only performed on a few horses. The horses had liver lesions, and their skin showed hyperkeratosis. The autopsies that were performed by veterinarians all reported gastric ulcers. Many of the animals had lung lesions and there were lesions in the kidneys. I am not sure whether some of these lesions were primary or secondary because of the debilitating effect that TCDD had on the horses. It impressed me that in the horses, which had been exposed over a period of time, a very pronounced fibrosis surrounding the central veins in the liver was present. Similar observations have been made in rabbits and in rats, but there the fibrosis was not as pronounced.

Because of time constraints, it will not be possible to discuss the considerations in determining that, in residential areas, levels above 1 ppb of TCDD in soil cannot be considered safe and represent a level of concern (Kimbrough et al. 1984).

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