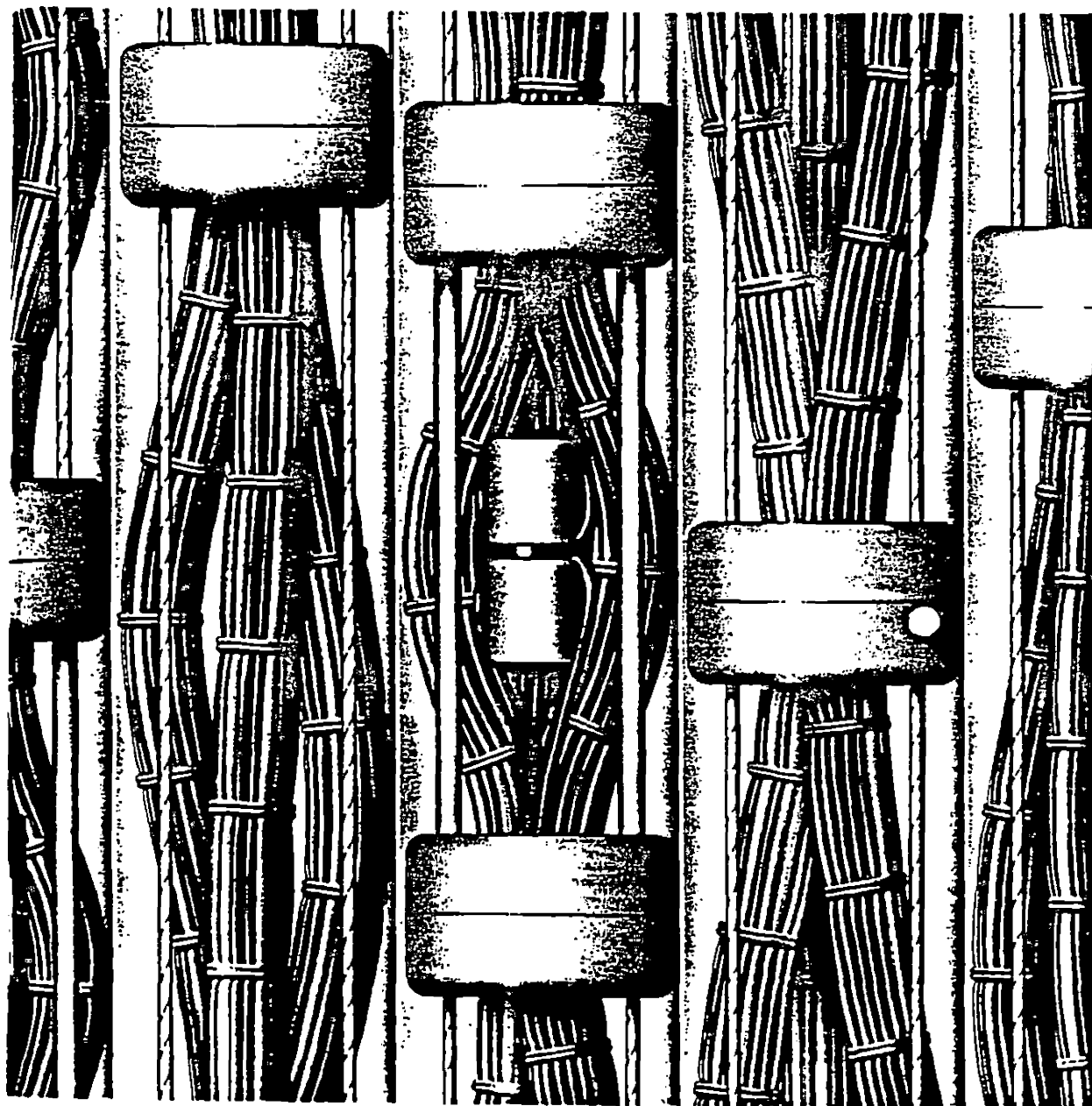


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Dioxin

Concern that this material is harmful to health or the environment may be misplaced. Although it is toxic to certain animals, evidence is lacking that it has any serious long-term effect on human beings

by Fred H. Tschirley

Dioxin. The word evokes a variety of reactions. Much of the public worries that the compound will cause poisoning even at minimal exposure. Toxicologists, knowing the severe toxic effects of dioxin in experimental animals but being uncertain about comparable serious effects on people, call for more research. Regulators, who must make decisions based on this conflicting evidence, are left wondering what to do. As one who has spent many years studying the dioxin issue, I hope in this article to provide a useful perspective for making judgments about the potential hazard of the material.

Dioxin is actually a name for a family of chemical compounds. The name refers to their basic structure: two oxygen atoms joining a pair of benzene rings. Substitution of chlorine atoms for hydrogen atoms on the rings produces a chlorinated dioxin, of which there are many. The chlorinated dioxin of interest here is 2,3,7,8-tetrachlorodibenzo-p-dioxin, usually abbreviated to TCDD. It is a by-product of the manufacture of trichlorophenol, which serves in the manufacture of two herbicides (the best-known being 2,4,5-trichlorophenol, or 2,4,5-T, one of the ingredients of Agent Orange) and the antibacterial agent hexachlorophene. TCDD is also produced in a variety of combustion processes.

The legacy of Agent Orange, Times Beach, Seveso, several industrial accidents and other instances of human exposure to significant amounts of TCDD is widespread concern about adverse health effects resulting from minimal exposure to the material. Yet

none of the many studies directed at this question have demonstrated that TCDD causes severe chronic human effects. Moreover, not one human death has been attributed to TCDD, even though exposure has been high in a number of cases. The issue points up the broader problem of the difficulty faced by regulators who must make judgments on the basis of incomplete scientific knowledge on the one hand and public fear on the other.

TCDD was first recognized in 1957 as a contaminant of 2,4,5-T, when 31 workers involved in the manufacture of the herbicide in West Germany developed the dermatologic affliction now called chloracne. It is a skin eruption resembling acne and takes its name from the fact that it is caused by exposure to various chlorinated organic chemicals.

General awareness that TCDD is a potential hazard to health and the environment arose in 1970, when a House subcommittee held a hearing on "Effects of 2,4,5-T on Man and the Environment." The hearing dealt among other things with a study by the Bionetics Research Institute showing that 2,4,5-T caused birth defects in animals. Testimony suggested that the teratogenic component of 2,4,5-T may have been TCDD. In the sample of 2,4,5-T tested by Bionetics the dioxin occurred as a contaminant at an extremely high concentration: 27 ± 8 parts per million.

Since then there has been a steady accumulation of information about the sources of TCDD, its environmental fate and its toxic effects. One

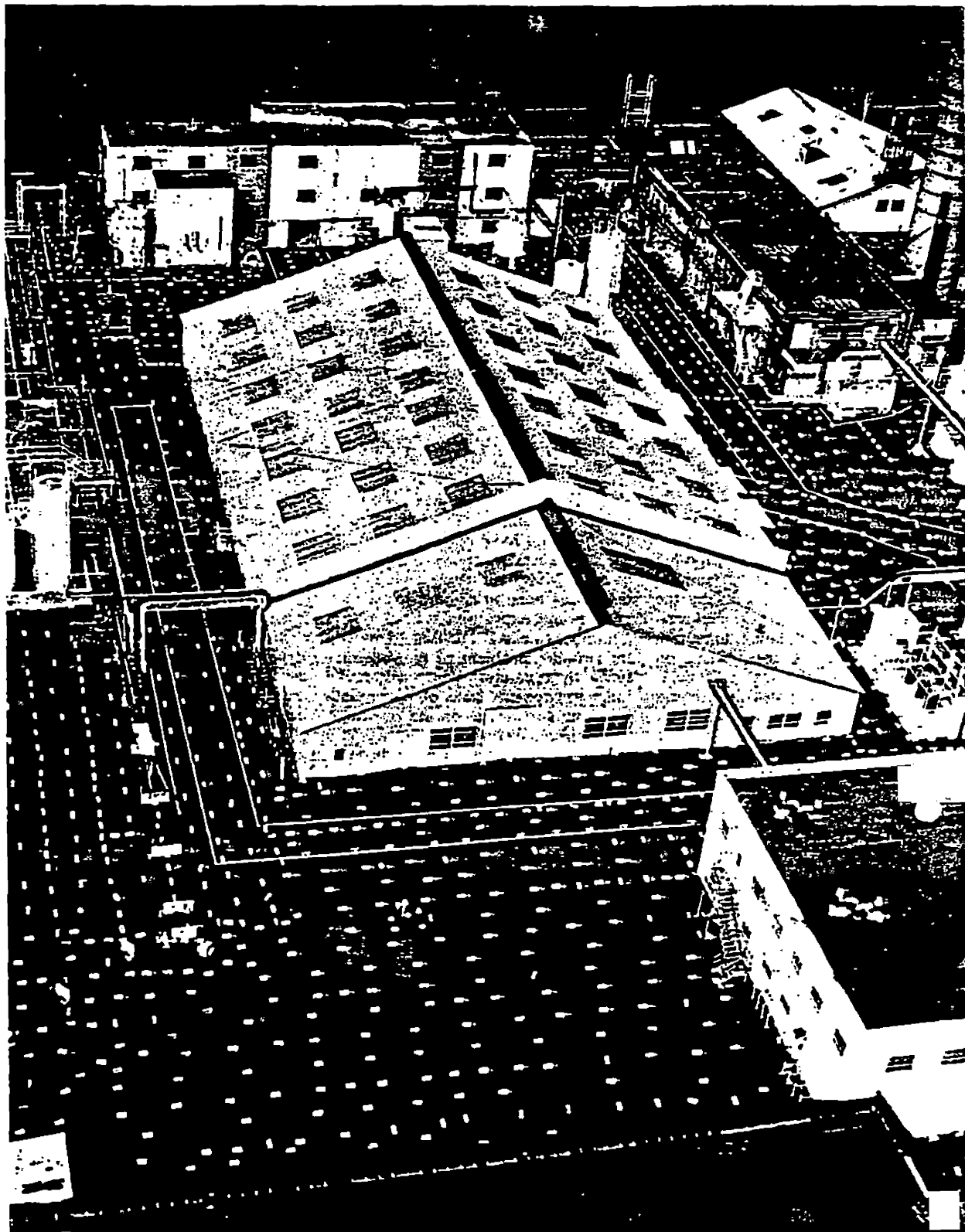
well-defined source is the formation of TCDD during the manufacture of 2,4,5-T. The amount of TCDD formed increases as the temperature of the reaction and the pH (degree of alkalinity) increase.

In 1977 investigators in the Netherlands reported that polychlorinated dibenzo-p-dioxins (PCDD's) were present in the fly ash from a municipal incinerator. Typically such an incinerator burns, among other things, organic wastes containing chlorine. Similar reports soon came from Switzerland, Canada and Japan. It was believed the compounds resulted from the condensation of chlorophenols. Later quantitative data demonstrated from a wide variety of combustion sources the presence of TCDD's that could not be explained on the basis of preexisting polychlorinated phenols.

These findings led R. R. Bumb of the Dow Chemical Company and 12 of his co-workers to put forward in 1980 the hypothesis that PCDD's can result from trace chemical reactions in fire. The hypothesis has been challenged because the reactions have not been defined. Nevertheless, PCDD's have now been found in the effluent and ash of so many combustion processes that there is no longer serious argument about their formation during combustion, even though the precise nature of the process remains obscure.

Moreover, TCDD has been specifically identified in soil and dust from numerous places, in soot from the chimneys of wood furnaces, as residues in river fishes (some from rivers whose watersheds do not have industrial operations known to form

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PLASTIC TARPAULINS cover much of the open area of the Diamond Alkali Co. plant in Newark, N.J., because the land may be contaminated by a chlorinated dioxin: 2,3,7,8-tetrachlorodibenzo-p-dioxin, usually abbreviated as TCDD. From 1943 through 1968 the company manufactured chemicals at the plant, including the herbicide 2,4,5-T. TCDD is a by-product of the manufacture of 2,4,5-T.

Federal and state officials had the tarpaulins put down as a precaution because TCDD is toxic to a number of animals tested in experiments. The material has not been shown to have severe chronic effects on human beings. It does produce some short-term effects.

TCDD), as residues in the eggs of herring gulls and recently in adipose tissue from more than 100 people in Canada, the U.S. and Vietnam. It appears that TCDD is a ubiquitous chemical, particularly in industrialized nations.

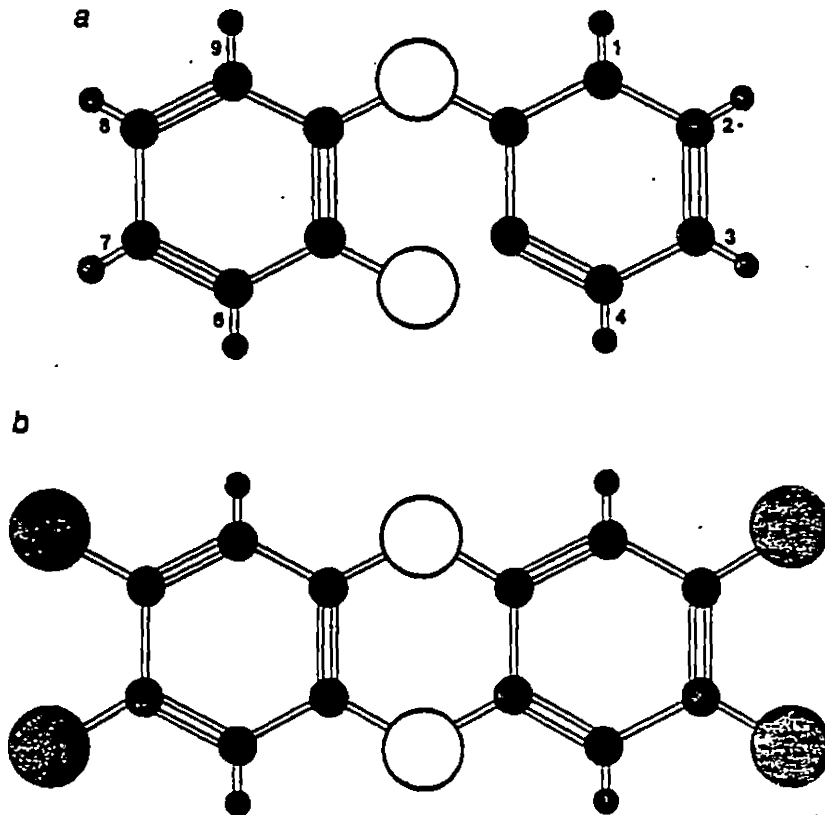
One might then ask why it was not detected sooner. For one thing, no one looked for it seriously before the 1970's. At the time it would not have been found anyway, except in unusual circumstances, because analytic chemists were only able to detect concentrations of a few parts per million. Since then the detecting equipment has improved at least a millionfold, so that concentrations of a few parts per trillion are now detected routinely. In addition dilution and the destruction of TCDD by light may reduce concentrations to undetectable levels. As analytic technology improves, one can expect that TCDD will be found in many more sites than are currently known.

In places where TCDD is protected from light it is an extremely persistent material. In the early 1970's it was thought the half-life of TCDD (the time required for half of a given amount to be degraded) was about a year; later studies in the U.S. suggested the half-life might be as long as three years. Recent reports from Italy raise the possibility that the half-life of TCDD in soil might be 10 years or even more.

Although precise data are meager, TCDD is known to be strongly held by most soils. The strength of the binding is inferred from the fact that known concentrations of TCDD applied to soil have remained near the surface. Even in the sandy soil examined in Florida the concentration of TCDD in the upper 15 centimeters was as high as 1,500 nanograms per kilogram 10 to 12 years after application.

In the most heavily contaminated zones near Seveso TCDD has been found at a depth of 136 centimeters. Moreover, the concentrations well below the surface were slightly but significantly higher in 1977 than they were in 1976, soon after the accident took place. The presence of soil fissures does not adequately explain this unexpected vertical distribution.

The processes that degrade TCDD in soil are poorly known. Microorganisms do degrade the substance, but at a low rate. S. D. Aust of Michigan State University found a wood-decaying fungus (the white mold *Phanerochaete chrysosporium*) that breaks down TCDD without observable mortality of the organism. The rate of degradation is low, but it is conceivable that contaminated sites could be inoculated



CHEMICAL STRUCTURE of a dioxin and of TCDD is depicted. The dibenzo-p-dioxin molecule (a) consists of two benzene rings joined by two oxygen atoms (light color). From one chlorine atom to eight atoms can substitute for hydrogen atoms (gray) attached to carbons (black) at the numbered positions to form any of the 75 chlorinated dioxins. The chlorinated dioxin known as TCDD (b) is shown with its four chlorine atoms (dark color).

with the mold to speed up the degradation process.

Sunlight degrades TCDD rapidly by splitting off the chlorine atoms. The reaction requires a hydrogen donor, which is usually available in water or in the wax on leaves. Experiments by Donald G. Crosby of the University of California at Davis showed that 40 percent of the TCDD layered on a glass plate remained after six hours in sunlight; the amount was from 25 percent to negligible when the material was applied as drops on leaves of the rubber plant, but on a loam soil the figure was 85 percent.

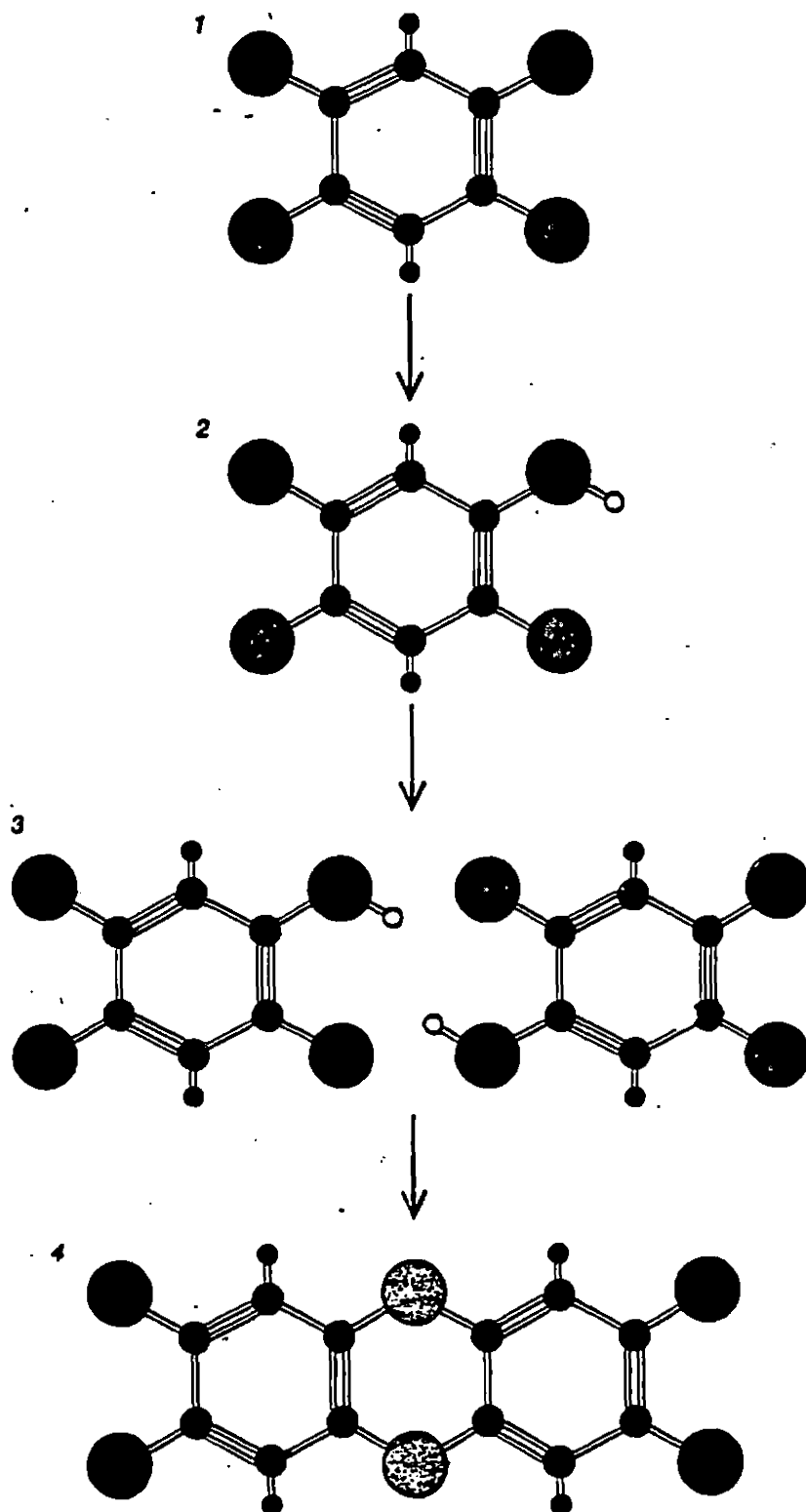
TCDD is a highly toxic chemical in experimental animals. The first animal-toxicity test performed is usually a determination of the LD_{50} : the dose that kills half of a test population. Between 1973 and 1978 the LD_{50} of TCDD was determined for eight species. The guinea pig was by far the most sensitive species tested: its LD_{50} for an oral dose was .6 microgram per kilogram of body weight. The hamster was the least sensitive animal tested: its oral-dose LD_{50} was about 1,900 times

as high as the guinea pig's. Its intraperitoneal level, 3,000 micrograms per kilogram, was about 5,000 times as high as the oral dose for the guinea pig.

The reasons for the extreme range of acute (short-term) toxicity may relate to the relative speed of clearance from the body. In the hamster half of a dose is removed within 15 days, compared with 30 days for the other species tested. Even though the hamster is much less sensitive than the guinea pig, an intraperitoneal LD_{50} of only 3,000 micrograms per kilogram signifies an extremely toxic material: the toxicity is comparable to that of the insecticide parathion.

Many essentially acute symptoms have been observed in human beings. They include chloracne, digestive disorders, effects on some essential enzyme systems, aches and pains of muscles and joints, effects on the nervous system and psychiatric effects. These symptoms have been transitory except for a few severe cases of chloracne.

Additional tests have measured the chronic, or long-term, effects of



STEPS IN FORMATION OF TCDD during the manufacture of 2,4,5-trichlorophenol (TCP) are shown. (TCP is used to make the herbicides 2,4,5-T and Silvex and the antibacterial agent hexachlorophene.) In the process of making TCP a molecule of 1,2,4,5-tetrachlorobenzene is hydrolyzed (1) in the presence of caustic soda to form 2,4,5-trichlorophenolate (2). Two molecules of the phenolate (3) combine to form TCDD (4). They lose atoms of sodium (white) and chlorine. The higher the temperature and the alkalinity are, the greater is the amount of TCDD that is formed. When the mixture temperature is above 180 degrees Celsius, a heat-forming reaction occurs; it has been the cause of industrial accidents.

TCDD in rodents, rabbits and nonhuman primates. Chloracne, the most sensitive indicator of human exposure to TCDD, has also appeared in rabbits, nonhuman primates and hairless mice. The skin and body can become dry and scaly. A few species lose hair. Some nonhuman primates lose fingernails and toenails without apparent evidence of pain.

TCDD also causes reproductive effects in experimental animals. Cleft palate and abnormalities of the kidney were caused in the offspring of exposed mice at dosage levels of from one nanogram to three nanograms per kilogram of body weight per day. Similar doses in rats caused the death of fetuses. In monkeys a dose of 1.7 nanograms per kilogram per day for two years caused abortions in four out of seven pregnancies.

TCDD is a proved carcinogen in rats and mice. Although the test results vary somewhat, there is fairly good agreement among tests by different investigators. The liver is the primary target in both rats and mice, although the brain, the respiratory system and the thyroid gland have also been involved in a few studies. It is important to recognize that an oncogenic response was reported only after the animal had ingested high doses of TCDD over a long period of time. Rats showed no oncogenic response at dosage levels of from one nanogram to 1.4 nanograms per kilogram per day; mice showed none at dosage levels ranging from one nanogram to 30 nanograms. Moreover, a study by R. J. Kociba of Dow Chemical and his co-workers showed that rats tolerated a daily dose of one nanogram per kilogram per day for two years without showing toxicologic effects.

Nevertheless, the findings from the tests on animals intensified concern about the effects of TCDD on people. On several occasions people have been exposed to "high" levels of TCDD. In this context "high" is a relative term because with one exception—a group of prisoners who volunteered for tests with TCDD—the amount of the material to which a person was exposed is not accurately known. The criterion I employ here to distinguish high from low exposure is whether or not the exposure results in chloracne.

The case of the prisoners is important because known amounts of TCDD were applied to their skin. In the first experiment 60 volunteers were treated with concentrations ranging from 200 to 8,000 nanograms (from three to 114 nanograms per kilogram for a 70-kilogram person), and the

dose was repeated two weeks later. The dosages chosen were those that had caused chloracne when they were applied to the ears of rabbits. None of the volunteers developed chloracne, and no other symptoms were observed. The second experiment involved 10 volunteer prisoners who were treated with 107,000 nanograms of TCDD per kilogram. Eight of them developed chloracne, but no other symptoms were noted.

From these experiments one can conclude only that TCDD does cause chloracne in humans when the dose is sufficiently high but that people are less sensitive than rabbits. The tests did not identify a threshold for the development of chloracne in human beings—a piece of information that would be of great value.

The number of people who have been exposed to high levels of TCDD cannot be determined accurately, but it must be in the thousands. Alistair Hay of the University of Leeds has estimated that in the chemical industry alone about 2,000 workers have had high exposure. Low levels of exposure have undoubtedly been experienced by people who handle the herbicides 2,4,5-T and Silvex, in which TCDD was a contaminant; by Vietnam veterans exposed to Agent Orange (50 percent of which was 2,4,5-T); by residents of Times Beach, Mo., where waste oil that contained TCDD was spread on the ground in several places; by chemical-industry workers making the products that include the material, and by many thousands of people who have eaten food (notably fish) containing trace amounts of TCDD or have been exposed to fallout from combustion processes that form TCDD. The total number of individuals with such low exposures probably runs well into the millions.

The possibility of chronic effects from exposure to TCDD causes far greater public concern than that of acute effects. An aspect of this problem about which little is known is the effect of protracted exposure to low levels of the material, as might occur in an occupational setting or from incidental exposures to, for example, the fallout of combustion effluents or to fish that contain low levels of TCDD.

A look at some of the major exposures to TCDD, approximately in order of their severity, reveals few if any unambiguous chronic effects. The industrial accident at Seveso in 1976 exposed some 37,000 people of all ages to considerable amounts of TCDD. A relatively small number of them showed transient effects such as chlor-

SPECIES	ROUTE	LD ₅₀ (micrograms per kilogram)
GUINEA PIG (MALE)	ORAL	.8
GUINEA PIG (FEMALE)	ORAL	2.1
RABBIT (MALE,FEMALE)	ORAL	115
RABBIT (MALE,FEMALE)	DERMAL	275
RABBIT (MALE,FEMALE)	INTRAPERITONEAL	252-500
MONKEY(FEMALE)	ORAL	<70
RAT (MALE)	ORAL	22
RAT (FEMALE)	ORAL	45-500
MOUSE (MALE)	ORAL	<150
MOUSE (MALE)	INTRAPERITONEAL	120
DOG (MALE)	ORAL	30-300
DOG (FEMALE)	ORAL	>100
FROG	ORAL	1,000
HAMSTER (MALE,FEMALE)	ORAL	1,157
HAMSTER (MALE,FEMALE)	INTRAPERITONEAL	3,000

ACUTE TOXICITY of TCDD in experimental animals is ascertained on the basis of the LD₅₀; the dose (in micrograms per kilogram of body weight) that kills half of a test group.

acne (184 cases, 164 of them children under the age of 15), headaches and digestive upsets, but no long-term effects such as birth defects and chromosomal damage have been identified. It is too early to tell whether the incidence of cancer is abnormal.

An accident in a Monsanto plant in Nitro, W.Va., in 1949 exposed more than 200 workers to TCDD. Of 122 who developed chloracne, 121 were monitored for the next 30 years. The total number of deaths in that group did not differ significantly from that expected in the population at large, and there were no excess deaths due to cancer or diseases of the circulatory system. Similar findings have been made after other industrial accidents, except for two in which an excess of deaths from cancer was found in small groups of the people exposed.

A particular type of cancer (soft-tissue sarcoma, a generic term for more than 100 different types of rare cancer) has become a focus of concern because of a survey of Swedish forestry workers by Lennart Hardell of the University of Umea. He concluded that their exposure to 2,4,5-T (and thus to TCDD) had caused six times the normal incidence of soft-tissue sarcoma.

This study led to an investigation of chemical-plant workers in the U.S. who had been exposed to 2,4,5-T and other chemicals. Seven apparent cases of soft-tissue sarcoma were discovered, raising the level of concern substantially. Subsequent events have emphasized the difficulties in accurate diagnosis of soft-tissue sarcoma and in accurate identification of exposed individuals. At a conference in 1983 Marilyn A. Fingerhut of the National Insti-

tute of Occupational Safety and Health reported that two of the seven people had in fact died of cancers other than soft-tissue sarcoma. Moreover, the exposure of three others to TCDD could not be documented. Such findings fall far short of being hard evidence for the proposition that TCDD causes soft-tissue sarcoma.

Other studies also fail to support Hardell's hypothesis. In the state of Washington no consistent pattern of death due to soft-tissue sarcoma was found among occupations in which workers would have been exposed to TCDD. A study in Finland found no cases of the disease among 1,900 people who applied herbicides, nor was their death rate from any natural cause different from that of the total male population in Finland. The U.S. Air Force, in its Ranch Hand study of about 1,200 military personnel who sprayed Agent Orange in Vietnam, found no cases of soft-tissue sarcoma. Finally, examinations by the Veterans Administration of 85,000 self-selected veterans showed fewer cases of these cancers than the national average would suggest.

Reproductive effects are also a subject of concern because of the animal findings. The most celebrated case alleging such effects in humans is commonly known as the Alsea II study, made by the U.S. Environmental Protection Agency. The study reported a link between the spraying of 2,4,5-T on foliage and spontaneous abortion among pregnant women in Alsea, Ore.

This study has come in for much criticism, notably by an interdisciplinary group at Oregon State University. The group concluded that an asso-

ciation between herbicide spraying and spontaneous abortion could not be shown from the data relied on by the agency. Other studies—in Australia, Hungary, New Zealand and the U.S.—failed to find a link between the use of 2,4,5-T and birth defects.

Because of the extreme acute toxicity and the multiple chronic effects of TCDD in animals, regulatory agencies have had to consider what to do in order to protect people from exposure to the material. Such agencies must extrapolate animal data to human beings in all but a few instances, in spite of the fact that the validity of this type of extrapolation has not been ascertained. Compounding the difficulty is the lack of a simple, accurate method for determining whether and at what level TCDD occurs in the tissues of exposed individuals. (The present test requires a surgical procedure to obtain

samples of the liver and fat tissues where TCDD resides.) Without such information a dose-response relation cannot be established.

TCDD has been called the most toxic synthetic chemical known to man. If its acute toxicity to the guinea pig, and even the rat and the mouse, is the criterion, the statement is probably correct. If its considerably lower toxicity to the hamster is the criterion, however, the statement would surely not be true. Yet there is no need to quibble: TCDD is unquestionably a chemical of supreme toxicity to experimental animals. Moreover, severe chronic effects from low dosages have also been demonstrated in experimental animals. Therefore the concern about its effects on human health and the environment is understandable.

When toxic chemicals are at issue, a regulatory agency has few options beyond extrapolating animal data to hu-

mans. Yet health effects on humans are rarely proved in the case of environmental chemicals to which the public is variably exposed at subacute levels that can only be estimated (and then only in the crudest approximation). A case in point is aflatoxin, the product of a mold that develops commonly in stored oilseed crops such as peanuts. In animal tests aflatoxin is one of the most potent carcinogens known, but it has not yet been proved to have this effect in human beings.

Diversity in reaction to stimuli is a hallmark of biological organisms. Reactions to toxins are no exception to the general rule. People may be more, less or equally sensitive to a given toxin than an experimental animal is. Extrapolation is neither art nor science; it is simply the most rational way to assess a hazard in the absence of definitive data. Hence regulatory actions continue to be based on the animal data even when the human data, although they are not definitive, may be sufficiently compelling to allow a scientific judgment that the hazard to people has been overestimated.

That appears to be the case with TCDD. Investigators are in general agreement that TCDD is less toxic to humans than it is to experimental animals, but the available information is not sufficiently compelling to stimulate a change in regulatory posture toward either more or less restriction of exposure to the material. I suspect that the direct evidence of TCDD's effects on humans will never be either more or less compelling than it now is.

The public's perception of a toxin is an important determinant of the posture taken by a regulatory agency. The public has heard a great deal about both the acute and the chronic effects of TCDD on experimental animals but little about the substantial body of data showing that human beings are less sensitive. The initial reports of TCDD's acute toxicity, followed by reports of its carcinogenicity and reproductive effects, have instilled a public fear that probably cannot be dispelled even by adequate information about the countervailing experience with human beings. The regulatory agency is therefore left in the position of having to deal with not only the available evidence but also the public's fear.

The U.S. Environmental Protection Agency has responded to the public's fear with a number of regulations intended to control the formation and release of TCDD and to limit individual exposure to it. Those regulations could be made stronger or weaker on the basis of new evidence. What the

DATE	WORKERS EXPOSED	LOCATION OF ACCIDENT	REMARKS
1949	250	Monsanto plant in Nitro, W.Va.	122 cases of chloracne being studied; 32 deaths v. 48.4 expected; no excess deaths from malignant neoplasms or circulatory disease
1953	75	BASF plant in Ludwigshafen	55 cases of chloracne, 42 severe; 17 deaths v. 11 to 25 expected (four gastrointestinal cancers and two oat-cell lung cancers); most common injuries were impaired senses and liver damage
1956	?	Rhone-Poulenc plant in Grenoble	17 cases of chloracne, also elevated lipid and cholesterol levels in the blood
1963	106	NV Philips plant in Amsterdam	44 chloracne cases (42 severe), of whom 21 also had internal damage or central-nervous-system disturbances; eight deaths (six possible myocardial infarctions); some symptoms of fatigue
1964	61	Dow Chemical plant in Midland, Mich.	49 cases of chloracne; four v. 7.8 expected deaths; three cancer deaths v. 1.5 expected, one a soft-tissue sarcoma
1965-69	78	Continuing leaks in Spolana plant near Prague	78 cases of chloracne; five deaths; many of the 50 workers studied for more than 10 years have hypertension, elevated blood levels of lipid and cholesterol, prediabetes; significant amounts of severe liver and neurologic damage
1966	?	Rhone-Poulenc plant in Grenoble	21 chloracne cases
1968	90	Coaltite & Chemical plant in Derbyshire	78 chloracne cases; one death from coronary thrombosis
1976	156	ICMESA plant in Seveso, Italy	Workers are being studied along with exposed townspeople; more than 500 residents treated for presumed toxic symptoms; 134 confirmed chloracne cases; overall mortality rate normal

INDUSTRIAL ACCIDENTS have exposed more than 800 workers to significant amounts of TCDD. The accident at Seveso in 1976 also exposed some 37,000 residents of nearby communities. The data are based on a study made by the American Medical Association.

agency has not done—and might be said to have a responsibility to do—is to try to dispel the public's fear on the basis of the evidence that exposure to low concentrations of TCDD in the environment appears not to have serious chronic effects on human beings.

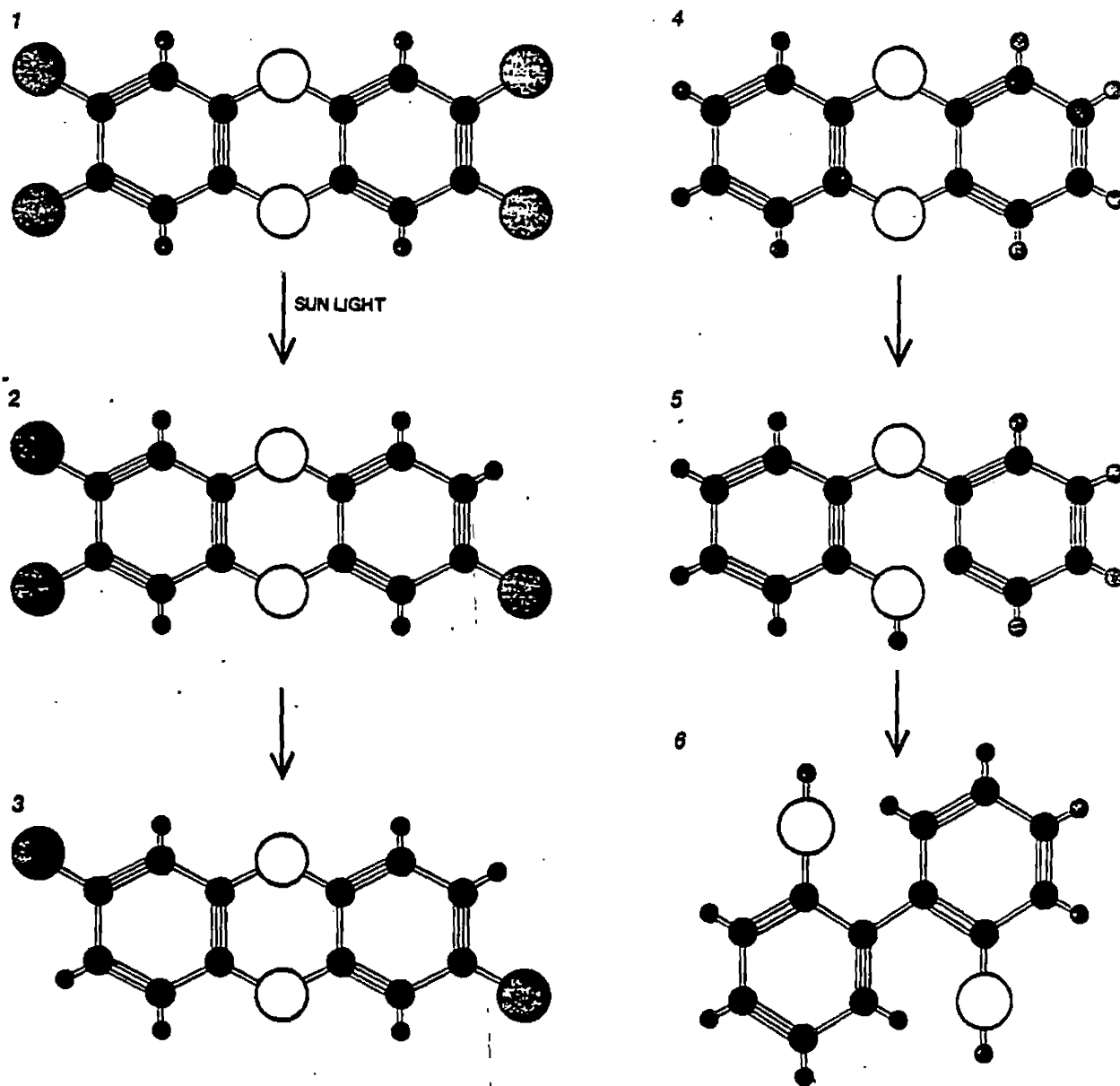
The TCDD case is further exacerbated by its relation to the defoliation program in Vietnam, an unpopular program in an unpopular war. The many and diverse health effects alleged by Vietnam veterans to have been caused by exposure to Agent Orange have been widely publicized. The public is generally aware that the complaints were settled out of court for

\$180 million, and many people believe the settlement was an admission of guilt by the chemical companies that manufactured Agent Orange. Apparently few people know of Federal Judge Jack B. Weinstein's statement to the attorneys for the plaintiffs that "in no case have you shown causality for the health effects alleged."

A troublesome matter exemplified by the TCDD issue is the appropriate utilization of scientific resources. A. L. Young of the Office of Science and Technology Policy has calculated that more than a billion dollars will have been spent by the Federal Government for research and other dioxin-related

matters before all the major studies now in progress have been completed. Additional expenditures of both time and money have been made by chemical companies, private organizations and government agencies. The total outlay is a tremendous amount for an issue of questionable importance.

Two years ago a conference on dioxin at Michigan State concluded that the TCDD case is relatively less important than a number of other issues and that the nation's limited scientific resources should be devoted to the issues posing a greater threat. On the basis of the evidence turned up so far, the conclusion is still valid.



DECOMPOSITION OF TCDD takes place when the ultraviolet in sunlight splits off the molecule's chlorine atoms. Six steps in the

reaction are shown. In soil, where sunlight cannot get at the material, TCDD tends to be quite persistent, enduring as long as 10 years.

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