

DIOXINS and FURANS

Todd Paddock

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**Dioxins and Furans:
Questions and Answers**

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Executive Summary

In the U.S., dioxin is infamous because it was the substance in Agent Orange blamed for a host of diseases in Vietnam veterans, and the substance that contaminated Times Beach, Missouri, prompting the federal government to purchase the entire town. Since then, the discovery of dioxins in incinerator emissions has caused further concern.

There are actually many kinds of dioxins. The chlorinated dioxins have caused the most concern. A related family of compounds called chlorinated furans are very similar to dioxins in their distribution, toxicity, and behavior, although not as much is known about them. The chlorinated dioxins and furans are the subject of this report.

One particular dioxin has received more attention than any other, because it was found in relatively large amounts in some widely used chemical products, and appears to be the most toxic. This dioxin is 2,3,7,8-TCDD. The word dioxin is commonly used to mean 2,3,7,8-TCDD. A great deal more research has been done on 2,3,7,8-TCDD than on the other dioxins and furans, and this report is based largely on studies of 2,3,7,8-TCDD.

How toxic are dioxins and furans?

Based on laboratory and field studies, 20 or so of the 210 chlorinated dioxins and furans are considered to be extremely toxic to animals. They accumulate in the tissues of organisms, and are often the only types found in organisms from the wild. Most dioxins and furans appear to be almost nontoxic, and do not accumulate.

What factors affect the toxicity of dioxins and furans?

The toxic effect of a dioxin or furan on an animal depends on more than the type of dioxin or furan. It also depends on the species of animal, the status of the animal, the route of exposure, and the substance in which the dioxin or furan is present. Some animal species are thousands of times more sensitive than others to the toxic effects of the same dioxin or furan.

How do dioxins and furans reach humans?

The major routes of exposure are generally considered to be eating contaminated food and breathing contaminated particles. Particles in air, especially near urban areas or large sources of combustion products, can be contaminated with dioxins and furans. Trace levels of

dioxins and furans have been found in a variety of foods in Japan, Canada, and Europe, and the same is probably true of foods in the U.S. Dioxins have also been found in fish from certain areas in the U.S.

Are dioxins and furans found in humans?

Dioxins and furans have been found in samples of blood and fatty tissue from persons in numerous countries, including the U.S., Canada, Japan, Vietnam, and several countries in Europe. Based on these findings, it is generally agreed that the population at large in many parts of the world has been exposed to low levels of dioxins and furans.

What are the health effects of dioxins and furans?

The long-term health effects of these compounds have been intensely investigated, and they are now among the most-studied substances with respect to their effect on animal and human health. Dioxins and furans cause mortality and/or cancer in many animals, but there is no conclusive evidence that they cause cancer or any other life-threatening health problem in humans. No documented human death has occurred because of an exposure to dioxins or furans.

People have been exposed to relatively large amounts of dioxins and furans (1 microgram or more) during industrial accidents, and other incidents of accidental contamination. The health effects were serious, but subsided with time. With the exception of severe acne, most researchers have found no serious, long-term health problems associated with exposure to dioxins, even at the highest reported levels, and after ten to thirty years have elapsed.

How are dioxins and furans created?

Dioxins and furans have no useful purpose and have never been manufactured deliberately, except in small amounts for research purposes. They are known to be created in two major ways: (1) they are created by unwanted side reactions, which take place during the chemical processes used to manufacture useful products such as biocides, paper, disinfectants, and preservatives; (2) they are created when a substance containing chlorine is burned, or when a substance is burned in the presence of chlorine.

Dioxins and/or furans have been found as contaminants in the following manufactured

products:

Product	Contaminants
PCBs	Furans
hexachlorophene	Dioxins*
2,4,5-T	Dioxins*
2,4-D	Dioxins*
chlorophenols with 3 or more chlorines	Dioxins and Furans
polychlorinated benzenes	.
diphenyl ether herbicides	.
hexachlorocyclohexane	.
paper products	.

* I could find no analyses of these products for furans.

Other products derived from chlorophenols have been identified as possibly contaminated and are under investigation by the U.S. Environmental Protection Agency (USEPA) and others.

What products can produce dioxins and furans when they are burned?

The following chlorinated products or substances can produce dioxins and/or furans when burned:

Product	Contaminants
PCBs	Furans
polybrominated biphenyls (PBBs)	Dioxins and Furans
polybrominated diphenyl ethers (PBDEs)	.
polychlorinated diphenyl ethers (PCDEs)	.
chlorophenols	.
tetrachloroethylene	.
polychlorinated benzenes	.
polyvinyl chloride (PVC)	.
Leaded gasolines	.
paper, wood, peat, and coal	.
dioxins and furans	.

Note: When a material is burned in the laboratory to determine whether it is capable of producing dioxins and furans, it is typically burned under those conditions most likely to produce dioxins and furans, or that produce the largest quantity of dioxins and furans. Therefore, the same substance may produce much smaller amounts of dioxins and furans under the uncontrolled conditions of a fire, or in the highly controlled conditions of an incinerator.

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Incinerators and other large combustion sources, sewage plants, waste streams, and landfills are also sources of dioxins and furans.

There are many sources of dioxins and furans. The combustion sources are widespread and numerous. Highly contaminated manufacturing and waste sites are fewer in number and usually local problems. The relative importance of the two major sources of dioxins and furans (chlorophenols vs. combustion) is not yet known. It is generally agreed that modern industrial activity, not the burning of wood, is the primary source of dioxins and furans to the environment.

Where are dioxins and furans found?

Dioxins and furans are present at trace levels in many places, and at relatively high levels at a small number of contaminated sites. The presence of dioxins and furans is usually associated with the production, storage, use, or disposal of chlorophenol-based compounds. In addition, they have been detected at low levels in urban areas, where they are believed to be the product of numerous combustion processes. As our ability to detect dioxins and furans improves, it is likely that they will be found in more places.

Dioxins and furans have been found in organisms from contaminated areas, and from fish in many areas of the U.S. Plants typically contain these compounds at levels much below the surrounding environment, and only when they are grown in highly contaminated soil. Fruits do not appear to contain dioxins, although root crops may sometimes contain them.

How long do dioxins and furans last in the environment?

2,3,7,8-TCDD can be broken down in a matter of days in the environment, if it is mixed with the proper organic solvent and exposed to ultraviolet light. On the surface of the soil, without a solvent, 2,3,7,8-TCDD has an environmental half-life of one year or less, due to slow photodegradation and evaporation. Underground and in sediments, this very stable compound degrades much more slowly, with a half-life of about 10 years. Very little is known about the half-lives of other dioxins and furans. In general, dioxins and furans with fewer than four chlorines are broken down more quickly than 2,3,7,8-TCDD. The dioxin or furan with eight chlorines is more resistant to breakdown.

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To what degree do dioxins and furans spread when they are introduced into the environment?

Dioxins and furans bind very strongly to the organic carbon present in particles of soil, in sediments, and to the particles found in the air. These particles can be lifted and carried by wind or moving water. Dioxins and furans can be transported great distances in air, and smaller distances in water. In soil and sediments, dioxins and furans appear to migrate very little or not at all. Areas of severe contamination have typically remained local problems, and most are not expected to spread the contamination to nearby areas.

What has been done about dioxins and furans?

Because they are very potent toxins and carcinogens in laboratory animals, regulatory agencies from various countries have issued guidelines for human exposure to dioxins and furans. These guidelines vary by more than a thousandfold, due to different interpretations of the same animal laboratory studies.

As dioxins and furans have been identified as contaminants in products, the manufacturers have lowered the levels of contamination. The USEPA has cancelled or restricted the manufacture, use, and disposal of many of the products containing hazardous levels of dioxins and furans, and the disposal of wastes from the manufacture of many products. Many contaminated sites have been cleaned up, and many more are on the Superfund list.

Conclusions and Recommendations

Based on the many studies already published, dioxins and furans do not appear to be a hazard to our health when we are exposed to the low levels typically present in the environment. Several groups of people need special attention because they may be exposed to greater than normal amounts of dioxins and furans. These include breast-fed babies (because dioxins and furans are usually present in breast milk), and workers in industries that use contaminated products.

We should continue to monitor the health of groups of people who were exposed to large amounts of these compounds, or who were exposed to smaller amounts for a long time. This will enable us to identify any long-term health effects not already recognized. Now that

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we have the ability to determine the extent of an individual's past exposure to dioxins and furans through a blood test, the identification of exposed persons is much easier and more accurate, making such studies more powerful.

We also need to determine how dioxins and furans cause the effects that they do, and why their toxicity varies so greatly between species. Such an understanding would not only have preventive or therapeutic value, but is also critical for accurate assessments of the risks these compounds pose to humans and other organisms.

Because of their demonstrated toxicity to laboratory animals, plus their distribution and persistence, some dioxins and furans are a potential hazard to organisms in the environment. There is a great need for more study in this area. We need to know what are unacceptably harmful levels for the various organisms in the environment, and the nature and amount of dioxins and furans from the various sources.

What appears to be the largest amount of toxic dioxins and furans is buried in landfills or stored at past or present sites of manufacture or use. We need to develop safe, yet practical ways to contain, or better yet destroy, this contaminated waste.

We may need to reduce the amounts of dioxins and furans occurring as unwanted contaminants of some products. Great reductions have been made in certain products in the past, and further reduction may be necessary. Unfortunately, such reduction can result in very highly contaminated waste streams, and proper disposal is difficult and expensive. Therefore, the emphasis needs to be on preventing their creation during the manufacturing process.

We also need to reduce the unwanted creation of dioxins and furans during combustion. For example, incinerators can be operated under conditions that reduce the creation of dioxins and furans.

More than one billion dollars has been spent in the U.S. alone for the research of dioxins and furans, and this research has greatly expanded our knowledge. With this knowledge, and with improved technologies for both reducing future sources of these compounds and cleaning up presently contaminated areas, dioxins and furans should be regarded as a manageable problem.

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Dioxins and Furans: Introduction and a Brief History

When most people use the term dioxin, they mean a single chemical compound, often referred to as "the most toxic substance ever made by man". In the U.S., dioxin is infamous because it was the substance in Agent Orange blamed for a host of diseases in Vietnam veterans, and the substance that contaminated Times Beach, Missouri, prompting the Federal Government to purchase the entire town. However, the dioxins (short for chlorinated dibenzo-p-dioxins) are a large family of compounds whose toxicity varies or, for many types, is unknown. A closely related and very similar group is the furans (chlorinated dibenzofurans).

Dioxins and furans have been discovered in unexpected places. They are in fish from lakes and rivers, in common paper products, in auto exhaust, and in the ash from municipal and industrial incinerators. Dioxins and furans will continue to be found in new places. In part, this is because they can be measured in extremely small amounts, and have been looked for in many places. Also, many dioxins and furans are very stable, can remain in the environment for years, and can accumulate in organisms.

One particular dioxin has received more attention than any other, because it was found in relatively large amounts in some widely used chemical products, and appears to be the most toxic¹. This dioxin is 2,3,7,8-tetrachlorodibenzo-p-dioxin, also known as 2,3,7,8-TCDD, or simply TCDD. The word dioxin is commonly used to mean 2,3,7,8-TCDD.

Much of the general public's knowledge of dioxins and furans was gained as a result of a few widely-publicized incidents or controversies. A brief history of dioxins and furans, with summaries of a few of the most publicized incidents, can serve to remind us of how these compounds became so well known.

¹ Here and in the rest of the report, "toxic" means that the substance is associated with adverse health effects, but not necessarily effects that are serious, or permanent.

What is the history of dioxins and furans?

Dioxins and furans were synthesized by organic chemists in the 1930s and were patented in 1939 as constituents in a product used for electric insulation (cited in Huff and Wassom, 1973). Different dioxins and furans were tested and in some cases patented as agents against bacteria, insects, and fungi, as intermediates in chemical processes, and as flame retardants, from the 1930s to at least 1970 (cited in Huff and Wassom, 1973).

Discovering their toxic effects on humans and animals

The toxic effects of dioxins and furans in humans were more or less unrecognized until 1957, when Dr. Karl Schultz, a dermatologist at the University of Hamburg in West Germany, tried to determine why workers at a nearby chemical plant were developing a severe form of acne, called chloracne (Gough, 1986: pp 29-33). After some careful tests, Schultz concluded that a contaminant in one of the plant's products (2,4,5-trichlorophenol) was responsible for the chloracne, and identified the contaminant as 2,3,7,8-TCDD. We now know that 2,4,5-trichlorophenol is always contaminated with 2,3,7,8-TCDD, and therefore trace levels of 2,3,7,8-TCDD are also present in the products made from 2,4,5-trichlorophenol.

Schultz and colleagues published several papers in 1957, showing that several dioxins and furans induced acne when applied to rabbit ears (the standard and most sensitive test at that time), and that small doses of 2,3,7,8-TCDD caused liver damage and death in rabbits. The plant chemists found a way to reduce the amount of the contaminants formed during the production of their 2,4,5-trichlorophenol, and the chloracne problem in their workers subsided.

Chick edema disease

Also in 1957, scientists in the U.S. Food and Drug Administration (USFDA) were trying to determine the cause of an outbreak of millions of deaths of chickens in the U.S. (Firestone, 1973). They determined in 1958 that the cause of the disease (chick edema) was toxic contaminants in commercial fatty acids that were part of the chicken feed. Symptoms included excessive fluid in the heart sac and abdominal cavity, and liver damage. Although the contaminant was not yet identified, the USFDA issued a regulation in 1960 that required fatty

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acids to be proven free of the contaminants through a 3-week chick-feeding bioassay. Advances in detection techniques made it possible to further identify the contaminants, and in 1966 it was determined that 1,2,3,7,8,9-hexachlorodibenzo-p-dioxin was one of the contaminants and that a synthetic hexachlorodibenzo-p-dioxin produced the disease in chickens (Firestone, 1973).

It had been shown as early as 1936 (cited in Huff and Wasson, 1973) that dioxins could be produced by heating chlorophenols, and the USFDA scientists proposed that chlorophenols were the source of the dioxins in the toxic fats being fed to chickens. Chlorophenols, including trichlorophenol and pentachlorophenol, were widely used as agents against slimes, bacteria, termites, and as herbicides. The USFDA scientists were able to produce a variety of dioxins by heating various commercial chlorophenols, and found these same dioxins in the toxic fat. They tested these dioxins on chickens, found that they produced chick edema, and found that the most toxic dioxin was 2,3,7,8-TCDD. Finally, it was determined in 1972 that the source of chick edema disease was fat derived from hides (from cattle, hogs, sheep, and other animals) that had been treated with commercial pentachlorophenol (Metcalf, 1972, cited in Firestone, 1973).

Concern about 2,4,5-T and related herbicides

In 1970, at hearings before the U.S. Congress, evidence was presented to show that the widely-used herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) was capable of causing birth defects in rats and mice (cited in Huff and Wasson, 1973). During that same year, a study showing similar results was published (Courtney et al., 1970). It was proposed that the relatively high levels (approximately 30 parts per million [ppm]) of 2,3,7,8-TCDD contamination in 2,4,5-T were probably responsible for the birth defects (cleft palate, cystic kidney) in mice and rats, and a study on 2,3,7,8-TCDD found that it affected reproduction in rats (Sperachn et al., 1970).

Based on these findings and the earlier findings of the toxicity of 2,3,7,8-TCDD to humans and animals, the U.S. Department of Agriculture (USDA) decided in 1970 to cancel registrations for the use of 2,4,5-T in certain areas, for example its use on human food crops, near bodies of water, and around homes (Gough, 1986: p 138). They did not cancel registration

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for other uses of 2,4,5-T if the levels of 2,3,7,8-TCDD were below 1 ppm (cited in Huff and Wasson, 1973). However, the USDA and U.S. Department of Health, Education, and Welfare issued a joint statement that 2,4,5-T and 2,3,7,8-TCDD may cause birth defects in mice and rats (cited in Huff and Wasson, 1973). Also in 1970, the U.S. Department of Defense stopped using the herbicide Agent Orange in Vietnam. Agent Orange was a half-and-half mixture of 2,4,5-T and 2,4-dichlorophenoxyacetic acid (2,4-D), and was contaminated with 2,3,7,8-TCDD.

In 1971, a Science Advisory Council from the U.S. National Academy of Sciences recommended to the U.S. Environmental Protection Agency (USEPA) that the registration of 2,4,5-T be restored for use on forests, rangeland, and rice fields, with certain restrictions on its use (Gough, 1986: p 138). For example, they required that present stocks of 2,4,5-T have less than 0.5 ppm 2,3,7,8-TCDD and that newly manufactured 2,4,5-T have less than 0.1 ppm (cited in Huff and Wasson, 1973). In 1973, the Science Advisory Council recommended that no more than 0.1 ppm 2,4,5-T be allowed in water or on edible food products, if they were for human consumption (cited in Huff and Wasson, 1973).

In 1979, the USEPA issued an emergency suspension of most remaining uses of 2,4,5-T, based on accumulating evidence that 2,3,7,8-TCDD caused cancer and birth defects in laboratory animals, and because of a 1979 study that showed elevated levels of spontaneous abortions among women near Alsea, Oregon, where 2,4,5-T was sprayed (Gough, 1986: p 138-145). A panel of scientists subsequently reviewed this 1979 study and concluded that because of a flawed design, the study was incapable of showing either the presence or absence of effects of exposure to 2,4,5-T (Coulston and Olajos, 1980, cited in USEPA, 1985: p 9-25). From 1979 until 1984, 2,4,5-T was used on rice and sugarcane fields, pending settlement of a suit between the USEPA and manufacturers of 2,4,5-T. All companies withdrew from the suit by 1984, and the USEPA then cancelled all uses of 2,4,5-T and the closely related herbicide Silver.

Times Beach and other areas in Missouri

(Much of the following discussion is based on a chapter in Gough, 1986)

Hexachlorophene, a germicidal product used as a skin disinfectant in hospitals, in germicidal soaps, and in some veterinary products, is produced from 2,4,5-trichlorophenol, the

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same chemical used to manufacture 2,4,5-T and related herbicides. When manufacturers of 2,4,5-trichlorophenol-based products became aware of the toxic properties of 2,3,7,8-TCDD, they found ways to greatly lower the concentrations in their final products. However, this purification process can create wastes with very high concentrations of 2,3,7,8-TCDD. If this waste is not disposed of properly, it can be a hazard to humans and other organisms.

Improper disposal of such wastes was the cause of the contamination of Times Beach, Missouri. A chemical plant in Verona, Missouri, produced hexachlorophene from 1970 to 1972. The purification of their product (by distillation) resulted in a thick, oily, 2,3,7,8-TCDD-contaminated waste called still bottoms. The plant's still bottoms were hauled away by a separate company, and sold in turn to a waste oil buyer. The waste oil buyer then used the still bottoms in a secondary business, in which he sprayed oil to keep dust down in horse arenas, private roads, and parking lots. Horses, birds, and other animals became sick and died following the spraying of one of the horse arenas in 1971, and a child who played in the horse arena was hospitalized with bladder inflammation and bleeding.

The U.S. Centers for Disease Control (CDC) began an investigation of the poisoning episode at that stable in August, 1971, three months after the spraying. They and local doctors diagnosed the episode as chemically related, but could not identify the disease or the contaminant. In the meantime, the owners of the first horse arena and another arena had suspected the cause of the illness was the sprayed oil, and had removed the top layer of soil from their arenas and placed it in a nearby landfill. The CDC investigation continued, and in 1973 they had identified 2,3,7,8-TCDD in samples of dirt from the arenas. They notified the Missouri Department of Health in 1974, and the CDC and state began a joint investigation of the episode.

The origins of the waste oil were quickly determined by the investigators, but identifying the many areas that had been sprayed with the oil was more difficult. Fortunately, the owners of the first arena had secretly followed and kept records of the spraying done by the waste oil buyer, and these records were used to locate other contaminated areas. Arenas and trailer parks had been contaminated by spraying, and soil from the arenas was removed and

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placed in landfills, on farms, and used as fill for building projects. Also, the waste oil buyer had sprayed 23 miles of unpaved streets in the town of Times Beach, Missouri, from 1972 to 1976.

The contamination of Times Beach was not confirmed by the federal government until December 1982, when their soil tests showed 5-300 parts per billion (ppb) 2,3,7,8-TCDD in the soil from the streets of Times Beach. Based on the results, the CDC recommended that the town of Times Beach was unsafe for its inhabitants, and in February 1983 the federal government announced it would buy the homes, properties, and businesses of Times Beach. The many other contaminated sites in Missouri (51 in all, according to USEPA, 1987a: pp 2.3-2.35) are being dealt with in various ways. The USEPA and CDC have removed soil, decontaminated the soil, restricted access, and advised minimal contact with soil, depending on the level of contamination and possibility of exposure (USEPA, 1987a: pp 2.18-19).

Based on studies of residents of the most highly contaminated areas in Missouri, it appears that the people exposed to 2,3,7,8-TCDD have suffered few if any long-term effects, although several commonly used areas were contaminated with extremely high levels of 2,3,7,8-TCDD (as much as 31 ppm in the soil of one horse arena). The people who were exposed to high levels of 2,3,7,8-TCDD in the arena soil suffered from a variety of effects, including nausea, headaches, diarrhea, nosebleeds, chloracne, and severe bladder inflammation. Their health subsequently returned to normal (reviewed in Reggiani, 1980).

A study of the residents of a trailer park that had 39-1100 ppb of 2,3,7,8-TCDD in the soil found abnormal levels of some blood constituents, that suggested long-term effects on the liver and immune system (Stein-Green et al., 1987). However, no liver changes could be directly detected, and no excess of illness was reported. The authors noted, "The effects we observed may be merely part of the normal, adaptive response to a toxicologic challenge, and well within the normal reserve capacity of the affected organ systems (i.e., they are markers of exposure and not signs of disease)."

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Agent Orange

Herbicides were used by the U.S. in the Vietnam War from 1962 to 1970. Agent Orange, a half-and-half mixture of the herbicides 2,4,5-T and 2,4-D, was sprayed over South Vietnam from 1965 to 1970, accounting for more than half of all herbicides used there. Earlier mixtures were called Agents Purple, Pink, and Green. Based on analyses of Agent Orange manufactured before 1970, the mixture sprayed on South Vietnam was contaminated with from 0.02-54 ppm 2,3,7,8-TCDD (Esposito et al, 1980: p 98). The U.S. Air Force (USAF) estimates that Agent Orange had a mean concentration of 2 ppm 2,3,7,8-TCDD, Agent Purple had a mean concentration of 33 ppm, and Agents Pink and Green were estimated to have 66 ppm (Albanese, 1988: p 3).

The large-scale use of herbicides in Vietnam ended in 1970 because of concern about the effects on the environment and inhabitants of South Vietnam. However, that concern has been almost entirely eclipsed by concern about the possible effects on the health of soldiers from the U.S. and other countries who were exposed to large amounts of the herbicides. Because of this concern, several large studies by the CDC and USAF have been conducted or are underway. The USAF study investigated the general health and rates of cancer and death among Vietnam veterans who were exposed to herbicides, as well as birth defects among children of the veterans. The CDC study investigated the health of Vietnam veterans in general, most of whom were not exposed to Agent orange, and therefore is not relevant to this discussion.

The USAF Health Study is investigating the health of USAF personnel who participated in the aerial spraying of herbicides over Vietnam. The spraying program was called Operation Ranch Hand; Ranch Hands include the men who flew the planes, and all men who worked with the herbicide and spray equipment used for the aerial spraying. The health of Ranch Hands is being compared to a carefully matched group of USAF personnel who flew in and out of Southeast Asia (but not Vietnam) during the same period. The most recent report from this study focused on eleven health effects that studies of animals and humans have associated with exposure to 2,3,7,8-TCDD (Albanese, 1988). They reported that for 6 of the 11 effects,

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differences were detected between the two groups, and for 5 of the effects the difference was in the direction that would be expected from current knowledge of the effects of 2,3,7,8-TCDD.

The six effects were increases in the rate of cancer, increases in the number of birth defects reported in children of the veterans, an increase of psychological changes, an increase of liver changes, an increase of cardiovascular changes, and an increase in changes in the endocrine system. However, no differences were detected in the sperm count or proportion of normal sperm, the rate of heart disease and heart attack, the immune system, overall mortality, and other health effects that studies of animals and humans have associated with exposure to 2,3,7,8-TCDD. Follow up studies, including an investigation of the birth certificates and health records of all children of the veterans, are now under way.

Albanese (1988) concluded that while "At this time one cannot ascribe the observed group differences to an effect of dioxin", the study also "...does not exonerate dioxin as a causative agent of these differences." He noted that the study did not find that the health effects increased in severity with a greater exposure to Agent Orange, and that some of the characteristic effects of exposure to 2,3,7,8-TCDD were not observed. He also noted that five of the six group differences were in the direction of 2,3,7,8-TCDD effects, and that the calculation of exposure was only an estimate. Finally, he noted that the sample sizes used in the study made it possible to detect common diseases and death, but almost impossible to detect rare diseases.

An important part of the controversy over the possible health effects of Agent Orange is the question of determining exposure: what veterans were exposed and what was the level of exposure? Recent studies indicate that 2,3,7,8-TCDD persists for decades in the fatty tissues of humans (Schecter and Ryan, 1988), and levels of 2,3,7,8-TCDD in the blood can be correlated with levels in the fatty tissues (Patterson et al., 1988). Measurements of 2,3,7,8-TCDD in the blood can therefore be used to determine a person's level of exposure to 2,3,7,8-TCDD, even if the exposure occurred many years before.

The CDC recently reported the levels of 2,3,7,8-TCDD in the blood of approximately 700 veterans who were part of the Vietnam Experience Study or the Ranch Hand Study. Ranch

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Ranch veterans had significantly higher levels of 2,3,7,8-TCDD in their blood (mean of 49 parts per trillion (ppt)) than did other Vietnam-era Air Force veterans (mean of 5 ppt). Seventy-nine percent of Ranch Hands had blood levels above 10 ppt, and many had levels of 100-300 ppt (CDC, 1988). However, other Vietnam veterans did not have higher levels of 2,3,7,8-TCDD in their blood (mean of 4.8 ppt) than did non-Vietnam veterans (mean of 4.9 ppt) (CDC, 1987). It appears that Ranch Hands, but not other Vietnam veterans, were exposed to significant amounts of Agent Orange.

To determine past exposure, the CDC used an estimated half-life² of about seven years (CDC, 1988), and therefore assumed that two to four half-lives have passed since Vietnam veterans were exposed to 2,3,7,8-TCDD in Agent Orange. Recent work by Kissel and Robarge (1988) suggests that the half-life of 2,3,7,8-TCDD is inversely related to the concentration of 2,3,7,8-TCDD in the body, and that the half-life is significantly shorter when concentrations are relatively high (e.g. immediately after exposure). If so, the CDC may be underestimating Vietnam veterans' past exposure to 2,3,7,8-TCDD in Agent Orange.

The Seveso accident

In 1976, a cloud of 2,4,5-trichlorophenol and caustic lime, contaminated with 2,3,7,8-TCDD, was released over the town of Seveso, Italy and nearby towns, when a chemical plant's reactor vessel went out of control. Approximately 700 acres inhabited by 38,000 people were contaminated with 2,3,7,8-TCDD (Mastroiacovo et al., 1988). The level of 2,3,7,8-TCDD ranged from greater than 150 ppt in the soil of the most contaminated area to less than 50 ppt in the soil of the least contaminated area (Wipf and Schmid, 1983). Vegetation (including garden vegetables and orchard fruits) was contaminated with from more than 1000 ppb 2,3,7,8-TCDD to less than 1 ppb, which was the limit of detection at that time (Wipf and Schmid, 1983).

The accident resulted in the deaths of about 3000 domestic animals (almost all rabbits and chickens); some of these animals died almost immediately after the accident, and their

² The half-life is the amount of time during which the 2,3,7,8-TCDD present in the body is reduced by one-half.

deaths were attributed not to 2,3,7,8-TCDD, but to the other chemicals in the cloud or to deliberate slaughter. (All animals given a lethal dose of 2,3,7,8-TCDD take at least two to three weeks to die after their exposure.) One hundred and eighty-three people, mostly children, were confirmed as having contracted chloracne, indicating that they were exposed to significant amounts of 2,3,7,8-TCDD. It was presumed that children were exposed to greater amounts because they played in the vegetation, and may also be more sensitive. All cases of chloracne cleared up within 5 years, although the 15 most severe cases resulted in permanent scars.

Aside from chloracne, no other health effects were confirmed by an investigation of the accident (Wipf and Schmid, 1983). However, there was concern that the effects of the exposure might include birth defects. The Italian health authorities advised the inhabitants of the area to avoid becoming pregnant, and many women requested abortions after the accident. A panel set up by the Italian government investigated, from the beginning of 1977 to the end of 1984, all suspected birth defects in children born to women who were inhabitants of the area at the time of contamination (Mastroiacovo et al., 1988). This study did not find an increased rate of birth defects in children born to the exposed women. The authors noted that rare defects could not have been detected because of the small number of births, and that it was possible that spontaneous abortions decreased the number of children born with defects. They cited one study that found an increase in spontaneous abortions after the accident (Santi et al., 1983), and one study that did not (Bianco et al., 1986).

Conclusion

The contamination of Times Beach and Seveso, and the health effects attributed to use of the herbicide 2,4,5-T, especially from Agent Orange, have made dioxin a household word with its infamous connotation. Much attention has been paid to the potential danger of dioxins and furans and their wide presence in very small quantities. Yet investigators of the health of the people exposed to relatively large quantities have found little evidence to justify the enormous reaction to these incidents. Nevertheless, dioxins and furans are present in our environment, in organisms, and in us, and can be extremely toxic, at least to other organisms. A great deal of money and other resources have been spent on the research of dioxins and

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furans, and will continue to be spent. The question then is, what do we know about dioxins and furans?

Detecting Trace Amounts of Dioxins and Furans

One of the difficulties of discussing dioxins and furans is the almost unimaginably small quantities we can detect with modern techniques: as little as one trillionth, or in some cases even a few quadrillionths of a gram. The following examples illustrate how little these quantities are. If we assume a drop of water to be equal to 0.05 milliliters (20 drops to a milliliter), then one ppb is equivalent to one drop of water in 13,200 gallons, or a pool 20-feet square and approximately 4.5-feet deep. One ppt is equivalent to one drop of water in 13,200,000 (thirteen million two hundred thousand) gallons, or a pool of water as long and wide as a football field, and approximately 28-feet deep. One part per quadrillion (ppq) is equivalent to one drop of water in 13,200,000,000 (thirteen billion, two hundred million) gallons, or a 6-square-mile lake, approximately 10.5-feet deep.

Dioxins and furans were among the very first compounds chemists could measure in one billionth of a gram (in 1970) and one trillionth of a gram (in 1976), and they are now approaching the detection of one quadrillionth of a gram. As the new techniques for detection were developed, dioxins and furans were used to test the techniques because they appeared to be toxic at extremely low levels. Before the detection techniques were developed, researchers used animals such as young chickens to test the toxicity of dioxins and furans (pers. comm., David Firestone, USFDA).

Dioxins lend themselves to the techniques used to detect amounts this small. They react with very few other chemicals, many last a long time, and they dissolve readily in organic solvents. Also, dioxins and furans are relatively simple molecules. The molecules of many other toxins are very complex (pers. comm., David Firestone, USFDA).

In order to detect amounts this small, it is first necessary to isolate the substance you want to measure from all the other substances that are present in a typical sample. This process

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is called analytical clean-up; the chemist puts the sample through a complicated and delicate preparation process, involving extractions, washings, and separations. Once the sample has been cleaned up, the separated materials need to be detected and their amounts measured. This can be done using several techniques, including an Electron Capture Detector, Flame Ionization Detector, or Mass Spectrometer, along with a Gas Chromatograph (pers. comm., Annette Guiseppi-Elie, Drexel University).

In addition to the difficulty of detecting these very small amounts, the toxicity of these compounds necessitates great care in their handling. Therefore, detecting the presence of dioxins and furans at levels approaching 1 ppt is a very time-consuming, expensive, and difficult undertaking. An experienced analytical chemist needs several months in order to prepare the laboratory for detecting a particular chemical at these extremely low concentrations. Once everything is in place, the analysis of just one sample costs about \$2000 in materials, requires the attention of an experienced analytical chemist, and typically consumes a half-day of work (pers. comm., Robert Baughman, Harvard University).

A much cheaper and quicker method has been developed for determining the level of toxicity of a mixture of dioxins and furans in a sample. It has been established that dioxins and furans induce a specific enzyme and bind to a specific protein in animals and humans (Poland et al, 1979). Rather than using analytical chemistry to determine the amounts of various toxic congeners¹ of dioxins and furans in a sample, cell cultures are exposed to the sample and the above biochemical responses are measured. The accuracy of these methods have been verified by comparing their results with the results of chronic toxicity tests using laboratory animals (Safe, 1987; Sawyer et al, 1983).

¹ A congener is a single, particular dioxin or furan, e.g. 2,3,7,8-TCDD.

Dioxins and Furans: What They Are, Where They Are Found, and How They Behave

What is dioxin?

The dibenzo-*para*-dioxin structure (see Figure 1), which provides the framework for tens of thousands of compounds, is made up of two benzene rings joined by two oxygen atoms (hence *dibenzo dioxin*). The "*para*" means the benzene rings are attached to opposite sides of the dioxin molecule, and it is usually designated as simply "*p*". Benzene is a ring of six carbon atoms (one at each corner) and six hydrogen atoms (one bonded to the carbon atom at each corner).

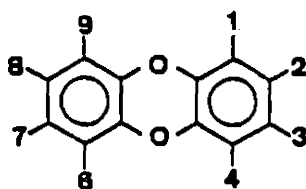


Figure 1. Dibenzo-*p*-dioxin

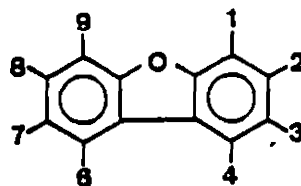


Figure 2. Dibenzofuran

In addition to dibenzo-*p*-dioxin, there is the related structure called a dibenzofuran (see Figure 2). A dibenzofuran, like a dibenzo-*p*-dioxin, is composed of two benzene rings. However, the benzene rings are joined by one oxygen atom, instead of two. The single oxygen that joins the two benzene rings forms the furan part of the molecule. A furan is a ring like benzene, but is made up of four carbon atoms plus one other atom (in this case, that other atom is the oxygen atom). Both dioxins and furans have eight corners (four on each benzene ring), free to react with other atoms. These other atoms can be, for example, hydrogen, chlorine, bromine, fluorine, iodine, or nitrogen. The corners can also react with groups made up of these atoms. The number of possible combinations is enormous.

There are 75 polychlorinated dibenzo-p-dioxins (PCDDs) and 135 polychlorinated dibenzofurans (PCDFs). PCDFs are similar to PCDDs in their distribution, toxic properties, and behavior, although not as much is known about them. While those dibenzo-p-dioxins and dibenzofurans with atoms other than chlorine on their corners (bromine, nitrogen, and so on) may have similar toxic potential (tests indicate this to be true for some types), they are not as common or numerous, and are not considered to be as important as chlorinated dibenzo-p-dioxins and dibenzofurans. However, there has been some concern about the polybrominated dibenzo-p-dioxins and dibenzofurans, because polybrominated compounds are used as gasoline additives, and have been widely used as flame retardants in plastics, carpets, textiles, and so on (Buser, 1987). It has been shown that when these compounds are burned, polybrominated dioxins and furans can form (Buser, 1986; Hagiund et al., 1988). Almost nothing is known, however, about the extent of their presence in the environment. For the rest of this report, only the chlorinated dibenzo-p-dioxins and dibenzofurans will be discussed.

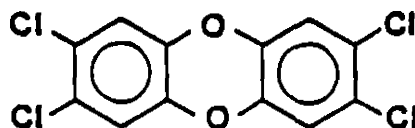


Figure 3. 2,3,7,8-TCDD

As illustrated in Figure 3, the numbers 2,3,7,8 refer to the positions on the benzene rings where the four (thus tetra) chlorine atoms are attached. 2,3,7,8-TCDD is the most toxic of the dioxins or furans, and can be formed in significant amounts during the production of trichlorophenol-based chemicals. Also, 2,3,7,8-TCDD is accumulated preferentially by animals and humans, compared to the other types of dioxins and furans. A great deal more research has been done on 2,3,7,8-TCDD than on the other dioxins and furans, and the following discussion is based largely on studies of 2,3,7,8-TCDD.

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Are all dioxins and furans dangerous?

Only 20 or so of the 210 chlorinated dioxins and furans are considered to be extremely toxic. These have 4 to 7 chlorines, with a chlorine in each of the 2,3,7, and 8 positions (2,3,7,8-substituted dioxins and furans). Table 1 lists these very toxic types of dioxins and furans, and all other dioxins and furans, along with their toxicity relative to the most toxic dioxin or furan, 2,3,7,8-TCDD.

Table 1. Relative toxicity of dioxins and furans

Compared to the most toxic, 2,3,7,8-TCDD.
From the USEPA National Dioxin Study (USEPA, 1987a: p 1.7)

Type of dioxin or furan		Relative toxicity
2,3,7,8-tetra-CDD	(4 chlorines)	1 (Most Toxic)
1,2,3,7,8-penta-CDD	(5 chlorines)	1/2 as toxic
2,3,7,8-tetra-CDF	(4 chlorines)	1/10th
1,2,3,7,8-penta-CDF	(5 chlorines)	"
2,3,4,7,8-penta-CDF	"	"
1,2,3,4,7,8-hexa-CDD	(6 chlorines)	1/25th
1,2,3,6,7,8-hexa-CDD	"	"
1,2,3,7,8,9-hexa-CDD	"	"
Other tetra-CDDs	(4 chlorines)	1/100th
1,2,3,4,7,8-hexa-CDF	(6 chlorines)	"
1,2,3,6,7,8-hexa-CDF	"	"
1,2,3,7,8,9-hexa-CDF	"	"
2,3,4,6,7,8-hexa-CDF	"	"
Other penta-CDDs	(5 chlorines)	1/200th
1,2,3,4,6,7,8-hepta-CDD	(7 chlorines)	1/1000th
Other tetra-CDFs	(4 chlorines)	"
1,2,3,4,6,7,8-hepta-CDF	(7 chlorines)	"
1,2,3,4,7,8,9-hepta-CDF	"	"
Other penta-CDFs	(5 chlorines)	"
Other hexa-CDDs	(6 chlorines)	1/2500th
Other hexa-CDFs	"	1/10,000th
Other hepta-CDDs/CDFs	(7 chlorines)	1/100,000th
Other CDDs/CDFs	(1-3, 8 chlorines)	Not toxic

Dioxins and furans usually occur in a mixture of several or many types, and the mixture varies with the source of the dioxins and furans. In order to arrive at a number that represents the total toxicity of the mixture, relative to 2,3,7,8-TCDD, the appropriate factor is applied to the amount of each type of dioxin or furan in the mixture and the result then added, for all the types present. The total amount is then expressed in "2,3,7,8-TCDD equivalents". This allows the direct comparison of the toxicity of different mixtures of dioxins and furans, from different sources.

For example, let us say we have analyzed samples of soil from two contaminated waste sites, and found the following:

Site One	Site Two
3 ppb 2,3,7,8-TCDD	1 ppb 2,3,7,8-TCDD
6 ppb 2,3,7,8-TCDF	4 ppb 1,2,3,7,8-penta-CDD
200 ppb other tetra-CDDs	100 ppb 1,2,3,7,8-penta-CDF

How can we compare the toxicity of these two samples? The toxicity equivalent method is one way. The toxicity of these two samples would be computed as follows:

Site One	Factor	Result
3 ppb 2,3,7,8-TCDD	X 1	3 ppb
6 ppb 2,3,7,8-TCDF	X 0.1	0.6 ppb
200 ppb other tetra-CDDs	X 0.01	2 ppb
		5.6 ppb

Site Two	Factor	Result
1 ppb 2,3,7,8-TCDD	X 1	1 ppb
4 ppb 1,2,3,7,8-penta-CDD	X 0.5	2 ppb
100 ppb 1,2,3,7,8-penta-CDF	X 0.1	10 ppb
		13 ppb

Therefore, the toxicity of the soil in Site One is equal to 5.6 ppb 2,3,7,8-TCDD equivalents and in Site Two is equal to 13 ppb 2,3,7,8-TCDD equivalents.

The USEPA used data from several kinds of studies to determine these factors (Barnes et al., 1986). Of first importance were data concerning cancer and reproductive effects in animals, based on long-term studies, but this information is available for only a few types of

dioxins and furans. Therefore, data from studies of the biochemical effects of these compounds on cell cultures were also used. These studies, called enzyme induction and receptor binding studies, measure certain biochemical responses that are related to the toxic effects of dioxins and furans. The USEPA chose not to use data from short-term animal toxicity tests, stating that such information is not useful for predicting the long-term health effects of dioxins and furans.

These factors are the result of interpretation, and agencies from other countries have released somewhat different guidelines (Barnes et al., 1986). This is an area of ongoing investigation, and the USEPA will probably revise this table. For example, a recent study indicates that oca-CDD/CDF are toxic, not non-toxic as this table shows (Couture et al., 1988). Other types of dioxins and furans have also been investigated and found to have toxicities higher or lower than the present factors indicate (Pleuss et al., 1988a; 1988b). The use of such factors to determine the toxicity of a mixture is somewhat controversial. The CDC, for example, feels that this method is not scientifically valid, given our limited knowledge of the health effects of the many dioxins and furans, especially in a mixture. However, Pleuss et al (1988b) investigated the toxicity of a mixture of dioxins and furans in rats, and found the USEPA's factors to be adequate for estimating the total toxicity.

What factors affect the toxicity of dioxins and furans?

The toxic effect of a dioxin or furan on an animal depends on more than the basic toxicity as expressed in the table above. It also depends upon the kind of animal being exposed, the condition of the animal, and the medium that the compound is mixed with. Some animals are thousands of times more sensitive than others to the toxic effects of the same dioxin or furan. For example, guinea pigs (the most sensitive animal tested so far) are approximately 3000-5000 times more sensitive to the lethal effects of 2,3,7,8-TCDD than are hamsters (the most resistant animal so far tested). Also, because they are very lipid-soluble (soluble in fats, oils, and solvents such as acetone), dioxins and furans have had a greater toxic effect on an

animal when they were administered in, for example, corn oil, than when they were administered in dry food.

Different kinds of dioxins and furans have different behaviors within animals; some are excreted rather quickly, while others are stored in the tissues for long periods of time. This may affect their toxicity to the animal. Laboratory studies showed that rats and carp fed a mixture of dioxins and furans accumulated higher amounts of 2,3,7,8-substituted types (these are the most toxic types of dioxins and furans) than other types (van den Berg et al., 1983; Kuehl et al., 1987a; 1987b). They also found that carp retained 2,3,7,8-TCDD and its counterpart furan (2,3,7,8-TCDF) for longer periods than dioxins or furans with fewer or more chlorines.

Researchers who have made congener-specific analyses of tissues from organisms in the wild have also found that the 2,3,7,8-substituted congeners of dioxins and furans are the only types found (Rappe et al., 1987a; Heida et al., 1986). Crustaceans appear to be an exception to this general rule; Rappe et al. (1987a) detected dioxin and furans congeners in crabs and lobsters that were not 2,3,7,8-substituted.

Soils from different 2,3,7,8-TCDD-contaminated sites show greatly varying toxicities. Researchers from the National Institute of Environmental Health Sciences and Rutgers Medical School fed guinea pigs 2,3,7,8-TCDD-contaminated soils from two different sites (McConnell et al., 1984; Umbreit et al., 1986). The animals showed greatly different reactions, although the amount of 2,3,7,8-TCDD given to them was similar. They concluded that the nature of the soil affected the toxicity of the 2,3,7,8-TCDD, presumably by determining how much of the 2,3,7,8-TCDD was absorbed by the animal (this is known as bioavailability). The researchers suggested that the difference between the toxicity of the soils was caused by the difference in the amount of carbon in the soil. It is known that dioxins bind strongly to carbon and are thus less likely to be absorbed during digestion.

Where are dioxins and furans found?

In soil, water, and air

There are areas contaminated with relatively high levels (1 ppb or more) of dioxins and furans; most are sites where 2,4,5-trichlorophenol and 2,4,5-trichlorophenol-based biocides were manufactured or processed, and/or their associated waste sites. Wood-preserving facilities that have used pentachlorophenol, and sawmills that have used chlorophenolic solutions to prevent staining, can be contaminated with dioxins and furans and in some cases have contaminated the local environment. In addition, there are many contaminated areas in Missouri where 2,3,7,8-TCDD-laden oil was sprayed on roads and horse arenas, and several military bases where Agent Orange was stored or heavily sprayed.

Apart from these recognized sites of contamination, 2,3,7,8-TCDD has not been found commonly in soil. As part of their National Dioxin Study, the USEPA randomly selected 221 urban sites and 142 rural sites where no previously known sources of dioxins or furans had been recorded. Seventeen of two hundred and twenty-one urban sites and one of one hundred and thirty-eight rural sites had detectable amounts of 2,3,7,8-TCDD in the soil (USEPA, 1987a: pp 3.26-32). The limit of detection was about 1 ppt, and levels ranged from 1-11 ppt.

Low levels of 2,3,7,8-TCDD have been found in areas that were sprayed with the herbicide 2,4,5-T. During their nationwide survey, the USEPA found 2,3,7,8-TCDD at 15 of 26 sites where 2,4,5-T was sprayed commercially; these sites included sugarcane and rice fields, rangeland, and forests (USEPA, 1987a: pp 3.12-21). The highest levels (1-6 ppb in soils or sediment) were generally found where spraying equipment was loaded, or where the herbicide accumulated. Where the herbicide was simply sprayed, levels were very low or below the limit of detection (1-5 ppt).

Dioxins and furans have also been found in sediments in the Great Lakes and some associated rivers, and in some large river systems near urban centers. They are ubiquitous in low ppb levels in the sediments of Lakes Erie, Ontario, Huron, and Michigan (Czuczwa and Hites, 1986). They have also been found in sediments of the Niagara River (Hallet and

Brooksbank, 1986). In many areas, samples of fish or other organisms have been used to detect the presence of dioxins and furans in the water ecosystem, rather than direct sampling of the sediments. (See the following section on dioxins and furans in animals and plants.)

Dioxins and furans have not been detected in treated drinking water in the U.S. However, furans have been found in tap water in Japan (Shiraishi et al., 1985). In the U.S., dioxins have been found in water of the Niagara River adjacent to the severely contaminated Love Canal area, and in groundwater near the canal (Hallet and Brooksbank, 1986). Groundwater and surface waters in the vicinity of wood-preserving facilities and sawmills, that use chlorophenol-based solutions to treat wood, have been contaminated with dioxins and furans (USEPA, 1988a: pp 53323-4). Both groundwater and surface waters can be sources for municipal drinking water, although the water is treated first. Those people who live near contaminated sites and use untreated well water have been notified.

Dioxins and furans have been detected in air in urban areas of the U.S. (Czuczwa and Hites, 1986), West Germany (Rappe and Kjeller, 1987; Rappe et al, 1988), and Japan (Nakano et al., 1987), in air near contaminated sites in the U.S. (Fairless et al., 1987), and in the air emissions from incinerators. It is suspected that incinerators and automobiles burning leaded gasoline are important sources of dioxins and furans in urban areas.

In conclusion, dioxins and furans are present in very low levels in many places, and at high levels at a small number of contaminated sites. Their presence is usually associated with the production, storage, use, or disposal of chlorophenol-based compounds. In addition, they have been detected in low levels in urban areas, where they are believed to be the product of numerous combustion processes. As our ability to detect dioxins and furans improves, it is likely that they will be found in more places.

Are dioxins and furans found in animals and plants?

Dioxins and furans are much more soluble in fats than in water and therefore tend to accumulate in the fatty tissues and organs of animals exposed to them. Levels of 1-200 ppt

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2,3,7,8-TCDD have been detected in fish and other aquatic organisms in some parts of the U.S., and fish from the Great Lakes and associated rivers generally contain higher amounts than elsewhere in the country (USEPA, 1987a: p 3.29-32). The USEPA detected 2,3,7,8-TCDD in 17 of 90 samples of fish from randomly selected national monitoring sites, at levels of 1-19 ppt. Samples were also taken from 305 areas of general interest, chosen because they were near population centers, were used for commercial or recreational fishing, or because other water quality information was already available. Of these samples, 95 of 305 from regionally selected sites had 1-85 ppt 2,3,7,8-TCDD. Of fish samples from the Great Lakes, 23 of 29 had 1-41 ppt 2,3,7,8-TCDD.

The USEPA also found as much as 85 ppt 2,3,7,8-TCDD in fish, from rivers that were receiving effluents from some pulp and paper mills (USEPA, 1987a: p 3.31). Since then, dioxins and furans have been found in the sludge, wastewater, and products of pulp and paper mills that use a chlorine bleaching process (Amendola et al., 1987).

A study of dioxins and furans in fish and Herring Gulls from the Great Lakes (Stalling et al., 1983) found a wide range of total levels of dioxins (undetectable to 223 ppt) and furans (15-290 ppt) in fish from various locations in the Great Lakes watershed. 2,3,7,8-substituted congeners were responsible for the bulk of the dioxins and furans present, and 2,3,7,8-TCDD was the predominant congener. The two Herring Gulls analyzed had 27 and 26 ppt total furans, and 196 and 110 ppt total dioxins, including 165 and 75 ppt 2,3,7,8-TCDD. 2,3,7,8-TCDD has also been detected in Herring Gull eggs from the Great Lakes, at levels ranging from 9-90 ppt (Norstrom et al., 1982).

Because 2,3,7,8-TCDD is a contaminant of the herbicide 2,4,5-T, there was concern about 2,3,7,8-TCDD being spread through the use of this herbicide (2,4,5-T is no longer produced or used in the U.S.) Therefore, a joint study by the USEPA and the University of Nebraska was undertaken to determine if animals showed detectable amounts of 2,3,7,8-TCDD after normal application of 2,4,5-T to Oregon forests (Gross, 1980, cited in Weerasinghe and Gross, 1985). Animal tissue and whole animals (mice, shrews, birds, and newts) were sampled

and, although 3 ppt were found in several samples by one laboratory, this could not be confirmed by the second laboratory.

However, some studies have detected low levels of 2,3,7,8-TCDD in organisms after normal applications of 2,4,5-T. In a 1984 study by the USEPA, deer were placed in a plot that was then sprayed with 2,4,5-T (Harless et al., 1983). They found 1-27 ppt 2,3,7,8-TCDD in the fat, muscle, and liver tissue of the deer, and the frequency of detection increased during the four-week sampling period. No 2,3,7,8-TCDD was found in the bone marrow of the deer, or in a deer placed in a separate area. Also, 2,3,7,8-TCDD in levels as high as 1 ppb have been detected in whole-animal samples of fish and shellfish from areas in South Vietnam (Baughman and Meselson, 1973) that were heavily sprayed with Agent Orange during the Vietnam War.

At exceptionally contaminated sites, such as an improperly managed waste site (Heida et al., 1986), a military base where Agent Orange was repeatedly handled and sprayed (Young and Cockerham, 1985), or where 2,3,7,8-TCDD was released during an industrial accident (Fanelli et al., 1980), 2,3,7,8-TCDD has been found in many different organisms, such as rodents, insects, lizards, earthworms, and birds. Researchers in Italy found that plants grown in soil contaminated with 2,3,7,8-TCDD accumulated the compound in their roots, and to a much lesser extent, in the above-ground portion of the plants (Facchetti et al., 1986). However, in Seveso, one year after the accident, no traces of 2,3,7,8-TCDD were found in the flesh of fruits or in corn kernels and cobs, from trees and plants grown in soil contaminated with approximately 10 ppb total dioxins. Dioxins were found in the peels of fruits; the researchers concluded that they were contaminated externally by dust, and not by dioxins in the soil (Wipf et al., 1982).

Dioxins and furans have been found in organisms from contaminated areas, and from fish in many areas of the U.S. Most animals do not appear to accumulate these compounds at levels greater than in their surrounding environment, although "bioconcentration" can occur. Plants typically contain these compounds at levels much below the surrounding environment, and only when they are grown in highly contaminated soil. The fruits do not appear to contain dioxins; however, root crops may be more susceptible to contamination.

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How long do dioxins and furans last in the environment?

Many factors influence the persistence of dioxins and furans in the environment: what kind of dioxin or furan it is, whether it is present as a solid or gas, what it is mixed with, and what kind of environment it is exposed to, among other things. Photodegradation (breakdown by light) is believed to be the most important environmental process for the breakdown of dioxins and furans. Crosby et al. (1971) and Crosby and Wong (1977) have demonstrated that ultraviolet (UV) light is responsible for the photodegradation of 2,3,7,8-TCDD. They also found that the rate of breakdown varied with the material the dioxins were mixed with, and the surface to which the mixture was applied.

They reported that 2,3,7,8-TCDD applied to wet and dry soil, or dissolved in water, showed no signs of breakdown after as much as four days of exposure to ultraviolet light. However, when it was mixed with the herbicide Agent Orange, the commercial herbicide Esteron, or a solvent such as methanol (wood alcohol), and applied to soil, glass, or plant leaves, the 2,3,7,8-TCDD was partially or totally degraded in less than eight hours. The authors noted that these conditions would often have been met during the application of 2,3,7,8-TCDD-containing herbicides such as 2,4,5-T, and may explain why the normal application of 2,3,7,8-TCDD-containing herbicides typically does not leave persistent, detectable amounts of 2,3,7,8-TCDD on soil or foliage.

In addition to photodegradation, there are other processes that can break down dioxins and furans. For example, some breakdown of these compounds in soil appears to be the result of digestion by microorganisms (Matsumura and Benzeat, 1973). However, this breakdown occurs much more slowly than the photodegradation process mentioned above. Efforts to isolate a microorganism that can digest 2,3,7,8-TCDD have met with little success: only a small percentage of the substance is broken down, even after months of incubation. It also appears that dioxins and furans bound to particles and dissolved in water are very slowly released to the atmosphere as a gas (Palansky et al., 1986; Nash and Beall, 1980). The significance of this

process is not yet agreed upon. Once released to the air by this process, it is expected that dioxins and furans are broken down by sunlight.

In sum, 2,3,7,8-TCDD can be broken down in a matter of days in the environment, if it is mixed with the proper organic solvent (not water, but acetone or even corn or olive oil) and exposed to ultraviolet light (Wipf et al., 1978). On the surface of the soil, without a solvent, 2,3,7,8-TCDD has an environmental half-life of one year or less, due to slow photodegradation and volatilization (Crosby and Wong, 1977). Underground and in sediments, this very stable compound has broken down much more slowly, with a half-life of about 10 years (DiDomenico et al., 1980a; 1980b). Very little is known about the half-lives of other dioxins and furans. In general, dioxins and furans with fewer than four chlorines are broken down more quickly than 2,3,7,8-TCDD (Crosby et al., 1971). The dioxin or furan with eight chlorines is more resistant to breakdown.

To what degree do dioxins and furans spread when they are introduced into the environment?

The most important manner of transport of dioxins and furans appears to be the physical movement of particles to which they are bound. Dioxins and furans have a great affinity for organic carbon; thus they bind very strongly to the organic carbon present in particles of soil, in sediments, and to the particles found in the air. These particles can be lifted and carried by wind or by water.

In the air, dioxins and furans can be transported considerable distances. For instance, they have been found in the sediment of a lake on Isle Royale, an island in Lake Superior (Czuczwa et al., 1984). It is believed that dioxins and furans could reach this lake only by transport in air. Also, dioxins and furans have been found in Arctic seals taken in the Arctic Circle, many thousands of kilometers from any known sources of the compounds (Oehme et al., 1988).

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There is also evidence of the transport of dioxins and furans in water. 2,3,7,8-TCDD has been detected in fish downstream from known sources, and in groundwater and river water near landfills in which large amounts of 2,3,7,8-TCDD-contaminated wastes were disposed (Hallet and Brooksbank, 1986). Dioxins and furans have also migrated from wood-preserving facilities and sawmills through surface waters and groundwater (USEPA, 1988a; pp 53323-4).

Measurements of the movement of 2,3,7,8-TCDD through soil indicate that the process is generally a very slow one, from one to ten centimeters per year. Palausky et al. (1986) reported that the initial depth to which the 2,3,7,8-TCDD contaminates the soil greatly influences the resulting movement by vapor phase. This depth of contamination is related to the type of solvent in which the 2,3,7,8-TCDD is carried: the volatility (at what temperature it evaporates) of the solvent, its viscosity (how easily it flows), and how it interacts with soil organic matter.

Because they are so insoluble in water, only very small amounts of dioxins and furans are washed from soil particles or released from sediments to the water above it (Isensee and Jones, 1975). Their extremely low solubility in water makes it very hard to measure just how much dissolves; consequently, there is a wide range of reported values. The recently accepted value for 2,3,7,8-TCDD is about 20 ppt in pure water (Marple et al., 1986).

Dioxins and furans can be transported as a gas, but Palausky et al (1986) detected this only at temperatures above 30°C (87°F); it was therefore concluded that this vapor phase transport of 2,3,7,8-TCDD takes place only in upper layers of soil, during hot weather.

In conclusion, dioxins and furans attached to particles can migrate considerable distances in the air, and to a lesser extent in water. But because these compounds are so insoluble in water, and because they bind so strongly to particles in the soil and water, they appear to migrate very little once they reach sediments and soil. Areas of severe contamination have typically remained local problems, and contamination appears to be limited to nearby areas.

Are dioxins and furans found in humans?

Dioxins and furans have been found in samples of human blood and fat tissues from numerous countries, including the U.S., Canada, Japan, Vietnam, and several countries in Europe. Based on these findings, it is generally agreed that the population at large in many parts of the world has been exposed to low levels of dioxins and furans.

In North America, for example, 2,3,7,8-TCDD is typically present in human fat, some other tissues, and breast milk, at the level of approximately 7 ppt (Ryan, 1986). In addition to 2,3,7,8-TCDD, penta-CDD is typically found at 10 ppt, penta-CDF at 15 ppt, and the hepta- and octa-CDDs/CDFs at levels approaching 1 ppb. In humans as in other animals, the most toxic dioxins and furans, with chlorines in the 2,3,7 and 8 positions, have been found in greater amounts than the other dioxins and furans with the same number of chlorines.

How do dioxins and furans reach humans?

Although we can be exposed to enough of these compounds to detect them in our bodies, the mechanisms of this process are still under investigation. Dioxins and furans are believed to reach humans in the following ways: when we inhale contaminated dust or vapors; when we contact or ingest contaminated water, sediment, or soil; when we eat contaminated vegetable, meat, or dairy products (Mukerjee et al., 1986). At the present time, the relative importance of these routes of exposure is not understood. However, drinking and contacting contaminated water is generally considered a minor route because dioxins and furans have not been detected in treated drinking water in the U.S., and our contact with untreated water and sediments is normally minimal (e.g. swimming, other watersports). Ingestion of and contact with soil is also considered a minor route, except for small children.

The major routes of exposure, then, are generally considered to be breathing contaminated particles and eating contaminated food. Particles in air, especially near urban areas or large sources of combustion products, can contain low levels of dioxins and furans, and

the accumulated lifetime exposure from inhaling these particles is considered a potentially important source (Marklund et al., 1986). Studies by Rappe et al. (1986a) and Travis and Hastenr-Frey (1987) compared breathing to food consumption, and estimated that breathing is far less important, even near a large source of combustion. However, very little is known about the actual amounts contributed by breathing air particles.

Dioxins and furans have been found in a variety of foods in Japan and Canada, in dairy products in Sweden, and in selected foods in the U.S. They have been found in fish from the Great Lakes and associated rivers, fish from many major rivers near urban centers, and fish from rivers below some pulp and paper mills. As a result, advisories for limiting consumption of fish in some of these areas have been issued (see Appendix).

In 1984, the USEPA found ppt levels of 2,3,7,8-TCDD in 3 of 85 samples of beef fat from cattle that had grazed on land sprayed with 2,4,5-T (USEPA, 1985: p 4-30). Dioxins and furans, but not 2,3,7,8-TCDD, have also been found in chicken livers and chicken eggs, and in gelatin from supermarkets (USEPA, 1985: p 4-31). In both cases, the sources of the contamination were hides (from cattle, hogs, sheep, and other animals), treated with pentachlorophenol, a product which is usually contaminated with dioxins and furans. Fat from the treated hides was used in the manufacture of the chicken feed and the gelatin (Firestone, 1973).

Investigators in Sweden found dioxins and furans (but not 2,3,7,8-TCDD or 2,3,7,8-TCDF) in levels below 1 ppb in cow fat, milk, cream, and liver (Nygren et al., 1986), and investigators in Japan (Ono et al., 1987) found similar amounts of dioxins and furans in a variety of meat and dairy products. A researcher in Canada also found ppt levels of dioxins and furans in fruits and vegetables (Davies, 1988).

2,3,7,8-TCDD has not commonly been found in food in the U.S.; its presence in selected foods has been related to specific sources, as above. However, it is probable that trace amounts of other dioxins and furans are present in common foods, as has been found in other countries. Similar tests have not yet been reported for the U.S.

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Breast milk, like many human tissues, has low levels of 2,3,7,8-substituted dioxins and furans, and they can be transferred to a baby through the mother's milk (reviewed in Lindstrom, 1988: p 34). Because a baby is tiny, undergoing rapid development, and may have breast milk as its sole source of nourishment, a breast-fed baby may be subject to a greater than normal risk (Tarkowski and Yrjanheikki, 1986; Schechter and Gasiewicz, 1987). Breast-fed babies may receive levels of dioxins and furans that exceed safe guidelines (Nygren et al., 1986). However, a study by the World Health Organization (WHO) Regional office in Europe determined that breast-fed babies receive dioxins and furans in amounts far below what are capable of causing adverse health effects (WHO, 1988, cited in Lindstrom, 1988).

Young children ingest more soil than older children and adults, and are probably subject to greater contact exposure as well (Houk, 1986). The Center for Disease Control took this greater exposure into account when they determined that 1 ppb or more of 2,3,7,8-TCDD in the residential soil of Times Beach suggested the need for corrective action.

Workers in several occupations are or have been subject to a greater potential exposure (Choudhary, 1983). These include: mills where wood is treated with pentachlorophenols or where treated wood is sawed; leather and tanning industries, which have used chlorophenols as preservatives; facilities that manufacture, ship, or formulate chlorophenols; pulp and paper mills that use chlorophenol-based fungicides; health-related facilities, where hexachlorophene is used as a bactericide; occupations where workers apply chlorophenol-based biocides.

In sum, it is generally believed that eating contaminated food and breathing contaminated particles are the most important sources of exposure. We need to know more about the routes of human exposure to dioxins and furans. Also, breast-fed babies, small children, and some workers in the industries that use contaminated products, are subject to greater than normal potential exposure. These cases merit special attention.

Sources of Dioxins and Furans

How are dioxins and furans created?

Dioxins and furans have no useful purpose and have never been manufactured deliberately, except in small amounts for research purposes. They are known to be created in two major ways: (1) they are created in trace quantities by unwanted side reactions, which take place during the chemical processes used to manufacture useful products such as biocides, paper, disinfectants, and preservatives; (2) they are created when a substance containing chlorine is burned, or when a substance is burned in the presence of chlorine (chlorine is a constituent element of many substances). In addition to the dioxins and furans from these two major sources, there is evidence that dioxins and furans can be created when certain mixtures of substances are exposed to sunlight. The importance of this process is not yet known.

Determining the relative or absolute importance of the various sources of dioxins and furans is complicated. Simply, the question is: What kind of hazard does the source represent to humans and other organisms? In order to estimate this, at least the following information should be considered:

- 1) What types of dioxins and furans are produced by the source?
- 2) What amounts of the different types are produced?
- 3) How will humans and other organisms be exposed?
 - For how long?
 - To what levels?
- 4) How many humans or other organisms will be exposed?

Because this information is unavailable for most of the sources of the dioxins and furans, it is impossible to make more than a rudimentary qualitative estimate of the importance of the various sources, relative to each other. For some sources, even this is unwarranted because of lack of information. Therefore, while a discussion of the sources is worthwhile, it should be noted that the various known sources may prove to be much more or less important

than our present understanding makes them appear. Also, new sources of dioxins and furans will continue to be identified.

What products can be contaminated with dioxins and furans?

Dioxins are formed as unwanted byproducts during the manufacture of some chlorophenols (especially those with three or more chlorines), and during the manufacture of chemical products that are derived from these chlorophenols: phenoxy herbicides such as 2,4,5-T, and biocides and preservatives such as pentachlorophenol. Manufacturers have greatly reduced the levels of dioxins and furans in their chemical products since they were identified as contaminants in the early 1970s. In some cases this resulted in much higher concentrations of dioxins and furans in the waste from these processes. The safe disposal of such waste is difficult, and inadequate disposal methods have resulted in environmental contamination.

Dioxins and/or furans have been found as contaminants in the following products:

Table 2. Products that can be contaminated with dioxins and/or furans

Product	Contaminants
PCBs	Furans
hexachlorophene	Dioxins*
2,4,5-T	Dioxins*
2,4-D	Dioxins*
chlorophenols with 3 or more chlorines	Dioxins and Furans
polychlorinated benzenes	" "
diphenyl ether herbicides	" "
hexachlorocyclohexane	" "
paper products	" "

* I could find no analyses of these products for furans.

Note: The above list is based on information available in journals or reports. Under the auspices of the Toxic Substances Control Act (TSCA), the USEPA published a larger list of chemical products that may be contaminated with chlorinated or brominated dioxins and furans (USEPA, 1987b). For more information, see under "What has been done about dioxins and furans?", page 69.

PCBs

PCBs and PCB-containing mixtures can be a source of furans and to a lesser extent a source of dioxins. They were widely used prior to 1977, primarily as dielectric fluids in electrical equipment such as transformers and capacitors. PCBs have also been used as plasticizers, hydraulic lubricants, and in a variety of other applications. PCBs are no longer produced in the U.S. or installed in new equipment, and their use and disposal is restricted (see under "What Has Been Done About Dioxins and Furans?", page 69).

Levels of furan contamination in PCBs vary with the manufacturer and the type of PCB (Bowes et al., 1975; Rappe and Buser, 1980). A recent and particularly sensitive study of both U.S. and Japanese PCBs found up to 60 different kinds of furans, including most of the 2,3,7,8-substituted types, in low ppb levels (Wakimoto et al., 1988). No dioxins were detected above the limit of detection of 2 ppb.

Used PCBs can have higher levels of furans. Apparently, the heat that they may be subjected to during use can promote the further formation of furans (pers. comm., P.E. des Rosiers, USEPA). However, several studies have shown that simple overheating or arcing in electrical equipment does not generate furans (des Rosiers, 1987). While dioxins generally have not been detected in PCBs, a recent study found relatively high levels of dioxins in used oil (R. Adams, et al., 1986). For many applications, such as dielectric fluids, PCBs are combined with other compounds such as chlorinated benzenes. These other compounds are believed to be responsible for the presence of dioxins (see discussion of chlorinated benzenes, below).

Approximately 1.4 billion pounds of PCBs were purchased by U.S. industries prior to 1977. Based on these sales, an estimated 84-94 kilograms (kg) of furans were present in the PCBs produced during this period, including 8 kg of 2,3,7,8-TCDF and 14 kg of 2,3,4,7,8-penta-CDF (Hutzinger et al., 1985). The authors noted that these were underestimates, because of missing sales information for some types of PCBs.

Most PCBs have been incinerated by licensed hazardous waste facilities or buried in designated landfills. However, a January 1988 U.S. General Accounting Office report estimates that 312 million pounds of PCBs still remain in millions of pieces of electrical equipment in the

U.S., and that as much as 150 million pounds of PCBs have been released to the environment (pers. comm., USEPA).

Low levels of PCBs are now ubiquitous in the environment, and it may be presumed that they are contaminated with trace levels of furans. In areas that are heavily contaminated with PCBs, it may be presumed that furans are present as well. Based on a comparison of the furan congeners in the tissues of aquatic animals (a snapping turtle, seal, and killer whale), to the furan congeners present in PCBs, several authors have concluded that PCBs were the source of the furans in the tissues (Rappe et al., 1981; Wakimoto et al., 1988). The release of PCBs is now highly restricted, and they are probably no longer a significant source of new releases of furans (the uncontrolled burning of PCB-containing fluids can be an exception; see "PCBs" on page 39).

Hexachlorophene

Hexachlorophene is a bactericide used in special soaps, veterinary medicine, and in restricted fashion as a surface disinfectant. It was once widely used in hospitals, in the cosmetics industry, and in some consumer products such as baby powder and skin cleansers. The USEPA no longer allows its use in non-prescription products. Very few measurements of dioxins in hexachlorophene have been made, but levels of from 0.2-0.5 ppb 2,3,7,8-TCDD were found in three samples (Baughman, 1974, cited in Rappe, 1984). Present levels have been reported as equal to or less than 30 ppb (USEPA, 1985: p. 4.12). Hexachlorophene is currently not produced in the U.S. (USEPA, 1986: p. 3.16).

2,4,5-trichlorophenoxyacetic acid (2,4,5-T)

The herbicide 2,4,5-T was used widely in the U.S. before 1980, and in a restricted fashion until 1983. It is no longer produced or used in the U.S. Dioxin concentrations as high as 100 ppm were found in 2,4,5-T produced in the 1950s and 1960s, with an estimated average of about 1 ppm (Rappe et al., 1982: p. 496). 2,3,7,8-TCDD was present in greater concentration than other isomers⁴ (Rappe, 1984). When this contamination was verified in the early 1970s,

⁴ An isomer is a single member of a homologue; a homologue is that group of dioxins or furans with the same number of chlorines.

manufacturers lowered the level of contamination considerably, and in 1984 producers of 2,4,5-T reported that the levels of 2,3,7,8-TCDD were below 0.1 ppm (Rappe, 1984).

The authors of one study estimated the maximum amount of 2,3,7,8-TCDD that could have been present in 2,4,5-T produced from 1960-1970 (Hutzinger et al., 1985). Based on total 1960-1970 production of 48.2 million kg, and a maximum concentration of 100 ppm 2,3,7,8-TCDD, they estimated a maximum total of 4800 kg 2,3,7,8-TCDD present in 2,4,5-T. The authors added that after 1970, both the level of contamination and level of production dropped sharply.

The defoliant Agent Orange, which was sprayed heavily over most of South Vietnam during the Vietnam war, was composed of a 50:50 mixture of 2,4,5-T and 2,4-D. Levels of 2,3,7,8-TCDD in Agent Orange were found to vary between 0.02 and 54 ppm, with an average of 2 ppm (reviewed in Esposito et al., 1980: p 98). The very heavy spraying of South Vietnam resulted in significant contamination of the environment with 2,3,7,8-TCDD (Baughman and Meadison, 1973).

In the U.S., normal spraying with 2,4,5-T appears to have contributed only trace levels of 2,3,7,8-TCDD to the environment, presumably because the 2,3,7,8-TCDD is present in a solvent (2,4,5-T) and therefore can be quickly broken down by sunlight. However, it is possible that the use of 2,4,5-T contributed to the low background levels of 2,3,7,8-TCDD in the fat of persons in the U.S.

The herbicide 2,4,5-T is no longer produced or used in the U.S. and is therefore no longer a source of dioxins here. However, a large amount of contaminated waste was created during the production of 2,4,5-T, resulting in many contaminated manufacturing and waste disposal sites (USEPA, 1987a). Some of these sites are still contributing dioxins to the environment, predominantly the local area (see "What about dioxins and furans from sewage plants, waste streams, and landfills?", page 45).

2,4-dichlorophenoxyacetic acid (2,4-D)

The widely used herbicide 2,4-D is made from dichlorophenol. Dichlorophenol has only rarely been found to be contaminated with dioxins and furans, and 2,3,7,8-TCDD is not

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formed in the manufacture of 2,4-D. However, other, much less toxic dioxin congeners have been found in 2,4-D at levels of from less than 1000 ppm to less than 10 ppm total dioxins (Cochrane et al., 1982). The authors of this study analyzed 2,4-D as acid, ester, and amine formulations. The ester formulations contained the highest levels of dioxins. The majority of the dioxin congeners identified in 2,4-D by this study and others are considerably less toxic than 2,3,7,8-TCDD (e.g. 1,3,6,8-TCDD), or not toxic (dioxins with 1-3 chlorines).

While the dichlorophenol from which 2,4-D is derived is not normally contaminated with 2,3,7,8-TCDD, isolated cases of 2,3,7,8-TCDD contamination of 2,4-D may have occurred when equipment formerly used to process 2,4,5-T was used to produce 2,4-D (USEPA, 1986: pp 3.21-3.23). The contaminated equipment would not be expected to contribute more than very low levels of 2,3,7,8-TCDD in the first few batches of 2,4-D.

In Canada, an annual production of 8 million kg of 2,4-D was estimated to be the source of 9 kg of dioxins with from 2-4 chlorines (Tosine, 1983). In the U.S., 7.1 million kg of amine formulations of 2,4-D were produced in 1986, and 6 million kg sold (U.S. Department of Commerce, 1987). No ester formulations were produced in the U.S. in 1986, but 3.7 million kg were sold. Because the level of production is similar to that in Canada, I assume it to be the source of a similar amount of dioxins. As in 2,4,5-T, dioxins in 2,4-D are present in a solvent (the herbicide) and therefore may be broken down by sunlight soon after their application. This possibility, along with proper disposal of the wastes from the production of 2,4-D, make it probable that the production of 2,4-D is a relatively unimportant source of dioxins in the environment.

Chlorophenols

Chlorophenols are a principal ingredient in the processes used to manufacture many of the above chemicals. They or their derivatives are used to preserve wood and drilling muds, and as biocides for process and cooling waters in some industries. Some of these uses may be phased out in the near future. In the past, chlorophenols and their derivatives have been used to preserve hides, textiles, paints, glues, and other materials, as disinfectants, and as biocides in fluids that aid in the cutting of metals.

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Chlorophenols with one or two chlorines (chlorophenol and dichlorophenol) have rarely been found to be contaminated with dioxins or furans. Chlorophenols with three or more chlorines have been found to be contaminated with many congeners of dioxins and furans, and 2,4,5-trichlorophenol is always contaminated with 2,3,7,8-TCDD (pers. comm., Rolf Hartung, University of Michigan). Chlorophenols with four or fewer chlorines are no longer produced in the U.S. (pers. comm., John Wilkinson, Vulcan Chemicals). There is only one current manufacturer of pentachlorophenol in the U.S., and pentachlorophenol and a product made from pentachlorophenol, sodium pentachlorophenate, are used almost entirely to preserve wood or prevent wood staining (USEPA, 1986: pp 3.17-21; USEPA, 1988a: pp 53286-7).

Pentachlorophenol has been commercially produced by two basic methods: the hydrolysis of hexachlorobenzene or the direct chlorination of phenol (Esposito et al, 1980: pp 78-88). Although both methods result in the formation of dioxins and furans, the hydrolysis of hexachlorobenzene can result in higher levels of dioxins and furans that are of most concern. In the U.S., pentachlorophenol has always been produced by the direct chlorination of phenol (Esposito et al, 1980: pp 78-88).

The USEPA has reported that solutions of U.S.-produced pentachlorophenol in use at wood-preserving facilities average approximately 300 ppb total dioxins and furans, in 2,3,7,8-TCDD equivalents (USEPA, 1988a: p 53301). 2,3,7,8-substituted hexa-CDDs are responsible for most of this calculated toxicity, and in the past were thought to be responsible for pentachlorophenol's demonstrated toxicity. However, the results of a recent bioassay (NTP, 1988) showed that pentachlorophenol alone is a carcinogen in mice, and the presence of 10 ppm hexa-CDDs in the pentachlorophenol made little or no difference. 2,3,7,8-substituted dioxins and furans with fewer than six chlorines are present in pentachlorophenol only at very low detectable levels or below the limits of detection. Tetra-dioxins, including 2,3,7,8-TCDD, have not been detected in numerous analyses of U.S.-produced pentachlorophenol (pers. comm., P.E. des Rosiers, USEPA).

A recent and particularly sensitive analysis of 10-year old pentachlorophenols and sodium pentachlorophenates, manufactured in Europe by the hydrolysis of hexachlorobenzene,

found very low ppb and ppt levels of 2,3,7,8-substituted tetra- and penta- dioxins and furans, in addition to 2,3,7,8-substituted dioxins and furans with six or more chlorines (Hagenmaier and Brunner, 1987). However, the low levels would have little impact on the estimated overall toxicity of the products; it would not differ significantly from that of U.S.-produced pentachlorophenols.

Hagenmaier and Brunner (1987) postulated that, in West Germany, the production and use of pentachlorophenol and sodium pentachlorophenolate may be, or have been in the past, the predominant source of dioxins and furans in their environment. The USEPA considers the wastes from wood-treatment facilities and sawmills to be sources of significant environmental contamination, and for that reason has regulated or proposed to regulate such wastes as hazardous (see "What Has Been Done About Dioxins and Furans?", page 69). It should be pointed out that alternative wood preservatives (creosotes and inorganic arsenicals) are considered human carcinogens (USEPA, 1988a), and a study by Carnegie-Mellon University concluded that pentachlorophenols are the safest wood preservatives available (Carnegie-Mellon University, 1982).

Chlorophenols, especially 2,4,5-trichlorophenol, were probably sources of large quantities of 2,3,7,8-substituted dioxins and furans in the past (Tosine, 1983; Hutzinger, 1985), and many contaminated sites remain from this era. However, levels of chlorophenol production and contamination have been greatly reduced. Based on a total annual production of pentachlorophenol in North America of 11 million kg (USEPA, 1988a), and an average 2,3,7,8-TCDD- equivalent content of 300 ppb, this production would be the source of 3.3 kg of 2,3,7,8-TCDD equivalents annually in North America. Most of this amount is present in used pentachlorophenol, and is incinerated as a hazardous waste.

Polychlorinated benzenes

Polychlorinated benzenes have been used as biocides, solvents, and in electrical and chemical industries. They were often mixed with PCBs in dielectric fluids. Dioxins and furans have been found in some chlorobenzenes at ppb and ppm levels, although no information is available on the specific types (reviewed in Heindl and Hutzinger, 1986).

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Diphenyl ether herbicides

Diphenyl ether herbicides can be derived from trichlorophenol and a variety of dioxins and furans were found in three types of diphenyl ether herbicides in one study (Yamagishi et al., 1981, cited in Rappe, 1984; p 83a). Total concentration of dioxins and furans ranged from less than 2 ppm to about 50 ppm. No 2,3,7,8-TCDD was found and the few individual congeners that were identified are not considered very toxic.

Hexachlorocyclohexane

Hexachlorocyclohexane is used primarily to produce the insecticide Lindane. Dioxins and furans are apparently formed by this process, and the waste has been found to be contaminated with ppm levels of dioxins and furans, including ppb levels of 2,3,7,8-substituted congeners (Scholz and Engler, 1987). The significance of this source is not known.

Paper mills and products

Pulp and paper mills that use a chlorine bleaching process have been identified as sources of dioxins and furans. Dioxins and furans are believed to be formed when naturally occurring phenolic compounds in wood called lignins react with chlorine during the bleaching operations in the manufacture of pulp (Beck et al., 1988). A preliminary study by the USEPA and the pulp and paper industry of five pulp and paper mills that use a chlorine bleaching process, found that the wastewater effluent from these mills had concentrations of less than 1 ppt total dioxins and furans, and the sludge had concentrations of less than 1 ppb total dioxins and furans (Amendola et al., 1987).

Because of the large volume of effluents from pulp and paper mills and the potential for the accumulation of dioxins and furans in organisms, even these low levels may pose significant risks to organisms exposed to the effluents. As noted earlier in this report, low levels of 2,3,7,8-TCDD were found in fish downstream from some pulp and paper mills and these findings are of concern to people who eat fish from these waters. The USEPA and the pulp and paper industry have a more extensive study underway.

Researchers in Sweden determined that the isomeric pattern of dioxins and furans from pulp plants is easily distinguishable from that of dioxins and furans from incinerators (Swanson

et al, 1988). They found that crabs and sediments near the pulp mill had dioxins and furans with an isomeric pattern similar to that in pulp, which then changed to the incinerator pattern as they moved away from the mill. The authors estimated that the pulp industry in Sweden was a source of 5-15 grams of 2,3,7,8-TCDD equivalents per year, and reported that the Swedish EPA estimates 1 kg of 2,3,7,8-TCDD equivalents per year for all sources of dioxins and furans in Sweden.

A study of West German paper products such as newsprint, coffee filters, and recycled paper found that they can contain a variety of forms of dioxins and furans. Total concentrations of dioxins and furans were below 1 ppb with concentrations of the more toxic congeners at levels below 50 ppt (Beck et al., 1988). A study sponsored by the National Council of the Paper Industry for Air and Stream Improvement (NCAST) determined that contact with paper products poses an insignificant health risk to humans (NCASI, 1987a). However, studies by researchers in Canada suggest that cardboard cartons made of bleached pulp can transmit dioxins and furans to certain food products, such as milk (Ryan et al, 1988). Any such assessments include a large number of uncertainties, and further research is necessary.

What products can produce dioxins and furans when they are burned?

Dioxins and furans can be formed when many materials containing some form of chlorine are burned, or when certain materials are burned in the presence of chlorine. The amount and kind of dioxins and furans produced varies greatly with the source and conditions.

The following chlorinated products can all produce dioxins and/or furans when burned.

Table 3. Chlorinated products that can produce dioxins and/or furans when burned

Product	Contaminants
PCBs	Furans
polybrominated biphenyls (PBBs)	Dioxins and Furans
polybrominated diphenyl ethers (PBDEs)	"
polychlorinated diphenyl ethers (PCDEs)	"
chlorophenols	"
tetrachloroethylene	"
polychlorinated benzenes	"
polyvinyl chloride (PVC)	"
Leaded gasolines	"

Note: When a material is burned in the laboratory to determine whether it is capable of producing dioxins and furans, it is typically burned under those conditions most likely to produce dioxins and furans, or that produce the largest quantity of dioxins and furans. Therefore, the same substance may produce much smaller amounts of dioxins and furans under the uncontrolled conditions of a fire, or in the highly controlled conditions of an incinerator.

PCBs

PCBs are fire-resistant compounds and do not readily support combustion. However, if they are incompletely burned in fires fueled by other materials, furans may be formed. More than 1 ppm of each of the most toxic congeners of furans (4-7 chlorines and 2,3,7,8 positions filled) have been produced by burning PCBs in the laboratory (Erickson et al., 1984; Swanson et al., 1985). Fires involving electrical equipment have contaminated buildings and other places with soot containing as much as 5000 parts per million total furans, including low ppm levels of 2,3,7,8-TCDF (Erickson et al., 1984; Rappe et al., 1983; p 121). In the U.S., PCBs are no longer produced or used in new equipment, and PCB-containing equipment in buildings is subject to strict regulation. However, large numbers of transformers and capacitors with PCB-contaminated dielectric fluids are still in use, and these contaminated dielectric fluids can produce furans when they are burned (Narang et al., 1988).

Polybrominated biphenyls (PBBs) and polybrominated diphenyl ethers (PBDEs)

Polybrominated biphenyls (PBBs) and polybrominated diphenyl ethers (PBDEs) have been widely used as flame retardants in textiles, carpets, and plastics. Although the addition of these substances makes products such as clothing and carpets less susceptible to igniting, the materials can burn in a building fire or incinerator. When burned in the laboratory, they have

produced brominated dioxins and furans, and smaller amounts of chlorinated dioxins and furans if they are burned in the presence of some form of chlorine (Buser, 1986; 1987; Thomas et al., 1987).

Polychlorinated diphenyl ethers (PCDEs)

Polychlorinated diphenyl ethers (PCDEs) are used as herbicides and have been found as low-level contaminants in chlorophenols (Soikkeli et al., 1986). When burned in the laboratory, they can produce significant amounts of dioxins and furans (Rappe, 1984: p 83a).

Chlorophenols

When burned, chlorophenols can produce significant amounts of dioxins and furans, especially those with from 4-6 chlorines, and including the toxic 2,3,7,8 congeners (Rappe et al., 1978; Rappe et al., 1983: p 108). An unknown amount of chlorophenol-treated wood is eventually burned, and may be a widespread source of significant amounts of dioxins and furans. Current USEPA registration for pentachlorophenol used in wood treatment specifies that the wood is not to be burned, although wood-treatment facilities may burn wood scrap in high-temperature boilers.

One study found that levels of octa-CDD were doubled when PCP-treated plywood was burned, and dioxins with six and seven chlorines were also detected (Crosby et al., 1973). Wood-treatment facilities often collect waste pentachlorophenol in ponds, and in the past they periodically set fire to the ponds to reduce their volume. This practice generated large amounts of dioxins and furans (P.E. des Rosiers, USEPA, cited in USEPA, 1986: p 3-18).

Tetrachloroethylene and polychlorinated benzenes

Tetrachloroethylene and polychlorinated benzenes are used as cooling fluids in electrical equipment, often in combination with PCBs. When burned in the laboratory, they can produce furans and lesser amounts of dioxins, including the most toxic congeners (Erickson et al., 1984). Polychlorinated benzenes produced less than 1/10th the amount of furans produced by PCBs, and tetrachloroethylene produced less than 1/1000th. However, these are significant amounts nonetheless. For example, polychlorinated benzenes are believed to be responsible for the dioxin contamination of an office building in Binghamton, New York, after a transformer fire.

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The soot produced by this fire had 20 ppb total dioxins, including 0.6 ppb 2,3,7,8-TCDD (Rappe et al., 1983: p 121).

Polyvinyl chloride (PVC)

Polyvinyl chloride (PVC) is a common plastic. When burned in the laboratory, it can produce low ppb levels of dioxins and furans (Marklund et al., 1986: p 90). Large amounts of PVC plastic are present in municipal waste, and are suspected of contributing to the dioxins and furans emitted from incinerators.

Leaded gasoline

Low levels of dioxins and furans have been detected in motor oil and in the exhaust of cars that use leaded gasoline (Marklund et al., 1987), but not cars that use unleaded gasoline. The authors noted that dioxins and furans may be destroyed in the catalytic converters of the cars burning unleaded gasoline. Dioxins have been found in mufflers from diesel trucks (Bumb et al., 1980), and dioxins and furans have been found in motor oils that are recycled from used motor and other oils (Rotard et al., 1987). Dichloro and dibromo ethane (DCE and DBE) are used as additives in leaded gasolines, and are thought to be the precursors to dioxins and furans.

Leaded gasoline is a very widely used product, and therefore even the low levels formed are potentially important. It was estimated that autos burning leaded gasoline in Sweden produce emissions with a total of 10-100 grams of 2,3,7,8-TCDD equivalents per year (Marklund et al., 1987). Using their emission values (30-540 picograms of 2,3,7,8-TCDD equivalents/kilometer) and assuming their test autos averaged 20 miles (32 kilometers) per gallon of gasoline (the models were a Saab 900, a VW Golf, an Opel Kadett, and a Volvo 245), total emissions from U.S. autos can be estimated. Based on an average figure of approximately 57 million gallons of leaded gas used per day in 1988 in the U.S. (pers. comm., American Petroleum Institute), and the values above, autos burning leaded gasoline in the U.S. may produce emissions with from (57 million gallons/day x 365 days x 32 kilometers/gallon x 30 picograms/kilometer) to (57 million gallons/day x 365 days x 32 kilometer/gallon x 540 picograms/kilometer), or 20 to 360 grams of 2,3,7,8-TCDD equivalents per year. The use of

leaded gasoline is steadily decreasing in the U.S. and much of Europe, thus reducing the contribution from this source.

The burning of dioxins and furans

The incineration of dioxins and furans in the laboratory has produced other dioxins and furans with fewer chlorines. For instance, incineration of octa-CDD or octa-CDF can produce dioxins or furans with from four to seven chlorines (Marklund et al., 1986; Swanson et al., 1986). This is a potentially significant process because the toxicity of dioxins and furans generally increases as the number of chlorines decreases from eight to four. Also, octa-CDD and octa-CDF are often the most numerous types of dioxin or furan in contaminated products or waste.

Does the burning of paper, wood, peat, or coal produce dioxins and furans?

Several studies have shown that wood, peat, and coal can produce dioxins and furans when they are burned. Apparently, naturally occurring phenolic compounds in these substances (lignins) can react with naturally present chlorine to form chlorinated phenols, which then form dioxins and furans (Beck et al., 1988). Measurements of dioxin and furan emissions from coal- and peat-fired power plants indicate that they emit only very small amounts of dioxins and furans, perhaps in part because the combustion conditions are carefully controlled for high efficiency (Kimble and Gross, 1980; Marklund et al., 1986; USEPA, 1987a: pp 4.1-26). Likewise, the combustion of paper has been found to produce only very small amounts of dioxins and furans (Olie et al., 1982; USEPA, 1987a: pp 4.1-26).

The combustion of wood, on the other hand, is a potentially significant source of dioxins and furans. Dioxins and furans, including the most toxic congeners, have been detected in small amounts in emissions from wood stoves and wood boilers (Nestrick and Lamparski, 1983; USEPA, 1987a: pp 4.1-26; Thoma, 1988). Because of the large number of wood combustion sources in the U.S., this could be a significant source. However, analyses of lake sediments from an island in Lake Superior did not find dioxins and furans in sediment layers

from before 1940, when wood combustion was prevalent in North America (Czuczwa and Hites, 1986).

Wood that has been treated with pentachlorophenol or sodium pentachlorophenate would be especially likely to emit dioxins and furans when burned. However, the major use of pentachlorophenol is for the treatment of utility poles, and few if any are burned in wood stoves.

Do municipal incinerators produce dioxins and furans?

Municipal solid-waste incinerators are recognized as important sources of dioxins and furans. They are found on the dust and in the gas emitted through the stack; on the fly ash and bottom ash that is collected and placed in landfills; and in the scrubber water that is part of the emission control system (Marklund et al., 1986; USEPA, 1987a: pp 4.1-26; Hiroaka et al., 1987). While municipal incinerators have been found to produce all types of dioxins and furans (Karasek and Hutzinger, 1986), the amounts and distribution of the different dioxins and furans produced by municipal incinerators vary widely and therefore so do estimates of the amounts of dioxins and furans produced in total by municipal solid-waste incineration. Incinerators operated under the proper conditions and equipped with the most modern emission control devices have greatly reduced dioxin and furan emissions (Hay et al., 1987; USEPA, 1988b).

Rappe et al. (1987a: p 1604) estimates that a normal-sized municipal solid waste incinerator (which burns 50,000-200,000 tons of garbage per year), operating under normal conditions, emits through the stack 1-100 grams of 2,3,7,8-TCDD equivalents per year (based on a range of 1-100 nanograms of 2,3,7,8-TCDD equivalents per cubic meter of stack effluent). This figure can thus be interpreted as 5 millionths ($1/200,000$) to 2 thousandths ($100/50,000$) of a gram of 2,3,7,8-TCDD equivalent emitted through the stack per ton of garbage burned. According to a recent USEPA report (USEPA, 1988b), 16.5 million tons of garbage are incinerated in the U.S. each year. Using Rappe's range as given above, municipal incinerators in the U.S. may be the source of from $(5 \times 10^{-6} \text{ grams/ton} \times 16.5 \times 10^6 \text{ tons})$ to $(2 \times 10^3$

grams/ton $\times 16.5 \times 10^6$ tons), or from 0.0825 to 33 kg of 2,3,7,8-TCDD equivalents per year, distributed in their stack effluents. This estimate does not take into account the dioxins and furans in the bottom ash, fly ash, and scrubber water, the majority of which are placed in landfills. In Canada, dioxin and furan emissions from municipal incinerators has been estimated to be 6.3 kg/year TCDD equivalent in the fly ash, and 6.1 kg/year TCDD equivalents in the stack emissions (Tosine, 1983).

A study in Switzerland showed that levels of dioxins and furans in cow milk were higher in samples collected near incinerators (Rappe et al., 1987b). However, in another study (Rappe et al., 1987c), the authors mention that while Sweden has 25-30 incinerators and Yugoslavia has none, similar levels of dioxins and furans are found in human milk from these countries. Apparently, incinerators are only one of many sources that contribute dioxins and furans to the environment in these countries.

Do other large combustion sources produce dioxins and furans?

There are other potentially large combustion sources of dioxins and furans. Hazardous and hospital waste incinerators, sewage sludge incinerators, and smelters and mills that recycle metals can all produce significant amounts of dioxins and furans, including the more toxic types (USEPA, 1987a: pp 4.1-26; Clement et al., 1987; Marklund et al., 1986). The dioxin and furan emissions from other large combustion sources have not been as well studied as those from municipal incinerators. The available data indicate that the emissions from a hazardous waste or sewage sludge incinerator are of the same magnitude as a municipal incinerator (USEPA, 1987a: pp 4.1-4.25; Tsuji et al., 1987; Clement et al., 1987). Because there are many more large industrial combustion sources than municipal incinerators, their total emissions of dioxins and furans could be greater than from municipal incinerators (Rappe, 1987).

What about dioxins and furans from sewage plants, waste streams, and landfills?

Dioxins and furans have been found in sewage sludge from municipal waste-water treatment plants in Germany, in levels below 100 ppb (Hagenmaier et al., 1986). The toxic varieties of dioxins and furans were present at levels below 1 ppb. Based on an analysis of the ratios of the various congeners of dioxins and furans present, the authors proposed that pentachlorophenol and its derivatives are the source of most of the dioxins and furans in the sludge.

In addition to the products themselves, the waste generated by the production of chlorophenol-based products is a potentially important source of dioxins and furans. Ironically, the contamination of the wastes is thought to have increased significantly as a result of efforts to reduce the contamination of the products: the dioxins and furans were concentrated further in the wastes. Landfills that contain the wastes from the manufacture of chlorophenols and chlorophenol-based products, that contain PCBs, or that contain fly ash, are suspected sources of dioxins and furans. The Love Canal and associated chemical landfills in New York, for example, have contaminated the adjacent Niagara River with dioxins, and the Vertac manufacturing and waste-disposal site in Jacksonville, Arkansas, has contaminated the nearby Bayou Meto and Arkansas River. Also, sites where chlorophenols and chlorophenol-based products were manufactured or processed are now considered sources of dioxins and furans (USEPA, 1987a: pp 3.1-26). As a result of these incidents, wastes containing dioxins and furans have been disposed of much more carefully.

Are there other processes that create dioxins and furans?

It has been shown that dioxins and furans can be broken down by sunlight (this is called photolysis) to other types of dioxins and furans with fewer chlorines. For example, the octachlorodioxin (OCDD), when exposed to UV light, can be broken down to potentially more toxic dioxins with fewer numbers of chlorines (Crosby et al., 1971). Combustion processes

often produce greater amounts of octa-CDD than all other dioxins combined, and it is often the most common dioxin in chlorophenols. However, the photolysis would then be expected to continue, eventually breaking down any toxic varieties into much less toxic forms.

Photolysis can also form dioxins and furans from other compounds. It has been shown that a mixture of polychlorinated benzenes and phenol, when exposed to UV light, can produce furans (Choudhary et al., 1983). Both polychlorinated benzenes and phenols are common environmental contaminants. Also, the photolysis of chlorophenols has been shown to produce octa-CDD (USEPA, 1985: p 4.17). Thus, wood and other materials preserved with chlorophenols and exposed to sunlight may result in the formation of dioxins. The significance of these photochemical processes is not yet known.

Conclusions on sources of dioxins and furans

There are many sources of dioxins and furans. Some of them, such as sources of combustion, are widespread and numerous. Others, such as contaminated manufacturing and waste sites, are fewer in number and usually local problems. The significance of the photochemical processes that can convert less toxic compounds to dioxins and furans is not yet known. Also, the relative importance of what appears to be the two major sources of dioxins and furans (chlorophenols and chlorophenol-based products, and sources of combustion) is not yet known.

It is generally agreed that dioxins and furans in our environment come primarily from recent human activities (chemical production and use, incineration, automobiles). Czuczwa and Hites (1985) analyzed sediment cores from the Great Lakes and a Lake in Switzerland. Dioxins and furans in these sediments were at or below the limit of detection until they reached the layers deposited after approximately 1940, a time that they say corresponds to the beginning of large-scale manufacture and disposal (often by incineration) of chlorinated aromatic compounds. Also, levels of dioxins and furans in human fatty tissue and breast milk from North Vietnam are the lowest yet measured while levels in South Vietnam are similar to the U.S., Japan, and

Europe (Schecter et al., 1986; Rappe et al., 1987: p 233). This indicates that modern industrial activity, not the burning of wood, is the primary source of dioxins and furans to the environment.

There is some evidence that the amount of dioxins and furans being released into the environment reached a peak in the mid-1970s and has declined since. The sediment cores analyzed by Cinczwa and Hites (1986) showed such a trend. An analysis of breast milk in Sweden also appeared to show this decline: the levels of dioxins and furans in combined samples of breast milk have dropped since the study was initiated in 1972 (Noren, 1988). However, studies of dioxins and furans in breast milk in Yugoslavia (1981 to 1987) and Japan (1978 to 1984) do not show changes over time (reviewed in Lindstrom, 1988: p 36).

The Health Effects of Dioxins and Furans, in Animals and Humans

What are the health effects on animals?

Some general features

Dioxins and furans have some very unusual features with respect to their toxicity to animals. Animals given fatal doses of dioxins and furans do not die immediately; several weeks elapse between the administration of the fatal dose and the death of the animal. Also, many of the acute (short-term) effects of less than fatal doses are temporary. When the animal stops receiving the substance, it recovers from most of the effects. The rate of recovery varies, and some animals have required more than six months to return to normal (USEPA, 1985: p 8.48).

The toxicity of dioxins and furans is highly variable. They produce a wide spectrum of effects, involving many different organs and body systems, and the affected areas usually vary with the species of animal. The toxicity of different dioxins and furans varies widely for a given species of animal, and the toxicity of a given dioxin or furan varies widely between different species of animals. See Tables 4 and 5 for acutely lethal (causes death quickly) doses of 2,3,7,8-TCDD for a variety of species. Finally, some individuals of a sensitive species (rats or mice, for example) do not die even when given doses as much as 100 times greater than the amount that is fatal to the other individuals in the same study.

Table 4. Acutely lethal single doses of 2,3,7,8-TCDD (LD50)
(from USEPA, 1985, Table 8.1)

Species	Gender	Dose micrograms per kg of body weight (ug/kg)
Guinea Pig	Male	0.6-2.1
Guinea Pig	Female	2.5-19
Rat	Male	22
Rat	Female	45
Monkey	Female	<70
Rabbit	Male	115
Rabbit	Female	115
Mouse	Male	114-285
Mouse	Female	>450
Hamster	Male	1157-5051

Note: The lethal values above represent doses that caused the death of 50 percent of the test animals. Such a value is known as an LD50, and is a standard endpoint in a toxicity test. For aquatic animals, different concentrations of the substance in water are used, instead of a dose. The concentration that causes death of 50 percent of the test animals is called the LC50 (see table below). There are also studies that use different endpoints, such as LD95 or LC95, where 95 percent of the test animals die.

Table 5. Lethal exposures to 2,3,7,8-TCDD in water (LC50)
(reviewed in Kieraga and Norris, 1983)

Species	Concentration in Water (ug/liter)	Duration (days)
Channel Catfish	0.0042 (4.2 ppt)	15
Coho Salmon	0.0056 (5.6 ppt)	1-3
Guppy	0.1-10 (ppb)	5

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Generally speaking, all toxic members of the dioxin and furan families produce similar effects in a given species of animal, and several effects are common to all mammals that receive a lethal dose of these compounds. Although most studies of the effects of dioxins and furans on laboratory animals have been done using 2,3,7,8-TCDD, these studies can be used to predict the toxic effects of other dioxins and furans. The chief difference is that a greater dose of other dioxins or furans is necessary to produce the same effects. Many dioxins and furans are so much less toxic than 2,3,7,8-TCDD that an experiment would require an impracticably large dose to produce lethal effects.

Doses that produce no observable adverse health effects

Long-term studies of mice and rats have shown that there are doses of 2,3,7,8-TCDD that produce no observed effects on the animals, even after receiving the substance for two years. The USEPA estimates the No Observed Adverse Effects Level (NOAEL) for toxic effects other than cancer to be approximately 0.001 ug/kg/day for both mice and rats. They also cited a need for long-term studies using lower doses (USEPA, 1985: p 14.10); some researchers feel that this dose can produce adverse reproductive effects (USEPA, 1985: p 14.10), and is therefore a Lowest Observed Adverse Effect Level (LOAEL). See Tables 6, 7, and 8 for NOAELs and LOAELs for other species. Also, the toxicity of 2,3,7,8-TCDD is at least partially cumulative; a smaller dose than the acutely lethal dose can cause lethal effects if the smaller dose is given for a longer period of time (McConnell, 1980: pp 110-111).

Table 6. Lowest dose with an observed adverse effect (LOAEL)
(from USEPA, 1985, Tables 8-4, 8-5)

Species	Dose	Duration	Effects
Rat	0.01 ug/kg/day	2 years	Liver damage
Mouse	0.001 ug/kg/day	1 year	Several
Guinea Pig	0.006 ug/kg/day	8 weeks	Several

(For the studies above, the animals received 2,3,7,8-TCDD in their food or were force-fed 2,3,7,8-TCDD once per week in a medium such as corn oil.)

Table 7. Lowest concentration with observed adverse effect (LOAEL)

Species	Concentration in Water ug/liter (ppb)	Duration days	Effect
Northern Pike (eggs)*	0.0001 (0.1 ppt)	4	Lowered Survival
Rainbow Trout*	0.0001 (0.1 ppt)	4	Lowered Survival
Fathead Minnows**	0.0017 (1.7 ppt)	28	Lowered Survival

* (Helder, 1982)

** (W. Adams, et al., 1986)

Table 8. Highest concentration with no observed adverse effect (NOAEL)
(reviewed in Kenaga and Norris, 1983)

Species	Concentration in Water ug/liter (ppb)	Duration days
Coho Salmon	0.00056 (0.56 ppt)	4
Rainbow Trout	0.0001 (0.1 ppt)	4
Mosquito larvae (<i>Aedes aegypti</i>)	0.2	17
Daphnia (<i>Daphnia magna</i>)	1.33	32
Alga (<i>Oedogonium cardiacum</i>)	1.33	32

The short-term health effects on animals

All mammals given an acutely lethal dose of a dioxin or furan suffer from wasting (losing weight), and it is sometimes the only effect leading to death. The animals simply waste away. This occurs primarily because the animals do not eat enough food to maintain their weight. Apparently, the animals' internal weight "setting" is lowered below normal, and so the animals do not eat enough food. However, there is evidence that this reduction of nourishment is not entirely responsible for the weight loss. Researchers who force-fed the animals could prevent some of the weight loss, but not all, and the animals died anyway (Gasiewicz et al., 1980).

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The thymus is affected in all mammals exposed to a toxic dose, and the liver is affected in most mammals. The thymus, and to a lesser extent the spleen and lymph nodes, typically suffer damage and a reduction in size, while the liver typically suffers damage and an increase in size. In rodents, liver damage is suspected to be a principle cause of death. Skin disorders have occurred in rabbits, monkeys, cattle, and hairless mice. The effects include severe acne, thickening of the eyelid, and abnormal growth or loss of hair, fingernails, toenails, or hooves. Dioxins and furans have also affected the cardiovascular system, gastrointestinal and urinary tracts, spleen, bone marrow, and gallbladder of animals.

For reviews of the above health effects, see Gupta et al., 1973; Poland and Knutson, 1982; USEPA, 1985.

Cancers

2,3,7,8-TCDD is a carcinogen in mice and rats, when fed to the animal or applied to the skin. Two-year studies at Dow Chemical Corporation (Kociba et al., 1978) and at the National Cancer Institute (NTP, 1980a; 1980b) found increased cancers of several types, resulting from chronic (long-term) doses as low as 0.01 ug/kg/day. Rats fed this dose for two years had, at the end of the Dow study, 1700 ppt 2,3,7,8-TCDD in their fat. The rats fed this dose also suffered increased mortality, decreased weight gain, and increased excretion of porphyrins (a pigment produced by the liver which indicates liver damage). Rats fed 0.001 ug/kg/day suffered no health effects of consequence, and had 340 ppt 2,3,7,8-TCDD in their body fat at the end of the study.

Long-term studies have also been conducted using a mixture of two hexa-CDDs, both containing chlorine atoms in the 2,3,7, and 8 positions (NTP, 1980c; 1980d). The mixture caused liver tumors in both mice and rats when administered orally in doses of 2.5-5.0 ug/kg/week (for female rats), 5.0 ug/kg/week (for male mice and rats), and 10.0 ug/kg/week (for female mice), but not at lower doses. The mixture was not carcinogenic when 0.1 ug was applied to the skin three times per week.

Many researchers have concluded that 2,3,7,8-TCDD is a promoting, rather than an initiating, carcinogen. A promoter provides a favorable environment for tumor growth, while an

initiator produces a change in DNA that causes tumorous growth. Tumor promotion is reversible and is not inherited, while tumor initiation is not reversible and is passed on through cell division (Paustenbach et al, 1986). Pitot et al (1980) used diethylnitrosamine to initiate tumors in mice, and found that 2,3,7,8-TCDD promoted the growth of the initiated tumors. Also, Kouri et al (1978) used 3-methyl-cholanthrene to initiate subcutaneous tumors in mice, and found that 2,3,7,8-TCDD promoted the growth of these tumors.

Reproductive effects

Dioxins and furans appear to be especially toxic to embryos and fetuses, and the reproductive system of adult animals appears to be especially sensitive as well. Mice and rats have produced litters with abnormally high rates of birth defects such as cleft palates, extra ribs, and deformed livers and kidneys, after receiving doses of 2,3,7,8-TCDD as low as 0.01 ug/kg/day, or a single dose of 1 ug/kg (reviewed in USEPA, 1985: pp 9.1-23). Reproductive effects such as smaller litters, lower birth weights, and premature abortions have been reported in monkeys and ferrets, as well as in rats and mice, that were administered 2,3,7,8-TCDD. When 2,3,7,8-TCDD was fed continuously to three generations of laboratory rats, reproduction was impaired by a dose of 0.01 ug/kg/day, but not 0.001 ug/kg/day (reviewed in USEPA, 1985: p D.1). Female Rhesus monkeys suffered reduced fertility after being fed 0.0015 ug/kg/day 2,3,7,8-TCDD (reviewed in USEPA, 1985: p D.1).

These effects have only been observed when the embryo or mother was exposed to 2,3,7,8-TCDD, and appear to be the result of direct exposure or transfer of the toxin from mother to embryo across the placenta. Birth defects have not been associated with exposure only to the father, nor has reproduction been reduced when only the father was exposed to 2,3,7,8-TCDD (reviewed in Kamrin and Matsumura, 1985; reviewed in Silbergeld and Marison, 1987: p 137). However, 2,3,7,8-TCDD can reduce the weight of testes, lower levels of testosterone, and impair the development of sperm, in rodents, monkeys, and chickens (reviewed in Poland and Kautson, 1982: p 524).

Mutagenic effects

An important question about any toxic substance is whether it causes changes in the DNA of exposed organisms, because such changes can then cause cellular mutations. Such a substance is called a mutagen. A small number of early studies found 2,3,7,8-TCDD to be a weak mutagen, while many subsequent studies have detected no evidence of mutagenicity. Most researchers have concluded that 2,3,7,8-TCDD is not a mutagen (reviewed in Hay, 1984; reviewed in Poland and Knutson, 1982: p 525).

Immune effects

2,3,7,8-TCDD has been shown to inhibit the immune system of mice, rats, and guinea pigs, at doses much below the fatal level. The thymus, spleen, and bone marrow have all been shown to suffer loss of tissue, and the enzyme immune system and cell immune system which normally react to a potentially toxic substance are inhibited (reviewed in Poland and Knutson, 1982; p 522; reviewed in USEPA, 1985: pp 8.85-86). Similar responses have been observed with 2,3,7,8-TCDF, at doses thirty times higher than for 2,3,7,8-TCDD. The effects of the 2,3,7,8-TCDF disappeared six weeks after dosing ended (Vecchi et al., 1983).

Effects on blood constituents

2,3,7,8-TCDD and 2,3,7,8-TCDF have been shown to affect a variety of constituents in the blood of test animals. 2,3,7,8-TCDD has been shown to reduce the number of red and white blood cells (Kociba et al., 1978), change the level of blood lipids such as triglycerides and esters, and change the levels of thyroid hormones such as thyroxine and thyrotropin (reviewed in Poland and Knutson, 1982: pp 526-529). Blood levels of progesterone and estrogen decreased in Rhesus monkeys fed 2,3,7,8-TCDD, and blood levels of testosterone decreased in rats (reviewed in Peterson et al., 1984). 2,3,7,8-TCDF has been shown to increase the level of serum globulin in mice, and decrease serum cholesterol and serum albumin in monkeys (Moore et al., 1979).

Are dioxins and furans hazardous to organisms in the environment?

Very little is known about the impact of dioxins and furans on organisms in the environment, especially at low levels. Many animals died after being exposed to relatively high levels of dioxins and furans, as a result of the accidental contamination of areas surrounding Seveso, Italy, and Times Beach, Missouri (reviewed in Reggiani, 1980: pp 318, 325). It was reported that six months after the Seveso accident, normal populations of wild and domestic animals were present in the contaminated area, and appeared to be in good health (Homberger et al., 1983, cited in OME, 1985: p 3.92). Fourteen rabbits from the zone of highest contamination were collected, sacrificed, and examined, three months after the accident. All had more than 300 ppb 2,3,7,8-TCDD in their livers, and 5 showed evidence of liver damage. Blood constituents were normal in all 14 rabbits, and no other health problems were observed (Abbruzzi et al., 1977, cited in OME, 1985: p 3.92).

2,3,7,8-TCDD is also suspected of causing reproductive failure in fish-eating birds of Lake Erie and Lake Ontario (Gilbertson and Fox, 1983). The reproductive failure was primarily the result of unusually high embryo and chick mortality. A study of several gull colonies found that the embryos and chicks were suffering from chick edema disease and hepatic porphyria, which are both indicators of poisoning by dioxins, furans, and related compounds such as PCBs. Relatively high levels of 2,3,7,8-TCDD were later detected in gulls from Lakes Ontario and Erie (Norstrom et al., 1982). Other contaminants such as PCBs, DDT, and hexachlorobenzene were also detected in relatively high levels in these birds, and may have been responsible for these health effects.

Several environmental studies of organisms exposed to 2,3,7,8-TCDD and other dioxins and furans have found little or no health effects. A 15-year study of beachmice at a highly contaminated site in Florida (Young et al., 1987) found that the 1 ppb levels of 2,3,7,8-TCDD in the soil had no observable effect on the birthrate of the mice, and enlarged livers was the only observed effect. Also, NCASI sponsored a five-month study of plants and animals exposed to dioxins and furans from paper sludge spread on a pine plantation (NCASI, 1987b). The 10

ppt 2,3,7,8-TCDD and 100 ppt 2,3,7,8-TCDF in soil had no observable effects on the health and reproduction of the organisms studied. More studies of the environmental effects of dioxins and furans are needed.

What are the pharmacokinetics of dioxins and furans?

In order to understand why many dioxins and furans accumulate and persist in animals and humans exposed to them, why the processes vary with the type of dioxin or furan, and how these characteristics relate to the varying toxicity of dioxins and furans, it is helpful to know something about the pharmacokinetics of dioxins and furans (their absorption, distribution, metabolism, accumulation, and elimination, in animals and humans).

Dioxins and furans are intermediate in their affinity for fat (this is known as lipid-solubility). They are soluble enough to be readily absorbed through the walls of the digestive tract, but not so lipid-soluble that, once absorbed, they are found only in the adipose (fatty) tissues of the body. They are also found in the liver and in other organs. Adipose tissue is the body's storage depot, and substances there are "in limbo". They are not interacting with the mechanisms that cause effects (toxic or otherwise), nor with the mechanisms that metabolize the substances. Therefore, the intermediate lipid-solubility of dioxins and furans makes it possible for them to persist in the body and be available to the mechanisms that cause toxic effects (Matthews and Birnbaum, 1983).

Studies with rodents show that 2,3,7,8-TCDD is absorbed primarily through the gastrointestinal tract, and to a much lesser extent through the skin and lungs. When 2,3,7,8-TCDD was administered orally in food or in corn oil, from 30-90% of the amount was then absorbed through the gastrointestinal tract (reviewed in USEPA, 1985: p 7.2). When applied to the skin in a solvent such as methanol, from 1-10% was absorbed. The absorbed 2,3,7,8-TCDD is distributed rapidly to many parts of the body, but the major sites of storage are almost entirely the liver and the fatty tissues (reviewed in Gasiewicz et al., 1983). The sites of storage vary somewhat with the species. 2,3,7,8-TCDD is stored in its original form, not as a changed

product of metabolism. Apparently, metabolites are excreted once they are formed. It appears that the absorption of dioxins and furans decreases as the number of chlorines increases (reviewed in Mathews and Birnbaum, 1983).

The metabolism of 2,3,7,8-TCDD has been studied primarily in rodents. Metabolism is affected by the number and position of chlorine atoms (reviewed in Mathews and Birnbaum, 1983). The critical factor for metabolism is the presence of two adjacent unsubstituted carbon atoms (not attached to a chlorine or other atom). When chlorines fill the 2,3,7, and 8 positions, no adjacent unsubstituted carbon atoms are left on the dioxin or furan molecule, and very little metabolism takes place. A year after people in Japan ingested a number of different types of furans that were accidentally present in rice oil (known as the "Yusho" incident), no furans with adjacent unsubstituted carbon atoms remained in their tissues. Apparently, these types had been metabolized and excreted (Rappe et al., 1979, cited in Mathews and Birnbaum, 1983). Furans with the 2,3,7, and 8 positions filled were still present in the tissues. In the general population, the only dioxins and furans found in people are those that are 2,3,7,8-substituted (Ryan, 1986).

The accumulation of dioxins and furans is the product of absorption and metabolism, and varies with the type of dioxin or furan. For instance, studies with carp and rodents have shown that they preferentially absorb those types with the 2,3,7, and 8 positions filled, and they absorb a greater proportion of the available dioxin or furan as the number of chlorines decreases (Kuehl et al., 1986; 1987a; 1987b; Opperhuizen et al., 1986; van den Berg et al., 1986). Although relatively small amounts of hepta- and octa-CDDs/CDFs are absorbed, these smaller amounts accumulate and persist in the body for longer periods of time.

2,3,7,8-TCDD has been eliminated slowly from the bodies of exposed animals; the half-life varies from 10 days to approximately one year, depending on the species. In humans, 2,3,7,8-TCDD appears to be eliminated quite slowly. Based on the rate of disappearance of one billionth of a gram of self-ingested 2,3,7,8-TCDD, Folger and Schlatter (1986) estimate a half-life of about six years. They also found that the dioxin was distributed quickly in the blood and stored almost entirely in the fatty tissues. A half-life of about seven years was

estimated by researchers from the CDC, based on measurements of 2,3,7,8-TCDD in the blood of Ranch Hand personnel (Pirkle et al., cited in CDC, 1988).

Recent work with pharmacokinetic models suggests that the half-life of 2,3,7,8-TCDD is inversely related to its concentration in human fatty tissue (Kissel and Robarge, 1988). They predict that the half-life is 4.4 years when 2,3,7,8-TCDD is present in fatty tissue at 100 ppt, but increases to 20 years as the tissue concentration approaches 10 ppt (a typical level in a person from an industrial country).

The rate of elimination of dioxins and furans increases as the number of chlorines decreases (reviewed in Mathews and Birnbaum, 1983; Kuehl et al., 1987b), and studies with rodents and fish have shown that furans are eliminated more quickly than their counterpart dioxins (van den Berg et al., 1983; Kuehl et al., 1987b). Apparently, 2,3,7,8-TCDD must be metabolized to different compounds in order to be excreted in the urine and bile (reviewed in Olson et al., 1983: p 97). However, unmetabolized 2,3,7,8-TCDD can be excreted in the feces (USEPA, 1985: p 7.20) and in breast milk (Moore et al., 1976; van den Berg et al., 1986). Studies of people exposed to furans in the Yusho incident showed that the furans were also stored in the fat tissue and in the liver, and were metabolized at a slightly faster rate than that found for 2,3,7,8-TCDD, above (reviewed in Reggiani, 1983: pp 59-61). It has also been shown that nursing women excrete both dioxins and furans in their breast milk, and there is some evidence that nursing can reduce the amounts of these compounds in the body (Noren, 1988; Ogaki et al., 1987, reviewed in Lindstrom, 1988: p 34).

In some cases, the toxicity of a dioxin or furan has been related to the rate of metabolism. For instance, the toxicity of 2,3,7,8-TCDF to different species was found to be inversely proportional to the rate of metabolism (reviewed in Mathews and Birnbaum, 1983). Also, a study of 2,8-di-CDD in goldfish found that, when the metabolism of this dioxin was prevented, it was 1/60th as toxic as 2,3,7,8-TCDD (Sijm and Opperhuizen, 1988). Normally, 2,8-di-CDD is metabolized too quickly to accumulate, and is almost nontoxic. Metabolism alone cannot explain the varying toxicities of dioxins and furans, however. For instance, rats metabolize 2,3,7,8-TCDD about three times faster than do guinea pigs, yet the LD50 for the rat

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is 3000 to 5000 times greater than that for the guinea pig (reviewed in Poland and Knutson, 1982: p 521). Also, octa-CDD is metabolized very slowly (Birnbaum and Couture, 1988), yet is very much less toxic than other dioxins and furans with chlorines in the 2,3,7,8 positions.

What are the effects of dioxins and furans on human health?

Our understanding of the effects of dioxins and furans on humans is not based on controlled studies such as were done with animals. Instead, it is based on studies of people who were inadvertently exposed to these substances, as a result of an accident, their occupation, or other circumstances. This presents two major difficulties: 1) we cannot control and often do not know the level of exposure (the dose); 2) people have almost never been exposed to these substances alone; the dioxins and furans have been mixed with other substances (PCBs, PBBs, chlorophenols, chlorophenol-based herbicides, and so on).

These other substances have been shown to cause some of the same health effects as dioxins and furans, but only when people have been exposed to much larger amounts. An important difference between the toxicity of dioxins and furans and these other substances is the comparatively small amounts of dioxins and furans that can cause serious health effects. In most cases, the level of exposure to the other substances has been too low to cause such effects.

The health effects of toxic substances can be divided into two major groups: 1) acute (short-term) effects, which occur soon after exposure and quickly subside; 2) chronic (long-term) effects, which can occur anytime during the life of the person and can be persistent. Our knowledge of the acute effects of dioxins and furans is based on studies of people who were exposed to relatively large amounts, usually as a result of an industrial accident. Our knowledge of the chronic effects of dioxins and furans is based on long-term studies of these same groups of people, or studies of people exposed to relatively small amounts for a long period of time. With these long-term studies, it is more difficult to remove the confounding effects of exposure to organic chemicals other than dioxins.

The short-term health effects on humans

Dioxins and furans have caused a host of reported acute effects on people who were exposed to relatively high levels. The reported clinical symptoms (directly observable or felt by the patient) include nausea and vomiting, headaches, irritation of the eyes, skin, and gastrointestinal tract, and a general feeling of not being well. Pain, especially in the limbs, has been reported as persisting for months, as has an enlarged and tender liver, and irritability and nervousness. There is no documented case of a person dying because of exposure to dioxins and furans.

In addition to the clinical symptoms, there are reported effects detectable by laboratory tests or study. They include liver damage, elevated levels of constituents of the blood such as triglycerides and lipids, and damage to the nerve fibers. Although most people recover quickly from the acute effects of dioxins and furans, there are reports that some of these effects have lasted for months or years. For reviews of the acute human health effects of dioxins and furans see USEPA (1985: pp 8.60-8.65); Hay (1982); Reggiani (1982).

The long-term health effects on humans

The most common chronic effect of exposure to dioxins and furans is severe and persistent acne, called chloracne, which can occur in many parts of the body. Excessive body hair and pigmentation, and elevated levels of blood constituents such as triglycerides, cholesterol, liver enzymes, and porphyrins have also been reported several years after the high exposure. Nerve disorders have been reported, including problems with or loss of some vision, hearing, taste, and smell. Also, general weakness and a loss of sexual drive has been reported to occur for some years after high exposure.

The reported symptoms and effects of exposure to dioxins and furans have been inconsistent, with the exception of chloracne. However, in most cases an enlarged and/or damaged liver and neuromuscular symptoms have also been reported. For reviews of the chronic human health effects of dioxins and furans, see USEPA (1985: pp 8.65-8.69); Hay (1982); Reggiani (1982).

Cancers

A few epidemiologic studies have found an association between cancers and occupational exposure to dioxins and furans. The studies that are generally considered to offer the best evidence were carried out in Sweden. Abnormally high levels of a rare type of cancer, called soft-tissue sarcoma, were found in men who were exposed to chlorophenols and chlorophenol-based herbicides (reviewed in Hardell, 1983). The Swedish studies have been criticized for unreliable diagnosis of soft-tissue sarcoma (Hajdu, 1984), and for relying on the workers' memory of their exposure to the substances (Cook, 1983). In general, the diagnosis and classification of this rare type of cancer is difficult, and relying on memory for an appraisal of a subject's health is an admitted weakness.

Similar studies have since been conducted in several countries, and no such association has been found (reviewed in USEPA, 1985: 11.64-91). Several of these studies are not considered sensitive enough to detect the small numbers of a cancer as rare as soft-tissue sarcoma (reviewed in USEPA, 1985: 11.64-91).

After the Swedish results were published, a review of the medical history of men in the U.S. who were occupationally exposed to chlorophenol-based chemical products showed an abnormally high number (seven cases) of soft-tissue sarcomas (Honchar and Halperin, 1981). The authors of the U.S. review subsequently helped to reexamine the data, and they determined that only two of the seven workers were both 1) exposed to dioxin- and furan-contaminated products and 2) correctly diagnosed as having soft-tissue sarcoma (Fingerhut et al., 1984). Nevertheless, two cases still represents a significantly higher number of soft-tissue sarcomas for this group (USEPA, 1985: p 11.91). A similar study in Sweden found no association between rates of soft-tissue sarcoma and exposure to phenoxy-acid herbicides, among 350,000 Swedish agricultural or forestry workers, when compared to 1.7 million Swedish workers in other industries (Wiklund and Holm, 1986, cited in Fishbein, 1987).

In their 1985 Health Assessment for dioxins, the USEPA stated that the Swedish studies offer "limited" evidence for the carcinogenicity of dioxin-contaminated chlorophenols and

chlorinated phenoxyacetic herbicides (such as 2,4,5-T), but "inadequate" evidence for the carcinogenicity of 2,3,7,8-TCDD alone (USEPA, 1985: p 11.138-140).

In addition to the association between exposure to dioxin- and furan-contaminated products and soft-tissue sarcomas, a few researchers have reported finding such an association with nasal cancer (reviewed in Hardell, 1983), stomach cancer (reviewed in USEPA, 1985: pp 98-107), and cancer of circulating cells (reviewed in USEPA, 1985: pp 92-98; reviewed in Hardell, 1983). Similar studies of workers exposed to dioxin- and furan-contaminated products have not found elevated levels of cancers (reviewed in Reggiani, 1983: p 483). The USEPA Health Assessment considered the available evidence for these other cancers to be inadequate, and this is an opinion shared by a majority of researchers.

The great majority of researchers in the field of toxicology or epidemiology feel that the numerous studies of the human carcinogenicity of dioxins and furans have provided inadequate evidence that they cause cancer in humans. Based on the epidemiological evidence and the knowledge that some dioxins and furans are proven carcinogens in animals, dioxins and furans are suspected human carcinogens.

Abortions, birth defects

A small number of researchers have found an association between exposure to 2,3,7,8-TCDD-contaminated products and abnormally high levels of abortions or birth defects (reviewed in USEPA, 1985: pp 9.23-36; reviewed in Hach, 1984; Albanese, 1988). Children of mothers who consumed rice oil contaminated with PCBs and furans (the Yusho incident) were born with dark pigmentation and deformed fingernails (reviewed in Kuratsune, 1980: p 299). Some of these babies also suffered from slowed growth, and chloracne. It has generally been concluded that furans were responsible for these effects (Kunita et al, 1984). Other researchers conducting similar studies have found no such association (reviewed in USEPA, 1985: pp 9.23-36; reviewed in Hach, 1984; Mastroiacovo et al., 1988). Many of these studies have been largely discounted because of weaknesses in the methodology (USEPA, 1985: pp 9.23-36).

There is thus far inconclusive evidence of an association between dioxins and furans and abortions, and an association with birth defects was detected only in the rare circumstance

where the mother was exposed to extremely large amounts while pregnant (the Yusho incident). If these substances are capable of causing such effects on humans, then either the level of exposure must be extremely high, or they cause rare types of birth defects that researchers have not been able to detect in significant numbers. Again, this is an area where further investigation is needed.

Immune effects

A few researchers have reported an association between long-term exposure to 2,3,7,8-TCDD and an impaired immune system (reviewed in Hay, 1982). Other long-term studies have found no effects on the immune system (Albanese, 1988; Fara et al., 1982). A study of people exposed to 2,3,7,8-TCDD in Missouri found evidence of an abnormal cellular immune system (Stehr-Green et al., 1987). However, the effects did not result in increased illness. Also, the authors noted that these effects may be part of a normal response to a toxin in the body, i.e., they could be considered indicators of exposure and not signs of disease.

Conclusions on health effects

The long-term health effects of these compounds have been intensely investigated, making them among the most-studied substances with respect to their effect on animal and human health. Dioxins and furans cause mortality and/or cancer in many animals, but there is no conclusive evidence that they cause cancer or any other life-threatening health problem in humans. No documented human death has occurred because of an exposure to dioxins or furans.

People have been exposed to relatively large amounts of dioxins and furans (1 ug or more) during industrial accidents, and other incidents of accidental contamination (Yusho, Times Beach). The symptoms of these high-level exposures include dizziness, headaches, liver damage, leg pains, and reduced sex drive. These symptoms, though serious, have typically subsided with time. An exposure to these amounts can also cause severe acne, called chloracne, which in some cases has persisted for decades. With the exception of chloracne, most

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researchers have found no serious, long-term health problems associated with exposure to dioxins, even at the highest reported levels.

However, some studies have found an association between long-term diseases and exposure to dioxins and furans. Several Swedish studies have shown an association between a person's exposure to 2,3,7,8-TCDD-containing herbicides and the incidence of a rare form of cancer. Other and subsequent studies have not confirmed this association, and the Swedish studies have been criticized on several grounds. Nevertheless, because they are very potent toxins and carcinogens in laboratory animals, the U.S. Environmental Protection Agency, Centers for Disease Control, Food and Drug Administration, and other groups, have issued guidelines for human exposure to dioxins and furans, based on the results of animal studies in the laboratory (see "How do government agencies arrive at acceptable human exposure to dioxins and furans?", page 65).

How do dioxins and furans cause the health effects that they do?

We don't know yet why dioxins and furans cause the health effects that they do. But because these substances affect so many systems of the body, it is expected that the mechanism of toxicity involves metabolism at the cellular level. For example, it has been proposed that many of the toxic effects of dioxins and furans are similar to vitamin A deficiency (Hakansson et al, 1988).

Some of the toxic effects of dioxins and furans (and other halogenated aryl hydrocarbons such as PCBs and PBBs) have been linked with the cellular machinery that makes and releases certain enzymes (Poland et al., 1979). Also, 2,3,7,8-TCDD has been linked with changes in the outer membrane of the cell (reviewed in Masumura, 1985). It is not likely, however, that these changes in the cell are directly responsible for the toxic effects. Instead, it appears that the toxic effects are somehow mediated by these enzyme systems and the cell membrane.

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Regulating Dioxins and Furans

How do government agencies arrive at acceptable human exposure to dioxins and furans?

Government agencies from many different countries have determined maximum acceptable doses of 2,3,7,8-TCDD for humans, which are then used to regulate practices that expose people to dioxins and furans. These acceptable doses (also called tolerable, allowable, and virtually safe) vary from country to country, and can vary from agency to agency within a country (see Figure 4, following page). This variation is primarily the result of differing interpretation of the same experimental animal data, and to a lesser extent the choice of different data. In order to understand how this comes about, a brief summary of how an agency determines an acceptable dose is in order.

First, suitable data must be chosen. The results of animal laboratory studies are relied upon most heavily and are often the only data considered. This is because human studies (epidemiological studies) are after-the-fact investigations of uncontrolled exposure, making it extremely difficult to confidently correlate a given dose of the substance with the observed health effects. Animal laboratory studies allow several controlled doses, including lethal doses, to be used, and allow the researchers to examine the health effects over most or all of the lifetime of the animal.

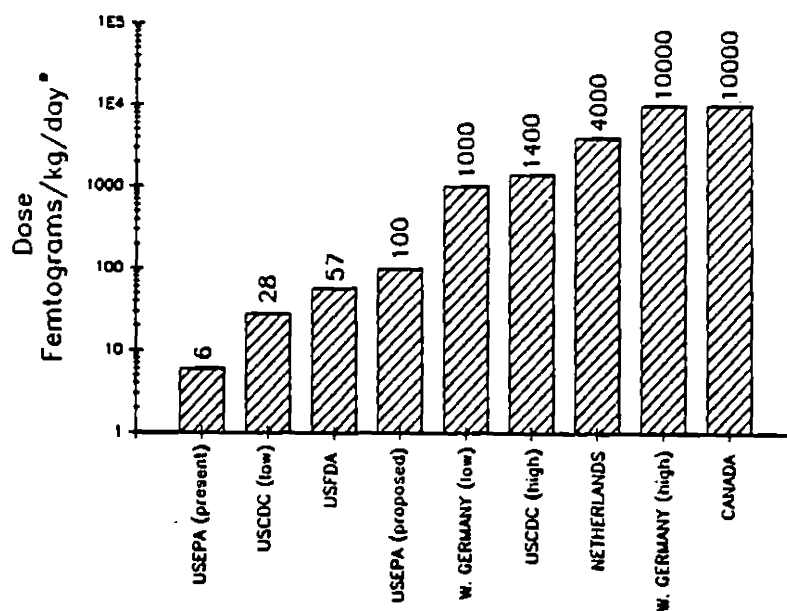
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Figure 4. Virtually safe lifetime daily doses of 2,3,7,8-TCDD from various agencies and countries.

from Figure 1 in USEPA, 1988c: p 4.



* A femtogram is one quadrillionth of a gram (1×10^{-15} grams)

The effects of different doses on long-term health aspects such as cancer, birth defects, and changes in the immune system are typically used by regulators, because they have very serious consequences. In the United States and Canada, for example, data from long-term studies of cancer in rats have been used to estimate an acceptable dose of 2,3,7,8-TCDD. Rats were chosen as subjects because they are physiologically similar to humans, reliable strains of rats have been developed for use in such studies, and large numbers of the animals can be used for the experiment.

Regulators must then extrapolate an acceptable dose for humans from the chosen data. It is this extrapolation that accounts for most of the variation in acceptable doses. The extrapolation can be done using two major methods: 1) applying safety factors to the largest dose that could be correlated with no observed adverse effect (the NOAEL); 2) using the various doses and their correlated adverse effects to extrapolate a dose that would be theoretically associated with an acceptably small risk of causing the effect. For example, the USEPA considers a risk of one tumor in one million people during an average lifetime of 70 years to be an acceptably small risk.

A safety factor (method 1) is used when the regulators decide that there is a threshold dose below which there is only a remote risk that the health effect will occur. The safety factor is then applied to allow for individuals that are more sensitive to the toxic effects than the average, and to allow for the possible difference between the test species and humans. Safety factors of from 10 to 1000 have been applied, depending on the confidence the regulators have in the available data.

The dose extrapolation (method 2) is used when the regulators decide that any dose, no matter how small, increases the risk of the health effect. Because the aim of this method is to quantify the risk and then choose an acceptable level of risk, such an approach is called quantitative risk assessment. There are many different mathematical models that can be used to extrapolate quantitative risks from a range of doses, and the extrapolated degrees of risk can vary considerably, depending on the model chosen.

The choices outlined above account for the range of acceptable daily lifetime doses of 2,3,7,8-TCDD as presented in Figure 4. The lowest (USEPA) and highest (Ontario Ministry of the Environment) doses in that table were derived from the same long-term studies of rats by Kociba et al (1978). The USEPA also used a similar study by the National Cancer Institute (NTP, 1980a); the Ontario Ministry of the Environment also used a similar study by Murray et al., (1979).

Because the USEPA feels that there is no threshold below which 2,3,7,8-TCDD does not cause an increased risk of cancer, they used a dose-extrapolation model to calculate the acceptable daily dose. The model they used to arrive at the present virtually safe dose is the most conservative of the five models they tested; it extrapolates a greater risk than do the other models at low doses.

The Ontario regulators recognize 2,3,7,8-TCDD as a promoting rather than an initiating carcinogen, and therefore feel that there is a threshold dose below which 2,3,7,8-TCDD probably does not increase the risk of cancer. They applied a safety factor of 100 to the dose that they felt represented the NOAEL in these studies, to calculate an acceptable daily dose. Thus, we have two very different interpretations of essentially the same data.

The USEPA's recently proposed virtually safe dose is greater because it reflects the median virtually safe dose from the different models, rather than the most conservative. As has been pointed out by Lave (1983), when the mechanism of action of a toxin is unknown, all applicable models are equally valid and should be used to derive a range of risk estimates. No single model should be chosen, because undue emphasis is then placed on one estimate in what is a large range of equally relevant estimates. At the same time, regulators should make conservative assumptions. Then, as their knowledge about the toxin increases and they replace their conservative assumptions with more accurate ones, the estimated risks should decrease. This provides an incentive for industry to conduct research on toxic substances.

Because of lack of information about dioxins and furans, the USEPA and other regulatory agencies have made very conservative assumptions when estimating the health risks of these compounds. Many researchers have argued that the assumptions are overly

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conservative, and these arguments have grown more persuasive as our knowledge of dioxins and furans has increased. For example, Paustenbach et al (1986) critically examine the assumptions used by the CDC and USEPA to determine the risk posed by 2,3,7,8-TCDD in soil. Their analysis indicates that the CDC and USEPA significantly overestimated the risk of 2,3,7,8-TCDD in soil. Also, although the CDC made it clear that their risk assessment was 1) specific to the residential area in Times Beach, Missouri and 2) not applicable for industrial sites, the USEPA subsequently adopted their guideline of 1 ppb 2,3,7,8-TCDD in soil to determine the need for cleanup at industrial sites, where the level of exposure would be much lower.

What has been done about dioxins and furans?

The manufacture and use of 2,4,5-T and the related herbicide Silvex in the U.S. was restricted in 1970, and prohibited in 1984. The manufacture and use of chlorophenols has been greatly reduced. No chlorophenols with four or fewer chlorines are being produced in the U.S. (pers. comm., John Robinson, Vulcan Chemicals), and hexachlorophene is not being produced because of the lack of 2,4,5-trichlorophenol (USEPA, 1986: p 3-16).

The USEPA requires that pentachlorophenol produced in the U.S. must now average no more than 2 ppm hexa-CDDs, and cannot have more than 4 ppm hexa-CDDs (Vulcan Chemicals, 1988). Approximately half of the hexa-CDDs present are 2,3,7,8-substituted (pers. comm., John Wilkinson, Vulcan Chemicals). The USEPA intends to cancel most non-wood uses of pentachlorophenol (USEPA, 1987b: p. 21413).

Wastes from the manufacture of tri-, tetra-, and pentachlorophenols, and from the manufacture of tetra-, penta-, and hexachlorobenzene under alkaline conditions, were designated as acutely hazardous by the USEPA in 1984. The regulations also apply to discarded, unused chlorophenols or products containing them, to products made with equipment previously used to manufacture the substances above (except pentachlorophenols), and to soil that has been contaminated by these substances. The manufacturers or owners of such wastes are required to notify the USEPA. These wastes cannot be placed in a landfill if they contain more than 1 ppb

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of certain dioxin and furans congeners (USEPA, 1986: p 2.5), and if incinerated, 99.9999% of the contamination must be removed (USEPA, 1986:p 2.3).

The USEPA has proposed that wastewaters and drippings, from wood-preserving facilities and sawmills that use chlorophenolic solutions, or that use equipment formerly used for such solutions, be regulated as hazardous wastes (USEPA, 1988a). Also, 2,3,7,8-TCDD is now listed under the Clean Water Act as a compound which the USEPA must control in industrial effluents (pers. comm., USEPA).

PCBs are no longer produced in the U.S., and any new use of them is strictly controlled and must be extremely well justified. A gradual phase-out of PCB-containing equipment is taking place. Transformers that contain fluid with more than 500 ppm PCBs are now prohibited where they can contaminate food or feed, must be registered and inspected, and leaks must be repaired within 48 hours. Capacitors with more than 500 ppm PCBs are also prohibited from areas where they might contaminate food or feed, and large capacitors had to be placed in enclosures by November 1988.

The disposal of PCBs is also highly restricted. Fluid contaminated with more than 500 ppm PCBs must be incinerated with a removal efficiency of 99.9999%, and fluid contaminated with more than 50 ppm cannot be placed in a landfill. It is a violation to store PCBs for more than one year before disposal (pers. comm., USEPA).

The USEPA has published lists of chemical products that may be contaminated with chlorinated or brominated dioxins and furans (USEPA, 1987b). Manufacturers or importers of the chemical products on these lists must test for and report to the USEPA on the presence of dioxins and furans in these products. The USEPA also published a list of precursor products, which are not contaminated themselves but may produce dioxins or furans if they are used to manufacture other products. Manufacturers or importers of products made with these precursors must notify USEPA of that fact (USEPA, 1987b).

The USEPA conducted a nationwide survey in order to determine the extent of contamination by 2,3,7,8-TCDD. The most severely contaminated sites were assigned to the Superfund List (most were already on the list because of the presence of other toxic substances).

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Where the USEPA found relatively high levels of 2,3,7,8-TCDD in fish, advisories were issued to limit consumption. Also, a program was put in place for cleaning up the many contaminated sites in Missouri, and many of the sites have since been cleaned up.

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Conclusions and Recommendations

We need to know more about the toxicity, distribution, and behavior of chlorinated dioxins and furans other than 2,3,7,8-TCDD, especially those that are found in relatively large amounts in the environment. For instance, current research indicates that the common ocre-CDD is biologically active, not non-toxic as has been believed (Couture et al, 1988).

Based on the many studies already published, dioxins and furans do not appear to be a hazard to our health when we are exposed to the low levels typically present in the environment. The epidemiological evidence indicates that dioxins and furans do not cause cancer, immune effects, or other serious, long-term health effects on humans, even at very high doses. Some groups of people, such as workers who are exposed occupationally to greater amounts over a long time, and breast-fed babies, need special attention. We should continue to monitor the health of those persons who have been exposed to large amounts of these compounds, or who are exposed to smaller amounts for a long time. This will enable us to identify any long-term health effects not already recognized. We also need to determine the mechanism of action. Such an understanding would not only have preventive or therapeutic value, but is also critical for accurate assessments of the risks these compounds pose.

Because of their demonstrated toxicity to laboratory animals, plus their distribution and persistence, some dioxins and furans are a potential hazard to organisms in the environment. There is a great need for more study in this area. We need to know what are unacceptably harmful levels for the various organisms in the environment, and the nature and amount of dioxins and furans from the various sources.

If we are to reduce the amounts of toxic dioxins and furans in our environment, we need to deal both with the large amounts already created, and the processes that continue to create them. What appears to be the largest amount of toxic dioxins and furans is buried in landfills or stored at former manufacturing sites. We need to develop safe yet practical ways to destroy this waste or ensure that it is contained. We may also need to reduce the amounts of dioxins and furans occurring as unwanted contaminants of some products. Great reductions

have been made in certain products in the past, and further reduction may be necessary. The emphasis needs to be on preventing their creation during the manufacturing process. Finally, we need to reduce the unwanted creation of dioxins and furans during combustion. For example, incinerators can be operated under conditions (high temperatures, complete burning) that reduce the creation of dioxins and furans (USEPA, 1988b).

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Appendix

The Virtually Safe Lifetime Daily Dose (VSD) of 2,3,7,8-TCDD is that quantity of 2,3,7,8-TCDD estimated to cause a maximum of one tumor in one million people who are exposed for 70 years. In other words, one person faces a maximum one in one million risk of a tumor due to 2,3,7,8-TCDD during their lifetime, if they are exposed to the VSD of 2,3,7,8-TCDD for their lifetime.

Virtually Safe Lifetime Daily Dose of 2,3,7,8-TCDD, from the U.S. Environmental Protection Agency

6 femtograms/kg/day

A femtogram is 1×10^{-15} grams or 1 quadrillionth of a gram. Note: The USEPA has proposed to increase this daily dose to 100 femtograms/kg/day.

Virtually Safe Levels of 2,3,7,8-TCDD in Soil and Water, from the USEPA

Soil: Below 1 ppb requires no immediate action (from the U.S. Center for Disease Control's recommendation for Times Beach, Missouri).

Water: 13 parts per quadrillion (1.3×10^{-14} grams/liter).

The Advisory for Fish Contaminated with 2,3,7,8-TCDD, from the U.S. Food and Drug Administration

Fish with levels of 2,3,7,8-TCDD above 50 ppt should not be eaten.

Fish with levels from 25 to 50 ppt can be eaten twice a month.

Fish with levels below 25 ppt can be eaten with no restriction.

(These levels can also be used for 2,3,7,8-TCDD in other foods).

Recommended Reading

For a succinct, informative pamphlet that summarizes the health risks of 2,3,7,8-TCDD in an easy-to-read style:

"Dioxin in the Environment: Its Effect on Human Health" 1986.
Available from the American Council on Science and Health,
47 Maple St., Summit, NJ 07901. Telephone (201) 277-0024.
Price is \$2 per copy.

For a well-written synopsis of the issues surrounding 2,3,7,8-TCDD and the relevant scientific information:

"Dioxin" by F. H. Tschirley, in Scientific American,
February, 1986, Volume 254, Number 2, pages 29-35.
Available from Scientific American, 415 Madison Ave.
New York, NY 10017, Attention Rosa Davis. Cost of issue is \$4.

For a book that discusses in detail the issues surrounding 2,3,7,8-TCDD, especially the incidents that received the most publicity in the U.S., and includes much of the relevant scientific information on 2,3,7,8-TCDD:

Dioxin, Agent Orange by Michael Gough, 1986.
Plenum Press, New York.

For a summary of the current research findings on dioxins and furans, consult the proceedings of the annual International Symposium on Chlorinated Dioxins and Related Compounds, published annually in the journal Chemosphere (Pergamon Press).

Glossary and List of Abbreviations

2,3,7,8-TCDD	2,3,7,8-tetrachlorodibenzo-para-dioxin
2,4-D	2,4-dichlorophenoxyacetic acid
2,4,5-T	2,4,5-trichlorophenoxyacetic acid
CDC	United States Centers for Disease Control
ADI	acceptable daily intake
CDD	chlorinated dibenzo-p-dioxin
CDF	chlorinated dibenzo furan
congener	a single, particular member of a chemical family
DNA	deoxyribonucleic acid
dioxins	chlorinated dibenzo-p-dioxins
furans	chlorinated dibenzo furans
homologue	a group of dioxins or furans with the same number of chlorine atoms in their structure
isomer	a single member of a homologue
kg	kilogram
LCSO	lethal concentration for 50% of test organisms
LD50	lethal dose for 50% of test organisms
LOAEL	lowest-observed-adverse-effects level
milligram	1 x 10 ⁻³ grams
microgram	1 x 10 ⁻⁶ grams
nanogram	1 x 10 ⁻⁹ grams
picogram	1 x 10 ⁻¹² grams
femtogram	1 x 10 ⁻¹⁵ grams
NCASI	National Council of the Paper Industry for Air and Stream Improvement
NOAEL	no-observed-adverse-effects level
NOEL	no-observed-effect level
NTP	National Toxicology Program
PBBs	polybrominated biphenyls
PCBs	polychlorinated biphenyls
ppm	parts per million
ppb	parts per billion
ppt	parts per trillion
ppq	parts per quadrillion
ug	microgram
USAF	United States Air Force
USDA	United States Department of Agriculture
USEPA	United States Environmental Protection Agency
USFDA	United States Food and Drug Administration
WHO	World Health Organization

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