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Dioxins: An Overview and History†

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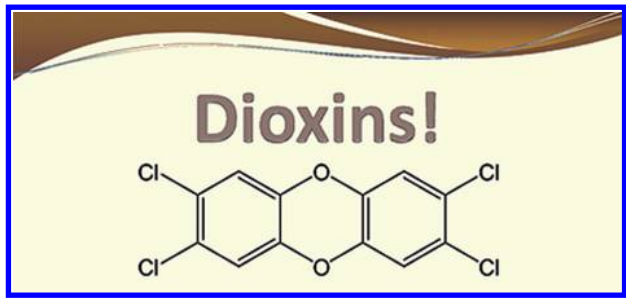

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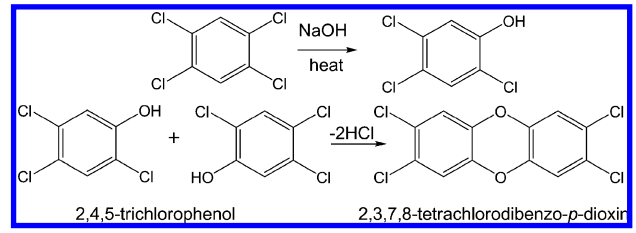
Polychlorinated dibenzo-*p*-dioxins (PCDDs) and their cousins, the polychlorinated dibenzofurans (PCDFs), are well-known environmental contaminants. Depending on where on the rings the chlorine atoms are attached, one can have 210 chemically different PCDD/Fs, each of which is called a "congener". Collectively the 210 compounds are often called "dioxins"—note the plural—even though the majority of them are actually dibenzofurans. PCDD/Fs have received considerable public and scientific attention because of the acute toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2378-TCDD), which has one of the lowest known LD_{50} (lethal dose to 50% of the population) values. It takes only 0.6 μg/kg of body weight to kill male guinea pigs (*1*). Thus, 2378-TCDD is frequently highlighted, at least in the popular press, as "the most toxic man-made chemical". The polychlorinated dibenzofurans are only slightly less toxic; for example, the LD_{50} of 2378-TCDF is about 6 μg/kg for male guinea pigs (*2*). Other dioxin and furan congeners are also toxic, and many of these compounds have both acute and chronic effects. Incidentally, the toxicity of dioxins varies dramatically from species to species; for example, 2378-TCDD is about 500 times less toxic to rabbits than it is to guinea pigs (*1*).

Unlike the polychlorinated biphenyls (PCBs), PCDD/Fs were never produced intentionally as marketable products. In fact, dioxins were unwanted byproducts of industrial and combustion processes. For example, dioxins were present in chlorinated phenols and in related compounds as accidental contaminants. The most classic example was the presence of 2378-TCDD in 2,4,5-trichlorophenol (also known as Dowicide 2), which was produced by the reaction of 1,2,4,5-tetrachlorobenzene with sodium hydroxide (NaOH). Dimerization of the resulting phenol produced small amounts of 2378-TCDD, which contaminated the chlorinated phenol product. Although dioxins were present at low levels in some commercial products, their widespread use resulted in the release of PCDD/Fs into the environment at levels that have sometimes required remediation.



This feature article will summarize some of the history concerning dioxins in the environment over the last 50 years and end with a commentary on the U.S. Environmental Protection Agency's (EPA's) approach to these problems.

Chick Edema Disease (*3*). In 1957, a mysterious disease was killing millions of young chickens in the eastern and midwestern U.S. The symptoms were excessive fluid in the heart sac and abdominal cavity, and the cause was traced to the fatty acids that had been added to the chicken's feed. Considerable efforts over several years lead to the isolation of one of the toxic materials and to its identification by X-ray crystallography; it was 1,2,3,7,8,9-hexachlorodibenzo-*p*-dioxin.

The source of this dioxin in the fatty acid material was traced to the tanning industry. Hides, after they are removed from the animal, have a layer of fat that must be removed. Until the midtwentieth century, the first step in the tanning process was to apply large amounts of salt (NaCl) to the hides as a preservative, but in the last 50−60 years, this approach was supplanted by the use of "modern" preservatives, such as chlorinated phenols, which we now know to have been contaminated with PCDD/Fs. As the fat was stripped from the hide, the chlorinated phenols and their impurities, both being relatively lipophilic, ended up in this so-called "fleshing grease". This material was saponified to produce fatty acids, which were purified by high temperature distillation. Both of these steps tended to dimerize the chlorinated phenols and to concentrate the resulting dioxin impurities in the fatty acid product, which was then used as a supplement in chicken feed. In fact, analysis of three contaminated fatty acid products showed the presence of 2,3,4,6-tetrachlorophenol (also known as Dowicide 6), which could dimerize by way of a Smiles rearrangement to form 1,2,3,7,8,9-hexachlorodibenzo-*p*-dioxin. Analysis of toxic fleshing grease samples also showed the presence of several other dioxins. Both 1,2,3,7,8,9- and 1,2,3,6,7,8-hexachlorodibenzo-*p*-dioxin are about 10% as toxic as 2378-TCDD (*2*), clearly contraindicating the use of chlorinated phenols in a material destined for food use or production.

Although an understanding of the chemical etiology of chick edema disease largely eliminated the problem in chickens by the early 1970s, the problem reappeared in the mid-1980s (*4*). This more recent problem was traced to pentachlorophenol (also known as Dowicide 7), which had

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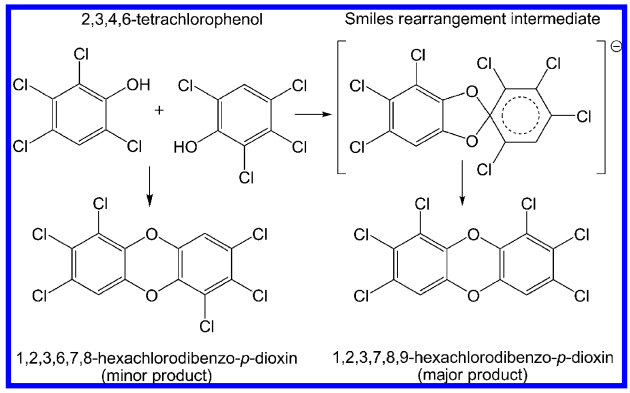
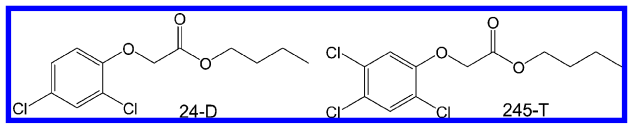


contaminated wood shavings used as bedding for chickens. In this case, the hepta- and octachlorinated dioxin and dibenzofuran congeners were relatively abundant, amounting to about 20 ppm in the wood shavings, but 1,2,3,6,7,8- and 1,2,3,7,8,9-hexachlorodibenzo-*p*-dioxins were also present in the chickens and wood shavings.

Agent Orange (*5*). During the war in Vietnam, the U.S. military used a herbicide dubbed Agent Orange as a defoliant. Spraying by airplanes and helicopters occurred in South Vietnam from 1965 to 1971. The intent was to kill food crops being used by the North Vietnamese and the Viet Cong and to kill foliage around U.S. military base perimeters (thus improving the defensibility of these bases). Agent Orange was a mixture of roughly equal amounts of the *n*-butyl esters of 24-D and 245-T, the latter of which was made from 2,4,5-trichlorophenol. As a result of the use of this starting material, 245-T and thus Agent Orange were contaminated with small amounts of 2378-TCDD. While it is now almost impossible to know what the concentrations of 2378-TCDD in Agent Orange were, the current estimate is an average of about 3 ppm. Given that a total of about 4.5×10^7 L of Agent Orange were sprayed, it follows that on the order of 150 kg of 2378-TCDD could have been added to the environment of southern Vietnam.



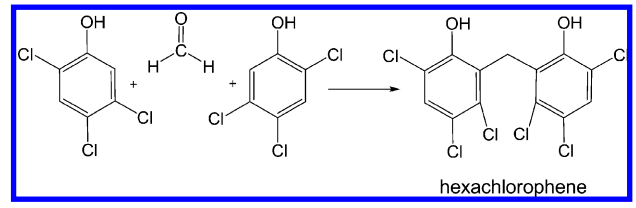
Often the scientific issues associated with Agent Orange have paled in comparison to the political issues, which have focused on U.S. Vietnam veterans and the Vietnamese people. Both groups have argued that health problems they have had since the 1970s have been caused by the dioxin impurities in Agent Orange.

In the case of the U.S. veterans, a large epidemiological study was organized starting in 1979. The idea was to associate Agent Orange exposure information with health effects as determined by medical examinations. This study soon focused on those veterans of the U.S. Air Force who had participated in the spraying program—the so-called Ranch Hands—who had presumably been exposed to Agent Orange. About 1000 such veterans and an equal number of veterans who had not been involved in the spraying operation were enrolled in this study, and their health status was assessed every 5 years. Early results found few statistically significant differences in the health outcomes of these two groups.

Later, exposure assessment was based on the measured tissue or blood concentrations of 2378-TCDD, and health differences between the exposed and unexposed populations began to emerge. This epidemiological study was terminated in 2006 over the protests of the scientific community, but all of the specimens, medical records, and data have been archived by the Institute of Medicine. The total cost of this 27-year project was about $140,000,000. The most recent assessment of the Ranch Hand and other data by the Institute of Medicine (*6*) indicates that there is "sufficient evidence of an association" between herbicide exposure and incidence of soft-tissue sarcoma, non-Hodgkin's lymphoma, Hodgkin's disease, chronic lymphocytic leukemia, and chloracne. Vietnam veterans can now be compensated if they have one of these health problems; for a 50% disability, this compensation is on the order of $800/month.

Agent Orange may also have had effects on the Vietnamese people and environment, but there are no plans to do an epidemiological study as was done with the U.S. veterans. Instead, efforts have focused on preventing further exposures by cleaning up "hot spots", where Agent Orange may have been spilled or dumped during U.S. operations in Vietnam. One estimate is that about 10^4 m^2 (1 ha) of soil will need to be remediated. This is about the size of two U.S. football fields, so this remediation should be feasible. It is interesting to note that some Vietnamese have sued the U.S. manufacturers of Agent Orange for health damages in a U.S. court; the case was dismissed in 2005, but the decision has been appealed (*5*).

Times Beach and Missouri (*7, 8*). In the 1960s and early 1970s, the Northeastern Pharmaceutical and Chemical Company (NEPACCO) operated a plant in Verona, MO, making hexachlorophene from 2,4,5-trichlorophenol and formaldehyde. Hexachlorophene's production rate soon reached 450 t (1 million pounds) per year. Unfortunately, 2378-TCDD was an impurity in the 2,4,5-trichlorophenol starting material used in this process; thus, the hexachlorophene product needed to be purified before sale. The waste from this cleanup process, with its relatively high load of 2378-TCDD, was stored in a holding tank on the NEPACCO property in Verona. Because of its neurotoxicity, the U.S. Food and Drug Administration restricted the use of hexachlorophene in 1971.



At about that time, Russell Bliss was contracted to "recycle" the chemical waste oil (also called still bottoms) from the NEPACCO holding tank in Verona. Bliss ran a small business in which he picked up waste oil from garages, airports, and military bases, and took it back to one of four 91,000 L (24,000 U.S. gal) holding tanks at his facility. He made his money by paying a small fee for picking up the oil and collecting a larger fee when selling it to petroleum reprocessors and by spraying the oil for dust control on dirt roads or in horse-riding arenas. The oil he usually dealt with was almost exclusively used crankcase oil from cars and trucks. Apparently no one realized that the oil he picked up from the NEPACCO facility was chemical waste oil as opposed to petroleum based oil, and as a result, about 70,000 L of this chemical waste oil with its dioxin impurities was mixed in with other oil in one or more of his holding tanks. NEPACCO claims Bliss was warned that this waste was hazardous, but he and his drivers insisted they were not. The 2378-TCDD concentration in this waste oil was about 300 ppm.

On May 26, 1971, Bliss took some oil from his holding tank and sprayed it at the Shenandoah Stables indoor horse-riding arena for dust control. The next day horses became ill; in the end, 75 horses had died or had to be euthanized. Within a week, small birds were found dead in the arena. Within two weeks, the same oil had been sprayed at the

Bubbling Springs arena and at the Timberline Stables arena, both of which soon had similar problems. Soil from these three arenas was removed within a few weeks, but the animal health problems persisted. At the Bubbling Springs site, 25−30 truckloads of dirt were removed and taken to several private building sites, thus spreading the contaminated soil to other parts of Missouri. Samples from the horse arenas were eventually analyzed by the U.S. Centers for Disease Control (CDC), who identified 2,4,5-trichlorophenol, hexachlorophene, and 2378-TCDD. By 1974, the CDC had traced the source of the contamination to the NEPACCO facility, which by this time was owned by another company named Syntex Agribusiness Inc. Several thousand gallons of chemical waste were still present at this facility, and this oily waste still contained about 8 kg of 2378-TCDD.

Between 1972 and 1976, Bliss also had been paid to spray oil for dust control on the unpaved streets of Times Beach, MO, and on other unpaved streets throughout the state of Missouri. Once it became clear that Missouri had a dioxin problem, and once typical bureaucratic in-fighting had cleared, the state government and the EPA began cooperating in 1982 to fully determine the spatial extent of the problem and to implement cleanup plans. In due course, the EPA published a list of 38 dioxin contaminated sites in Missouri, including Times Beach. By the end of 1982, the Missouri Department of Health recommended that the entire town of Times Beach be evacuated, and it was. By February of 1983, the EPA announced that $33,000,000 would be spent to buy all the homes and businesses in Times Beach. In April 1986, the aldermen voted to dis-incorporate and everyone left Times Beach. This site was eventually remediated and removed from the Superfund list in 2001 (*9*).

In addition to the soil cleanup, the ~8 kg of 2378-TCDD in the former NEPACCO holding tank (now owned by Syntex) had to be remediated. Syntex first protected the tank from storms and vandals by building a concrete dike around tank and fencing the area. Incineration in Minnesota was considered, but groups in Iowa threatened to call out the National Guard to block transport of this material through their state. Instead, a waste-management company developed a technique for breaking down 2378-TCDD by direct ultraviolet photolysis. The process was tested successfully in 1979; the waste began to be treated in May 1980; it ran full time for 13 weeks; and by August 1980, all the waste had been treated with 99% destruction of 2378-TCDD.

Seveso, Italy (*10*). In the mid-1970s, a Swiss company, Roche Group, operated a small chemical production plant, known as Industrie Chimiche Meda Società Anonima (ICMESA), in the northern Italian town of Meda. Among other products, this plant made 2,4,5-trichlorophenol by the reaction of 1,2,4,5-tetrachlorobenzene with NaOH. On Saturday, July 10, 1976 at about noon, the vessel in which this reaction was being carried out overheated, and its pressure increased. This caused the rupture disk in a safety valve to burst, and the contents of the vessel were released to the atmosphere and transported south by the wind. Most of the contamination landed in the town of Seveso.

On Sunday, July 11, ICMESA managers informed local authorities of the escape of a chemical cloud and that it might contain "toxic substances". These plant managers requested that local authorities warn the residents, and they sent soil samples to Roche in Switzerland for analysis. By the next day, nearby residents were warned not to eat vegetables from their gardens. Within a few days, more than 1000 chickens and rabbits had died, and Roche informed the ICMESA plant manager that the soil samples contained traces of 2378-TCDD. The next day, the mayors of Seveso and Meda declared the area south of the ICMESA plant to be contaminated, and warning signs and fences were erected.

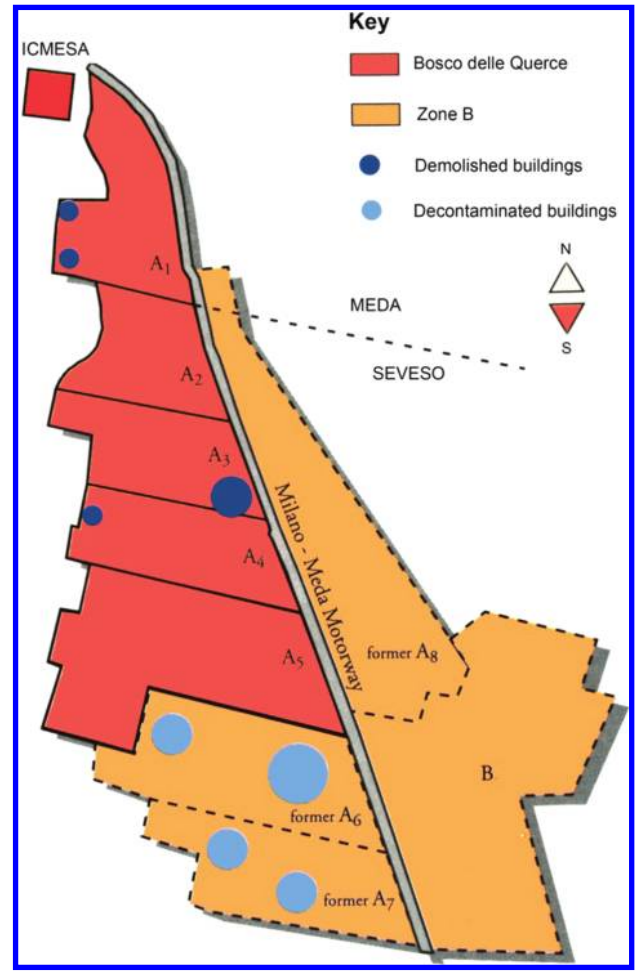


FIGURE 1. Map of the dioxin contaminated zones in Seveso, Italy. Zone A (red) was the most contaminated with soil levels of 2378-TCDD of >50 μg/m^2) and Zone B (yellow) was less contaminated with soil levels of 2378-TCDD of 5−50 μg/m^2. This map is reprinted from ref *11* with permission.

By July 16, several children had been hospitalized due to skin reactions. The mayor of Seveso informed a national newspaper about this chemical disaster, and on July 19, the first articles about it appeared in the national press and on television. At about this time, the government sealed the building where the accident occurred, and the mayor of Meda ordered that all other ICMESA buildings be sealed as well. On July 20, Roche notified the Italian authorities that 2378-TCDD had been found in the soil samples. This information caused a sensation in northern Italy, and the next day the ICMESA Technical Director and the ICMESA Director of Production were arrested. Roche provided a preliminary map of concentrations as a function of location on July 23 and suggested closing the area closest to the plant and evacuating the people living there.

On July 24, two weeks after the accident, various governmental officials, provincial and national scientists, and industrial representatives met. One result of this meeting was to set up a team of Italian scientific institutions to establish sampling and analytical protocols. This team also recommended the evacuation of people living closest to the ICMESA plant. On July 26, 230 people were evacuated, and by the end of July, more than a thousand 2378-TCDD measurements of soil and vegetation had been made. These data led to the geographical definition of the most contaminated area, named Zone A (1). This zone covered an area of 87 ha, and about 730 people were evacuated from this area. Estimates of the total amount of 2378-TCDD in Zone A soil are imprecise, but more than 2 kg is the best guess.

By August, following further soil measurements, Zone B was defined (Figure 1). It is interesting to note that the dividing line between Zones A and B is the Milano-Meda Motorway. About 4600 people lived in Zone B. These people were not evacuated, but they were asked to follow some restrictions. They could not eat produce grown in Zone B, and their children were sent to schools outside of the area. In addition, many businesses in Zone B were closed for several years. Decontamination of both zones began in August 1976, and an agreement was reached between the Regional Government and Roche for removal and disposal of chemicals from the plant. Roche covered the costs.

By 1977, decontamination of Zone A had been completed. The entire top 40 cm of soil was removed, and the contaminated ICMESA plant and several contaminated houses were demolished. All of this waste was buried in two new 300,000 m^3 hazardous waste facilities built near the accident site. Decontamination of zone B started next. In this case, the contaminated surface layer of soil was simply mixed with deeper uncontaminated soil by repeated plowing of the fields. By 1987, Zone A had been converted to a park known as the Bosco delle Querce (Oak Woods).

Epidemiological monitoring programs were established to follow possible metabolic modifications, spontaneous abortions, malformations, tumors, and deaths among the exposed population. Health monitoring of the workers at the ICMESA plant and on the decontamination projects was also established. An International Steering Committee was formed to assess toxicological and epidemiological data and findings of the monitoring program. In 1984, this Steering Committee reported that there were no human effects other than ~200 cases of chloracne. Nevertheless, longer term epidemiological studies have continued. One of the most interesting such studies is the "where the boys aren't" effect reported by Mocarelli et al. (*12*). They observed that the sex ratio in the children of fathers who had high levels (>118 ppt) of 2378-TCDD in their blood in 1976 was significantly skewed toward female children. This is an example of a subtle biological effect that did not become apparent until over 20 years after exposure.

Although the human health effects continue to be studied, it is important to note that the people who lived in Seveso also suffered significant economic effects. For example, within Europe, the term "made in Seveso" became pejorative—who would want to buy a product that had been so closely associated with a famous toxic substance? As a result of this public antipathy, many people in Seveso lost their jobs. Seveso's property values became depressed—who would want to buy housing or land there? These economic effects were as real as health effects and deserved equal attention, and a reimbursement plan was established to cover these individual and social costs.

Combustion Sources of Dioxins (*13*). All of the incidents described above were ultimately the result of dioxin impurities in commercial chemical products, especially chlorinated phenols, but in 1977 Olie et al. noticed that dioxins were present in fly ash from an industrial heating facility (*14*). In 2000, Bumb et al. in a famous paper titled "Trace chemistries of fire: A source of chlorinated dioxins", showed that dioxins were present in particles from the combustion of most types of organic material, including the combustion of municipal and chemical waste (*15*). This was an important discovery. No longer could the simple presence of dioxins in a sample be blamed on the chemical industry. Indeed, it was suggested that "dioxins have been with us since the advent of fire" (*16*).

It seemed that this "advent of fire" idea was subject to experimental verification, and my laboratory began work on this issue (*13*). We started by developing the following operational hypothesis: Chlorinated dioxins and furans are formed during combustion and are emitted into the atmosphere. Depending on the ambient temperature, some of these compounds are adsorbed to particles and some are in the vapor phase. In either case, these compounds travel through the atmosphere for some unknown distances and are deposited by various routes. Particles with their load of adsorbed compounds settle out of the air, and precipitation scavenges both particle-bound and vapor-phase compounds.

We tested this hypothesis by measuring dioxins and furans in the ambient environment. Our first step was to look at historical aspects. What was the history of chlorinated dioxin and furan concentrations in the atmosphere? Were these compounds really present in the environment since the "advent of fire"? Since it was not possible to retroactively sample the atmosphere, we resorted to an indirect strategy by sampling lake sediment. This technique is based on the rapid transport of material deposited on the top of a lake to its bottom and on the regular accumulation of sediment at the bottom of the lake. Thus, the sediment preserves a record of atmospheric deposition. Experimentally, we obtained cylinders of sediment (called "cores") from the bottom of several lakes, sliced them into 0.5−1 cm layers, and analyzed each layer for the tetrachloro- through octachlorodibenzo-*p*-dioxins and dibenzofurans by gas chromatographic mass spectrometry. Using radio-isotopic methods, we determined when a particular layer of sediment was last in contact (through the water column) with the atmosphere.

We analyzed many sediment cores from the Great Lakes and from a few alpine lakes in Europe, but the site that we consider the most significant is Siskiwit Lake on Isle Royale (*13*). This island is in northern Lake Superior; it is an infrequently visited U.S. national park; it lacks roads and other development; it is a wilderness area and a Biosphere Reserve. Siskiwit Lake is the largest lake on Isle Royale, and its water level is about 17 m higher than that of Lake Superior. Clearly, the only way for dioxins and furans to get into this lake is through deposition from the atmosphere.

Our measured concentrations of dioxins and furans in this sediment core were dominated by octachlorodibenzo-*p*-dioxin, and 2378-TCDD was a minor component. The heptachlorinated dioxins and furans were the second most abundant set of congeners. These relatively high levels of the octa- and heptachlorinated congeners are different from what had been observed in soil samples from Missouri and Seveso, which were dominated by 2378-TCDD. In terms of absolute levels, we found that the concentrations of the dioxins and furans were not much higher than the limit of detection in sediment layers corresponding to deposition dates prior to about 1935. At this time, the concentrations began to increase and maximized in about 1970, after which they decreased to about two-thirds of their maximum levels. From these data, we concluded that atmospheric dioxin and furan levels increased slowly starting in about 1935 and have decreased considerably since about 1970.

What happened in about 1935 that led to the emission of dioxins? Clearly it was not the "advent of fire." We suggest that it was a change in the chemical industry that took place at about this time. Before World War II (1939−1945), the chemical industry was commodity based, selling large amounts of inorganic products. During WWII, organic products were introduced; for example, plastics became an important part of the chemical industry. Some of these products were organochlorine based, and in fact, some of them were chlorinated phenols. As waste materials containing these chemicals were burned, dioxins and furans were produced and released into the atmosphere. These compounds deposited to the water and ended up in lake sediments. Incidentally, coal combustion could not account for the historical record that we observed. Coal combustion was almost constant between 1910 and 1980; there was no major shift either in amount burned or in combustion technology around 1935.

We observed the 1970 maximum in almost all of the sediment cores we analyzed for dioxins. This suggests that

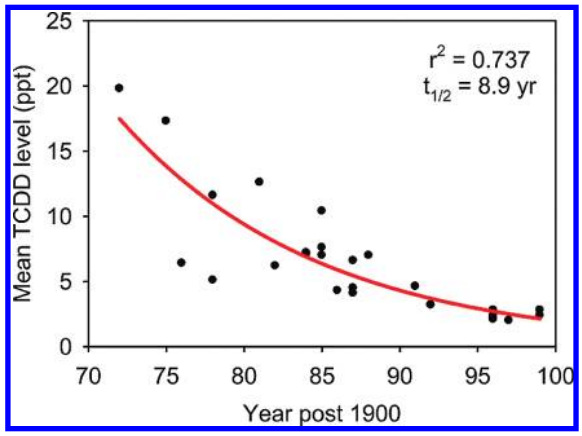


FIGURE 2. Concentrations of TCDD (parts per trillion lipid) in human tissue and serum as a function of when the samples were taken. Each point is the mean of, on average, ~50 samples; plotted from ref *19*.

emission control devices, which were beginning to be widely installed at about this time, were effective in removing dioxins and furans as well as more conventional air pollutants. Subsequent work in my laboratory on another set of cores from Siskiwit Lake has confirmed these results and shown that dioxin levels in surficial sediment have decreased to about one-half of their maximum levels (*17*). This suggests that emissions of dioxins have decreased even more between the time of our first study (cores taken in 1983) and our second study (cores taken in 1998).

Dioxin Reassessment. By the mid-1980s, it was apparent that dioxins from both chlorinated phenols and from combustion were a potential public health issue, and the EPA sprang into action. In 1994, a massive report, called the "Dioxin Reassessment" was generated and reviewed by the EPA's Science Advisory Board (*18*). This report included detailed reviews of the scientific literature and presented a comprehensive assessment of dioxin exposure and human health effects. This report more or less languished in the files of the EPA (although parts have been published in the peer-reviewed literature) for 15 years, but an official draft version of this report has been released recently.

As a result of this delay, few regulations limiting dioxin emissions have been issued in the U.S. Nevertheless, things have changed. The continued reduction in particle emissions from large combustion systems, the elimination of chemical waste burning, and the abandonment of the chlorinated phenol business by large sectors of the chemical industry have meant that lower amounts of dioxins are entering the environment over time. This almost incidental reduction of dioxin emissions has had an effect. For example, Figure 2 shows the average lipid adjusted TCDD levels in people from the U.S., Canada, Germany, and France as a function of time, starting in 1972. The reduction in TCDD shown by this meta-analysis is substantial, decreasing by about a factor of 7 over a 25-year period. One might call these reductions "inadvertent regulation", which is a good thing.

Because of the acute toxicity of dioxins, the environmental problems outlined in this article have received a fair amount of public attention and have contributed to the public's demand for an environment free of toxicants. In a sense, dioxins have been a catalyst for environmental policy makers: Dioxins themselves have not been extensively regulated, but they have led to the regulation of other chemicals.

Ronald Hites is a Distinguished Professor at Indiana University in the School of Public and Environmental Affairs. His research focuses on the behavior of toxic organic compounds in the environment. He has published six books and almost 400 scientific papers and supervised over 70 postdoctoral associates and graduate students. He is a Fellow of the ACS, the winner of the 1993 Founders Award from the Society of Environmental Toxicology and Chemistry, the winner of the 1991 ACS Award for Creative Advances in Environmental Science and Technology, and an Associate Editor of Environmental Science & Technology.

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