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Review Article

Prolegomena to Seveso*

Ecclesiastes I 18

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Introduction

Worldwide attraction was bestowed upon the accident that occurred at the ICMESA factory in the small Italian community of Meda/Seveso at 12.30 on July 10th, 1976. This has resulted in a host of publications, including half a dozen books, at the time of writing. The pre-history of this event is also discussed in many publications, as is the use of the herbicide 2,4,5-T in agriculture and as a defoliant in the Vietnam war.

This present account will not attempt to go into detail except for some aspects of the protohistory of Seveso and the chronology of the events occurring immediately after the explosion at the ICMESA factory.

The author has interviewed several people and consulted a number of publications in an effort to try and throw some light on facts such as why the publication of the formula of one of the most toxic compounds ever described and published in 1957, attracted so very little attention for so many years, and why the more than 20 cases of intoxication with TCDD, which had occurred prior to the Seveso (Italy) disaster, had remained relatively unknown in spite of information found in open literature. In the case of ICMESA, representatives have been interviewed from both the research workers of the chemical companies concerned and Italian scientists dealing with the problems of chemistry and toxicology occasioned by the Seveso accident.

The author has also taken information from a report made by an independent Swedish commission sent to Seveso (Italy) shortly after the accident (Karnedö report). This commission was triggered by an organization that has the ability to send experienced people to investigate without delay any reported medical catastrophe in the world. Many letters sent to the author will also be quoted in this account. Because of the nature of this paper relatively few references will be found in the text. Instead, the list of references has been partly annotated.

The present report does not discuss the problem of dioxins as contaminants in defoliants used in the Vietnam war. In this case the reader is referred to the publications of

* A report written on behalf of the Advisory Subgroup on Toxicology of the European Medical Research Councils (EMRC)

Meselson and Baughman. The thesis of the latter constitutes one of the best and most comprehensive treatise of the subject in general but has, unfortunately, never been printed.

Nomenclature

The term "chlorinated dibenzo-p-dioxins" or, more simply, "chlorinated dioxins" refers to 75 compounds or any combination of the 75. It is theoretically possible to have 75 different chlorinated dioxins each having its own identity and special properties. The term "chlorinated dibenzo-p-dioxins" or, more simply, "chlorinated dioxins" refers to all 75 compounds or any combination of the group.

Only very few of these 75 compounds have been synthesized and studied for their chemical and physical properties, and only 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) has been examined comprehensively for its toxicological effects. However, sufficient biological effects of various chlorinated dioxins have been measured to allow theories to be proposed and generally accepted that 2,3,7,8-TCDD is 3-1,000 times more toxic than the other tetra isomers or any of the other chlorinated dioxins.

There are 22 possible isomers of tetrachlorodibenzo-p-dioxin. TCDD has been commonly used to mean 2,3,7,8-tetrachlorodibenzo-p-dioxin without recognizing the existence of the other 21 tetra isomers. At the time of printing all of them have been synthesized (Nestrick et al., 1979).

Synthesis of TCDD

The sequence of events that led to the synthesis of TCDD has been related by Rappe in the book *Dioxin* 1978, and can also be found in Table 1.

The first chlorinated dioxin, the octachlorinated compound, was prepared as far back as 1872 by two German chemists, Merz and Weith, but the structure of this product was not clear until 1957. In the 1930s a Japanese group under Tomita started synthesizing chlorinated dioxins, but they did not prepare TCDD.

In 1957 Gilman and Dietrich reported that they had prepared the tetrabromodioxin, and in the same year Sandermann et al. published the first synthesis of TCDD. These two compounds were both prepared by halogenation of the unchlorinated dioxins. In both cases the respective laboratory worker was hospitalized.

Table 1. Chlorinated dioxins

1872	Merz and Weith	Synthesize octachlorodioxin structure elucidated only in 1957
1906	Ullmann and Stein	Synthesize unchlorinated dioxin
1932	Tomita et al.	Synthesize chlorinated dioxins but not TCDD
1957	Gilman and Dietrich	Synthesize halogenated dioxins but not TCDD tetrabromodibenzo-dioxines (TBDD) were, however, synthesized
1957	Sandermann, Stockmann and Carter	Synthesize TCDD

Accidents

TCDD can also be prepared by pyrolysis of 2,4,5-trichlorophenol (TCP) and 2,4,5-trichlorophenoxy acids. Uncontrolled conditions during the industrial preparation of 2,4,5-trichlorophenol from 1,2,4,5-tetrachlorobenzene have resulted in severe accidents on several occasions. A list of both accidents and involuntary contamination can be found in Table 2, which also gives references. Some of these accidents deserve special comment.

It is important to note that information on the toxicity as well as on the stability (long persistence and slow degradability) of TCDD was not available at the time the first reports of acute toxicity were observed, and no measures were taken to decontaminate the factories and control the residue levels of TCDD. In fact, the presence of this and related substances was not even suspected. Workers, therefore, were probably exposed for a considerable time following the first observations of acute toxic effects, usually chloracne.

Nitro, West Virginia, USA 1949

The first reported cases of industrial poisoning, due to the formation of TCDD in uncontrolled exothermic reactions occurring during the manufacture of TCP, were seen in 1949 at a 2,4,5-T-producing factory in Nitro, West Virginia, USA. The temperature in one of the reactors containing tetrachlorobenzene, methanol and sodium hydride arose, a relief valve opened and the contents of the vessel was discharged into the interior of the building and over a wide area outside of the building. Two hundred twenty-eight persons were affected.

Symptoms included chloracne, nausea, vomiting, headaches, severe muscular aches and pains, fatigue, emotional instability and intolerance to cold. Laboratory findings showed raised total lipids and raised prothrombin time. Among those affected were not only workmen but also laboratory personnel, medical personnel, and even the Safety Director who visited the area of exposure. Several wives who had never visited the plant also developed acne, usually at the same time as their employee husbands. A man from the nearby town who purchased a truck which was parked in the vicinity of the accident at the time it occurred, and his child, also developed chloracne. The disabling symptoms which kept men from their jobs for as long as 2 years were severe aches and pains and fatigability, the manifestations of peripheral neuropathy. Liver tests were negative 4 years later. Mild residue of acne were, however, common.

Very little was heard about this accident at the time but a standardized mortality analysis has recently been conducted on the workers (Zack and Suskind, 1980). One-hundred-twenty-one workers who developed chloracne resulting from this accident on March 8, 1949, were selected for study. Follow-up of this group was 100% complete. The standardized mortality ratio for all causes of death was shown to be 0.69 with 32 deaths observed and 46.41 expected. For the categories of malignant neoplasms and circulatory diseases, the standardized mortality ratios were 1.00 and 0.68, respectively. Because of the small size of the cohort and the relatively small number of deaths observed, the results of this study cannot be conclusive. However, it is important that no apparent excess in total mortality or in deaths from malignant neoplasms or dis-

Table 2. Industrial incidents associated with the manufacture of chlorinated phenols. Essentially after Young et al., 1974.

Year	Country	Manufacturer/Location ^a	Production/Product ^b	Primary source of exposure	Number of cases
1949	United States	Monsanto/ Nitro, West Virginia	TCP	Explosion	228
1949	Federal Republic of Germany	Nordrhein-Westfalen	PCP, TCP	Occupational	17
1952	Federal Republic of Germany		TCP	Occupational	60
1952-1953	Federal Republic of Germany	Boehringer/ Ludwigshafen	TCP	Occupational	37
1953	Federal Republic of Germany	BSAF/ Ludwigshafen	TCP	Explosion	75
1953-1971	France	Rhone Poulenc/Grenoble	TCP	Occupational and explosion	17
1954	Federal Republic of Germany	Boehringer, Ingelheim/Hamburg	TCP 2,4,5-T	Occupational	31
1956	United States	Diamond Alkali/ Newark, New Jersey	2,4-D, 2,4,5-T	Occupational	29
1956	United States	Hooker/ Newark, New Jersey	TCP	Occupational	Many
1959	Italy	Industria Chimica Melegnano/Saronno	TCP	Occupational	5
1960	United States	Diamond Shamrock/ Newark, New Jersey	TCP	Occupational	Many, 1 fatal
1963	Netherlands	Phillips-Duphar/ Amsterdam	TCP	Explosion	100
1964	USSR		2,4,5-T	Occupational	128
1964	United States	Dow Chemical/ Midland, Michigan	2,4,5-T	Occupational	30

but with modifications

216

Years from incident to last observation ^a	References
30	[28, 30, 59, 68]
1	[3]
—	[4]
—	[23]
24	[21, 22, 30, 61, 62]
2	[16]
9	[36, 37, 37A]
13	[7, 48]
—	[23]
20	[25]
—	[23]
14	[6, 13, 14, 30]
—	[28, 60]
6	[19, 63]

B. Holmstedt

1964-1969	Czechoslovakia	Spolana	TCP	Occupational	NO, 2 fatal	6	[31, 32, 33, 47]
1968	United Kingdom	Coalite and Chemicals Products/ Bolsover, Derbyshire	TCP	Explosion	90	9	[30, 38]
1970	Japan		PCP 2,4,5-T	Occupational	23	3	[44]
1972	USSR		TCP	Occupational	1	1	[69]
1972-1973	Austria	Linz Nitrogen Works	2,4,5-T	Occupational	50	-	[20, 23]
1974	Federal Republic of Germany	Bayer/Ueddingen	2,4,5-T	Occupational	5	-	[20, 23]
1975	United States	Thompson-Hayward/ Kansas City, Kansas	TCP	Occupational	-	-	[23]
1976	Italy	ICMESA/Meda	TCP	Explosion	134	3	[34, 51, 52, 53, 54, 55]

Prolegomena to Seveso

* The name of the factory or company and its location was cited whenever it was available because considerable confusion exists in the published literature as to what incident is addressed. The absence of data indicates the information was not available

* TCP = trichlorophenol, PCP = pentachlorophenol

* Frequently individuals involved in an incident, and who were examined initially, may have also been examined at a later date. The years that lapsed from the exposure until the most recent examination are cited in this column. The absence of a number indicates that only an initial examination was reported in the referenced literature

cases of the circulatory system was observed in a group of workers with a high peak exposure to tetrachlorodibenzodioxin followed over a period of nearly thirty years. A morbidity study of the same group is in progress.

BASF, 1953

In November 1953, an accident occurred at a TCP factory in Ludwigshafen, FRG; 75 workers were exposed to the reaction products during the accident and the subsequent cleaning work. A detailed description has been given by Goldmann (1972). Most workers were affected by chloracne, 42 severely; 21 of the 42 suffered consequent damage to internal organs or disturbances of the nervous system. The most relevant features were polyneuritis, sensorial impairments and liver damage. The son of one of the workers developed chloracne following contact with his father's workclothes. An additional case of poisoning occurred 5 years later concerning a worker who was involved in repair work (welding one of the autoclaves) at the contaminated site; subsequently this worker died with necrotic pancreatitis.

All the 75 workers could be traced in a cohort study 25 years later; mortality was compared both with the regional and national mortality and with a control group of workers from the same factory. In the exposed group, 17 deaths were observed (11-25 expected depending on the control population): six from cancer (four or less expected), five from cardiovascular diseases (as expected), two from suicides (0.2-0.6 expected), one from liver cirrhosis, one from a urogenital tract disease, and two from traffic accidents (Thiess et al., 1976, 1977).

At the beginning the injuries were ascribed to "unknown toxic chlorinated hydrocarbons". Cages containing rabbits were therefore placed at the exposed localities. The animals put in the autoclaves died of liver necrosis after many days delay. Several kinds of cleaning and repainting were tried in view of the recurring cases of chloracne but unsuccessfully. Finally, it was decided to dismantle the factory. This took place under the strictest measures of security in the winter of 1968 to the spring of 1969. The broken-down parts of the building were put into airtight chests and deposited in a deserted saltmine. The metallic parts were melted down.

Schulz, Sorge, and Sandermann

Sometime in the year 1956, K. H. Schulz in the department of dermatology at Eppendorfer Krankenhaus, Hamburg, received a patient with chloracne from the chemical company Boehringer, Hamburg, FRG. This led him to study other workers at the same company and he identified some 30 cases with this disease.

Later on, several cases of chloracne were also identified at the main plant of Boehringer in Ingelheim, FRG. The people in question had all been handling the sodium salt of 2,4,5-trichlorophenol. This compound was manufactured at the main plant of Boehringer in Ingelheim (FRG) and shipped to Hamburg for further processing. In Hamburg (FRG) the shipments received from Ingelheim were reloaded from barrels with shovels, without much attention to the dust clouds arising. No closed system was available and only rudimentary precautions were taken.

In Germany, chloracne had been known of since 1899 and epidemics of the disease had been called "Pernakrankheit" when it was caused by PERchlorated Naphthalenes. To study this disease experimentally, Schulz used the rabbit ear test, originally developed by Adams et al. (1941). He soon found out that pure 2,4,5-trichlorophenol and pentachlorophenol were not chloracnegenic, whereas the technical product of 2,4,5-trichlorophenol was highly active and responsible for the symptoms observed in the workers.

Schulz established a collaboration over several years with Georg Sorge, who was the chemist responsible for the local chemical laboratory of the Boehringer Company in Hamburg, FRG. Sorge played a decisive but neglected role in the subsequent developments but, for reasons of company policy, was not allowed to take part in the publications. Schulz and Sorge tested a number of chlorinated compounds that could possibly be contaminants of the technical product. They established, e.g., that the dibenzofurans were highly active in the rabbit ear test, although they could not be found as impurities in the technical 2,4,5-trichlorophenol.

This is how things stood when another case of dermatitis, type hyperkeratosis and chloracne, was admitted into the department of dermatology, Eppendorfer Krankenhaus in Hamburg, FRG. The person in question was an assistant of Professor Sandermann in the institute of wood chemistry. Sandermann and co-worker had synthesized no less than 20 g of TCDD during their studies of chlorophenols as wood preservatives. The assistant had become contaminated on the face by a cloud of TCDD when opening a desiccator. This unlikely coincidence gave the clue to the possible impurity in the chemical product produced by Boehringer, FRG.

TCDD was previously unknown. Sorge immediately understood that it could be the contaminant responsible for the chloracne among the workers. Although it has never been published, he managed to isolate and identify TCDD in the technical product. He also synthesized TCDD in his fairly primitive laboratory and compared it to the isolated product, establishing unequivocally its presence as a contaminant.

TCDD was found by Schulz to be highly active in the rabbit ear test. Schulz also applied the compound to a spot on his left lower underarm and in 2 weeks developed hyperkeratosis and chloracne. The skin of the spot was excised, studied histologically, and showed the typical lesions.

Sandermann and co-workers published their synthesis in 1957, and in the same year Schulz summarized the toxicology of TCDD (Kimmig and Schulz, *Die Naturwissenschaften*, 1957). It was pointed out that pure 2,4,5-trichlorophenol and pentachlorophenol were not chloracnegenics, that TCDD was both the most toxic and the most powerful chloracnegenic agent of the series of compounds studied, that peroral doses of 0.1–0.5 mg/kg bodyweight in the rabbit were lethal in 1–2 weeks and that the animals, upon autopsy, showed necroses and fatty liver. This succinct summary, although taken notice of by some toxicologists did not lead to any action generally.

Sorge understood the temperature dependence for the formation of TCDD in the process, and developed a low-temperature procedure for the synthesis and production in closed system. Thus, Boehringer's product became more expensive but the manufacture less dangerous (Table 3).

For 5–6 years all batches produced by Boehringer (FRG) were continuously controlled for purity by the simple rabbit ear test. The old factory in Hamburg (FRG)

Table 3. Technology for synthesis of trichlorophenol

Method	Conditions of synthesis	Comments
Dow Chemical	High temperature "without pressure" > 200° C Ethyleneglycol NaOH	In ICMESA NaOH was added to tetrachlorobenzene. In the presence of traces of heavy metals possible condensation to polyethyleneglycol. Exothermal reaction
Boehringer	High pressure in autoclaves 19.5 atm. 157° C Methanol NaOH	Reaction under conditions of controlled temperature. Possibly isothermal

The DOW procedure is economically more advantageous. The necessary temperature is reached in the ethyleneglycol without pressure

was broken up and destroyed. After the occurrence of the cases of chloracne at Boehringer (FRG) and the introduction of the low temperature procedure, there have reportedly occurred no cases of chloracne.

It is quite remarkable that some of the accidents could happen subsequently, in spite of all the warnings. In 1957 the Boehringer Company (FRG) informed other producers using the high temperature method for the manufacture of TCP about the risks and how they could be successfully avoided.

Phillips-Duphar, 1963

An accident occurred at this 2,4,5-T-producing factory in Amsterdam, The Netherlands, during March 1963. After the start of the synthesis, the reaction became uncontrollable. An explosion blew the safety valve as well as the lid of an autoclave, and the contents of the vessel contaminated the inside of the 4,000 m³ building, which became covered with soot. Nobody was injured by the explosion and there was no fire.

At the Phillips-Duphar 2,4,5-T factory, sodium trichlorophenate was synthesized by the hydrolysis of 1,2,4,5-tetrachlorobenzene using sodium hydroxide and methanol at a temperature of approximately 170° C and a pressure of approximately 22 atm. It was estimated that the final temperature in the autoclave was 400–450° C and the pressure > 80 atm. Concerning the cause of the accident, no mechanical failure could be found, but a mistake on the part of the operators could not be excluded.

Hundred and six men are likely to have been exposed to TCDD as they were in the building where the accident occurred during the subsequent period, March–July, 1963. These workers were factory employees, a clean-up crew (non-factory personnel) and plumbing, painting and insulating personnel (non-factory workers).

The personnel has been carefully investigated and it was found that chloracne was the most common and prominent lesion observed following exposure. Liver function tests did not indicate liver damage. A few men complained of fatigue. The latent period

ween exposure and the appearance of chloracne, characterized by comedones, stules and cystes on the face and sometimes on other parts of the body, was proximately 4-6 weeks. A follow up study of the exposed personnel is under

Immediately after the accident, the building was closed. Animal experiments were started since the management knew of problems encountered with 2,4,5-T production in the USA and in the Federal Republic of Germany. Rodents died from dust, peeled off skin, etc. In March 1963, the compound TCDD was said to be unknown to the plant management in spite of reference to the work in Germany! No mention is made of Schulz's 1957 paper. Spectrophotometric analysis was of little use but in 1966, a GLC method for TCDD analysis, developed by Dow Chemical Co, the Netherlands, was introduced. It was estimated that 200-500 g TCDD were released in the building.

The activities in the building included removal of paint from machinery, walls, etc. At the end of 1963 a final decision was reached to close the building since decontamination was deemed impossible. After the unsuccessful decontamination, the plant remained closed for 10 years. In 1973 the factory building was dismantled, embedded in concrete and dumped in the Atlantic Ocean. A question in the Dutch parliament remains the only official document concerning this accident in the middle of a world city (Nagel, 1972).

Two extremely detailed reports regarding safety measures have been published by Daldorup (1974). The workers were using fully protective clothing (air supplied suits). The report shows that in this case advantage was taken of the experience in Germany.

"For the particular purpose with which it all started we received much advice from the medical and safety services of the BASF in Ludwigshafen am Rhein, FRG, where a similar factory building had been disposed of without untoward events a few years ago."

"We are much indebted to Dr. P. J. Goldmann and the chief safety engineer Birkhafin for their kind expose on working procedures and preventive measures, access to documentation, such as films and photographs, and useful advice."

The actual demolition of the factory was carried out in April through the first half of June 1973. An impression of the amounts to be disposed of produced from a building 18 x 125 x 11.5 m with full process equipment together with tools, protective gear and everything that is to be considered contaminated, can be given from the tonnage of the dump ships. Three ships of about 330 tons were filled up to full tonnage, which means 80% of the available volume (all former equipment removed). A harbour had especially to be made for these ships and in such a way that they could be moored parallel to the longest walls and separated from the nearest wall by the crane track (the floor of a non-contaminated wing of the building). A pontoon was used as a windbreaker leaving room for two of the ships together.

Daldorup's papers are full of the most detailed and curious information such as: "If old ships are used, provisions should be made beforehand to ensure proper sinking at the given site by letting water in, but letting nothing of the (solid) contents out."

"Employees with claustrophobia should not be admitted in the working team, and specially for the first working shifts emergency measures should be discussed and agreed upon. Since the suits had the zipper on the back, nobody could free himself with-

out help. Therefore, permission was given to keep a knife within the suit to make a direct escape possible. No one actually took the knife with him."

It even goes as far as to discuss "unexpected events to be expected".

Coalite, England, 1968

Coalite & Chemicals (England) had been manufacturing 2,4,5-trichlorophenol since 1965 and the solvent in this case was ethylene glycol. A detailed description has been given by May, 1973. 1,2,4,5-tetrachlorobenzene and ethylene glycol were charged to the reactor together with ortho dichlorobenzene and caustic soda solution. The vessel was heated by oil and reaction took place at about 180° C with an arbitrary upper limit of 200° C. Since about 1966-1967 caustic soda flake had been charged directly to the reactor, no water being added at this stage.

At midnight on 23rd April 1968, the reaction temperature reached 175° C and thereafter it rose continuously for 50 min. When it had reached a point somewhere in excess of 250° C an explosion of considerable violence occurred and the supervising chemist was killed by falling masonry.

The manufacturing procedure at Coalite (England) did not utilize either pressure or agitation in the autoclave stage. Explosions elsewhere, of which the research staff were aware, used both but at a lower temperature. It was believed that the Coalite (England) method could not produce an explosion and, further more, in the event of an unforeseen temperature rise, "that there would be fewer and less dangerous toxic by-products".

The workers were immediately subjected to a clinical examination but nothing in particular was found. In view of these "satisfactory findings" the building was reopened after 10 days. All damaged and obviously dirty areas were sealed off to be decontaminated properly and at leisure, while the remainder of the building was subjected to a thorough spring clean. Production was then resumed in the greater part of the plant.

For a time work continued normally. Process operators were watched particularly carefully but they all remained well. However, certain men, all of whom had been in Fine Chemicals Unit (England), developed a mild but peculiar skin condition. This took the form of a slight malar erythema and the eruption of tiny vesicles around the borders of the pinnae. The conditions developed and the diagnosis quickly established itself as chloracne. It became widespread. These skin conditions developed among the employees between May and December of 1968 and 79 cases of chloracne were recorded. Within the next 4-6 months the greater majority of cases made an almost complete recovery.

The Fine Chemicals Unit (England) was again closed and no one was allowed into it without special protective clothing, including full face mask, gloves and boots. It was obvious that the entire building would have to be thoroughly cleaned and resurfaced. Heavy and expensive equipment which had been affected by blast or was badly contaminated was buried 45 m deep at the base of an opencast coal mine. Two unexplained cases of chloracne indicating reinfestation occurred when a new factory was constructed at the site.

At the time of the accident it seems that May was unaware of Schulz's 1957 publication.

Other Incidents from Table 2

Concerning most of the other incidents listed in Table 2, much scantier evidence is available. For example, it is known that a number of cases of chloracne occurred at the Dow Chemical Co. (USA) in 1964 and that this led to the termination of the high temperature procedure and the adaption of the Boehringer technique. In connection with this, V. K. Rowe carried out a number of toxicity experiments with chlorinated dioxins on various species and seems to have been the first person to arrive at the extraordinary toxicity for TCDD of an LD_{50} perorally in the guinea pig of $0.6 \mu\text{g/kg}$ bodyweight. The author has seen the original laboratory records and the toxicity tests have since been repeated elsewhere. Early toxicity experiments were sometimes hampered by the long delay between time of administration and time of death.

In February, 1970, the Dow Chemical Company (USA) wrote up instructions for the safe handling of TCDD in the laboratory. These instructions were reissued almost *verbatim* in 1978 on October 10th, and include a description of a "wipe test" to be used in contaminated areas.

Seveso, 1976

As is now well known the only accident where detectable traces of TCDD have been released into the environment happened at the ICMESA plant at Meda/Seveso (Italy), 20 km north of Milan (Italy), and resulted in a most serious environmental contamination. On July 10th, 1976, as a result of this accident, a chemical cloud consisting primarily of 2,4,5-trichlorophenol but also containing some TCDD was released into the atmosphere and over the surrounding area. The plant produced 2,4,5-trichlorophenol by hydrolysis of 1,2,4,5-tetrachlorobenzene with caustic in ethylene glycol at an elevated temperature. Due to so far unknown reasons, a safety valve ruptured and released part of the reactor content. Analysis of the solids from the reactor head showed the presence of TCDD.

The 2,4,5-trichlorophenol was produced for use in the synthesis of hexachlorophene, a bactericide. The process used at ICMESA was similar to the one used in the plant destroyed in 1968 at Coalite, England. The reason why the synthesis went astray is still debated and one of the main issues of the court case now in process in Italy. Another issue concerns the disputed lack of information to the workers and authorities about the potential danger of the operation before and after the explosion.

The sequence of events during the hectic days after the discharge is difficult to follow but two official chronologies issued by the Region of Lombardy (Italy) have partially cleared the picture. In the following the Swiss version (Roche, Reggiani) and the Italian version (Cattabeni, Dept. of Pharmacology, Milan, Italy), and the two chronologies from the Region of Lombardy (Italy) will be given consecutively for the sake of clarity.

From many interviews, unpublished and published documents, the author has formed the following opinion:

ICMESA is a subsidiary of Givaudan, in turn owned by the Swiss company Hoffman La Roche. We are informed that the ICMESA plant started to manufacture TCP in 1972 and that the product was shipped to the US for the manufacture of hexa-

chlorophene. We are also informed that TCDD analyses were continuously performed on the batches of TCP produced. Baughman (1974) in his thesis, also mentions analysis of the American hexachlorophene product made from the TCP shipped to Delaware.

At the time of the explosion the Medical Director of Roche, G. Reggiani, was informed about the situation. According to personal communication he did not know anything about TCDD at that time but acquired information from G. Zbinden, the toxicologist in Zürich, and also through a telephone call to Dow Chemical Company. From Zbinden he received the EPA report on dioxines (Environ. Health Perspectives, Exp. Issue No. 5, 87, 1973). Thus equipped, he set out for Milan, Italy. Upon arrival in Seveso (Italy) on Friday, July 16th, 1976, he was mainly alarmed by the skin damage in children caused by the alkaline chlorophenolates. At that time no other skin damage had occurred.

Before the arrival of Reggiani in Milan, Italy, some important events had taken place. The effect on the vegetation could be observed on July 13th. On July 14th the first cases of intoxications and death occurred among animals and, on the same day, several children were hospitalized with skin lesions. July 15th, the Lord Mayor of Seveso (Italy) issued a decree prohibiting the consumption of all vegetables and food within the area of the factory and the selling of all provisions. On July 17th, the workers of ICMESA stopped working and went on strike. Regarding what happened on July 17th, Dr. Reggiani states the following in a letter to the author:

"The physicians taking care of the children hospitalized on 16th July after the first signs of a skin lesion appeared and who had been confronted with the clinical picture of chemical burns were informed by me on the following day, 17th July, that the lesions were possibly caused by the potentially caustic nature of the reactor contents (sodium hydroxide, sodium salt of ethylene glycol, trichlorophenol etc.) but that a contact with an unknown quantity of dioxin had to be considered too. Literature on this product was therefore handed over to them and I requested them to keep all organic functions of the hospitalized children including blood count and coagulation under close control. They passed on the information in writing to their health authorities."

At the time immediately after the accident, the first and uppermost task assigned to the Givaudan laboratories for analytical chemistry in Dübendorf near Zürich, Switzerland, was to examine the possibility that a certain amount of the contaminant TCDD had been produced and emitted.

The first samples of dust and soil collected with the Dow wipe test procedure on July 14th, 16th, and 18th, did not yield reliable and reproducible results but the samples of grass collected on the following days allowed a good evaluation of the concentration of the dioxin and the mapping up of the contaminated zone. The laboratory chief of Givaudan, Dr. Vaterlaus, came down on the 19th July.

In the meantime, further analytical data were coming from the laboratories in Switzerland, and with their help it was then possible for Reggiani to submit to the Italian authorities a plan for the evacuation and protection of the population. This he did on Friday, 23rd July, as follows:

"That day I requested that the population of the zone we were outlining be immediately evacuated and that the people be prevented from entering it. Furthermore, I suggested that the people evacuated and those living around the area be kept under medical control and weekly follow-up base line examinations for toxic effects be

regularly performed, furthermore, that all personal belongings be left behind in the houses and that fruits, vegetables or animals belonging to this area be not consumed. Pregnant women were to be informed of the remote possibility of an embryotoxic effect" (Reggiani letter, 1977-02-21).

Friday, July 23, represents the turning point for the event "dioxin of Seveso". In the building of the regional Authorities were convened medical specialists from the Region of Lombardy, Italy, and the top officers of the provincial Health Authorities. Chaired by Domenico Amari, Prefect of Milan (Italy) and by the regional minister of health, Rivolta, the meeting carried on the whole day. A statement was issued at the end of the meeting: "The convention is of the opinion that no measures are required for the protection of the population". The experts agreed unanimously that further steps were neither urgent nor necessary. During the television news the Health Director, A. Rivolta, declared on the same day that "everything is under control" (Mazotta, 1976).

The original analytical results as well as the state of the art of analysis of soil and vegetables carried out by Givaudan have been put at the disposal of the author by Drs. N. Neuner (1976) and J. Hostynec (1977). A copy of the paper to the Italian authorities (in French) which was submitted to the Italian authorities on Saturday morning, July 24th, and signed by Waldvogel, director of Givaudan, is also in the possession of the author. Evacuation was commenced that very same day.

Meantime, the scientific activities of the Italians during this period of time is closely connected with two people. Professor Cavallaro, Director of the local Laboratory of Hygiene in Milan (Italy) and Professor F. Cattabeni of the Dept. of Pharmacology of the University of Milan (Italy). Cavallaro paid a visit to the factory on the 16th of July. On the 17th July, Cavallaro was approached by Dr. Ghetti who came to him with a sample of leaves informing him that animals were dying. This led Cavallaro to visit the ICMESA factory also on the 18th July. He wanted to enter the area of TCP production. One Mr. Paoletti in charge of TCP production did not, however, want him to go into the area¹. According to one version he told Cavallaro nothing about TCDD. When Cavallaro went back to the laboratory he looked in the literature (the same day) and found out that TCDD could be formed. The book where Cavallaro found for the first time the information on TCDD is the following:

Chemical analysis of the environment and other modern techniques.

Progress in Analytical Chemistry, vol. 5.

S. Ahuja, E.M. Cohen, T. J. Kneip, J. L. Lambert and G. Zweig (eds.), Plenum Press, 1973.

In this book there is the chapter by J. R. P. Plimmer: The significance of pesticide contaminants. In the chapter there is a paragraph on TCDD, its origin and toxicity (Cattabeni letter, 1978-01-30).

However, according to the Kameda Report, already on the 17th July the factory management confirmed the possible formation of TCDD. This seems to be the first time TCDD was brought up in connection with the accident — 7 days after the explosion.

According to the official version of the Region of Lombardy (Italy), Prof. Cavallaro, on the 18th July, suspected the presence of a substance more toxic than TCP and

¹ In February 1980, Paolo Paoletti, one of the directors of ICMESA, was killed in an ambush by the Italian urban guerrilla group Front Line

suggested TCDD and ICMESA made the first concession to the Health Authorities that same day. However, they did not admit in an explicit way that it was TCDD but they let it be understood that this could be the case. The Kamedo Report confirms that on July 18th, the Laboratory of Hygiene in collaboration with the Institute of Pharmacology at the University of Milan (Italy) commenced analytical work but does not say what this consisted of.

On July 19th Prof. Cavallaro and Prof. Ghetti, on the instructions of the Provincial Medical Officer and the Assessors' Council, left for Zürich (Switzerland), Givaudan's headquarters — the parent company of ICMESA — to ascertain the first results of the analyses carried out on the samples collected by ICMESA's technicians following the accident. On the 20th July they obtained TCDD-standard for analysis and at the same time got the information that a maximum of 2 kg. TCDD had been discharged (Kamedo Report).

In Zürich (Switzerland) the analytical methods were demonstrated to Cavallaro and the toxicity of the dioxin was underlined. As yet, he was not fully aware of the great toxicity of TCDD. Upon returning to Italy, various specialists were called into Seveso (Italy) and the Department of Pharmacology of the University of Milan (Italy) were asked to control the results from Dübendorf and verify the presence of TCDD. (Event: ICMESA, Region of Lombardy, Italy). The sample of TCDD given to Cavallaro probably got into the hands of Cattabeni on July 22nd or somewhat earlier. (Cattabeni interview).

On Thursday, 22nd July, Cavallaro contacted Cattabeni who luckily mastered the mass fragmentographic technique and had access to an instrument. He was, however, as ignorant about the toxicity and chemical properties of TCDD as was Reggiani in the beginning. Cavallaro wanted to know whether a sample of leaves from a tree close to the exhaust contained TCDD. He said it was *dioxin* but gave no formula or other information. A technician from Cavallaro's lab. came 2 h after with a paper about TCDD. The general ignorance about these types of compounds is evidenced by the actions of another scientist who collected leaves with his bare hands 23–24 July and who still suffers from chloracne.

Before the arrival of Cavallaro's technician Cattabeni had already recorded a mass spectrum without observing any precautions whatsoever. From its fragmentation pattern and the characteristic molecular cluster he nearly arrived at constructing the correct formula, as evidenced by documents shown to the present author.

At 23:00 h on the 23rd of July, Cavallaro was able to give the first results obtained from the Department of Pharmacology concerning TCDD analysis, about vegetation and ground in the vicinity of ICMESA. Since this date more than 10,000 determinations of TCDD in soil have been carried out, strangely enough in a department of pharmacology.

Comments

In hindsight many things can be learned from Seveso (Italy) and previous accidents.

The word "catastrophy" is usually associated with sudden (or violent) death or injury. The Seveso (Italy) incident illustrates a completely different type of catastrophe —

with a latency varying from months to decades — organic injuries with teratologic, carcinogenic and genetic manifestations. A discharge of this character is therefore similar to that of radioactive material.

Based upon the many human accidental exposures, it is fair to assume that TCDD has a low acute toxicity to man compared to certain animal species e.g. the guinea pig. The Seveso (Italy) incident confirms this but the delayed appearance of chloracne indicates that man is a sensitive species and the development of this lesion is a sensitive indicator of exposure.

The high animal toxicity and general properties of TCDD were clearly pointed out by Schulz in 1957. Yet in 1976 many scientists were ignorant about the extreme toxicity and even the existence of this compound. Serious work on the mechanism of action started around the 70's and was then prompted more by the discussion of the use of defoliants in the Vietnam war than by accidental exposure in factories. The lack of knowledge about Schulz's paper can only partly be explained by the fact that it was a short note written in German.

The many accidents mentioned in Table 2, some of which have been commented upon in this paper, did not seem to create the necessary awareness outside some specialists in toxicology, industrial hygiene and dermatology. On the other hand, one has to keep in mind the fact that the awareness of the general public with regard to environmental pollution was not great when these accidents occurred, neither was the legislation the same as it is now in most of the countries concerned. It is inconceivable to think that at the present time a factory in a major city could remain closed, contaminated with a deadly poison, for 10 years and then become dismantled and dumped into the sea without the authorities, the general public and the news media, becoming aware of the fact.

The overall information to scientists about potential toxic compounds is also different now: in fact, it is almost overwhelming in its indiscriminate magnitude. There is clearly a case for more cooperation between scientists in the various fields of toxicology, particularly to digest the literature and present conclusions in a form suitable for the non-specialist e.g. industrial chemists.

Although some toxicologists took careful notice of Schulz's 1957 paper, the problem was that no consequences were drawn and no effective distribution of the message was organized. Somehow they were unable, or did not feel called upon, to make proper use of their knowledge in terms of effective warning. The lesson to be learned is improvement of the channels for the distribution of knowledge about, and recognition of compounds with outstanding toxic potentials. In the future a roster of people with both a detailed and broad toxicological knowledge, managed by an international organization like the WHO, would serve a useful purpose provided that it is kept up to date continuously.

As will be apparent from this review, the communication between the chemical companies with regard to the risks of TCDD contamination has been much better.

The Boehringer Company, FRG, already in 1957, informed its competitors about a safer procedure for the production of TCP which was subsequently adopted by many of them. However, even so, major accidents have occurred, e.g., Conitex, England, in 1968; and Seveso (Italy) in 1976. In the latter case a proportion of the general public, for the first time, became involuntarily exposed to the toxic compounds.

The author does not feel called upon to discuss technical details about synthesis but wants only to point out that "run away" exothermal reactions seem to have occurred regardless of starting temperature and solvents used.

In Seveso (Italy) there is no doubt whatsoever that the Swiss firm was fully aware of the potential risks in the manufacture of TCP. Notwithstanding this, the process was carried out in a clearly risky manner, the most obvious evidence being that the safety valve opened out straight into the air, indicating gross negligence.

At the time of the discharge the authorities were faced with the problem of obtaining quickly information about the toxicity of different conceivable toxic substances discharged into the surroundings. At the initial stage they were apparently restricted to local libraries to obtain information that could serve as a basis for action, this, of course, was a time consuming task. In retrospect, this is remarkable in as much as the Dept. of Dermatology of the University of Milan, Italy, in 1962, summarized five cases of chloracne occurring in workmen involved in the manufacture of trichlorophenol from tetrachlorobenzene (Hoffmann and Meneghini, 1962). This was an occupational exposure in 1959 at "Industrie Chimiche Melegnanesi Saronio" in Milan. Through a former co-worker the author has found out that one of the exposed workers is still suffering from outbursts of chloracne 20 years later.

Authorities usually have some supervisory system to protect industrial labour, and the population in general, from injury. Information regarding the general labour protection at ICMESA is extremely incomplete and information to the local people involved may have been voluntarily or involuntarily neglected. The Italian law has articles regarding the obligation of firms to inform their employees about risks in their place of work. The number of the law is DPR (Decreto Presidente Repubblica) 303, Art. 4, the date is March 19, 1956.

Under all circumstances one has to agree with Hans Paul Bosshardt from the Swiss Laboratory of Plant Protection, who in 1973 wrote an article about dioxins, in the *Neue Zürcher Zeitung*, stating among other things:

"In the future, to prevent damage, the technical production of chlorinated phenols and formulations will have to be improved so that polychlorinated-dibenzo-p-dioxins no longer occur. If this is not possible the use of these compounds will have to be drastically limited or totally forbidden.

According to a new Swiss law about poisonous substances, valid for about one year, rules have been laid down which will allow a quick amelioration of these problems. Undoubtedly, the producers of chlorinated phenols, within a reasonable time limit, will be willing to accept this and, without objection, institute changes in their production.

It goes without saying that such problems do not have to be solved in Switzerland alone. Even in this instance an *international collaboration* is indispensable and, luckily, already partly realised.

It behoves our country to be ahead of these questions and to suggest possible solutions of problems concerned with the prevention and decontamination of chemical environmental pollutants."

Acknowledgements. The literature on TCDD is already extremely lengthy. Therefore, the author has not found it reasonable to include references to everything included in this editorial, since he has relied much upon correspondence and personal interviews. In as far as letters are available, they are quoted below. The author would like to express his gratitude to the following people who have contributed to the compilation

I have also greatly relied on the so-called Kamedo report on Seveso and this, perhaps, requires an explanation. Kamedo is a Swedish organization of catastrophe medicine. It consists of a number of preselected scientists in various fields, the number of which can be increased ad hoc by suitable experts. The purpose of Kamedo is primarily to gain experience on how to handle medical catastrophes. To this effect, when an accident happens experts can be immediately and promptly sent to the area where it has occurred. Decisions are made by only a few people, mostly a chairman and secretary of the organization. The missions are expedited without it being necessary to go through various channels. Passports, visas and money are available at the airport. A report is submitted later. In the case of the Seveso catastrophe the Swedish mission's report is dated 1976 not long after the incident and has also been translated into German.

The author would also point out that in addition to the literature given below, he has also relied upon the two official chronologies, completed in 1978, of the ICMESA accident, provided by the Region of Lombardy, Italy.

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