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BRIEF REVIEW OF HEALTH AND ENVIRONMENTAL DATA
FROM THE SEVESO, ITALY, TCDD EPISODE

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NOTE: The following review of scientific data collected by the Seveso Authority was prepared by this author following a visit to Seveso, Italy, June 9-16, 1983.

The exposure of the Italian Community of Seveso to 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD) has provided a valuable data base on which to evaluate the impact of TCDD on human health and the environment. On July 10, 1976, an uncontrolled exothermic reaction during the synthesis of trichlorophenol at the Givaudan - La Roche ICMESA plant at Meda, 30 km north of Milan, resulted in a release of a toxic cloud containing reactor material heavily contaminated with TCDD. The assessment of environmental contamination area downwind from the plant (the community of Seveso) is noted in Table 1.

TABLE 1. ASSESSMENT OF SEVESO ENVIRONMENTAL CONTAMINATION

Date of accident - July 10, 1976
Total TCDD released - 165 gm
Total area impacted - 1800 ha
Number of people evacuated - 733 (July 26 - Aug 2, 1976)
Soil contamination - <5 ppt (Zone R) - 55 ppb (Zone A)
Atmospheric contamination (Dust) - 0.06 - 2.1 ppb (Zone A)
Vegetation contamination- 1.3 - 15.8 ppm (6-13 days, Zone A)

Within a few days of the accident, vegetation, birds and courtyard animals near the ICMESA plant were seriously affected. At the same time, dermal lesions began to appear among the inhabitants of the area. Nine days after the accident it was assessed that TCDD was present in various types of samples collected near the ICMESA plant. As a first step, on July 26, 1976, Italian Authorities evacuated 179 people from a 15-ha area

immediately southeast of the plant. A few days later, further sampling of soil and vegetation indicated the presence of TCDD, which prompted Italian Authorities to evacuate all the inhabitants (733 people) in a wide area, coded Zone A (approximately 110 ha). Zone B (270 ha), the natural extension of Zone A along the main diffusion pathway of the cloud, exhibited lower dioxin contents. Both Zones A and B were enclosed by a larger territory, coded Zone R (1430 ha). Zones B and R were subjected to a number of hygienic measures.

The impact of the TCDD and reactor product on the domestic animals is shown in Table 2. The animals slaughtered in June 1978 were killed

TABLE 2. TOXIC IMPACT OF TCDD ON DOMESTIC ANIMALS IN SEVESO, ITALY

	Died After Accidents	Slaughtered June 1978
Small animals (rabbits, fowl, rats and mice)	3,281	77,078
Cattle	6	298
Horses/Donkeys	2	47
Swine	3	227
Sheep/Goats	1	66

because of the need to control large numbers of rodents capable of carrying TCDD from the contaminated zone into the surrounding community and because of the initiation of large scale clean-up operations.

HEALTH STUDIES

Two factors characterize the history of health surveillance and epidemiologic studies conducted in Seveso: the lack of proper studies in the early phase and problems in defining exposure. Regarding the former point, it is useful to illustrate the characteristics of the area in which the ICMESSA plant is located. It is densely populated area with a mixed social and economical structure: family agriculture, homeyard animals breeding, small handicraft shops and industries, wood and furniture factories, and chemical plants of various types. The suddenness of the

ICMESA accident literally upset both the social and economical structure of this area. During the initial period, when animals were dying and children were developing skin problems, it was expected that the whole population was going to show major health short- and long-term effects. The attitude which then evolved was a kind of a "self-defense", a psychological refusal for everything connected with dioxin. This attitude caused and is still causing many difficulties in executing clinical studies. It is in this atmosphere that the epidemiological studies in Seveso area had to be designed and started. This atmosphere was also reflected in the actions undertaken during the period immediately following the incident. Following the evacuation of the most polluted A Zone, an intensive screening program was started, in which blood tests and clinical examinations were freely offered to anyone living in the polluted area, or to those that had been potentially exposed to TCDD. An intensive campaign of chemical analysis of ground samples from a wide area for presence of TCDD was also undertaken. No standardized protocols or control groups were identified. The population was expected to show many effects and it was expected that refined studies were unnecessary.

During the summer of 1979, it was clear that, fortunately, a major disaster of population-size had not taken place. On the other hand, the lack of well-designed epidemiological studies had made it impossible to rule out that minor health effects had affected large portions of the population of the area or that very serious effects had occurred in very limited subgroups.

Human health monitoring data were collected on the parameters noted in Table 3. As was noted many of the monitoring programs were designed to assess acute effects. The need for long-term health studies was not formally acknowledge until 1979. Registries for mortality and cancer were not established until 1980.

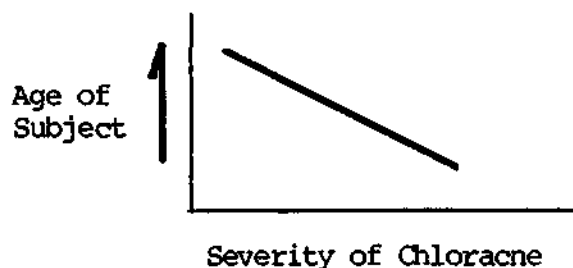
TABLE 3. HUMAN HEALTH MONITORING STUDIES OF THE SEVESO, ITALY POPULATION

<u>Acute</u> (Short-term)	<u>Chronic</u> (Long-term)
Dermal	Chloracne
Neurological	Cancer
Immunological studies	Mortality
Involvement of organs and systems	
Cytogenetic studies	
Pregnant women and newborns	
Abortions	
Congenital malformations	
Neonatal growth	
Embryomorphological studies	

Dermal. As can be seen in Table 4, most of the 187 cases of chloracne occurred in children; however, only school-aged children and not adults, were systematically screened for chloracne. Although these data suggest that children may have greater sensitivity to the acnegenic effects of TCDD than adults, the potential in exposure, between children (who were likely to have played outside) and adults, may have contributed to the differences in symptoms between children and adults.

TABLE 4 THE OCCURRENCE OF CHLORACNE FOLLOWING
"ACUTE" EXPOSURE TO TCDD IN SEVESO, ITALY

<u>Age of Subjects</u>	<u>Number</u>	
0 - 4	19	
5 - 9	108	160 "young" children
10 - 14	33	
15 - 21	20	
>21	<u>7</u>	
	187	32,000 children screened



Neurological. Neurological effects were reported and a summary of the neurological findings are shown in Table 5. As noted only a small percentage of those evaluated were diagnosed as having polyneuropathy of peripheral nerve and fibers. Three individuals were hospitalized and diagnosed as having polyneuropathy of the lower extremities.

TABLE 5. NEUROLOGICAL FINDINGS IN SELECTED SUBJECTS, SEVESO, ITALY

190 Children (52 with chloracne)

432 Adults

Subjected to clinical and neurophysiological examinations

10% disclosed evidence of impairment

Question etiologic relationship

Children with chloracne showed no impairment of nervous system functions.

Immunological. The study of immunological capability was repeated several times between 1976 and 1979. The results are shown in Table 6. Although in vitro tests produced evidence of decreased immune competence, the affected children at Seveso did not experience a higher incidence or severity of childhood diseases than children from other parts of Italy.

TABLE 6. RESULTS OF THE IMMUNE CAPABILITY STUDIES PERFORMED BETWEEN 1976 AND 1979 ON SEVESO CHILDREN WITH AND WITHOUT CHLORACNE

Investigation of immune capability (1976 - 1979)

Results

For children with and without chloracne

- increased complement hemolytic activity in six out of six examinations, higher for chloracne cases
- increased mitogenic response (PHA and PWM) in three out of six examinations
- increased peripheral blood lymphocytes number in two out of six examinations

No consistent difference from control for the remaining tests

Involvement of Organs and Systems. The chloracne cases in Seveso provided biological evidence of a toxic effect of TCDD. Thus, chemical analysis of several functions repeated several times during the years following the accident permitted an opportunity to evaluate permanent abnormality of those functions which did not exist before the accident. In such an evaluation of the chloracne cases, no clear cut pathological condition developed of the liver or of carbohydrate, fat, protein or porphyrin metabolism as a consequence of the exposure.

Cytogenetic. Chromosome analyses have also been performed on the blood of people belonging to a group of 145 acute cases and 69 chronic exposure cases. The cases included 73 ICMESSA plant workers and 14 children with and 15 without chloracne. These exposed cases were compared to 87 control group cases. The average frequency of gaps, breaks and structural rearrangements found were within the accepted standard frequency.

Pregnant Women and Newborns. Intense efforts have been made by the Italians to examine the effects of TCDD on pregnant women and newborns. Although many reports have been published, definitive answers are yet not available for the following reasons: (1) lack of reliable indicators of exposure; (2) problems of sample size; (3) delay in implementation of the studies; and (4) the results of the studies on abortivity and birth defects which started on separate protocols, have not yet been collated. Considering all these limitations, the data for pregnancy from October 1976 to September 1977 show higher rates of abortivity in Zones A and B compared with that observed in the Zone R and in the out area, which are quite similar. In the third trimester 1976, many exposed women had induced abortions. Many pregnancies started outside the area because of holidays and evacuation. The abortivity rates observed in Zones A and B during these four trimesters were the highest observed in any period and in any zone.

The rates for the second period (1978 and 1979) which are much more reliable, show a declining trend in Zones A, B, and R in contrast with stable rates in unpolluted zones. The trend does not reach statistical significance, but it is quite suggestive. A clear seasonal variation was observed both in 1978 and 1979 in the polluted zones but not in the out area. The difference between abortivity rates during 1978 in Zones A, B, and R versus the out area reaches statistical significance. This difference disappeared in 1979.

In conclusion, the available data provide evidence suggesting an increase in abortivity rates in the polluted zones, from September 1976 to 1978, possibly attributable to the accident. Values returned to normal after 1978.

The data concerning birth defects are also confusing. Birth defects, which appear, as a whole, with a frequency varying from 25 to 150 every 1,000 newborns, are relatively rare when considered separately, with frequencies varying from 0.1 to 10-20 per thousand newborns. Therefore, if the 2,700 births per year in the whole area are stratified by pollution zone, very small numbers are obtained of little, if any, statistical meaning. Furthermore, before the accident, birth defects in this area were largely under-reported. Thus, data cannot be compared with those of previous years. Comparisons with data from other registries are affected by possible differences in the various operations of each registry and by the geographical variation in baseline birth defect rates.

Most of the rates of birth defects fall within international ranges. Furthermore, the possibility of an association with TCDD pollution is supported by the overall evidence of polydactily and Down's Syndrome. Nevertheless, an association is suggested by the available evidence concerning hemangiomas and, perhaps, neural tube defects. It is more clearly indicated for hypospadias, because of a strong consistent excess over other registries and a weak correlation with potential TCDD exposure, and for both cardiovascular and multiple defects, because of a reasonably good correlation and a possible time trend.

Neonatal Growth. The examination of 2,000 newly born infants of the Seveso region has revealed no abnormalities with respect to the somatic and psychic development of the child.

Embryomorphological Studies. Embryomorphological studies were performed on 34 cases of abortion. In the majority of these cases, the pregnancy had been interrupted at the gestational age of 5-6 to 15-16 weeks. Direct examination and radiophotography did not detect any gross or clear signs of damage brought about by the action of an exogenous agent. The cases of spontaneous abortion showed different morphological alterations obviously due to a variety of causative factors. Nevertheless, increases in the frequencies of aberrant cells and in the average number of aberrations per damaged cell were found in the fetal tissues of exposed pregnancies. Continued study is indicated.

Cancer Incidence. Cancer incidence studies have now been established in order to obtain stable and reliable baseline rates. The main problem which now exists is to verify the diagnosis of cancer and to connect this with specific individuals in order to avoid inclusion of multiple hospital admissions for same case in these data. Data are being collected on several selected types of cancer, cancer among children under 15 years of age and other types of cancer that can be considered more interesting on the basis of the animal experiments, epidemiological data or, possibly, a shorter latency period. Although only preliminary manually processed data are available, most of the cancers were considered "rare". It is not known whether, and how, at this point, the data reflects prevalence and/or incidence rates. In general, the data reflect the rates observed in the Registry of Varese, a town close to the Lombardy Region.

Mortality. Mortality studies on a general population exposed to a chemical are not very powerful tools for detecting health effects, but are necessary for two reasons: (1) to establish a baseline, in which the general mortality pattern of that population is defined in relation to possible relevant deviations, and (2) as a source of data for organ-specific incidence or mortality studies (cancer registry, liver disease, etc.).

The mortality pattern of the Seveso area from 1975 to 1980 reflects that of industrial countries, with cardiovascular diseases and cancer as leading causes of death. Mortality from liver diseases was higher than in the rest of the Lombardy Region, but this phenomenon was found in 1975. No remarkable differences between zones at different populations were observed, or was there acute deaths attributable to TCDD exposure in Zone A residents. There was one case of liver cancer death in 1977 but it was not attributable to TCDD exposure due to the ICMESA accident, because of a too-short latency period.

Concluding Environmental Assessment. In 1980-1981 the TCDD contamination in safety Zone R was no longer measurable. Vegetables and agricultural crops grown in Zone R for experimental purposes have invariably been found to be free of 2,3,7,8-TCDD at the 1 ppt level. About one-third of Zone R has been released for agricultural purposes and official liberalization of the rest of Zone R is expected soon.

In Zone B the ban on the use of the land continues. Measurable amounts of TCDD are still found in the soil, typically in the order of 10-50 ppt. Measurements of plant samples showed in 1977 and 1978 that TCDD was not present at the 1 ppt level.

Part of Zone A was decontaminated in 1977 and two-thirds of the evacuated houses were reinhabited. Clean-up standards used at Seveso are shown in Table 7. An area of about 50 ha is still fenced-in and decontamination operations are underway. The topsoil in the most contaminated parts of Zone A are being removed and buried locally in plastic-lined basins. The less contaminated parts have been treated by agronomic methods. Finally, the entire zone will be covered with new topsoil and the resultant green area will be donated to a foundation.

TABLE 7. CLEAN-UP STANDARDS USED BY THE SEVESO AUTHORITY

Contaminated areas were established based on analytic sensitivity of 0.01 ug TCDD/kg soil.

1977 regional law barred areas having more than 50 ug/m² (0.5 ppb) to human habitation.

"Insides" of homes - 10 ng TCDD/M²

Agricultural soil - 5 ppt TCDD

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