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Chloracne Following Environmental Contamination by TCDD in Seveso, Italy

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Data are presented on the occurrence of chloracne, clinical symptoms and biochemical changes in 164 children following environmental contamination by TCDD from an industrial accident in Seveso, Italy. An overall positive association was found between the territorial distribution of chloracne cases and the different levels of soil contamination in the affected area. Individual risk factors such as condition and length of exposure, intake via contaminated foods, etc. were evaluated; no single factor appeared to be associated with chloracne. Disturbances of the gastrointestinal tract were more frequently observed in children affected with chloracne than in those from the same areas having no skin lesions. However, no clinically definable systemic disease has been diagnosed.

On July 10, 1976, an accident occurred in the ICMESA plant in Meda during the production of trichlorphenol. This resulted in widespread contamination of parts of the towns of Seveso, Meda, Cesano Maderno and Desio by 2,3,7,8 tetrachlorodibenzo-para-dioxin (TCDD).

Knowledge of the effects of TCDD on man comes mainly from studies of industrial accidents. Chloracne, first described by Herxeimer[1] has been frequently observed.[2–16] Chloracne is a syndrome characterised by the presence of comedos of various sizes and symmetrically distributed corneal cysts, not usually associated with inflammatory phenomena. Lesions are generally localised on both sides of the face, beginning from the temporal regions, and caused by the elimination of chlorinated compounds through the pileus-sebaceous apparatus. In more severe cases, lesions may also occur on other parts of the body and then they have an inflammatory or pustular appearance (Puccinelli, personal communication). Chloracne may be caused by various chemical compounds such as chlornaphtalenes, polychlorbyphenils (PCB), polychlordibenzofuranes (PCF), contaminants of chlorphenols (TCDD and other dioxins) and chlorbenzenes.[17,18,19]

In addition to chloracne, porphyria cutanea tarda,[3,10,11] hyperpigmentation and hirsutism[3,13,14] have also been reported. Morphological damage to the liver has been observed with moderate fibrosis and steatosis, hepato-cellular degeneration and hemofuxine deposition, and an increase in hepatic enzymes.[2,3,5,7,8,10,11] Reported frequencies range from 9 to 36%.[3,10,11,15,16] An increase in hepatic enzymes was also noted by Poland et al.[14] Changes in lipid metabolism have been reported,[10,13,14] as well as changes in carbohydrate metabolism.[7,8,10,11,14]

Studies of porphyrins showed changes in exposed subjects not necessarily affected with chloracne. Bleiberg et al[3] noted some increase in uroporphyrins in 37% of the workers exposed to 2,4 DCF and 2,4,5 TCF, but concluded that there was no correlation between an increase in porphyrins and the extent of exposure to the poisonous compounds, or between the severity of chloracne and the presence of porphyria. Poland[14] also found that the occurrence of chloracne was not correlated with the concentration of porphyrins excreted, but Jirasek[10,11] described the simultaneous presence of chloracne and a marked, long-term increase in porphyrin metabolism in 14% of the individuals examined. With regard to Ala-U, Jirasek[10,11] noted a considerable increase in concentration in subjects with

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chloracne as compared to a control group. The increases, however, did not correlate with porphyria cutanea tarda. A slight increase in Ala-U in a group of workers exposed to TCDD was also observed by Poland.[14]

Goldman[7] reported a short-term involvement of the myocardium, respiratory tract, pancreas and urinary tract, and Jirasek,[11] a case of atherosclerosis. Involvement of the respiratory tract was also observed by Bauer et al,[2] and that of the urinary tract by Carter et al.[4] Insofar as neurological disturbances are concerned, there are descriptions of cases of neuropathy,[7,8,10,11] weakness of the lower limbs,[2,6,7,8,10,13,14] abnormalities of sight, hearing, taste and smell,[7,8,13,14,20] and depression and neurasthenia.[2,6,7,8,10,11,13,14]

Kimming and Schulz,[12] referring to chloracne subjects with previous aspecific acute skin lesions, noted the presence of subjective symptoms of the gastrointestinal tract, without objective clinical evidence of general impairment. Lack of such evidence was also reported by May[15] and Poland et al.[14]

In 1971 a 6 year old girl reported headaches, diarrhoea, nosebleeds, blood in urine and painful micturition, whilst her sister (10 years) and her mother reported abdominal pain, diarrhoea and recurrent headaches following the use of waste oil as a dust-control measure in an indoor horse-arena. All symptoms disappeared in a few months: 5 years later a full examination yielded negative results.[21]

Studies carried out on Vietnamese exposed to defoliants used for war operations claimed an increase in birth defects and premature deliveries[22] and liver tumours.[23] The results of these studies are inconclusive, however, due to the inadequacy of the data-collecting methods, particularly for birth defects,[24] the poor quality of epidemiological data and the presence in the defoliants of a great number of compounds other than TCDD.

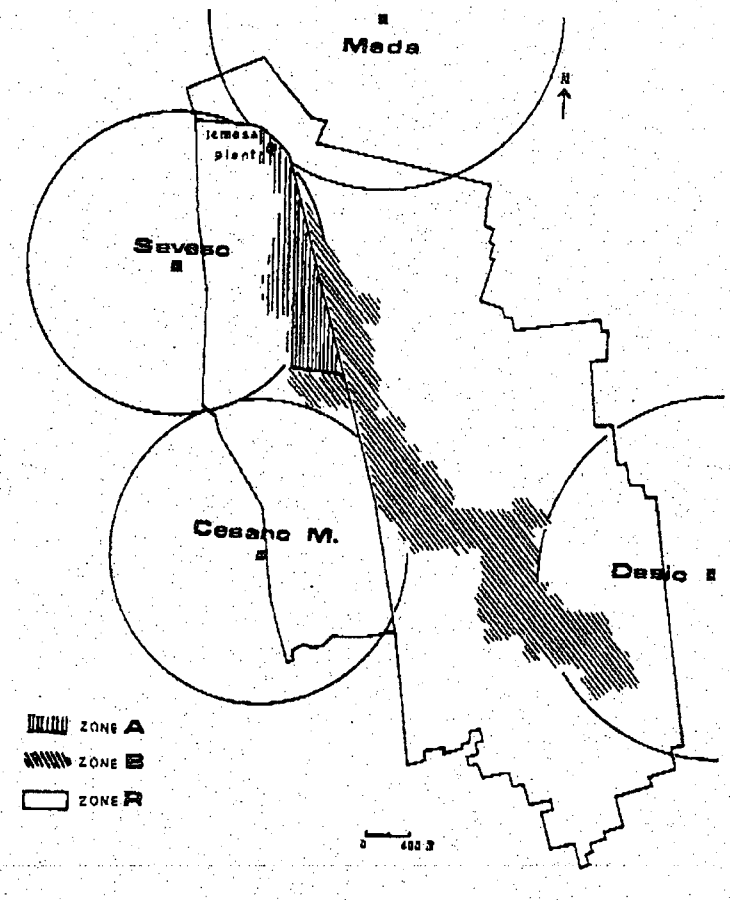

FIGURE 1 *Map of Seveso area by pollution zones.*

The aim of the present paper is concerned with the distribution of cases of chloracne following the industrial accident of Seveso and the association between chloracne and general clinical impairment.

STUDY POPULATION AND METHODS

On the basis of analysis of contamination in the soil, the affected area was divided into 3 zones, as shown in Figure 1. More detailed analytical results are provided in Table 1.

Zone A. 80.3 hectares, 730 inhabitants. This zone, which was the most highly contaminated, was divided into 7 sub-zones, A_1 to A_7, A_1 being closest to the ICMESA plant.

Zone B. 269.4 hectares, 4737 inhabitants. Average contamination levels lower than those of zone A.

Zone R. 1430 hectares, 31 800 inhabitants. This zone which surrounds zones A and B showed low, scattered contamination.

Zones A, B and R span parts of 3 Local Health Districts (CSZ Brianza di Seveso): such districts (220 100 total population) are all included in the health surveillance programme. Therefore, a fourth zone, non-ABR, is considered. In this zone the TCDD contamination in the soil was not evaluated.

Population data up to July 10, 1976, were provided by the Local Register Office for each town in zones A and B, whereas those for zone R and non ABR were estimated from the last National Census in 1971 (Table 2).

The inhabitants of zone A were evacuated between July 24 and August 2, 1976. In zones B and R only children and pregnant women were evacuated: others were allowed to remain and instructed to follow a number of hygienic rules, including temporary advice not to start pregnancies. No particular rule was established for the inhabitants of zone non ABR.

In September a household questionnaire collecting information on each family member was administered to people coming from zone A and B by public health nurses. The following questions were asked:

- Was the individual in the contaminated area on July 10, 1976?
- Did the individual continue to live in the contaminated area during the month following the accident?
- Did any farm animals owned by the family die due to poisoning?
  Did the individual consume any food (fruits, vegetables, animal products) produced on his own land, following the accident?
- Did the individual (if adult) work or (if child) play in the contaminated area following the accident?

The information collected was analysed for both the frequencies of single risk factors and the exposure characteristic for the population of each zone.

TABLE 1 *Distribution of TCDD contamination ($\mu g/m^2$) in the A, B, R areas on the basis of GC-MS analysis of soil samples (data provided by Regione Lombardia, Piano Operativo no. 1)*

Zone	Size (ha)	$\mu g/m^2$ TCDD values average	$\mu g/m^2$ TCDD values highest value	No. samples	Negative samples* No.	Negative samples* %
A	80.3	192.8	5447	306	12	3.9
A1	10.7	580.4	5447	51	1	1.9
A2	5.1	421.1	1700	19	0	0
A3	9.2	350.5	2015	34	3	8.8
A4	7.2	134.9	902	26	3	11.5
A5	16.3	62.8	427	50	2	4.0
A6	14.0	29.9	270	61	2	3.2
A7	17.8	15.5	91.7	65	1	1.5
B	269.4	3.0	43.8	106	26	24.5
R	1430.0**	0.9	9.7	449	308	68.6

* less than 0.75 $\mu g/m^2$

** only 950 hectares examined

TABLE 2 *Distribution of population by pollution zones and age*

Age	A*	B*	R**	non A,B,R**
0 – 14	214	1 468	8 680	48 263
15 and over	516	3 269	23 120	134 580
Total	730	4 737	31 800	182 843

* Actual figures at July 10, 1976
** Estimated population on 1971 census

At the same time a wide health surveillance plan was established as reported in a previous paper.[25]

A few days after the accident several people began to complain of burning skin lesions and asked to be examined by dermatologists. Between September and December 1976, 34 cases of chloracne were diagnosed by dermatologists in children under 15 years of age who presented themselves to the clinics. Dermatological data were collected by the Department of Dermosyphilopatic Diseases of the University of Milan (Director: Professor V Puccinelli). Between February and April 1977, dermatological screening was carried out on all children under 15 years of age attending nurseries, infant and primary schools of the 3 Health Districts. Children were submitted to a full examination. Out of 522 children selected as positive, on further examination 392 were considered negative whereas 130 were diagnosed as having chloracne, according to the clinical classification, approved by EEC Commission during the 1st Chloracne Panel (Milan, 11–12 July 1977).[26]

This classification is based on the type of lesions (comedos, cysts, pustules) and their site (face, neck, chest, back, other). In addition 5 categories of severity were established in attempting to quantify the stages of the lesions as follows:

- 0 : no lesion.
- 1 : a few comedos (up to 10) – minimum stage.
- 2 : numerous comedos and cysts – light stage.
- 3 : comedos and cysts in specific regions – medium stage.
- 4 : comedos and cysts spreading from the face to other regions of the body – serious stage.

From September 1976 to July 1977, 23 more cases of chloracne were registered in adults over 15 years of age distributed as follows: 19 in zone A, 1 in zone B, 1 in zone R, 1 in zone non ABR and 1 outside the 3 Health Districts.

A clinical follow-up was undertaken on 146 (89%) of the 164 affected children. 182 children of the same age from zones A,B,R and from the surrounding area within the three Consorzi Sanitari di Zona (Health Districts) Brianza di Seveso, voluntarily submitting to examinations and having no skin lesions are used as a comparison group. 45 of the 182 children came from zone A, 12 from zone B and 125 from zone non AB (zone non AB includes zone R and non ABR).

Medical examinations of children of both groups took place for the most part at varying intervals in 1977. In addition, there was a lack of uniformity in recording data on the 2 groups. Classification of clinical signs and symptoms was carried out retrospectively on the basis of available records.

The following biochemical tests, selected by the Regional Medical Commission on the basis of the current literature, were performed:

- γ – glutamil-transpeptidase (γ-GT);
- glutamate oxalate transaminase (GOT);
- glutamate piruvate transaminase (GPT);
- total cholesterol (CHOL);
- δ – aminolevulinic acid (Ala-U);
- alkaline phosphatase (ALP);
- total bilirubine (BIL);

For each test, the frequency of individuals exceeding the threshold limits in at least one specimen was calculated. Simple statistical procedures, such as the χ^2 test and epidemiological indices (odds ratios[27,28]) were calculated. The association of TCDD concentration in the soil and the stages of severity of chloracne was examined using a χ^2 test derived from an extension of the Mantel-Haenszel procedure.[29]

RESULTS

Distribution of chloracne cases

Table 3 shows the distribution by sex and age of chloracne cases detected during the ambulatory care and the screening. 95 cases (59 boys and 36 girls) aged 5–9 years were identified by screening.

TABLE 3 *Distribution of chloracne cases by sex and age and mode of ascertainment*

Age Groups	Chloracne cases presenting Sept–Dec 1976			Chloracne cases identified Feb–Apr 1977		
	m	f	mf	m	f	mf
0 – 4	6	5	11	4	4	8
5 – 9	6	7	13	59	36	95
10 – 14	4	6	10	18	9	27
TOTAL	16	18	34	81	49	130

TABLE 4 *Chloracne subjects age 0 14. Number by zone and percentage of child population*

Zones	No. of cases of Chloracne	Total population 0–14 yrs	%
A	42	214	19.6
B	8	1 468	0.5
R	63	8 680	0.7
non ABR	46	48 263	0.1
others	5	–	–

It is difficult to explain the excess in this age group, particularly as it is not present in those who came to the dermatological clinics in the first months following the accident.

Of the 5 cases of chloracne from 'other' zones reported in Table 4, 3 were diagnosed between September and December 1976 in children from far-away communities who were involved while spending their holidays in zone A, and 2 were in children living outside the area of the 3 Health Districts but attending the schools involved in the screening. The highest frequency of chloracne was seen in zone A and the lowest in zone non ABR, while in zones B and R the frequencies were low and almost the same despite the different mean levels of TCDD contamination of the soil (3.0 vs. 0.9$\mu g/m^2$). Since zones R of Seveso and Meda are closer to zone A than many parts of southern zone B, it is likely that people from such zones could have had direct or indirect contact with zone A before it was evacuated and fenced off. This trend is confirmed by the odds ratios calculation (Table 5) by paired zones. The OR of zone A vs. zone non ABR is the highest; the OR of B and R vs. non ABR is still around 5 and 7; while the OR of R vs. B is close to 1.

An analysis was carried out in order to investigate a possible association between the severity of each case of chloracne, ranking from severity stage 1 (least severe) to 4 (most severe) and the ground concentration of TCDD measured at the sampling point

TABLE 5 *Odds ratios for pairs of groups (zones)*

Pairs of groups		OR*	p**
A vs.	non ABR	205.9	<0.01
B vs.	non ABR	5.7	<0.01
R vs.	non ABR	7.7	<0.01
A vs.	B	36.1	<0.01
A vs.	R	27.0	<0.01
R vs.	B	1.33	>0.20

* These figures were obtained by comparing the proportion of chloracne subjects 0–14 years to total population 0–14 years, in pairs of zones

** 2 x 2 Mantel-Haenszel chi-square test[28]

closest to each case's residence. Only cases in zones A, B and R were considered: 2 cases had to be excluded as corresponding analytical values were not available leaving a total of 111 cases. Ranking scores[29] were assigned to 4 ranges of TCDD concentration and degree of severity of chloracne. Table 6 shows a marked and highly significant relationship between them.

Chloracne and clinical findings

A special study was carried out on 146 (89%) of the 164 chloracne cases under age 15 in comparison with 182 children without skin lesions from the same area.

Table 7 shows the frequency of positive signs and symptoms present for children with and without chloracne in at least one examination. The symptoms are divided into 10 categories. A significant difference ($p=1.6\times10^{-4}$) between the two groups was found with respect to symptoms of the gastrointestinal tract (lack of appetite; nausea; vomiting; abdominal pain; gastritis). The odds ratio (children

TABLE 6 *Distribution of severity of chloracne by range of TCDD concentrations*

Severity of chloracne	Score	TCDD conc. $\mu g/m^2$ n.d.*–14 (0.35)	15 – 59 (0.73)	60 – 240 (0.79)	>240 (0.905)	Total
Chl.1	(1)	67	5	1	4	77
Chl.2	(2)	9	4	1	4	18
(Chl.3+Chl.4)	(3.5)	–	–	2	14	16
TOTAL		76	9	4	22	111

Mantel χ^2 test with 1 d.f.[29] : $P = 2 \times 10^{-10}$

* Below the level of detectability ($0.75 \mu g/m^2$)

TABLE 7 *Frequency of positive clinical reports in children with and without chloracne*

Clinical Reports		Subjects with chloracne No. 146	% 100	Subjects without chloracne No. 182	% 100	p*
1.	Urinary tract	8	5.5	3	1.6	0.06**
2.	Inflamed joints	4	2.8	1	0.5	0.12**
3.	Upper respiratory tract	9	6.2	6	3.3	0.16
4.	Gastrointestinal tract	19	13.0	4	2.2	1.6×10^{-4}
5.	Headache	7	4.8	3	1.6	0.01
6.	Eye irritation	9	6.2	4	2.2	
7.	Impaired vision	11	7.5	8	4.4	0.16
8.	Liver enlargement and/or scleral jaundice	12	8.2	10	5.5	0.23
9.	Paleness	1	0.7	5	2.7	0.03
10.	Other dermatological symptoms	2	1.4	8	4.4	

* one-sided χ^2 test

** one-sided Fisher exact test

affected with chloracne vs. children without) was therefore calculated with the corresponding confidence limits at the 95% probability level (OR=6.65; log SE=0.562 confidence limits: 1.612–27.491). Headache and eye irritation, considered together, were also more frequent in chloracne subjects ($p=0.01$), while paleness and other skin symptoms were more frequent in subjects without skin lesions ($p=0.03$). These findings are also confirmed when the 2 groups are compared by zones. Disturbances of the gastrointestinal tract were more frequent among chloracne subjects living in zone A than among those in zone non AB ($p<0.05$). These 2 zones theoretically represent the maximum and minimum levels of TCDD exposure.

Table 8 shows a comparison of selected biochemical tests in children with and without chloracne. More instances of abnormal γGT, GPT and Ala-U were found in children with chloracne than in those without (respectively: $p=2.3\times10^{-4}$, $p=0.035$ and $p=1.2\times10^{-5}$). For the Ala-U test, the odds ratio for the chloracne group vs. the comparison group is 5.80, with log SE=0.436 and confidence limits: 2.038–16.518. The Ala-U abnormalities were not, however, large. These results are also confirmed when the chloracne groups are compared by zones. Children with chloracne living in zone A show a higher frequency of abnormal values than those living in zone non AB (14 out of 39 vs. 17 out of 91). Although this difference is not statistically significant ($\chi^2=3.55$; 1 degree of freedom; $0.05<p<0.10$), it is coherent with the observations discussed earlier.

DISCUSSION

Interpretation of these findings is difficult. Several factors which could limit the validity of the conclusions should be pointed out.

All cases of chloracne were studied as a single group, despite the fact that they were identified in 2 ways, firstly by presentation to dermatologists and secondly by screening of the school population. All cases identified during the period September–December 1976 were detected in children of zone A (or those living there during the accident). In spite of the general recommendation to call the physician, no case was reported in other zones. In addition, in zone A 31 (74%) out of 42 total cases were identified during this period. In zones B, R and non ABR chloracne cases were discovered only by the screening. Therefore the validity of the case findings could be affected by the different criteria of detection.

It was impossible to get reliable information on time of onset since these data were available only in a small proportion of cases. It is not possible, therefore, to calculate a true incidence of chloracne, or to compare the duration of clinical manifestations with episodes previously reported.[5,13,14,18] Lack of information on the times of onset of individual cases makes it impossible to predict the likelihood of occurrence of further cases after April 1977. Following the initial screening, no further examinations were undertaken.

Actual figures on population data for the 3 Health Districts could not be obtained: it was only possible to have actual data as at July 10, 1976 for zones A and B by means of a special process. Popul-

TABLE 8 *Frequency of children with biochemical tests exceeding threshold limits*

Biochemical tests (Threshold limits)		Subjects with chloracne (146) No. Subjects	No. over threshold	%	Subjects without chloracne (182) No. Subjects	No. over threshold	%	p**
γGT	(≥ 37 U/l)	141	4	2.8	138	–	–	2.3×10^{-4}***
COT	(≥ 27 U/l)	141	16	11.3	138	14	10.1	0.45
GPT	(≥ 24 U/l)	141	5	3.5	138		–	0.035***
CHOL	(≥ 231 mg %)	138	21	15.2	120	15	12.5	0.32
ALA–U	(≥ 6.1 mg/l)	137	33	24.1	135	7	5.2	1.2×10^{-5}
ALP	(≥ 151 U/l)	142	7	4.9	148	8	5.4	0.47
BIL	(≥ 1.2 mg %)	142	0		145	0	–	–

* Number of subjects from whom at least one specimen was obtained
** One-sided χ^2 test
*** One-sided Fisher exact test

ation of other zones were estimated using 1971 national census information which every 10 years updates population data by age, sex and all other variables. Also, because of the poor reliability of the record system of school population it was necessary to use estimates.

The comparison between children with and without chloracne could have been affected by an important bias: the children who formed the comparison group were obtained only because clinical documentation and/or biochemical data were available. Clinical data for cases and controls were collected without a definite preliminary standardisation: the classification of signs and symptoms was carried out retrospectively on the basis of the available records. Lack of uniformity in the collection of clinical data for cases in respect to controls is a possible bias, as well as the irregularity of the timing of clinical examinations.

For the analysis of the distribution of chloracne cases in zones with different levels of soil contamination several statistics were calculated. Frequencies and odds ratios, while confirming a substantial agreement with the distribution of ground contamination values in zones A and non AB R, show a very similar risk of chloracne in children of zone R and B (OR=1.33). Therefore, one may hypothesise that the exposure to contamination in zone R was higher than soil concentrations in the same zone would indicate. The presence in the toxic cloud of volatile compounds, easily transported by air and suspended at length in the atmosphere, could have allowed inhalation.

Exposure of the chloracne group, as determined by questionnaire, did not present any characteristic pattern. No single risk factor appeared to be associated with chloracne. Deaths among farm animals were more frequently reported by subjects with chloracne, but as these data were collected for administrative purposes (eventual reimbursement) definite conclusions cannot be drawn.

It was also noted that chloracne often affected whole family groups. In fact, in 17 (53%) out of 32 families of zone A, involved in the chloracne outbreak, 2 or more cases were observed. This could be explained by an exposure to a 'local' risk due to the particular whereabouts of certain family groups at the time of the accident, or the extent of adoption of hygienic norms suggested by the health authorities, or a possible contamination via personal belongings.

The most notable finding from a clinical point of view is the involvement of the gastrointestinal tract, more frequently observed in children affected with chloracne, and living in the most highly contaminated area. Children with chloracne also presented more frequently γGT, GPT and Ala-U abnormalities, as previously recognised by Poland et al[17] and Jirasek.[14] The results of other biochemical tests did not appear to be associated with dermatological manifestations.

No clinically definable systemic disease has been diagnosed to date in children of the Seveso area. This is in line with the data of Kimming and Schulz,[15] Poland et al[17] and May,[18] who found no systemic clinical involvement in subjects affected with chloracne.

The present paper demonstrates that the chloracne subjects of Seveso deserve careful attention for both epidemiological and primary health care purposes. This group, along with the comparison group, will be the object of a thorough follow-up as detailed in the Health Surveillance Programme for Seveso.

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