

Chapter 18

**ADVERSE HEALTH EFFECTS IN HUMAN POPULATION EXPOSED TO
2,3,7,8-TETRACHLORODIBENZO-PARA-DIOXIN (TCDD) IN SEVESO:
AN UPDATE**

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INTRODUCTION

On July 10, 1976, an explosion at the Industrie Chimiche Meda Società Azionaria (Icmesa) plant in the Northern Italian town of Meda released a cloud of aerosol which contaminated the surrounding area. The aerosol contained 2,4,5-trichlorophenol (TCP), sodium hydroxide and the by-product, 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD). Starting in 1947, the Icmesa plant produced a variety of chemicals (acetates, benzyl chloride, benzyl cyanide, phthalates, etc.). In 1970, pilot production of TCP began, and in 1974 full scale operation of TCP was set up. The incineration of production wastes was done by a very rudimentary combustion oven without any environmental control. During the years before the accident, many animal deaths were observed but local authorities were never informed about these. Moreover, local authorities were never informed about the TCP production at the Icmesa plant despite the fact that the TCP operation was considered notifiable by Italian Environmental-Occupational Laws (Acts of Parliamentary Commission, 1978).

THE ACCIDENT

The accident occurred six and a half hours after the Icmesa factory had closed down for the weekend. It is generally accepted that there was a "runaway reaction" in the reactor producing TCP. The pressure increased as the reaction became exothermic and reached the critical limit, causing the safety disk to rupture and the discharge of the reactor contents. The safety valve, situated outside the plant, discharged the aerosol directly into the atmosphere and it then drifted over a highly inhabited area.

THE AREA

The affected area (92.85 km²) was subsequently divided into three zones on the basis of gas chromatography-mass spectrometry analysis of soil samples (Fig. 1) (di Domenico et al., 1980). Zone A, an area of about 1.2 km² in the town of Seveso just south of the plant, was contaminated with the highest levels of TCDD (from .75 to 20,000 µg/m²). Zone B, covering about 2.3 km², was contaminated with lesser amounts: 5 to 50 µg/m² of TCDD in the soil was found. Zone R (14.8 km²), further south and including both Zone A and B, usually had a concentration of less than 5 µg/m² of TCDD in the soil.

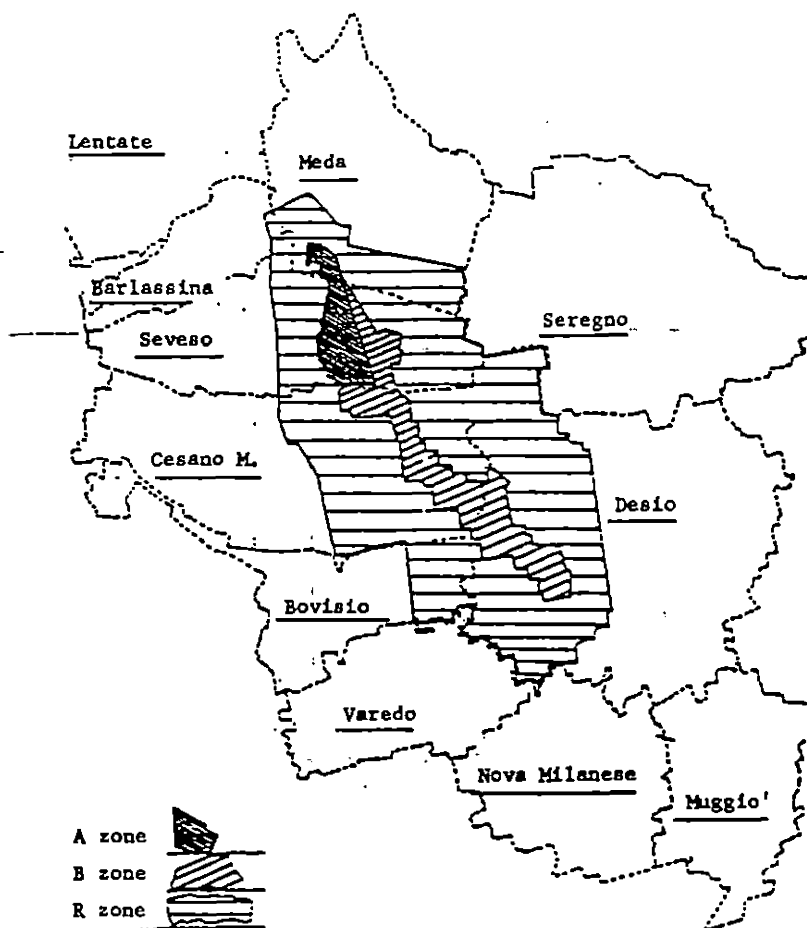


Figure 1. Map of the Contaminated Area by Polluted Zones

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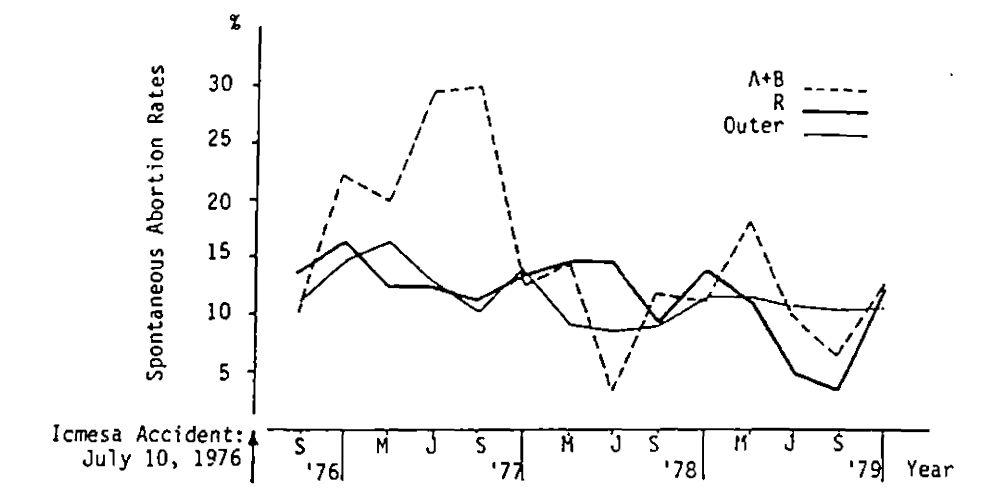


Figure 2. Time trends of spontaneous abortion rates by quarters and by polluted zones (1976-1979) (Strigini *et al.*, 1982).

POPULATION(S) AT RISK BASED ON TCDD SOIL CONTENTS

By the end of July 1976, 16 to 23 days after the accident, 735 people were evacuated from Zone A, and the area was fenced off. About 4,300 people lived in Zone B and 40,000 in Zone R. None of the people died from acute exposure to TCDD, but of the people who were exposed to TCDD, about 500 were treated for acute skin irritation. From September to December 1976, 44 children were diagnosed with chloracne. To date, the number of cases of chloracne amounts to a total of 193. No cases of chloracne were observed among the Icmesa workers, even though they continued to work for one week following the accident.

SPONTANEOUS ABORTIONS AND BIRTH DEFECTS

A health monitoring program (HMP) was established in July 1976 by the local regional authorities. The data collected during a five-year follow-up by the obstetric and gynecologic teams have been analyzed (Strigini *et al.*, 1982). Due to the lack of abortion baseline values prior to the accident, only a backward analysis of the embryotoxic effects in different areas has been possible. A statistically significant increase in the spontaneous abortion rate has been detected in those areas in which higher levels of TCDD were found (areas A and B). This temporary rise in spontaneous abortions, as shown in Figure 2, reached a peak in the second half of 1977, about one year after the accident. This rise in the abortion rate among exposed pregnant women was observed despite the fact that more than 90 pregnant women from those areas obtained a clinical abortion.

Data from the Birth Defects Registry established during 1978 do not show an association between malformations and exposure to TCDD except for hemangiomas and benign neoplasms (Table 1). This association becomes statistically significant ($\chi^2 = 5.97$, $p < 0.05$) when data are analyzed considering the distribution of chloracne rates (see later in text) as risk markers for potential TCDD exposure instead of the simple analytical detection of TCDD on the soil.

TABLE 1. Observed and expected birth defect cases by area of residence of the mother during the pregnancy (1976-1980)

<u>Congenital Anomalies</u>	Cases	
	Whole Area	Zones A+B+R Observed Expected*
Central Nervous System Anomalies	27	6 5.19
Central Nervous System and Eye Anomalies	39	8 7.49
Anomalies of the Ear	27	4 5.19
Heart Anomalies	44	6 8.45
Heart and Circulatory System Anomalies	53	8 10.18
Anomalies of Respiratory System	14	3 2.69
Hypospadias	39	8 7.49
Hip Dislocation	38	8 7.30
Talipes Equinovarus	27	4 5.19
Polydactyly, Syndactyly	16	3 3.07
Anomalies of Integument	30	6 5.76
Benign Neoplasm - Hemangiomas	228	50 43.81
Chromosomal Anomalies	27	4 5.19
Anomalies of the Musculoskeletal System	19	3 3.65
<u>All others</u>	<u>30</u>	<u>4</u> <u>5.76</u>
<u>Total</u>	<u>587</u>	

* On the basis of the birth defect rates in the whole area

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CHLORACNE GROUPS

In order to establish adverse health effects among people who developed chloracne as a consequence of TCDD absorption, 164 affected children and 182 children of the same age, living in A, B, and R areas and without chloracne, were studied. The results of this study were published in 1981 (Caramaschi *et al.*, 1981). Unfortunately, the "control" group was not randomly selected: only children having medical examinations and without skin irritation became part of the "control" group. The children selected as a comparison group were not representative of the unexposed children. They were a self-selected group of people who voluntarily submitted to the health monitoring program established by the Regional Health Minister to assist and test people living in the contaminated area. Recognizing the bias in selection, higher frequencies of GGT, GPT and Ala-U abnormalities were detected in the chloracne group when compared to the "control" group (Table 2).

TABLE 2. Frequency of subjects with abnormal values among chloracne and "control" group*

Test	Threshold Values	Chloracne Group no=164	"Control" Group no=182	P Value
GGT	>37 U/L	2.8% (4/141)	— (-/138)	<0.001
GPT	>27 U/L	3.5% (5/141)	— (-/138)	<0.005
ALA-U	>6.1 mg/L	24.1% (33/137)	5.2% (7/135)	<0.001

* Reproduced with permission from Caramaschi *et al.*, 1981.

The response rate to the health monitoring program decreased from 1976 through 1980 among the chloracne group, as well as among the general population and the occupational groups followed. In late 1982, 6 years after the accident, a 3 year prospective follow-up study of the whole chloracne group (193 people) and of a comparison group (193 people matched by age, sex and history of exposure to TCDD) began. One of the major efforts in this study was to define unpolluted areas from which the comparison group was selected.

In early 1982, at the time the study design was prepared, the epidemiologic team in charge asked the Scientific Governmental Commission to follow at least two controls for each chloracne case in order to avoid problems due to a possible refusal to participate in the study. As of today, because of the low response rates to the first calls (November 1982 - March 1983) for the medical examination among chloracne and control groups (82.4% and 67.9% respectively), it is difficult to analyze and interpret the data.

OCCUPATIONAL STUDIES

An occupational health surveillance, according to the HMP was established soon after the accident. Its prevailing clinical characteristics and the lack of adequate study design limited any conclusions from the large amount of data collected from 1976 through 1980. Table 3 indicates the groups of people with potential occupational exposure to TCDD as specified by the HMP and the response rate to the control calls in 1980 among these groups. Although such initial participation followed by discontinuous participation to the clinical follow-up do not allow any epidemiological processing, in five out of 23 ex-cleanup workers hospitalized from October 1976 to May 1981, a diagnosis of liver disease suspected to be of toxic origin was made (Table 4).

TABLE 3. Occupational groups potentially exposed to TCDD and their response rates in 1980

Groups	Subjects	Examination Response Rate in 1980
Icmesa workers	191	62%
Encol workers*	92	75%
Public Service employees	2035	50%
Soldiers	342	61%
Clean-up workers	926	47%

* Response rate in 1981

TABLE 4. Liver diseases diagnosed among 23 ex-cleanup workers hospitalized from October 1976 to May 1981

Diagnosis	Number of Subjects
Virus hepatitis	15
Alcoholic liver disease	2
Liver diseases (negative HBSAg)	1
Liver diseases suspected of toxic origin	5
Total	23

The participation of the Icmesa workers in the medical monitoring program decreased over time. This drop in the response rate makes the follow-up evaluation difficult. The five year time trends have been analyzed. Statistically significant downward trends for GGT and alkaline phosphatase were seen (Table 5). These results seem to indicate that since 1976, for the study population, those conditions which caused the observed high frequency of abnormal liver function tests just after the accident, ceased.

TABLE 5. Frequency of subjects with abnormal laboratory values among the Icmesa workers with one clinical examination every year

	Year	Alkaline Phosphatase cut-off = 50 U/L *	Gamma GT cut-off = 50 U/L *
	1976	22.22%	27.77%
	1977	8.89%	24.44%
	1978	8.63%	22.47%
	1979	8.63%	20.00%
	1980	8.53%	15.93%
	Chi square for the Trend	8.23	4.23
	P level	.005 > P > .0001	.01 > P > .005

* Suggested by the International Steering Committee

A neurologic study done by the Clinica del Lavoro Luigi Devoto of Milano (Ghezzi, 1981) indicated that among the ICMESA workers there were four cases of slight polyneuropathy in the lower limbs with clinical and electrophysiological alterations. Three subjects showed a reduction of the motor and/or sensory nerve conduction velocity. Another 16 subjects presented subclinical signs of neuropathy of the distal muscles of the limbs. Interpretation of these findings is not possible because of the lack of a control group and because alcohol consumption and/or history of diabetes was not determined.

In late 1980, a cross-sectional study was designed to evaluate hepatotoxic and neurotoxic effects in the Icmesa population (188 subjects). A control group was identified consisting of 305 workers of a metallurgical and mechanical industry out of the polluted area and in which there were no known hepatoneurotoxic risk factors. Clinical examinations were carried out among all the workers at the Occupational Health Department of Desio Hospital. A standardized questionnaire was administered at the time of this examination by trained interviewers in order to investigate universal variables, confounders and/or

modifiers. Lung function tests (FVC, FEV₁), SPE and ulnar nerve electromyography, SGOT, GGT, alkaline phosphatase, total bilirubin, cholesterol serum level, triglycerides, total serum protein and electrophoresis, prothrombin time, hematocrit, hemoglobin, WBC and differential and total urinary porphyrin were carried out in both groups. The response rate was higher than 90% for the Icmesa workers and reached 100% for the control group. No statistically significant differences were found between the two groups examined. This means that five years after the July 1976 Icmesa accident, no particular health effects were detected in the Icmesa workers compared with a selected control group.

A mortality study on the 1947-1976 Icmesa cohort, consisting of 746 workers employed for at least six months, began in late 1980. Two control groups were composed of 1,659 people who worked for at least six months in two plants located in an unpolluted area. It was difficult to trace the Icmesa workers because of the unusually high turnover in this plant. The causes of death among the Icmesa workers are shown in Table 6. An interpretation of significance can only be made after a mortality analysis of the control group is completed. In 1980, a study was initiated to evaluate the effectiveness of the safety measures adopted during the cleanup of the highest polluted sub-area A₁. The lack of relevant differences between the cleanup workers and a selected control group make it possible to assume the effectiveness of the safety measures used. However, long-term adverse health effects related to a potential TCDD exposure can not be excluded (Ghezzi *et al.*, 1982).

TABLE 6. Causes of Death Among the "1947-1976 Icmesa Cohort"

ICD Code 9th Revision		
(140-208)	Malignant neoplasms including neoplasms of lymphatic and hematopoietic tissues	42
(162, 163)	Cancer of trachea, bronchus, lung and pleura	16
(161)	Cancer of larynx	2
(200-208)	Cancer of lymphatic and hematopoietic tissue	3
(140-149)	Cancer of lip, oral cavity and pharynx	1
(150-159)	Cancer of digestive organs and peritoneum	14
(155)	Cancer of liver and intrahepatic bile ducts	3
(151)	Cancer of stomach	5
(191)	Cancer of brain	3
(189.2)	Cancer of ureter	1
(172, 173)	Cancer of skin	2
(310-448)	Major cardiovascular diseases	43
(571)	Chronic liver diseases and cirrhosis	19
(E800-E949)	Accidents and adverse effects	17
	All others	22
	Total	143

TABLE 7. All causes of death: Age adjusted rates per 100,000 inhabitants by residence, sex and year of death (1975-1980)

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TABLE 7. All causes of death: Age adjusted rates per 100,000 inhabitants by residence, sex and year of death (1975-1980)

Zones	1975		1976		1977		1978		1979		1980	
	C.R.	A.R.	C.R.	A.R.	C.R.	A.R.	C.R.	A.R.	C.R.	A.R.	C.R.	A.R.
A and B	265.60	362.22	763.61	960.96	697.21	834.24	464.81	565.36	630.81	763.13	830.01	996.14
F	307.06	427.81	341.18	492.82	307.06	395.01	341.18	434.18	409.42	565.96	375.30	455.67
R	692.21	764.71	803.46	909.18	679.85	778.55	852.90	932.33	781.10	915.61	630.41	749.45
F	606.50	731.18	624.77	738.18	630.04	740.17	600.51	705.36	582.31	688.33	630.84	751.29
Outer Area	891.17	871.33	892.30	868.38	870.07	847.90	867.60	844.62	883.32	859.54	900.17	875.60
F	701.95	776.99	792.35	766.61	689.19	666.46	729.60	704.45	692.30	669.15	700.88	677.23
Whole Area	847.29	847.29	875.90	875.90	837.13	837.13	856.52	856.52	862.98	862.98	857.34	857.34
F	678.47	678.47	759.33	759.33	672.30	672.30	701.38	701.38	668.78	668.78	681.99	681.99
Italy	1076.71	785.28	1076.71	785.28	1076.71	785.28	1076.71	785.28	1076.71	785.28	1076.71	785.28
1975 F	906.33	721.73	906.33	721.73	906.33	721.73	906.33	721.73	906.33	721.73	906.33	721.73

C.R. = Crude Rate
A.R. = Adjusted Rate
M = Male
F = Female

TABLE 8. Causes of death: Malignant tumor of larynx, trachea, bronchus and lung (I.C.D. 8th; 161,162): Crude and adjusted rates per 100,000 inhabitants by zone of residence, sex and year of death (1975-1980)

Years		1975		1976		1977		1978		1979		1980	
Zones		C.R.	A.R.	C.R.	A.R.	C.R.	A.R.	C.R.	A.R.	C.R.	A.R.	C.R.	A.R.
A and B	M	0	0	33.20	48.77	66.40	83.96	33.20	40.66	33.20	40.66	66.40	83.96
	F	0	0	34.12	53.92	0	0	0	0	0	0	0	0
R	M	61.80	68.82	98.89	106.78	49.44	56.33	55.72	62.84	74.17	84.05	37.08	41.23
	F	12.13	12.24	0	0	6.07	6.87	12.13	13.96	24.26	28.64	6.07	7.59
Outer Area	M	62.85	61.51	71.83	70.09	81.93	79.96	70.71	69.05	93.16	91.09	97.65	94.96
	F	5.32	5.11	9.57	9.30	7.44	7.20	10.64	10.25	11.70	11.34	12.76	12.50
Whole Area	M	60.92	60.92	74.96	74.96	76.61	76.61	67.38	67.38	88.61	88.61	85.84	85.84
	F	6.17	6.17	8.81	8.81	7.05	7.05	10.57	10.57	13.22	13.22	11.45	11.45
Italy 1975	M	67.58	53.48	67.58	53.48	67.58	53.48	67.58	53.48	67.58	53.48	67.58	53.48
	F	8.56	7.29	8.56	7.29	8.56	7.29	8.56	7.29	8.56	7.29	8.56	7.29

C.R. = Crude Rate
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 M = Male
 F = Female

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MORTALITY STUDY AND CANCER REGISTRY

In order to set up a mortality study and a cancer registry, the population living in the area at the time of explosion has been computed starting from residents in 1979 and going back to July 10, 1976. This was possible with the cooperation of the eleven Municipalities' Demographic offices. The "July 10, 1976 Seveso Cohort" was identified retrospectively, and since 1979 it has been kept up-to-date prospectively month by month. The completeness of the mortality data collected from 1975 through 1980 was more than 99% of the deaths. In the analysis, the mortality rates of the polluted areas were compared with the 1975 Italy mortality rates (the most recent available). The total population of 22,837 in the eleven Municipalities up to December 31, 1979, has been used as a standard population for making the age adjustment. In Table 7, mortality rates for all causes of death refer to the subdivision by zones of residence at the time of death. With regard to those long-term health effects correlated with TCDD exposure based on observation in animals and humans, it is obvious that no conclusion can be reached five years after the Icmesa accident due to their long latency period. However, an increasing trend has been detected in 1979-1980 in the age adjusted mortality rates for cancer of the larynx, trachea, bronchus and lung (Table 8). A statistically significant difference was also observed in the time trend for the eleven Municipalities between 1976 and 1980 in mortality rates for hypertension.

More suggestive data comes from the "Seveso Cancer Registry" established on January 1981. A statistically significant excess has been found in the incidence of soft tissue sarcomas in the population living in Zone R. Eight histologically confirmed cases have been observed from 1977-80; the expected number based on the population of eleven Municipalities was 3.23 with a risk ratio of 2.48. Comparison with national mortality rate was excluded due to the varying quality of the data.

It has to be pointed out that no conclusions can be drawn from the cancer data because of the recognized latency period for cancer induction and the fact that in this instance the risk-assessment base used only one risk marker (TCDD in the soil). There are at least three other possible markers of exposure: chloracne, acute skin irritation and animal deaths occurring as a consequence of the accident. The geographical distributions of these TCDD related adverse health effects are shown in Figures 3, 4 and 5. In order to define the real population potentially exposed to TCDD, the whole area has been divided into sub-areas of one square kilometer (Figure 6). Chloracne, acute skin irritation and animal mortality rates have been computed for each sub-area. In this approach, high rates for these adverse effects must be considered to define sub-areas in which a high risk of TCDD related health effects would be expected. Differences in rates for the markers considered are shown in Figures 7, 8 and 9.

C.R. = Crude Rate
A.R. = Adjusted Rate
M = Male
F = Female

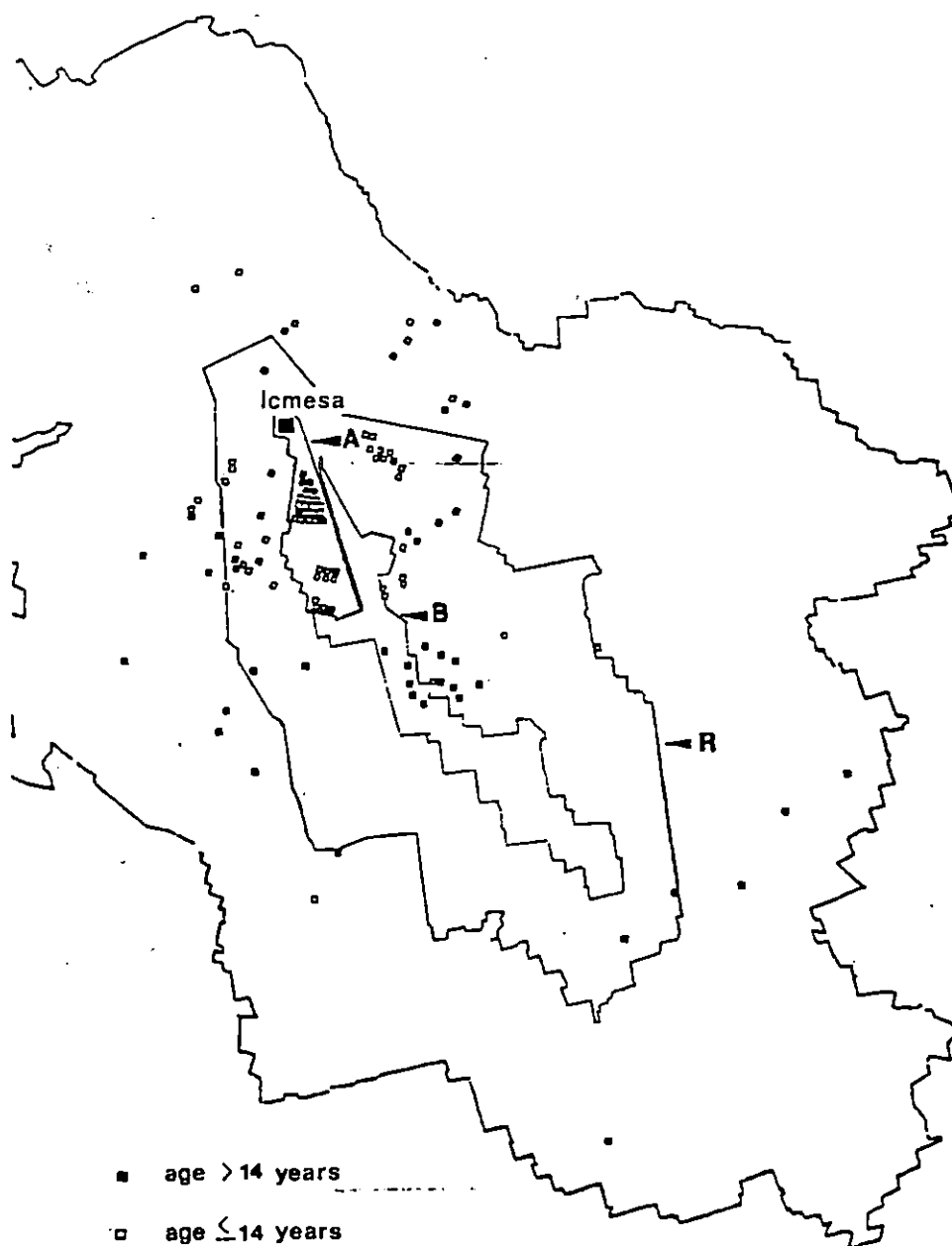
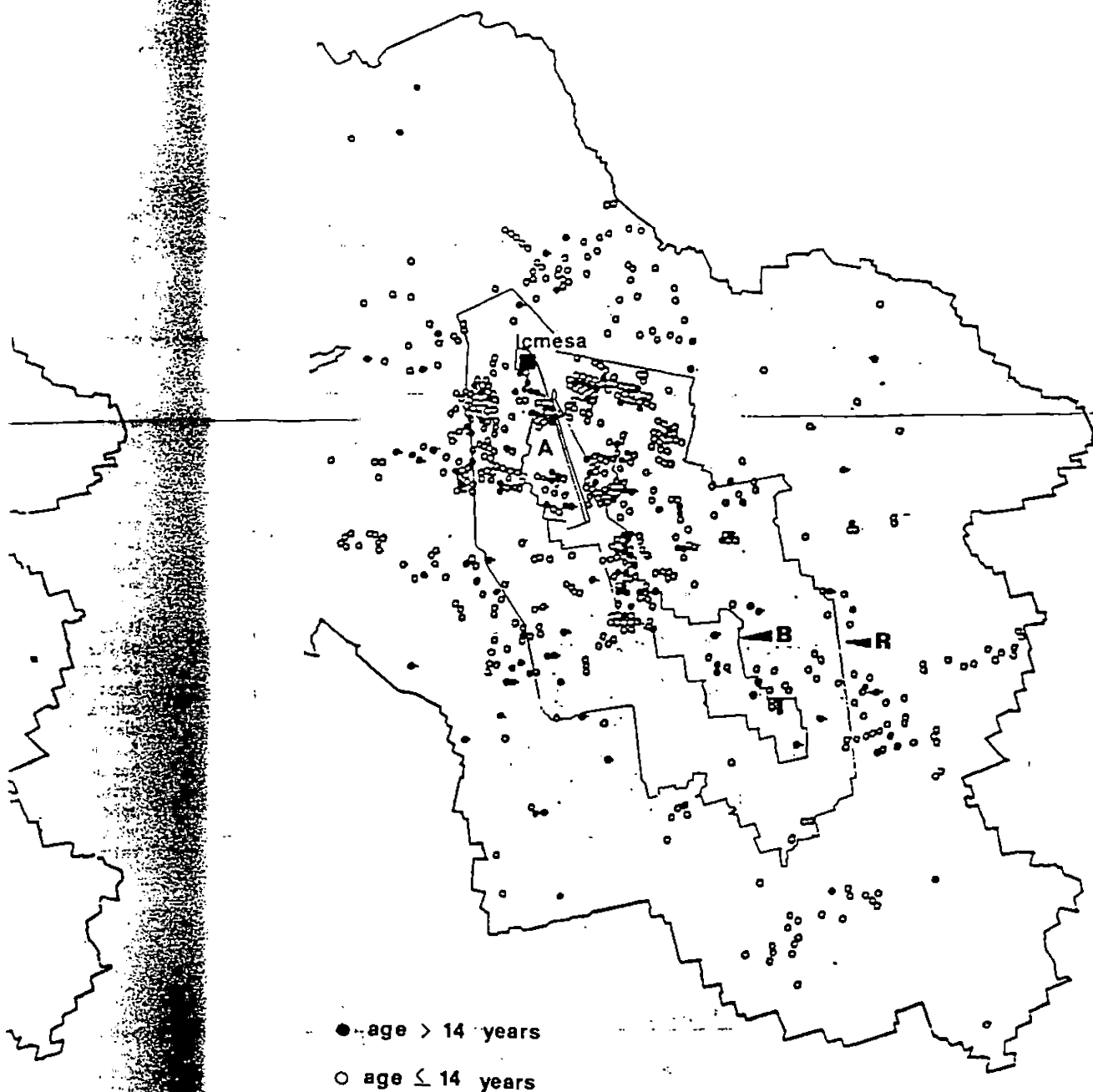


Figure 3. Geographical distribution of chloracne cases (males) notified after July 10, 1976 in the polluted area.

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Figure 4. Geographical distribution of acute skin lesion cases (males) notified after July 10, 1976 in the polluted area.

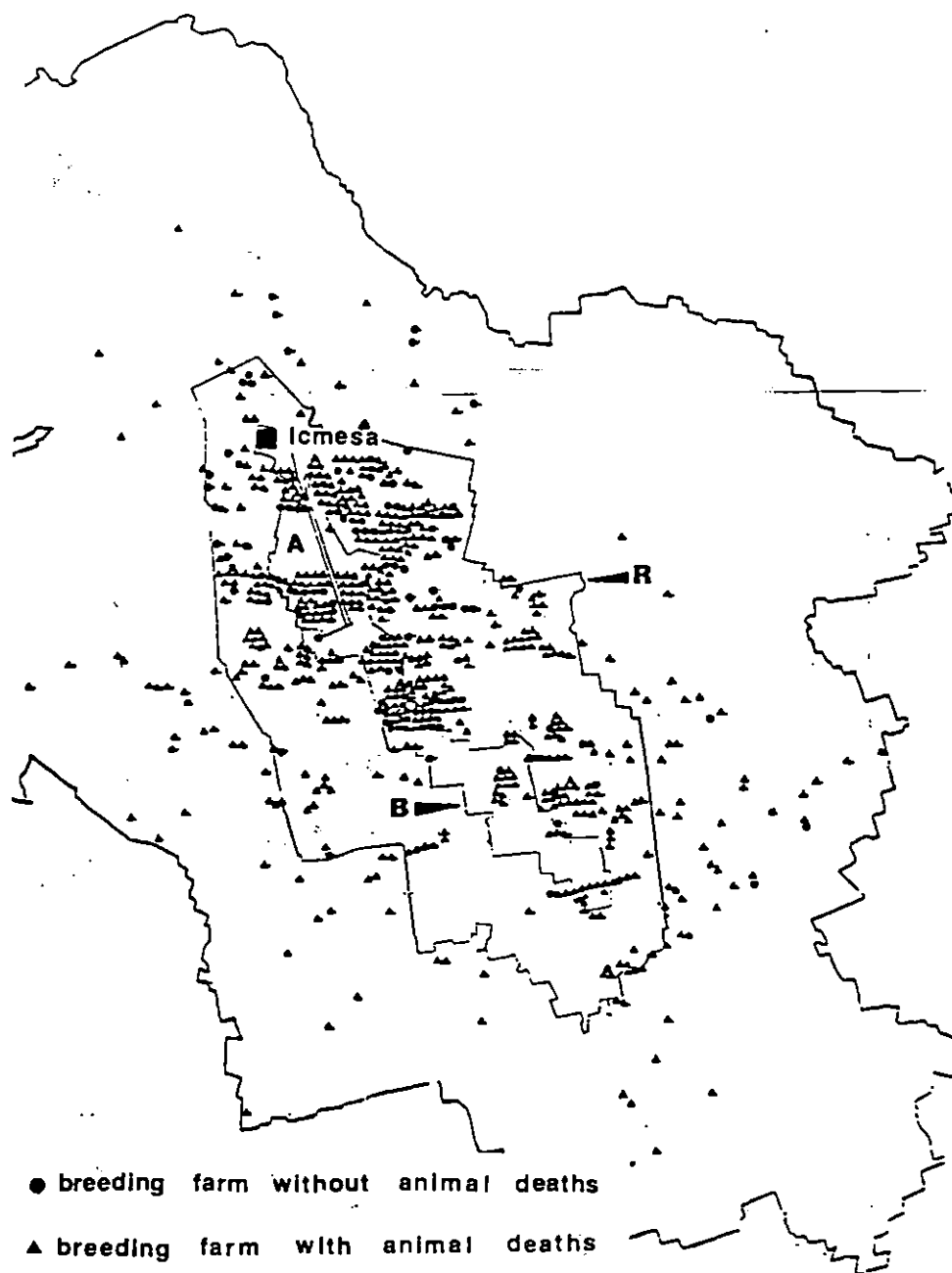


Figure 5. Geographical distribution of animal deaths occurred after July 10, 1976 in the polluted area.

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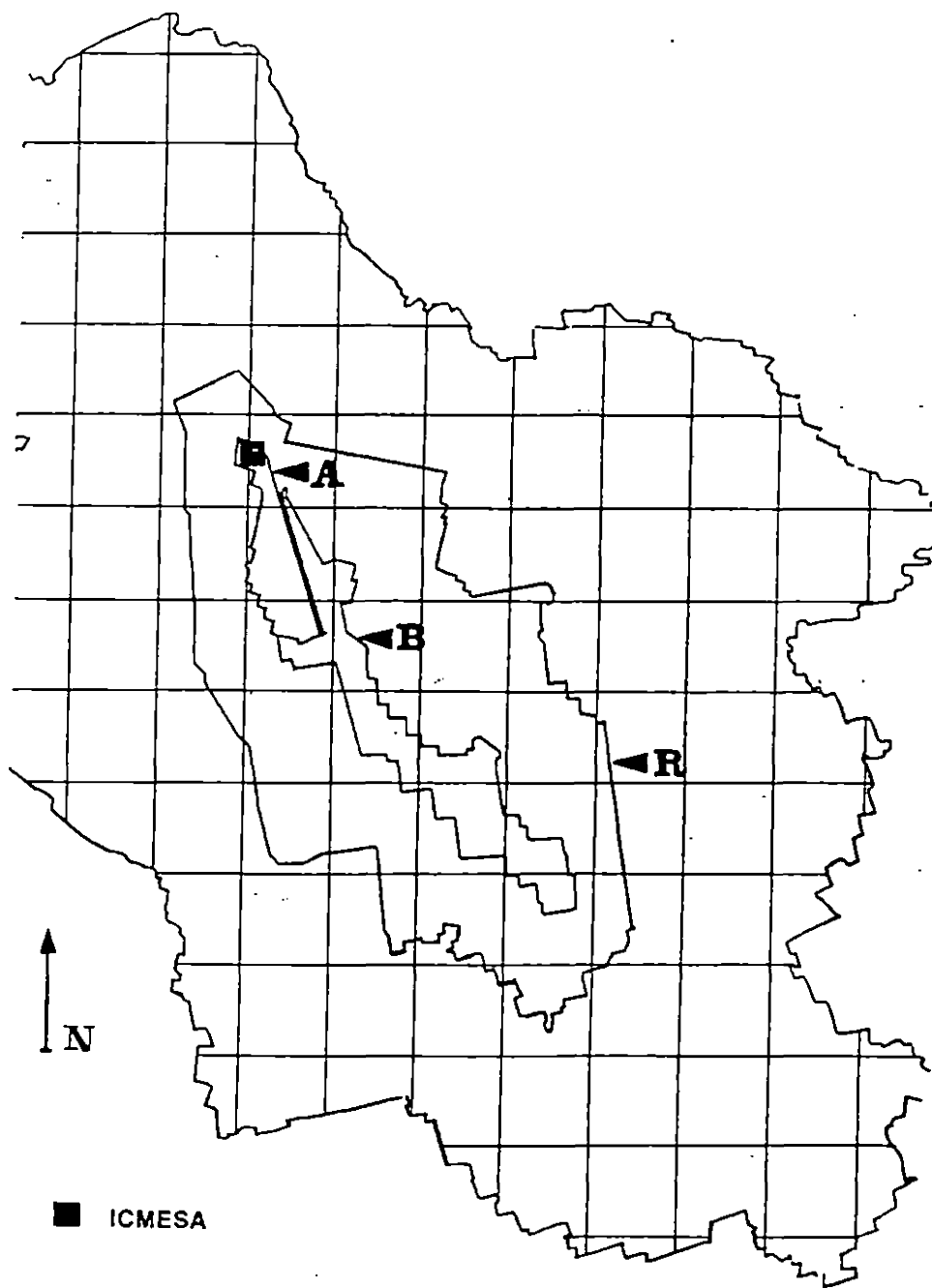


Figure 6. Map of the Seveso area by square kilometers

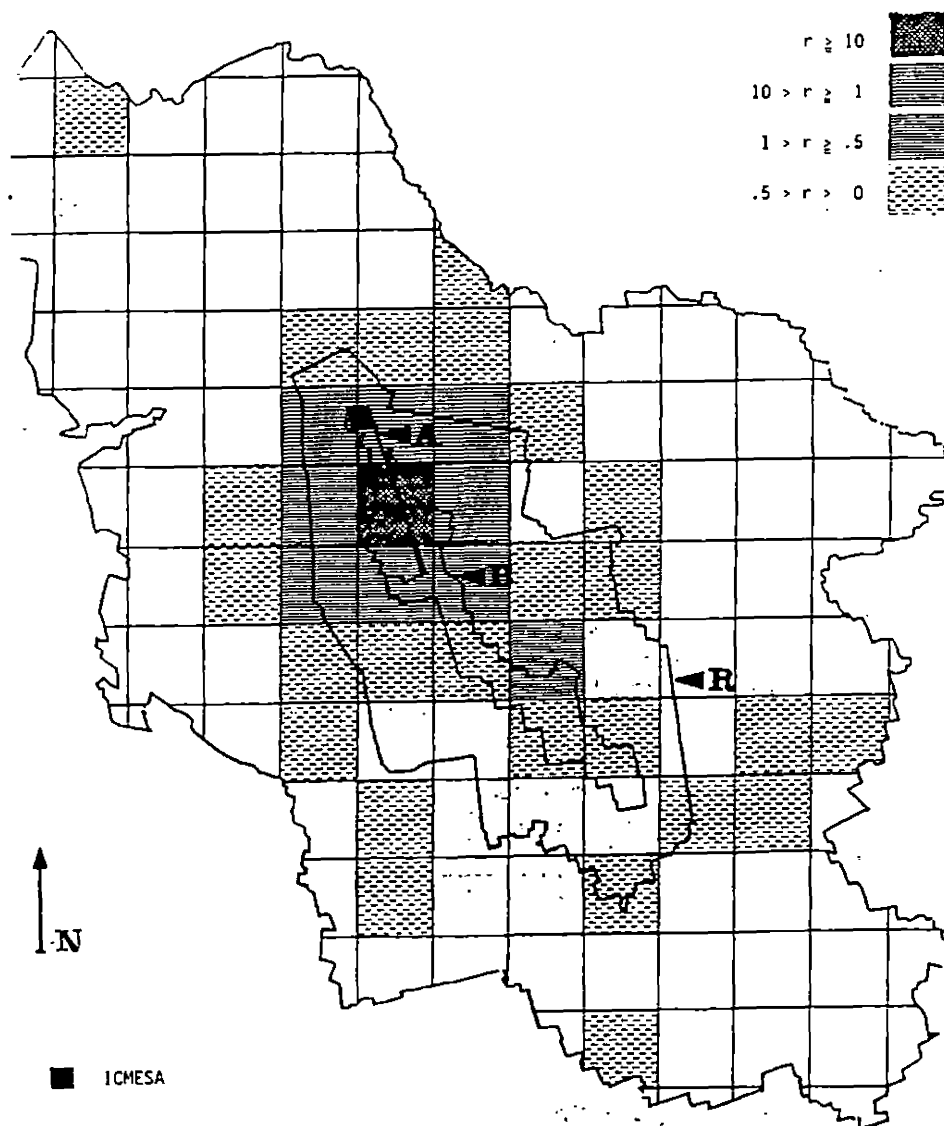


Figure 7. Geographical Distribution of Chloracne Rates (r) $\times$ 1000 per Km²

Figure 8

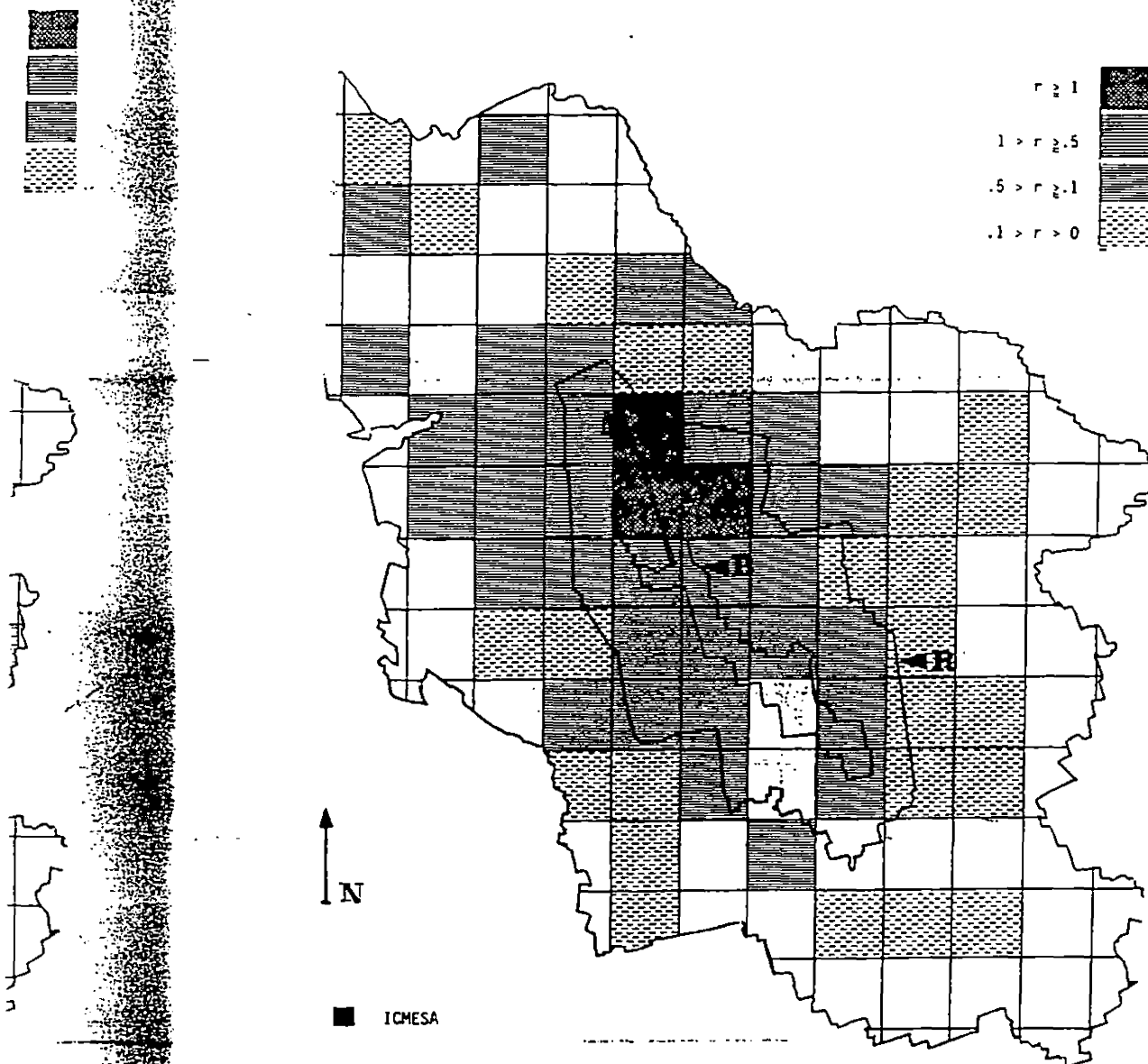


Figure 8. Geographical Distribution of Acute Skin Lesion Rates (r) x 1000 per Km^2

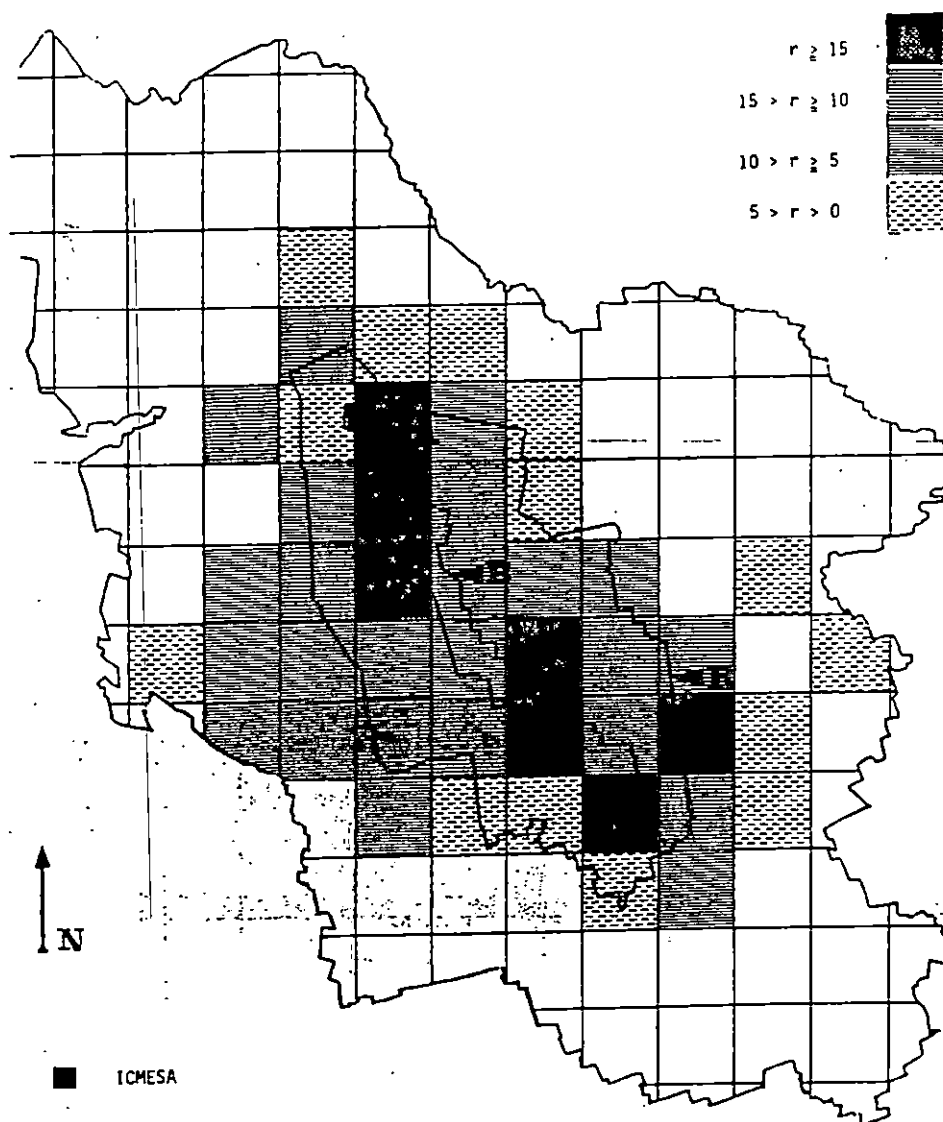


Figure 9. Geographical Distribution of Animal Death Rates (r) x 100 per Km²

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CONCLUSION

Knowledge of the adverse health effects of TCDD comes from animal studies and human occupational exposures occurring during the manufacture of trichlorophenol. Short term effects have been identified. Long term effects are still under study.

The high persistence of TCDD bound to the soil, and its absorption and translocation in vegetables and fruit trees, represent serious problems in Seveso. In this highly populated area, two major kinds of exposure occurred after the accident: 1) an acute high-level exposure in which larger quantities of TCDD were probably absorbed directly and through the food chain; 2) a chronic low-level TCDD exposure that could still be present in those subjects who have lived and are still living in areas that were never cleaned up such as Zones B and R. Several efforts have been made in the last two years to identify the populations most likely exposed to TCDD in order to plan methodologically correct studies for mid and long term effects. There is an urgent need to define and quantitate exposure in order to improve the quality of the epidemiological investigation. In Seveso, no systematic analyses of human tissue were done. Only one analysis of TCDD in human tissues was carried out among the thousands of people exposed (Fachetti et al, 1980). This was from an autopsy of a woman who lived in Seveso's highly polluted Zone A. She died in October 1976 of pancreatic cancer. It has to be underlined that she was a grandmother of two of the more severe cases of chloracne that occurred and that she never developed either chloracne or skin irritation. 2,3,7,8-TCDD was detected in all tissues at levels ranging from 6 to 1840 pg/g (Caramaschi et al., 1981). It is clear that although chloracne is an indicator of absorption and biological effects, it is not a sensitive marker of TCDD exposure. Other parameters have to be considered to identify exposed and control groups.

Unfortunately, due to the lack of proper studies in the early phase of the "Seveso Program", reevaluation of these data, such as has been done with the Hiroshima and Nagasaki study records, has to be excluded.

Only well designed carefully executed epidemiologic studies will enable us to draw conclusions about the occurrence of chronic health effects and their relationship to TCDD exposure.

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