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Veronika Weyer, Maria Blettner, Constanze Cholmakow-Bodechtel & Ursel Heudorf

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LETTER TO THE EDITOR

Chemical accident at Hoechst AG Frankfurt/Main, Germany, 1993: a 15 year follow-up analysis of mortality

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On 22nd February 1993 a major chemical accident occurred at the chemical plant of the Hoechst AG Frankfurt (Main), Germany (FFM). Approximately twelve tons of a complex chemical mixture [27 different substances, many of them nitroarenes; main substance o-nitroanisole (ONA)] were released into the air via a safety-valve. A part of the substance came down as "yellow rain" and lead to severe contamination in an area of allotment-gardens (up to 2,000 mg ONA/m^2) and in a nearby housing area in the district Schwanheim near FFM. Soil samples were taken in several parts of the area. Cleaning and redevelopment measures started promptly after the accident. One month later no more contamination was detected in the district of Schwanheim. Further details of the pollution see [1].

Short-term health effects of the accident had been documented in 83 adults and 15 children and were reported [2]. Neurotoxic, cardiotoxic, and hematotoxic effects of nitroarenes were not observed [3].

Some of the nitroarenes in the fallout are known genotoxins and some are carcinogenic in animal tests causing bladder, kidney or colon tumours in rodents [4]. Therefore a follow-up of all persons living in the area at the time of the accident was performed to investigate cancer mortality rates. The results of this follow-up study until Feb 2008 are presented here.

The study cohort included all subjects with an address in the residential area Schwanheim/Goldstein (Fig. 1) according to the municipal population register, at the time of the accident. The "*cone*" zone was defined by chemical contamination detected via soil analysis. For further evaluation the whole region was divided into several zones: centre, zone 2 East/West, and zone 3 East/West according to potential exposure. At the time of the accident, 2,049 people were residents in the "*cone*" zone, 3,525 in the centre, 5,577 in the zone 2 East/West, and 8,579 in the zone 3 East/West.

For all members of the cohort, the last known address and the vital status as well as date and cause of death were obtained until February 22nd 2008, i.e. up to 15 years after the accident.

For data analysis ICD codes from all diagnoses were transformed in the current ICD version 10. Following groups of death were considered: All deaths, cardiovascular diseases including myocardial infarct (I00–I99) and neoplasm in total (C00–C97) as well as definite cancer types, according to the toxicological expertise from Neumann [5].

Death rates from Hessen by 5-year age groups and 5-year calendar groups were obtained from Statistisches Landesamt, Wiesbaden, Germany.

Exposure was defined in four categories according to the place of residence on February 22nd 1993: the "*cone*" zone, the centre, the zone 2 East/West and the Zone 3 East/West. The zone 3 East/West is considered as unexposed reference group. According to detected chemical soil contamination only "*cone*" zone was exposed to o-Nitroanisole and the other compounds of the chemical contamination [1].

First, for external comparison person years were computed for 5 years age groups and for male and female

V. Weyer (✉) · M. Blettner
Institute of Medical Biostatistics, Epidemiology and Informatics, University Medical Center Mainz, Obere Zahlbacher Straße 69, 55131 Mainz, Germany
e-mail: weyer@uni-mainz.de

C. Cholmakow-Bodechtel
Kantar Health GmbH, Munich, Germany

U. Heudorf
Public Health Department of the City of Frankfurt/Main, Frankfurt, Germany

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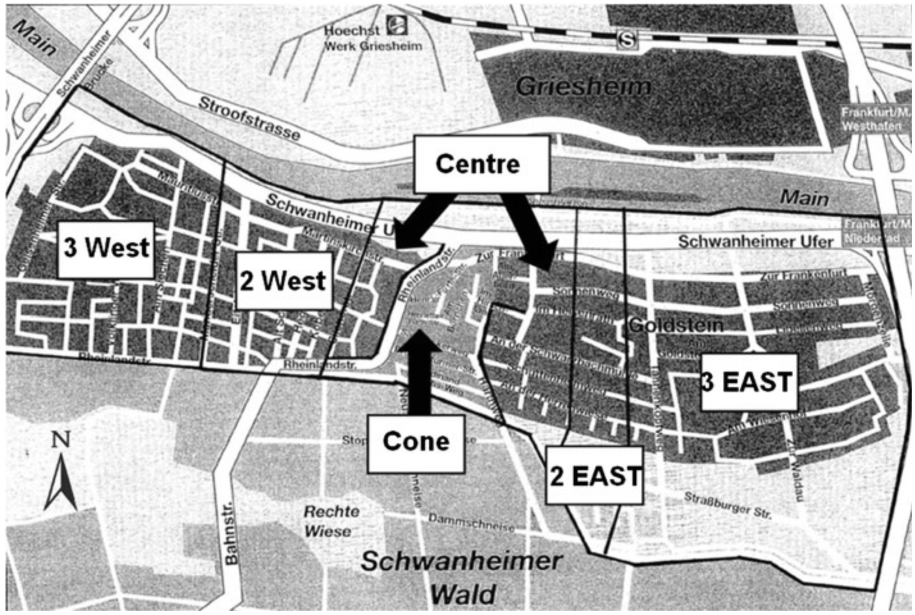

Fig. 1 Map of research area subdivided in four zones: "*cone*", centre, 2 East/West and 3 East/West (Amt für Gesundheit 2009)

separately. The start time was defined by the day of the accident on February 22nd 1993, the end of follow-up was either the end of the study on 22nd Feb 2008, death or "lost to follow-up" whatever occurred earlier.

The standardized mortality ratio (SMR) and its 95 % confidence interval were calculated. The expected deaths were calculated using mortality rates from the Hessian population. SMR was calculated for the total cohort (Schwanheim) as well as for the "*cone*"-category only [6].

For internal comparison, a Cox regression model was used to analyse the association between areas of residence and mortality. Entry date was the date of the accident and end of follow-up was either date of death, lost to follow-up or 22nd Feb 2008, whatever occurred earlier.

For persons who were documented as "lost to follow-up" the date of last known vital status was used. For the Cox regression the time since "exposure" was used as time scale in the model. Hazard ratios and 95 % confidence intervals (95 % CI) for "*cone*" zone, centre and zone 2 East/West with zone 3 East/West as reference zone were estimated. All models were adjusted for gender and age.

The computation was done with SAS, version 9.1.

The cohort includes all persons registered 1993 in the Schwanheim area.

In the population of 19,730 persons [9,447 (47.9 %) men and 10,283 (52.1 %) women] 3,034 (15.4 %) had died. 692 (3.5 %) were lost to follow up and 3 persons who had died (two men and one woman) were not included in the analyses because information on their date of death could not be identified.

Table 1 shows the SMRs of the study population in total and of the "*cone*" subgroup in comparison to the Hessian standard-population. No increase in total cancer mortality was observed, neither in the Schwanheim population in total nor in the "*cone*" subgroup alone. For the Schwanheim population SMRs for cancer of specific sites (lung, intestine, bladder, liver, leukaemia or kidney) was also calculated and no statistically significant increase was observed.

Table 2 shows the hazard ratios (HR) and 95 % confidence intervals for the total mortality rates and for cancer deaths in the different zones. HR in the most exposed group ("*cone*") was less than 1.0 for all causes of death and for cancer and varying between 0.34 and 1.12 for cancer subgroups. For none of the groups a trend was observed (HR increasing from non-exposed to high exposed group).

The total mortality and the cancer mortality for the "*cone*" zone was less than in the reference zone 3 East/West. Regarding the specific cancer sites (Table 2), no statistically significant increase in cancer mortality was observed for the "*cone*" zone. Also for the other exposed zones (centre and 2 East/West), HR showed no statistically significant higher risk to cancer mortality.

In our study we found no evidence for elevated overall mortality or cancer mortality in persons living in the most severely exposed area compared to persons living in other places in Schwanheim. Although some of the nitroarenes exhibit carcinogenic effects in animal tests causing bladder, kidney or colon tumours [7] we do not expect a recognizable higher rate of cancer in the

Table 1 SMR of the Schwanheim population as well as the "*cone*" population compared with standard mortality in the county of Hessen (1998)

	Schwanheim population		"*cone*" population	
	SMR	95 % CI	SMR	95 % CI
Mortality total				
All	0.95	0.92–0.99	0.88	0.78–0.98
Men	0.93	0.88–0.98	0.84	0.71–1.00
Women	0.97	0.96–1.02	0.91	0.78–1.06
Mortality cardiovascular				
All	0.84	0.80–0.89	0.76	0.63–0.91
Men	0.82	0.76–0.89	0.71	0.52–0.93
Women	0.85	0.79–0.92	0.80	0.63–1.01
Mortality cancer				
All	0.95	0.88–1.02	0.80	0.63–1.02
Men	0.92	0.83–1.01	0.76	0.53–1.07
Women	0.99	0.89–1.09	0.85	0.59–1.18
Among them cancer of				
Intestine				
All	0.75	0.60–0.92	n.a.	n.a.
Men	1.02	0.77–1.32	n.a.	n.a.
Women	0.51	0.35–0.72	n.a.	n.a.
Lung and bronchiae				
All	0.97	0.82–1.14	0.79	0.41–1.38
Men	0.83	0.67–1.01	0.76	0.34–1.45
Women	1.48	1.09–1.96	0.89	0.17–2.62
Liver				
All	0.76	0.42–1.26	n.a.	n.a.
Men	0.69	0.30–1.37	n.a.	n.a.
Women	0.86	0.34–1.78	n.a.	n.a.
Kidney				
All	0.68	0.39–1.11	n.a.	n.a.
Men	0.45	0.16–0.98	n.a.	n.a.
Women	0.99	0.47–1.84	n.a.	n.a.
Urinary tract				
All	1.16	0.74–1.73	n.a.	n.a.
Men	0.99	0.54–1.66	n.a.	n.a.
Women	1.53	0.73–2.82	n.a.	n.a.
Leukaemia				
All	1.13	0.92–1.83	n.a.	n.a.
Men	1.20	0.72–1.89	n.a.	n.a.
Women	1.46	0.87–2.32	n.a.	n.a.

n.a.: not analysed because of limited number of cases

cohort according to the toxicological expertise from Neumann [5].

Assessment of environmental contamination due to the accident showed a clearly defined area of about 0.2 km^2, inhabited by 2,048 people ("*cone*" area). Outside of this area ONA contamination could not be detected in several hundred soil samples.

The strength of our study and mortality analysis is the excellent follow-up of all persons in the study region (only 3.5 % were lost to follow-up) and the availability of individual death certificates. However, there are some limitations as well: only death—due to all causes and specific cancer causes—could be considered as an outcome. For cancer with good prognosis the risk may be underestimated. As in all environmental studies, exposure assessment is crucial. In our study, exposure assessment was only based on home address, because data of an exposure registry were not available and data on the human biomonitoring which had been obtained immediately after the accident in February 1993 [8] focussed on children only. So there is always a potential misclassification problem, simply because it is uncertain whether the people were present in Schwanheim at the chemical accident.

However, our approach is in line with many other epidemiological studies following industrial accidents. Addresses in regions with different exposures are commonly used in epidemiological studies as surrogate markers for exposure, i.e. in the Seveso and the Bhopal studies [9–11].

It is an interesting point that the area with the highest exposure results in a lower SMR and hazard ratio like the other areas.

In this context a further limitation is that no other risk factors or confounding factors were available. As the social structure of the persons living in the four areas is rather similar, one could argue that the distribution of other risk factors is not varying substantially. Although the division of the area into sequents is only based on distance to the chemical plant the population of Schwanheim is rather homogeneous.

The power of the study is a further limitation of our data set. Although the cohort includes nearly 20 000 persons, the number of death for specific cancer sites is small and the confidence intervals are rather broad.

A 15 year follow-up might be quite short with respect to the latency periods for many cancers. Therefore a 20 year

Table 2 Hazard ratio for the people living in the different zones ("*cone*", centre and 2 East/West) compared to the reference zone (3 East/West)

	N	Hazard ratio ("*cone*") Incl. 95 % CL	Hazard ratio (centre) Incl. 95 % CL	Hazard ratio (2 East/West) Incl. 95 % CL
Mortality total	3,031	0.97 (0.86–1.10)	1.14 (1.03–1.25)	1.14 (1.04–1.24)
Mortality cardiovascular	1,237	0.91 (0.75–1.10)	1.03 (0.88–1.20)	1.08 (0.94–1.24)
Mortality cancer	778	0.88 (0.68–1.13)	1.15 (0.96–1.39)	1.10 (0.93–1.32)
Among them cancer of				
Intestine	87	1.12 (0.58–2.17)	0.65 (0.33–1.25)	1.05 (0.63–1.75)
Lung and bronchiae	153	0.94 (0.53–1.67)	1.18 (0.77–1.81)	1.28 (0.87–1.88)
Liver	16	1.07 (0.23–5.06)	0.63 (0.14–2.99)	0.79 (0.21–2.99)
Kidney	16	0.73 (0.09–6.02)	2.49 (0.80–7.73)	0.99 (0.25–3.97)
Urinary tract	28	0.79 (0.18–3.56)	1.61 (0.63–4.16)	1.51 (0.61–3.74)
Leukaemia	33	0.34 (0.04–2.56)	1.75 (0.75–4.10)	1.60 (0.70–3.66)

follow-up has already been suggested around the end of 2013 with a final mortality analysis.

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