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Leukemia Risk in Caprolactam Workers Exposed to Benzene

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PURPOSE: To investigate the leukemia risk in a group of benzene exposed workers.
METHODS: We conducted a retrospective cohort mortality study on 311 men who worked between January 1, 1951 and December 31, 1968 in a Caprolactam plant in the Netherlands. In the production of Caprolactam (the Nylon 6 monomer) pure benzene is used as an extracting agent and the workers at this plant have been exposed to substantial concentrations of benzene. The cohort was followed for mortality until January 1, 2001. The total mortality was below the expected number, which was mainly caused by a deficit of cardiovascular disease mortality.
RESULTS: In the total group, there was one death from leukemia, compared with an expected number of 1.17. Despite the substantial exposures to benzene (on average 159 ppm-years per person) there was no indication for increased leukemia mortality within the cohort. We have applied earlier quantitative risk assessments to our cohort and conclude that some of these assessments overestimate the risk observed in our cohort of Caprolactam workers.
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KEY WORDS: Benzene, Leukemia, Risk Assessment, Epidemiology, Occupation.

INTRODUCTION

It is clear that high levels of benzene exposure increase the risk of leukemia in humans (1). IARC has classified the evidence for a carcinogenic risk from benzene exposure in humans as sufficient (2). However, actual measurements or quantitative exposure estimates are available in only a few studies on the leukemia risk from benzene exposure. A number of characteristics of these studies are briefly summarized in Table 1. In summary, clear increased risks have been found in workers employed in production processes in which benzene was used as a solvent, processes that inevitably will result in high peak exposure if no personal protection equipment or source shielding was applied.

We identified a group of workers who have been exposed to benzene in the past and followed them over a long period of time to observe the cause-specific mortality in this group. We considered this group to be of particular interest for benzene risk assessment, since it was anticipated that their exposure would be lower than that of the Pliofilm cohort, but significantly higher than exposures encountered in oil refineries or gasoline distribution operations.

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METHODS

Plant and Cohort Selection

The DSM Business Unit Caprolactam Europe agreed to perform a benzene cohort study after receiving a letter from the Dutch chemical industry association (VNCI) stressing that in the coming Occupational Exposure Limit discussion in the Netherlands, epidemiology data were needed on workers exposed to pure benzene only. The cohort is enrolled from a Caprolactam production plant. *e*-Caprolactam (2-oxohexamethylenimine, hexahydro-1*H*-azepin-2-one) is the commercial feedstock for Nylon 6. Thirty-three production locations worldwide produce about 4×10^6 metric tons of Caprolactam per year. Virtually all industrialized nations possess Caprolactam facilities of their own. In this Dutch plant, Caprolactam is synthesized via the cyclohexanone oximation and Beckmann rearrangement route using oleum, followed by neutralization with ammonia. DSM has a long history with Caprolactam. A pilot plant was constructed in 1951 followed by a production plant in 1952 which is still in production. Pure benzene is used to extract the Caprolactam from the neutralized Caprolactam ammoniumsulphate solution.

Benzene

Benzene extraction was performed indoors and rather primitive in the early years. According to information given by former employees, this provided a high background exposure and peak and skin exposure occurred often due to technical problems and limitations. In Table 2 three periods are distinguished based on the technological improvements in benzene extraction within the observation period. The

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TABLE 1. Brief overview of all cohort studies on benzene exposed workers for which quantitative exposure assessments are available

Cohort and type of work	Cohort size and length of follow-up	Probability of peak exposures	Anemia excess observed	Obs/Exp = RR	Description of conclusion by researchers
Pliofilm, cohort (7) (9)	1868 1936–1987	Yes	Yes	14/3.9 = 3.6 (TL)	-coating workers, indoor, benzene used as rubber solvent -A clear excess of leukemia -Incorporation of intensity dependent factor improved the model (9)
Chemical workers cohort (11)	4602 1946–1976	yes	no	7/6.0 = 1.2 (TL)	-only an excess was found in the highly exposed subgroups
Canadian distribution workers cohort (12)	6672 1964–1983	No high peaks	No	14/10.4 = 1.35 (TL)7/7.2 = 1 (ML)	-no indication for an excess of leukemia, most benzene exposure originated from gasoline vapors
UK petroleum distribution cohort (13)	23300 1950–1990	Peaks defined as exposure over 3 ppm	No	OR = 1.004 per ppm-y (TL)OR = 1.000 per ppm-y (AL)	-inconclusive results, perhaps some relevance of peak exposures, these were relatively low
China cohorts (14)	74828 1972–1987	Yes,	Yes	38/15.2 = 2.5 (TL)21/7 = 3 (ANLL)	-a statistically significant increase in leukemia was reported in exposed workers -benzene used as solvent genetic factors involved in metabolism and detoxification of benzene
Monsanto cohort (15)	4417 1940–1998	Yes		12/9.3 = 1.3 (TL)5/2.3 = 2.2 (ANLL)	-highest relative risk for workers with over 40 peaks over 100 ppm -peaks appear to be a better predictor of myeloid leukemia risk than cumulative exposure
Dow cohort (17)	956 1938–1982	Yes, peaks up to 900 ppm	Yes	4/2.1 = 1.9 (ML)	-although not statistically significant, the study is in support of an increased leukemia risk in these workers
Caprolactam cohort	311 1951–1969	Yes, peaks were present	Never reported	1/1.17 = 0.85	-no excess leukemia despite substantial exposure to benzene

TL: total leukemia, ML: myeloid leukemia, ANLL: acute non-lymphatic leukemia.

TABLE 2. Observed number of total deaths, cancer and leukemia deaths and corresponding SMRs in six exposure groups

		Total mortality			Cancer mortality			Leukemia mortality		
Exposure group	N	Obs/exp	SMR	95% CI	Obs/exp	SMR	95% CI	Obs/exp	SMR	95% CI
(1951–1957) pilot plant French extraction	93	41/48.42	0.85	60.1–114.9	12/16.73	0.72	37.0–125.1	0/0.40	–	–
(1958–62) Comprimo extraction	67	42/48.83	0.86	62.0–116.3	17/17.35	0.98	57.0–156.8	1/0.41	2.44	3.2–1232.4
(1962–68) Outdoor Lurgi/RDC extraction	115	24/27.04	0.89	56.9–132.0	11/9.11	1.21	60.2–215.7	0/0.22	–	–
Lowest tertile with average mean exposure of 3.4 ppm-year	94	31/36.83	0.84	57.2–119.4	14/12.69	1.08	60.3–184.9	0/0.30	–	–
Middle tertile with average mean exposure of 68.8 ppm-year	88	35/38.40	0.91	63.5–126.7	14/13.56	1.03	56.4–173.0	1/0.32	3.13	4.1–1579.0
Highest tertile with average mean exposure of 401.5 ppm-years	93	41/48.42	0.85	60.8–114.9	12/16.73	0.72	37.0–125.1	0/0.40	–	–
No exposure assessment	36	14/24.21	0.58	31.6–96.6	5/ 6.0	0.84	27.0–194.0	0/0.1	–	–

retrospective exposure assessment performed on the Caprolactam workers has been extensively described in a report published by TNO (3). Individual exposure estimates have been constructed for 275 of the 311 workers. We have treated the group of workers for which no exposure estimate has been made as a separate group in the analysis with a supposed equal exposure distribution.

Exposure Assessment Algorithm

A method developed by Armstrong et al. was selected for the assessment of the individual exposure to benzene (4). Cumulative individual exposure was assessed as the summation of exposures per cohort year. For each cohort year, exposure is generated using the following equation:

$$WE_i = BE * K_{job\text{-}location} * K_{workplace}$$

where WE_i = worker exposure in year i; BE = base estimate distribution of benzene exposure (ppm); $K_{job\text{-}location}$ = modifying factor for job-location combinations; and $K_{workplace}$ = modifying factor for the workplace.

Modifying factors for environment and substance are assumed to be 1 and therefore are not included in the equation.

The modifying factors were derived from the expert judgment process (see below). The factors 1 (low) to 6 (high) exposure are assigned to the percentiles of the BE distribution of available exposure data (1970s–1990s). The factors 2 to 6 are assumed to be within the 25 to 75 percentile range of the exposure distribution, which corresponds with the approach used in EASE (5)—the computerized expert system to assess exposure.

For $K_{Workplace}$ three additional factors are assigned to take into account major changes in the production process between 1951 and 1968 (see Table 2). The modifying factors, representing a reduction in exposure are: 8 from 1960 onwards; 4 from 1964 onwards; and 2 from 1968 onwards based on the expert judgment of former employees. The reduction of a factor 2 for any year after 1968 links the cohort period with the 1978 to 1995 period for which exposure data for benzene are available.

Expert Judgment Process

A group interview was held with seven former employees to reconstruct past exposure to benzene of workers at the Caprolactam factory. The panel consisted of the following employees: two Heads of shift, Instructor, Chemical analyst, Chief of production, and two Production workers. The following four issues were discussed:

- A job-location and time frame at the Caprolactam factory from 1951 to 1968;
- The influences of process and work practices changes on benzene exposure;
- Workplace air exposure to benzene during regular production, incidents, and stops;
- Ranking of jobs related to the workplace air concentrations.

First, the opinion of the employees was asked by means of a questionnaire. Next, the same questions were discussed by the group to settle differences in opinion. In general, no large differences were seen. Therefore, the overall opinion of the group was used.

The time span of the cohort (1951–1968) was split in three periods on the basis of major changes in the production process: period 1: 1951 to 1957; period 2: 1957 to 1962; period 3: 1962 to 1968.

In total, 30 changes that had an effect on benzene concentrations in the Caprolactam factory were identified. The former workers were asked to assess the magnitude of the effect on benzene exposure by a factor. This factor was used as a modifier in the assessment of the background concentration to benzene in the Caprolactam factory. The intensity of the benzene exposure was divided into three classes: low, middle, and high. To achieve consensus in the interpretation of the exposure classes, the following definitions were employed—"none to low exposure": no smell of

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benzene; "middle": a weak benzene smell; and "high": strong benzene odor. However, it should also be noted that the odor threshold for benzene varies between persons.

The type and number of jobs changed over the cohort period due to changes and expansions of the factory over the years. In the Caprolactam factory a planning board with an overview of the jobs and the names of the persons working was used. A photo album was available with photographs of these planning boards for each cohort year. To derive individual exposure estimates the main task named in the descriptions of the job as it appeared on the planning board were used.

The job/time concentrations were established and checked using: 1) the exposure assessment expert system EASE (5) for the first period (1951–1957), 2) the exposure factors determined at the panel meeting, 3) the history of recommended workplace levels, and 4) the exposure measurements conducted in the factory from 1978 to 1988.

The benzene measurements of 1978 and later were used to establish BE, the base estimate distribution of benzene exposure (ppm). The K factors were used to establish the exposure of a certain function in a certain year. EASE and the trend in recommended workplace levels were used only to compare the trend and the calculated exposure levels in the early fifties.

The exposure could be established for only 275 cohort members.

Air Exposure

The total cumulative exposure of the 275 cohort members over the observation period from 1951 to 1968 was 43,725 ppm-years (49,500 ppm-years when extrapolated to the total cohort). The daily mean workplace air exposure was 20.9 ppm per person. The average number of exposure years was 9.6, with a standard deviation of 6.0 and a range from 1 to 18 years. A clear reduction in exposure occurred over the years (see Fig. 1). For example, average daily mean exposure in the early period (1951–1957) was estimated to be over 26 ppm compared with 0.6 in the 1963 to 1968 period. For 47% of the workers the cumulative exposure was less than 50 ppm years and for 28% higher than 200 ppm-years (maximum 1080 ppm-years).

For 12 out of 46 job-location combinations no contribution to benzene exposure was expected to have occurred. The highest contribution in ppm-years was found for the "operator extraction" (see Fig. 1). The highest contribution in terms of number of years contribution was observed for the job descriptions "reserve" (219 years) and "chemical analyst" (168 years).

Dermal Exposure

According to former employees, in some jobs, certainly in the early years, it is likely that there was extensive and frequent dermal exposure to benzene. The contribution of dermal exposure was also assessed and included in the model. With the help of some members of the former employee group, jobs and time periods were identified with daily and weekly skin contact. Relevant skin exposure occurred predominantly in the early years. An arbitrary 2% to 10% ppm-years of the air exposure was added if the job was identified with a weekly or daily skin contact. This approach led to the addition of 1654 ppm years to the cohort. It was felt, by the researchers, however, that the contribution of benzene skin exposure to the total body burden was still underestimated this way.

Epidemiology

The first step in the epidemiology part of the study was to compile a list of former and current workers of the Caprolactam plant. This was done by means of the employee

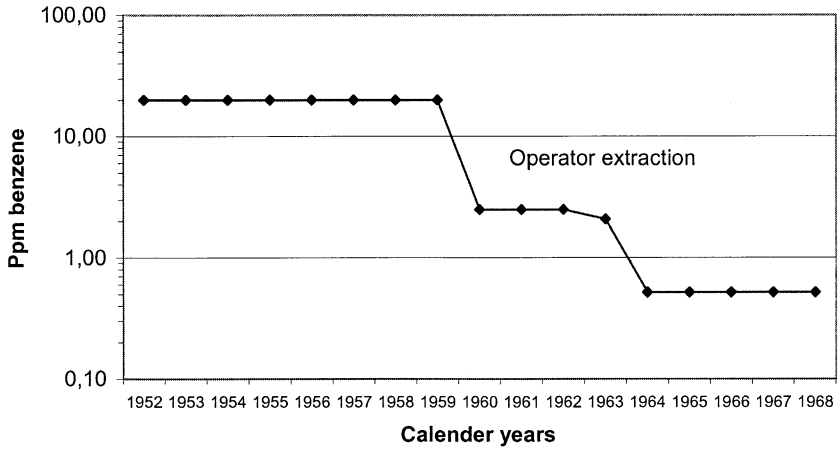

FIGURE 1. The estimated benzene workplace air concentrations during the cohort observation period of the Operator extraction.

rosters of the plant, which were available for the period between January 1, 1951 and December 31, 1968. All the names and ID-numbers that appeared on these worker rosters were written down and the personnel files of the employees were traced in the archives of the company. This procedure resulted in a list of 311 Caprolactam workers who had been employed in the Caprolactam plant at some time between January 1, 1951 and December 31, 1968. These workers were followed for mortality and the end date of the follow-up was January 1, 2001, covering a maximum risk period of follow-up of 40 years and a minimum risk period of 32 years in case a person survived until the end date of the study. The observed cause-specific mortality was compared with the expected number based on background cause specific and age specific mortality of the total male Dutch population. Standardized Mortality Ratios (SMRs) were calculated by dividing the observed number of deaths by the expected number and multiplying the result with 100. 95% confidence intervals were calculated by the method proposed by Ulm (6).

The exposure assessment data were linked to the individual employees on the basis of the job, workplace, and time interval. An exposure matrix was made for each combination of a specific job, specific workplace, and specific time interval. This matrix was linked to the job history of all 275 cohort members for whom a complete job history was available. This process resulted in an exposure estimate for each worker in terms of cumulative exposure and exposure peaks. Next, all exposed workers were classified into three cumulative dose groups: low, medium, and high. The cut-off points of the three dose groups were chosen in such a way that all three dose groups contained one third of the cohort.

RESULTS

Of the 311 workers included in the study, 121 had died before the end date of the follow-up period, 180 (57.9%) were still alive on that date, and 8 (2.6%) had emigrated. For workers who emigrated, the person-years at risk accumulation was stopped at emigration date. Two (1.1%) employees were lost to follow-up. The workers who had emigrated or were lost to follow-up had no particular exposure pattern. Next, the numbers on the death certificates were linked with the Dutch electronic causes of death file, which was maintained by the Dutch Central Bureau of Statistics (CBS). Of the 121 deceased workers, 5 (4.1%) could not be linked to the CBS causes of death file.

The total and cause specific mortality of the cohort is given in Table 3. One hundred twenty-one Caprolactam workers had died before the end date of the follow-up, compared with an expected number of 140.9, giving an SMR of 85.9 (95% CI, 71.3–102.6) Table 4. This healthy worker effect is mainly attributable to lower mortality rates from diseases of the circulatory system and to a lesser extent to a deficit in mortality from external causes. Mortality from neoplasms was also lower than expected (SMR, 91.9; 95% CI, 67.1–123.0). An unexpected finding was the statistically significant excess of brain cancer mortality (SMR, 634.2; 95% CI, 231.6–1372.8). The mortality from leukemia was in fact lower than the expected number. Only one death form leukemia was observed compared with an expected number of 1.17. The leukemia found was a non-AML type. The subclassification of the cohort into three groups either according to cumulative dose or peak exposure (data presented in Table 3) shows that the one leukemia death

TABLE 3. Observed numbers of death and Standardized Mortality Ratios for 311 Caprolactam workers followed until January 1, 2001

Causes of death	Observed/ expected	SMR	95% CI
Total mortality	121/140.9	85.9	(71.3 – 102.6)
Main categories			
I Infectious diseases (1)	0/0.95		
II Neoplasms (2)	45/48.95	91.9	(67.1–123.0)
III Circulatory system (3)	39/56.06	69.6	(49.5–95.1)
IV Respiratory system (4)	11/10.27	107.1	(53.4–191.4)
V Digestive system (5)	4/4.30	93.0	(25.0–235.4)
VI Others (6)	13/14.22	91.4	(48.6–156.1)
VII External causes (7)	4/6.14	65.2	(17.5–165.0)
Unknown	5		
Mouth cancer & pharynx (8)	1/0.61	163.7	(2.1–827.0)
Esophagus (9)	1/1.23	81.2	(1.1–410.5)
Stomach & small intestine (10)	4/3.46	115.6	(31.1–292.6)
Large intestine (11)	3/3.27	91.6	(18.4–262.9)
Rectum (12)	1/1.19	84.2	(1.1–425.7)
Liver & biliary passages (13)	1/0.85	117.5	(1.5–593.8)
Pancreas (14)	2/2.11	94.7	(10.7–330.1)
Larynx (16)	1/0.46	215.5	(2.8–1089.0)
Trachea & lung (17)	15/19.53	76.8	(43.0–126.5)
Prostate (22)	1/3.51	28.5	(0.4–144.2)
Bladder (24)	3/1.62	185.3	(37.2–531.5)
Brain (25)	6/0.95	634.2	(231.6–1372.8)*
Hodgkin's disease (29)	1/0.27	373.1	(4.9–1885.4)
Multiple myeloma (31)	1/0.71	140.8	(1.8–711.7)
All leukemia (32)	1/1.17	85.6	(1.1–432.6)
Unspecified neoplasms (34)	3/1.96	153.3	(30.8–439.7)

Causes of death with zero observations have been omitted.
*$P < 0.05$.

TABLE 4. Endpoints of the follow-up in terms of vital status of the 311 Caprolactam workers

Vital status in January 1, 2001	N	%
Alive	180	57.9%
Deceased	121	38.9%
Emigrated	8	2.6%
Lost to follow-up	2	1.1%
Total number	311	100%

occurred in the comprimo group and in the middle tertile of the cumulative dose group. So, although no excess leukemia is found, the single non-AML leukemia case is not found in the highest exposure group. We observed six deaths from brain tumors compared with an expected number of 0.95. The excess was found in all three caprolactam processes and all three tertiles of the cumulative dose groups. Several of the brain tumors had been the subject of an investigation of a brain tumor cluster within the company. This cluster was not confined to a particular area of the company and former analyses did not lead to the identification of a risk factor for this excess of brain tumors within the company as a whole.

DISCUSSION

We conducted a retrospective cohort mortality study of 311 Caprolactam workers exposed to substantial concentrations of benzene in the past. In the cohort, there was no indication of any excess risk for leukemia due to the benzene exposure. From earlier epidemiological studies it is clear that benzene is a human carcinogen. Many well-conducted studies document this risk. In several of these studies exposure measurements and/or exposure assessments have been used to quantify exposure to benzene. In this respect, the studies and further analyses of a cohort of Pliofilm workers in the United States play an important role (7). In the Pliofilm cohort a statistically significant excess of leukemia mortality has been observed. A few documented exposure measurements of limited information and further extrapolations have been used to estimate dose–response curves on several occasions (8–10). There is quite some debate about whether or not the Pliofilm cohort data provide evidence for a threshold or not, and if so at what level. Wong for instance concluded that in the Pliofilm cohort there was no evidence of a risk for acute leukemia under 200 ppm-years of exposure and that a significant excess of leukemia mortality was only present in workers with a cumulative exposure of over 400 ppm-years (10). In a further analysis of the Pliofilm data Crump (9) concluded: "There was evidence of an intensity dependent non-linearity reaching borderline significance." Paxton, who studied and extended the follow-up of the Pliofilm cohort, noted that the leukemia risk was only present in workers hired before 1950 and interpreted this finding as evidence indicating the existence of a threshold (8).

A second retrospective cohort mortality study for which quantitative exposure estimates were available was conducted by Wong (11) who followed 4602 workers from seven companies who had been exposed to benzene between 1946 and 1975. Average 8-hour concentrations varied from < 1 to over 50 ppm. Peaks of over 100 ppm had also occurred. Overall, no increasing trend was observed for leukemia. In the workers who had experienced peaks of over 100 ppm, 4 leukemia deaths were observed compared with an expected number of 3.01. A four-fold excess risk of leukemia was found for employees with more than 60 ppm-years of exposure.

A third cohort for whom exposure estimates and measurements are available is a cohort of 6672 Canadian petroleum distribution workers (12). The benzene exposures in this cohort were in the lower range. Daily concentrations reached 6.1 ppm. The authors concluded that the study did not show a relation between lympho-hematopoietic cancer and low-level exposure to benzene.

A fourth cohort for whom exposure measurements or estimates were available is the UK marketing and distribution workers cohort. The cohort had been assembled in the seventies and later exposure estimates were added and an extension of the follow-up was conducted (13). Exposure estimates were made using the same procedures as applied to the Canadian cohort. Ninety cases of leukemia were observed and together with a matched control group, were studied in a nested case/control design. The authors reported a suggestive dose–response trend between acute myeloid leukemia and categorical exposure metrics. However, in further sensitivity analyses by degree of confidence in exposure information the dose–response trends became weaker. The authors interpreted the study as weakly suggestive of an effect, but noted that because the study lacked internal consistency no firm conclusions could be drawn.

A fifth large cohort has been studied in China, in the form of a close collaboration between the US National Cancer Institute and several Chinese investigators (14). This cohort consisted of 74,828 workers employed in 1427 departments with benzene exposure including painting, printing, manufacture of footwear and other chemicals. A large number of concurrent benzene measurements were available, and past exposure was assessed and extrapolated from the measurements and categorized into 6 concentration ranges over 7 calendar periods. Increased risks for leukemia were found even in the lowest exposure group, under a cumulative exposure of 10 ppm-years. However, peak exposures in this group are likely to have occurred.

A sixth cohort for whom exposure data are available is the Monsanto cohort of 4172 workers employed between 1940 and 1997 (15, 16). Exposure measurements were available since 1980. For all jobs the potential for peaks was evaluated. The authors concluded that there was little evidence of an increasing risk with increasing cumulative exposure for acute non-lymphocytic leukemia and that peak exposure appeared to be a better predictor of risk than cumulative exposure.

A seventh cohort of benzene-exposed workers with quantitative exposure assessments was assembled at the Dow Chemical Co. in the United States (17). It included 956 workers employed in three production areas (chlorobenzyl,

alkyl benzene, and ethyl cellulose plants) of a chemical plant using benzene. The cohort was followed up to 1982 and four deaths from leukemia were noted compared with an expected number of 2.1. Despite the lack of statistical significance the authors concluded that the study is in support of an association. All these studies provide information that can form the basis of a quantitative risk assessment for benzene and leukemia. So far however quantitative risk assessments for benzene have been based on the results of the Pliofilm cohort. A more balanced approach would be to include all seven studies and perhaps perform a pooled analysis on the original data of these studies. Perhaps a pooled analysis of these studies could also address the issue of a threshold for benzene exposure to act as a carcinogen.

In the past, several quantitative risk assessments have been made in which the additional risk of leukemia due to long-term benzene exposure was calculated. We applied these quantitative risk estimates to the data of the Caprolactam cohort to see which of these earlier risk estimates are compatible with the findings in the Caprolactam cohort:

- Austin (18) estimated the additional leukemia mortality as 53 per 1000 deaths in a population exposed to 300 ppm-years. In the Caprolactam cohort we found an average exposure of 43725/275 = 159 ppm-years. According to this approach the number of benzene-induced additional leukemia cases in this cohort should have been 159/300 * 121 * 53/1000 = 3.3, compared with the zero number of additional deaths we found ($p = 0.03$).
- Rinsky (19) concluded that the leukemia risk in the Pliofilm cohort was best described by the model: OR = Exp (0.0126 * ppm-years). This would lead in the Caprolactam cohort to an OR = exp (0.0126 * 159) = 7.4, and to 1.17 * (Exp(0.0126 * 159)-1) = 7.5 additional benzene-induced leukemia cases ($p = 0.0001$).
- The Dutch Health Council (20) estimated that a 10-year occupational exposure to 128 mg/m^3 (= 420 ppm-year) would result in a relative risk of 5 for acute nonlymphatic leukemia. Using the simple linear model RR = 1+ bxc in which c is the cumulative exposure and b is the tangens (b equals 0.0095) of the slope, it can be calculated that an average exposure of 159 ppm will result in a relative risk of 2.5 for acute non-lymphatic leukemia mortality. Thus, departing from the risk assessment of the Dutch Health Council, an excess acute non-lymphatic leukemia mortality as a result from the benzene exposure in the Caprolactam cohort would have been expected to be 0.58. (Of the 1.17 expected leukemia deaths, a third will be acute non-lymphatic leukemias.) An expected number of 0.58 + 1.17 = 1.75 compared with an observed number of 1 is not statistically different ($p < 0.17$) and thus statistically compatible with the findings in the Caprolactam cohort.
- In 1984, the United States Environmental Protection Agency estimated that lifetime continuous exposure to 0.046 ppb benzene would result in one additional death from leukemia per million lives. This unit of risk expressed as a lifetime and continuous exposure was converted to ppm-years of occupational exposure to benzene 8 hours per day, 5 days per week. This unit risk then was applied to the Dutch national mortality rates to calculate the expected number of excess leukemia deaths in the Caprolactam cohort if the EPA risk assessment were true. On the basis of the EPA risk assessment we expected 1.92 excess deaths from benzene-induced leukemia in the Caprolactam cohort, which is not statistically significantly different from our findings. ($p < 0.14$).

Of the four risk models applied to the Caprolactam cohort two overestimate the leukemia risk from benzene exposure in such a way that they predict benzene induced excesses from leukemia that are statistically significantly different from our findings.

It must be clear that our study is limited because of its size. However, a strong point of this study is that it adds information in an exposure range between the very high exposure encountered in the Pliofilm cohort and the very low exposures encountered in the petroleum industry. Thus it contributes information in the exposure range that is most important with respect to the ongoing debate about the existence of a threshold for the leukemogenic effect of benzene. We believe that our study adds some support to the hypothesis that the risk for leukemia from benzene exposure is not a linear relationship, but one that has a threshold. Certainly our study is too small for the exact determination of the exposure range in which the threshold should be. A pooled analysis of all currently available epidemiological studies of benzene exposed workers, for which exposure data are available could help determine if these studies are in support of a threshold and in which exposure range the threshold should be expected.

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