Leukaemia risk in Caprolactam workers exposed to benzene

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We conducted a retrospective cohort mortality study among 311 men who worked between 1-1-1951 and 31-12-1968 in a Caprolactam plant in the Netherlands. In the production of Caprolactam (the monomer of Nylon 6) pure benzene is used as an extracting agent and the workers at this plant have been exposed in this period to substantial concentrations of benzene.

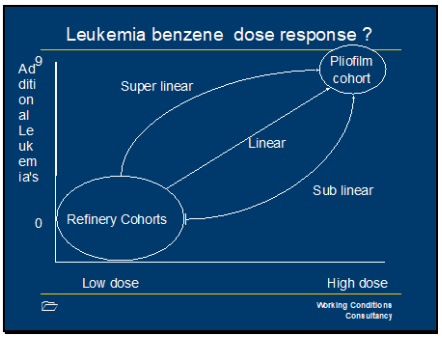
The study was performed by TNO Chemie the Netherlands (dr. J. de Cock and co-workers, Exposure assessment) and the University of Maastricht (dr. G. Swaen and co-workers, the mortality follow up).

The Dutch Chemical Industry Association (VNCI) asked in 1999 there members if they could provide epidemiological evidence for the ongoing discussion with governmental organizations and the Dutch health council on the existence of a threshold level for the carcinogenic effects of benzene and the safe levels for exposure.

Because DSM foresees feasibility problems with a further reduction of the Occupational Exposure Level (OEL or MAC) and has on the average positive experience with the conclusive epidemiological research done by the University of Maastricht, the management of the Caprolactam plant was asked to participate.

The history of the use of pure benzene since 1952 and the information available on the plant (EPO archives going back to 1978) made the Caprolactam plant in Geleen (the Netherlands) a good candidate for such a study. The CAP management responded positive and agreed after consulting the works council.

The current Dutch OEL of benzene is based on data from 1 study (pliofilm cohort) with extreme high exposures and substantial number of additional leukemia's. On the other hand there is overwhelming evidence that low exposures to benzene does not cause sufficient damage to the bone marrow to cause leukemia.



Since no reliable cohort studies exist on intermediate exposure levels, it is assumed in risk analysis, despite information indicating a sub linear trend, that a linear dose response relationship exists between benzene and leukemia.

The study was performed in three steps:
First TNO established if sufficient data could be gathered to estimate exposure.
When it was concluded that sufficient information was available it was decided to ask TNO to perform exposure assessment.
After TNO concluded that the exposure was sufficient to detect at least two additional leukemia's it was decided to ask the University of Maastricht to perform the mortality follow-up

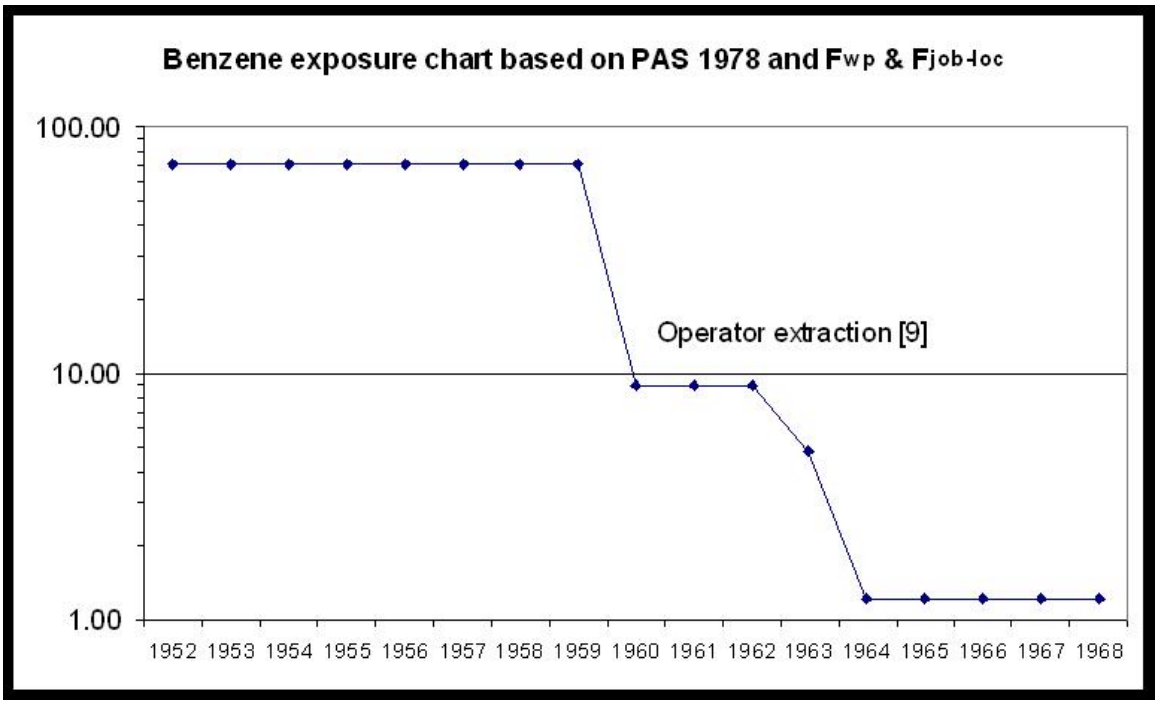
With the use of the checklist developed by Pat Stewart key data were checked on availability, completeness en quality. Samples of personnel files were checked. TNO concluded that sufficient information was available to perform a good exposure assessment.

Individual exposure estimates were made using the retrospective exposure assessment method developed by Armstrong (1996). This method combines base estimates of exposure with multiplying factors for workplace (hardware) and job/location (organization).

$$Exposure_i = \sum^j Base^* F_{workplace_j} * F_{job\text{-}loc_i}$$

The workplace and job-location factors necessary for the model were based on the plant lay outs, engineering reports on changes in the hardware, standard operational procedures (SOP), process flow charts, operations descriptions, job descriptions and industrial hygiene data and established with the assistance of a panel of former employees who had worked in the plant in the 50-ties and 60-ties. For both multiplying factors time tables were constructed.

The base estimate was made from the so-called “Epo” exposure data base. This is a site database containing outcome and other key information on all the TWA 8 hours, Personal Air Sampling results within Similar Exposure Groups collected since 1978.



The level and major discrete jumps in the workplace exposure through time were estimated using the PAS exposure distribution of 1978 combined with the workplace factors. The outcome were compared with:

- the results of industrial hygiene exposure assessment program EASE, taking into account the process conditions in the different periods.
- the EASE estimate of 1952 with the workplace factors,
- the trend in the Benzene’s Occupational Exposure Limit (OEL) over the cohort period.
- the results of backward extrapolation of logarithmic regression of the Personal Air Sampling (PAS) outcome of the eighties and nineties to the period 1951 and 1968.

Pictures taken yearly over the period 1951-1968 of the plant’s personnel planning board were the source to identify the person/job combinations and the way work was organized (jobs, tasks and shifts). Cohort input data (identity, dates of birth, hire, job mutation and leave) were collected from plants personnel records. Although the personnel records of 36 workers could not be used for the individual exposure assessment, we concluded that the exposure distribution of the complete cohort is well described by the information of the 275.

The exposure ranking of the 48 job/locations by the panel, was converted to zero exposure or to one of six discrete percentile points (10, 25, 37.5, 50, 62.5, 75%) in the air exposure distribution. Some members of the panel also determined jobs with weekly or daily, hand contact, arm contact and/or soaked clothing with the benzene liquid (dermal exposure).

The cumulative exposure per employee is than established by the summation of the job-location percentile point concentration per year over all the individual working years. The average daily workplace air exposure of the total group is 20.9 ppm (standard deviation 28). The mean number of exposure years is 9.6 (range 1-18) years. For 47% of the cohort cumulative exposure is less than 50 ppm-years and for 28% higher than 200 ppm-years with a maximum of 1080 ppm-years.

The total number of ppm-years of workplace air exposure to benzene for the 275 cohort members is 43,725 ppm-years. Extrapolation to the complete cohort brings the total cohort benzene air exposure to 49500 ppm-years. The skin exposure is estimated to add 1885 ppm years, which leads to a total of 51385 ppm years or 165 ppm years per person.

The two EASE approaches resulted in much higher exposure levels. They are considered to be not representative for the regular production at that time, but maybe representative for shut-down and start-up periods in turnarounds (once or twice a year) and incidents (often occurring in the fifties). The non-Dutch OEL's before 1960, which were probably unknown in the plant at that time and are considered to underestimate the workplace exposure. The backward regression indicated that the workplace factor of two used for the decrease in exposure between 1968 and 1978 is probably a factor 1.9 too low.

The estimation of the exposure is considered to be at the lower side of the exposure confidence interval.
The University of Maastricht followed the cohort for mortality until 01-01-2001 and asked the Dutch Central Bureau of Statistics causes of death.

Cause	Obs/Exp	SMR
All	121/140.9	0.86
Cardiovasculair	39/56.06	0.70
All cancer	45/48.95	0.92
Leukaemia	1/1.17	0.85

The total mortality was below the expected number, which was mainly caused by a deficit of cardiovascular disease mortality (Healthy worker effect).

In the total group there was one death from leukemia, compared to an expected number of 1.17. If the cohort was divided in three groups of ppm-years exposure (low, medium, high) the leukemia case was in the medium group

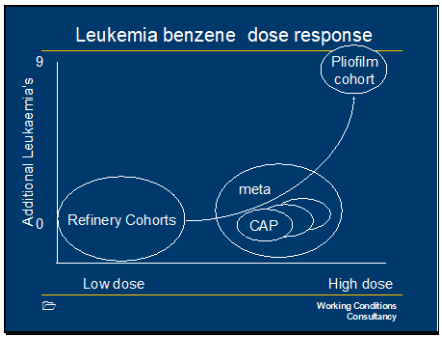
Despite the substantial exposures to benzene (159 ppm-years per person on the average) there was no indication for increased leukemia mortality within the cohort.

We have applied earlier quantitative dose response risk assessments to our cohort.
The most conservative do not comply with the results we found.
Based on Rinsky's approach we should have found 7.5 additional leukemia cases. The change that our findings are caused by change is less than 0.01%. The same accounts for the approach of Austin. We conclude that these assessments overestimate the risk observed in our cohort of Caprolactam workers. Our result do not reject the US EPA linear dose response approach.

Reference	Additional cases	P value
Rinsky	7.5	<0.0001
Austin	3.3	0.03
US EPA	1.92	<0.14

Based on a short review of other human studies of benzene exposed workers we hypothesize that the estimated exposure levels in the Caprolactam plant were below the levels that cause bone marrow toxicity and thus do not cause leukemia.
The cohort study supports the findings that for benzene a sub linear dose response relation exists.

We recommend:
- to pool the data of the chemical industry cohorts presented today
- to initiate more cohort studies among Caprolactam plants, using the HSO (HyamSulphate) route with pure benzene as the extracting agent.



References

Armstrong TW, Pearlman ED, Schnatter AR, Bowes SM, Murray N, Nicolich MJ. Retrospective benzene and total hydrocarbon exposure assessment for a petroleum marketing and distribution worker epidemiology study. Am Ind Hyg Assoc J. 1996; 57(4):333-343.
Rinsky RA, Young RJ, Smith AB. Leukemia in benzene workers. American journal of industrial medicine 1981;2(3):217-45.