

# German Investigations on Morbidity and Mortality of Workers Exposed to Vinyl Chloride

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Two studies on mortality and morbidity of workers exposed to vinyl chloride monomer (VCM) which have been carried out on behalf of the Ministry of Labour, Health and Social Affairs on Northrhine-Westphalia are reported.

## Vinyl Chloride Mortality Study

The aims of this study were to determine standardized mortality ratios (SMR) for male workers exposed to VCM, using the mortality rates of the West German male population as reference, to study the SMRs of a cohort of workers of the chemical industry comparable concerning age distribution and observation period but not exposed to VCM and to determine the SMR of a cohort of workers in PVC-processing plants.

The study was designed as a historic cohort study, covering the period from the beginning of the VCM- and PVC-production in all of the German plants till the end of 1974.

Table 1 shows the main characteristics of the three cohorts investigated. Only Germans and Austrians were included in data analysis because of insufficient mortality data on various foreign nationals employed in German factories. To determine the mortality rates of Austrians, West German rates were used. To calculate expectations of total mortality, the mortality rates of the adequate years have been used. To calculate expectations of specific causes of death for all years before 1968, the rates of 1968 have been used; for the following years the rates of the corresponding years. Following the procedure applied by Tabershaw (1),

weighting of observed cases of specific causes of death according to unknown causes of death has been done with weighting factors calculated separately for three observation periods (up to 1959, 1960-1969, 1970-1974) as well as for six age groups.

In all of the cohorts, follow-up rates have been near or above 90%. The percentage of causes of death that could not be investigated due to loss or deletion of death certificates varied from 7.3% to 13.1%. To calculate age-standardized mortality ratios of specific causes of death, weighting has been done according to the procedure used by Tabershaw and Gaffey (1) to compensate for unknown or unidentified causes of death.

Table 2 displays total mortality as well as some of the relevant specific causes of death. It can be observed that the otherwise observed "healthy worker effect" cannot be demonstrated in the German cohorts exposed to VCM or employed in PVC-processing plants.

In the VCM cohort there are significant elevations of SMR of malignancies of the lymphatic and hematopoietic tissues (ICM 200-209), and of malignancies of the GI tract (ICD 150-159). The latter is due to the paramount elevation of SMR of tumors of the liver (ICD 155).

It must be noted that there is a modest elevation of SMR of tumors of the liver also in the cohort not exposed to VCM nor employed in PVC-processing plants. No obvious explanation for this observation can be offered. In addition elevated SMRs for ischemic heart disease (ICD 410-414) can be found in all of the three cohorts. Due to methodological

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shortcomings of the study no assessment of cardiovascular risk factors has been made. Therefore these results are of minor interest.

When subdividing the VCM-exposed cohort according to time of exposure there is a clear-cut increase of the SMR of liver tumors with time (Table 3). This seems to be highly suggestive of a

time-response pattern. As it has been impossible to determine concentrations of VCM retrospectively due to technological and methodological problems, no dose-response pattern can be established. However time of exposure seems to be the best available guess for dose.

Subclassification according to observation period

Table 1. Characteristics of study cohorts.

|                                               | Group I, VCM/PVC production | Group II, reference group | Group III, PVC processing |
|-----------------------------------------------|-----------------------------|---------------------------|---------------------------|
| Population (Germans + Austrians)              | 7,021                       | 4,910                     | 4,007                     |
| Man years                                     | 73,734                      | 76,029                    | 52,896                    |
| Follow-up completed till 12/31/74. % deceased | 93.2                        | 89.5                      | 92.1                      |
| Observed                                      | 414                         | 417                       | 360                       |
| Expected                                      | 435                         | 533                       | 350                       |
| Unknown causes of death                       |                             |                           |                           |
| No.                                           | 30                          | 47                        | 47                        |
| %                                             | 7.3                         | 11.3                      | 13.1                      |
| Total mortality (SMR)                         | 95                          | 78                        | 95                        |
| Foreigners (excluding Austrians)              | 882                         | 711                       | 1,454                     |
| Deceased                                      | 6                           | 6                         | 10                        |

Table 2. Standardized mortality ratios.

| ICD 9           | Cause of death                                      | VCM/PVC production |                   | Reference group |                  | PVC processing |                  |
|-----------------|-----------------------------------------------------|--------------------|-------------------|-----------------|------------------|----------------|------------------|
|                 |                                                     | Obs.               | SMR               | Obs.            | SMR              | Obs.           | SMR              |
| Total mortality |                                                     | 414                | 95                | 417             | 78               | 360            | 95               |
| 140-209         | All malignant tumors                                | 94                 | 112               | 83              | 83               | 62             | 65               |
| 140-199         | Malignant tumors of organs                          | 79                 | 103               | 77              | 83               | 60             | 89               |
| 200-209         | Malignancies of lymphatic and hematopoietic tissues | 15                 | 214 <sup>b</sup>  | 6               | 77               | 2              | 34               |
| 150-159         | Malignant tumors of GI tract and peritoneum         | 45                 | 149 <sup>a</sup>  | 27              | 71               | 15             | 56               |
| 155             | Malignant tumors of the liver                       | 12                 | 1523 <sup>b</sup> | 4               | 401 <sup>a</sup> | 3              | 434              |
| 191             | Malignant tumors of the brain                       | 2                  | 162               | 2               | 184              | 5              | 535 <sup>a</sup> |
| 410-414         | Ischemic heart disease                              | 91                 | 127 <sup>a</sup>  | 115             | 131 <sup>a</sup> | 96             | 158 <sup>b</sup> |
| 410             | Acute myocardial                                    | 66                 | 114               | 83              | 120              | 69             | 143 <sup>b</sup> |
| 800-949         | Accidents                                           | 61                 | 137 <sup>a</sup>  | 44              | 99               | 32             | 110              |

<sup>a</sup>Beyond 95% confidence interval (2).

<sup>b</sup>Beyond 99% confidence interval (2).

Table 3. Standardized mortality ratios by duration of exposure.

| ICD 9           | Cause of death                                      | Duration of exposure, months |     |       |                  |        |                   |       |                   |
|-----------------|-----------------------------------------------------|------------------------------|-----|-------|------------------|--------|-------------------|-------|-------------------|
|                 |                                                     | < 12                         |     | 13-16 |                  | 61-120 |                   | > 121 |                   |
|                 |                                                     | Obs.                         | SMR | Obs.  | SMR              | Obs.   | SMR               | Obs.  | SMR               |
| Total mortality |                                                     | 53                           | 93  | 138   | 102              | 93     | 87                | 130   | 96                |
| 140-199         | Malignant tumors of organs                          | 6                            | 74  | 20    | 86               | 22     | 116               | 31    | 115               |
| 200-209         | Malignancies of lymphatic and hematopoietic tissues | 1                            | 92  | 4     | 186              | 5      | 287               | 5     | 249               |
| 150-159         | Malignant tumors of GI tract and peritoneum         | 3                            | 101 | 12    | 135              | 13     | 173               | 17    | 158               |
| 155             | Malignant tumors of the liver                       | 0                            | -   | 2     | 874 <sup>a</sup> | 3      | 1525 <sup>b</sup> | 7     | 2528 <sup>b</sup> |
| 191             | Malignant tumors of the brain                       | 0                            | -   | 0     | -                | 1      | 350               | 1     | 278               |

Table 4. Standardized mortality ratios by period of observation.

| ICD 8   | Cause of death                                      | Observation period |                  |         |                  |         |                   |       |                   |
|---------|-----------------------------------------------------|--------------------|------------------|---------|------------------|---------|-------------------|-------|-------------------|
|         |                                                     | To 1959            |                  | 1960-69 |                  | 1970-74 |                   | Total |                   |
|         |                                                     | Obs.               | SMR              | Obs.    | SMR              | Obs.    | SMR               | Obs.  | SMR               |
| 140-199 | Malignant tumors                                    | 12                 | 160              | 29      | 84               | 194     | 103               | 414   | 95                |
| 200-209 | Malignancies of lymphatic and hematopoietic tissues | 1                  | 147              | 9       | 275 <sup>b</sup> | 5       | 168               | 15    | 214 <sup>b</sup>  |
| 150-159 | Malignant tumors of GI tract and peritoneum         | 8                  | 270 <sup>a</sup> | 13      | 94               | 24      | 177 <sup>b</sup>  | 45    | 149 <sup>a</sup>  |
| 155     | Malignant tumors of the liver                       | 1                  | 1282             | 3       | 834 <sup>a</sup> | 8       | 2264 <sup>b</sup> | 12    | 1523 <sup>b</sup> |
| 191     | Malignant tumors of the brain                       | 1                  | 557              | 0       | -                | 1       | 223               | 2     | 162               |

<sup>a</sup>Beyond 95% confidence interval.<sup>b</sup>Beyond 99% confidence interval.

Table 5. Standardized mortality ratios by age.

| ICD 8   | Cause of death                                      | Age group |     |       |     |       |                   |       |     |       |                  |      |                   |       |                   |
|---------|-----------------------------------------------------|-----------|-----|-------|-----|-------|-------------------|-------|-----|-------|------------------|------|-------------------|-------|-------------------|
|         |                                                     | ≤ 24      |     | 25-34 |     | 35-44 |                   | 45-54 |     | 55-64 |                  | ≥ 65 |                   | Total |                   |
|         |                                                     | Obs.      | SMR | Obs.  | SMR | Obs.  | SMR               | Obs.  | SMR | Obs.  | SMR              | Obs. | SMR               | Obs.  | SMR               |
| Total   | mortality                                           | 10        | 68  | 45    | 111 | 65    | 104               | 90    | 101 | 105   | 80               | 90   | 103               | 414   | 95                |
| 140-199 | Malignant tumors of organs                          | 0         | -   | 4     | 141 | 13    | 188 <sup>a</sup>  | 19    | 141 | 22    | 76               | 21   | 100               | 79    | 103               |
| 200-209 | Malignancies of lymphatic and hematopoietic tissues | 0         | -   | 2     | 194 | 4     | 303               | 4     | 264 | 3     | 162              | 2    | 197               | 15    | 214 <sup>b</sup>  |
| 150-159 | Malignant tumors of GI tract and peritoneum         | 0         | -   | 3     | 397 | 10    | 365 <sup>b</sup>  | 10    | 145 | 10    | 89               | 12   | 140               | 45    | 149 <sup>b</sup>  |
| 155     | Malignant tumors of the liver                       | 0         | -   | 0     | -   | 6     | 6865 <sup>b</sup> | 0     | -   | 3     | 934 <sup>b</sup> | 3    | 1664 <sup>b</sup> | 12    | 1523 <sup>b</sup> |
| 191     | Malignant tumors of the brain                       | 0         | -   | 0     | -   | 0     | -                 | 1     | 254 | 1     | 362              | 0    | -                 | 2     | 162               |

<sup>a</sup>Beyond 95% confidence interval.<sup>b</sup>Beyond 99% confidence interval.

Table 6. Groups for subdivision of laboratory examinations.

| Group | Specification                                                      |
|-------|--------------------------------------------------------------------|
| A-1   | VCM/PVC production                                                 |
| A-11  | PVC processing                                                     |
| B-1   | VCM/PVC production and PVC processing.<br>work capacity loss < 20% |
| B-11  | VCM/PVC production and PVC processing.<br>work capacity loss ≥ 20% |
| C-1   | Germans and Austrians                                              |
| C-11  | Foreigners (Excl. Austrians)                                       |
| D-1   | Plants with high morbidity                                         |
| D-11  | Plants with low morbidity                                          |

Table 7. Bromsulfalein retention.<sup>a</sup>

|                    | VCM/PVC<br>Production | PVC<br>Processing | Total |
|--------------------|-----------------------|-------------------|-------|
| Retention normal   | 26                    | 21                | 47    |
| Retention abnormal | 44                    | 10                | 54    |
| Total              | 70                    | 31                | 101   |

<sup>a</sup>Chi square, = 8.09 ( $p < 1\%$ ).Table 8. Bromsulfalein retention.<sup>a</sup>

|                    | Germans<br>and<br>Austrians | Foreigners | Total |
|--------------------|-----------------------------|------------|-------|
| Retention normal   | 17                          | 30         | 47    |
| Retention abnormal | 33                          | 21         | 54    |
| Total              | 50                          | 51         | 101   |

<sup>a</sup>Chi square, = 6.25 ( $p < 2.5\%$ ).Table 9. Bromsulfalein retention.<sup>a</sup>

|                    | Work capa-<br>city loss<br>< 20% | Work capa-<br>city loss<br>> 20% | Total |
|--------------------|----------------------------------|----------------------------------|-------|
| Retention normal   | 41                               | 6                                | 47    |
| Retention abnormal | 32                               | 22                               | 54    |
| Total              | 73                               | 28                               | 101   |

<sup>a</sup>Chi square, = 9.81 ( $p < 1\%$ ).

(Table 4) reveals a rather inconsistent pattern: malignancies of the lymphatic tissues (ICD 200-209) are significantly elevated in the sixties only, whereas SMRs for tumors of the liver increase till the end of the study period. This might be referred to different latency periods for both kinds of malignancies, but other causes might likewise have contributed to these results. However, it has to be reported that the number of angiosarcomas confirmed histologically in the Federal Republic of Germany in patients previously exposed to VCM has actually come to 17 in contrast to mere 4 at the endpoint of the mortality study (12/31/1974).

The distribution of SMRs by age (Table 5) demonstrates an obvious susceptibility of males aged 35-44 for malignancies in general as well as for malignancies of the liver.

The data base for the German morbidity study consists of all of the reports of suspected cases of occupational disease due to VCM or PVC production or PVC processing. The reference population for these reports has to be defined as the total

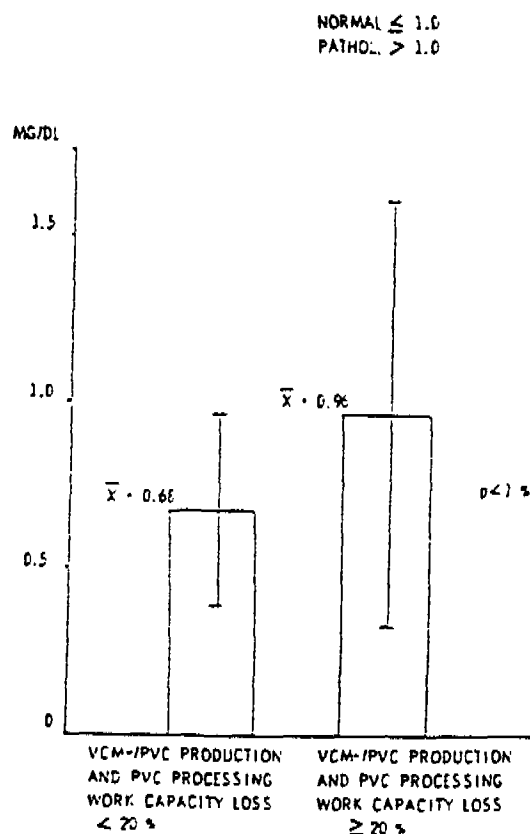


FIGURE 1. Vinyl chloride morbidity study: total bilirubin (normal 1.0).

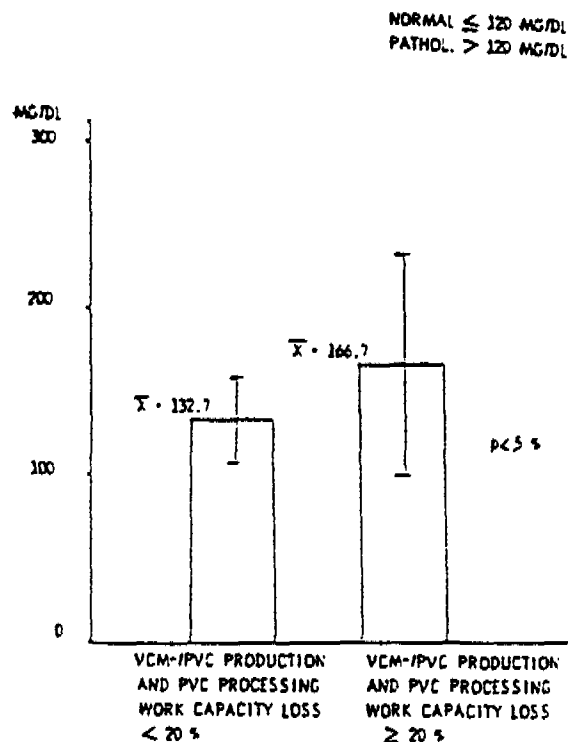


FIGURE 2. Vinyl chloride morbidity study: oral glucose tolerance test, 120 min after loading (normal 120 mg/dl).

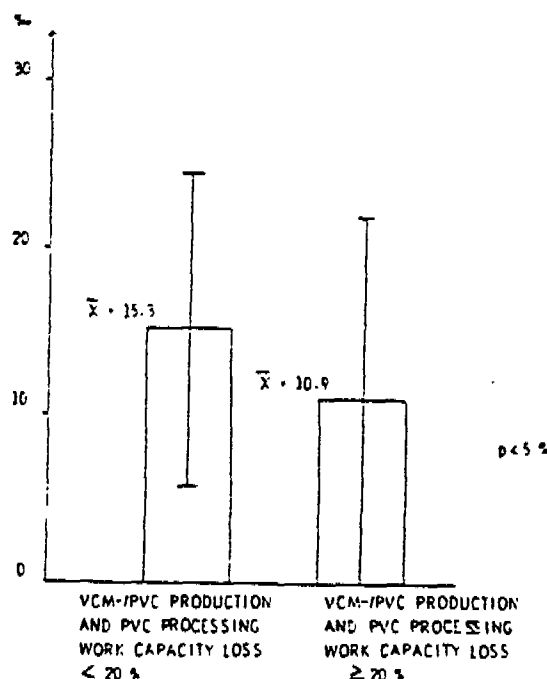


FIGURE 3. Vinyl chloride morbidity study: reticulocytes (normal 15%).

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working population in 1974 in the above mentioned branches, i.e., 6,500 workers in VCM or PVC production and 42,800 workers in PVC processing (as given by the German Association of Plastic Producing Industries). Till the end of 1974, 269 reports of suspected cases of occupational disease had been received. As there has been no consistent set of examinations performed on each of the cases, numbers of observations for various variables analyzed vary according to examination method performed. Insofar as the results of this study are of much lower validity than those of the mortality study, one should regard them as hints for further investigations.

Four attempts to subclassify observation on the 269 cases have been undertaken (Table 6). Only those results showing significant differences when applying t-tests or chi-square tests are so classified. Amazingly none of the more sensitive lab examinations of liver functions showed a marked difference in all of the subclassifications besides bromsulfalein retention. In this instance there is a significant difference when subdividing by VCM/PVC production versus processing (Table 7), as well as by

nationality (Table 8) and most pronounced when subdividing by extent of work capacity loss (Table 9). This latter result, however, must be expected when an effect of exposure on liver function is anticipated. An impairment of the excretory liver function is suggested by elevated total bilirubin values in the subgroup with work capacity loss greater than 20% (Fig. 1). There seems to be an impaired glucose tolerance in this group, although observed in a small subsample only (Fig. 2), as well as a lower number of reticulocytes (Fig. 3). The thromocyte count in both groups was the same. These results, however, lead to no sensible interpretation, as all results attempts failed to standardize the methods applied for thrombocyte counts by various laboratories.

#### REFERENCES

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2. Bailar, J. C. Significance factors for the ratio of a Poisson variable to its expectation. *Biometrics* 20: 639-643 (1964).