# Analysis of a Case-Control Study Concerning Bladder Cancer and Occupational Exposures*

by

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### Abstract

This work presents the results from a case-control study about occupational exposures as risk factors for bladder cancer. Odds ratio analysis and logistic regression give results, which show the influence of different exposures to polycyclic aromatic hydrocarbons and an exposure to paints on bladder cancer etiology. Further an outlook on the upcoming studies about genetic predispositions as additional risk factors is given.

## 1. Introduction

### The Study

The relationships between assumed carcinogenic substances and bladder cancer were assessed from a case-control study conducted between 1992 and 1996 in Northrhine-Westphalia, Germany. The analysis was conducted by means of smoking-adjusted odds ratios and logistic regression.

The study concerned 156 cases with bladder cancer and 336 controls with prostate cancer. The main focus was the role of polycyclic aromatic hydrocarbons (PAH), since most of the considered exposures contained substances of this group. Data were collected from male patients who had applied for a cancer rehabilitation treatment. A questionnaire was sent to all patients, containing questions about occupational history, occupational exposures to potential carcinogenic substances, smoking habits, diseases of relatives and hobbies. The exposures to chemicals, paints, bitumen, tar, pitch and other combustion fumes were divided into seldom, often and permanent. Problems occured for pitch and chemicals. The question about pitch was placed unfortunately on the questionnaire leading to many missings. For chemicals a huge variety of substances was stated, including common detergents. The physician reported medical informations, including height, weight, further diseases and staging and grading of the tumor.

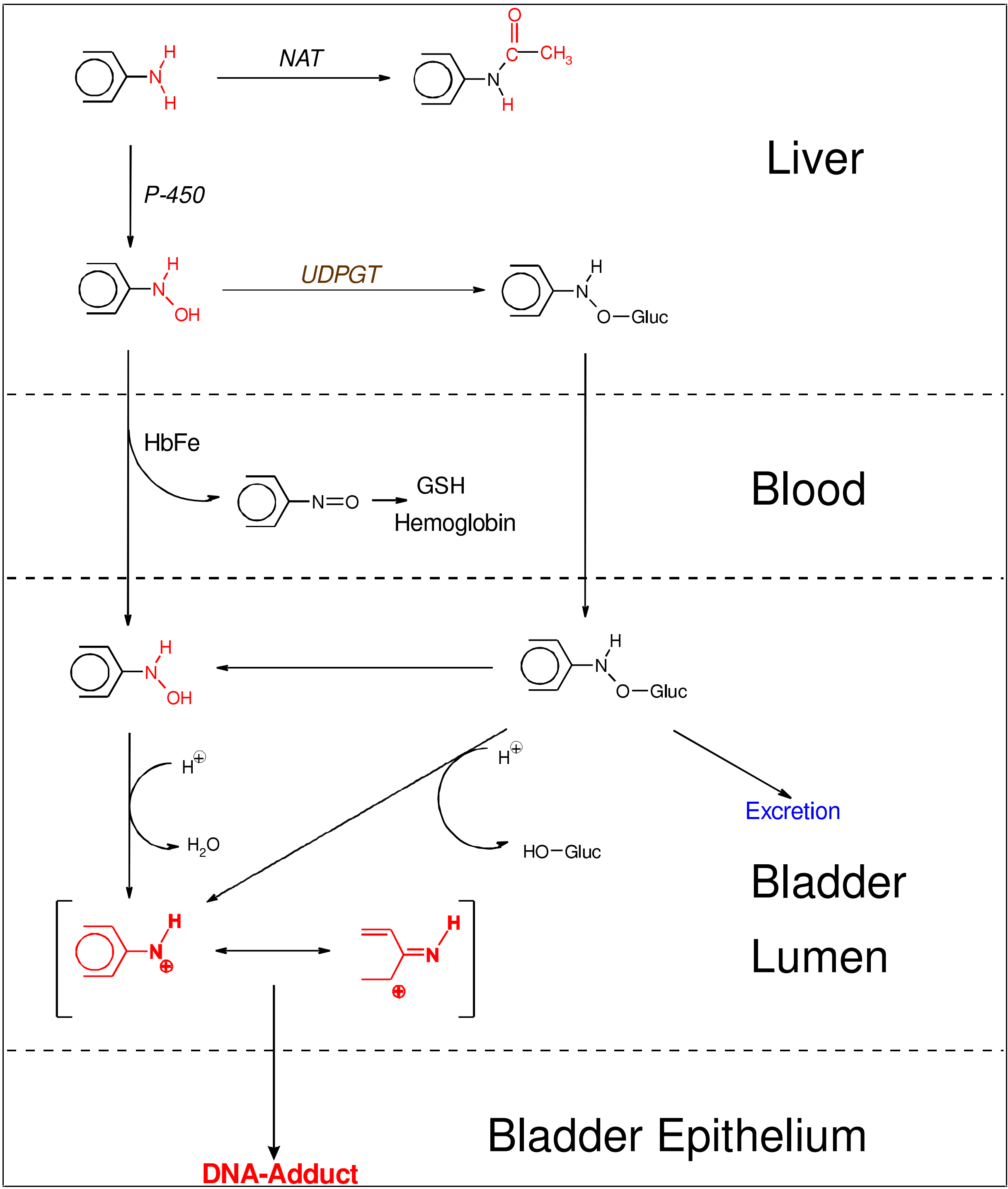


Fig. 1: Proposed aromatic amine bladder carcinogenesis pathway (modified from Lang and Kadlubar, 1991).

**Occupational Exposures as Risk Factors for Bladder Cancer**

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The relationship between occupational exposures and bladder cancer is examined since Rehn (1895) reported an undue incidence of bladder tumors in a group of men employed in the manufacture of fuchsine. He concluded that aniline was the most suspicious of the substances used in this process. Up to now it is known that an exposure to aromatic amines or bioavailable azo dyes (which are cleaved in the human body to aromatic amines) lead to an elevated bladder cancer risk. The simplifying two stage model of carcinogenesis divides the whole process in two phases:

- the initiation sets the stage for carcinogenesis by changing the genetic information. Initiating agens bind to DNA and cause an irreversible genetic damage. In the further development of the tumor these substances may play no role.
- the promotion is necessary for an onset of disease within life time. The effect of promotors is reversible. After cessation of exposure the effect vanishes over time.

Aromatic amines have to be considered as initiating agens. Especially the pathway from the initiating agens in the liver to the formation of the DNA-adduct in the bladder epithelium is shown in fig. 1.

The role of polycyclic aromatic hydrocarbons is mainly on the stage of promotion. Therefore the frequency of exposure is more important than for aromatic amines.

## 2. Evaluation of Non-Occupational Factors

There were differences in the distribution of non-occupational factors for age, smoking and further tumors in the two groups. The cases had a mean age of 62.5 compared to 65.4 years for the controls. The differences became obvious when four age groups were considered. The youngest patients, under 55 years, contained 17% of the cases and only 7% of the controls. While 49% of the cases had an age between 55 and 64, 36% of the controls fell in this age group. For an age between 65 and 74 years the effect was contrary, with frequencies of 25% for the cases and 49% for the controls. The age group above 74 years showed no differences. The smoking habits underlined the role of smoking for bladder cancer etiology. For the cases there were 43% smokers reported compared to 31% for the controls. Further tumors were observed for 10% of the cases and 5% of the controls. For obesity, measured by a Broca-index greater than one, a non-significant odds ratio smaller than one was observed, since obesity is an assumed risk factor for prostate cancer.

## 3. Odds Ratio Analysis

The analysis of the crude and smoking-adjusted odds ratios was divided in frequent and ever exposure. “Frequent“ exposure compared the answers often and permanent with seldom and no exposure. “Ever“ exposure combined seldom, often and permanent exposure. The ratios for the PAH-group were always higher for a frequent exposure. For paints an ever exposure had the higher value. Table 1 shows the crude and smoking-adjusted odds ratio estimates for the exposures and the significant non-occupational factors. Significant odds ratios were obtained for the three exposures paints (1.69), bitumen (2.93), tar (2.49) and the cumulative measure any PAH (1.67). For work in a coke oven plant an exceeded crude odds ratio of 2.16 was calculated.

| Risk Factor | Crude Odds Ratio | 95% - CI | Smoking-adjusted Odds Ratio (Mantel-Haenszel) | 95% - CI |
|---|---|---|---|---|
| **Occupational Factors** | | | | |
| Aromatic Amines | | | | |
| - ever exposed to paints | 1.69 | 1.12 - 2.55 | 1.69 | 1.10 - 2.61 |
| Polycyclic Aromatic Hydrocarbons | | | | |
| - frequently exposed to bitumen | 2.93 | 1.34 - 6.41 | 2.92 | 1.32 - 6.48 |
| - frequently exposed to tar | 2.49 | 1.27 - 4.89 | 2.09 | 1.04 - 4.21 |
| - frequently exposed to pitch* | 3.49 | 0.89 - 13.62 | 3.06 | 0.77 - 12.10 |
| - frequently exposed to other combustion fumes | 1.35 | 0.77 - 2.38 | 1.21 | 0.68 - 2.15 |
| work in a coke oven plant | 2.16 | 0.76 - 6.13 | 1.92 | 0.58 - 6.29 |
| work at a blast furnace | 1.62 | 0.75 - 3.49 | 1.73 | 0.77 - 3.90 |
| - frequently exposed to any PAH | 1.67 | 1.08 - 2.60 | 1.56 | 0.98 - 2.47 |
| Chemicals | | | | |
| - frequently exposed to chemicals* | 1.36 | 0.88 - 2.12 | 1.29 | 0.81 - 2.05 |
| **Non-Occupational Factors** | | | | |
| Smoking | 1.79 | 1.20 - 2.68 | | |
| Age : younger than 65 years | 2.59 | 1.75 - 3.83 | 2.28 | 1.51 - 3.44 |
| Obesity ( Broca-Index > 1 ) | 0.70 | 0.43 - 1.13 | 0.73 | 0.44 - 1.24 |
| Further tumors | 2.29 | 1.13 - 4.63 | 2.12 | 0.99 - 4.54 |

Legend:
* - uncertain information

Table 1 : Crude and smoking-adjusted odds ratio estimates with 95% confidence intervals.

### Results

The estimated smoking-adjusted odds ratios were significantly higher for

- an ever exposure to paints, $\hat{OR}=1.69$, 95%-C.I.=(1.10, 2.61),
- a frequent exposure to tar, $\hat{OR}=2.09$, 95%-C.I.=(1.04, 4.21).

– a frequent exposure to pitch, $\hat{OR}$=3.06, 95%-C.I.=(0.77, 12.10),

Elevated risks were observed for these occupational exposures:

– work in a coke oven plant, $\hat{OR}$=1.92, 95%-C.I.=(0.58, 6.29),

– work at a blast furnace, $\hat{OR}$=1.73, 95%-C.I.=(0.77, 3.90).

The occupational exposures to other combustion fumes and chemicals showed only slightly increased odds ratio estimates about 1.2 .

When the power of the study is considered, the low frequencies of exposed in the control group made it hard to detect significant ratios. The frequencies for bitumen, tar, pitch, work in a coke oven plant and work at a blast-furnace were smaller than 0.1 and led to poor values for the power, see Geller (1997).

The analysis of odds ratios for smokers and non-smokers did not provide uniform results, see Geller (1997).

## 4. Logistic Regression Analysis

A logistic regression model was fitted to the data, including the non-occupational factors age, smoking and further tumors. Age group 2 (55 - 64 years) was chosen as reference group since the most cases reported an age in this group. For 52 patients important informations were missing, leaving 137 cases and 303 controls. Table 2 shows the model of the main effects. The only occupational factors which met the entry criteria of a p-value less than 0.2 in the multiple model were paints and bitumen.

| Variable | Estimated Odds Ratio | Parameter Estimate $\hat{\beta}$ | Standard Error $\hat{S}$ | P-value of the $\chi^2$-Test |
|---|---|---|---|---|
| Intercept | | -1.001 | 0.210 | 0.0001 |
| Age group 1 ( younger than 55 years) | 2.02 | 0.704 | 0.354 | 0.047 |
| Age group 3 ( 65 - 74 years ) | 0.41 | -0.896 | 0.253 | 0.0004 |
| Age group 4 (older than 74 years) | 1.09 | 0.082 | 0.400 | 0.837 |
| Smoking | 1.70 | 0.532 | 0.226 | 0.018 |
| Ever exposed to paints | 1.53 | 0.422 | 0.242 | 0.081 |
| Frequently exposed to bitumen | 2.35 | 0.853 | 0.447 | 0.056 |
| Further tumors | 2.43 | 0.888 | 0.412 | 0.031 |

Table 2 : Logistic regression model for main effects.

Since age and smoking often interact with other factors, two important questions arise:

- Are the bladder cancer patients with an occupational exposure younger than those without ?

- Does smoking strengthen the effect of occupational exposures ?

Table 3 contains the model with interactions, which led to the following conclusions:

- The occupational exposures interact with younger ages at first diagnosis.
- Smoking is related with further tumors and also with younger ages at first diagnosis but shows no association to the exposures.

| **Variable** | **Parameter Estimate** $\hat{\beta}$ | **Standard Error** $\hat{S}$ | **Coeffizient** $\hat{\beta}/\hat{S}$ | **P-value of the $\chi^2$-test** |
|---|---|---|---|---|
| Intercept | -1.121 | 0.239 | -4.68 | 0.0001 |
| Age group 1 ( younger than 55 years) | 0.240 | 0.452 | 0.53 | 0.596 |
| Age group 3 ( 65 - 74 years ) | -0.496 | 0.315 | -1.58 | 0.115 |
| Age group 4 (older than 74 years) | 0.419 | 0.429 | 0.98 | 0.329 |
| Smoking | -0.183 | 0.408 | -0.45 | 0.654 |
| Ever exposed to paints | 0.297 | 0.265 | 1.12 | 0.263 |
| Frequently exposed to bitumen | 0.195 | 0.862 | 0.23 | 0.821 |
| Further tumors | 0.373 | 0.534 | 0.70 | 0.485 |
| Younger than 65 × smoking | 0.982 | 0.498 | 1.97 | 0.049 |
| Younger than 55 × paints | 1.299 | 0.763 | 1.70 | 0.089 |
| Younger than 65 × bitumen | 1.049 | 1.036 | 1.01 | 0.311 |
| Smoking × further tumors | 1.710 | 0.947 | 1.81 | 0.071 |

Table 3 : Logistic regression model with interactions.

The interactions caused substantial changes in the parameter estimates for the main effects. The parameter estimates went down and the standard errors grew. Especially for smoking and bitumen the p-values increased above 0.5 , underlining the importance of the interactions for these effects. There were three interactions for the younger patients, diminishing the effect of age group 1. The effect of further tumors was to a certain extent explained by the interaction with smoking.

## 5. Summary Measures for the Fit of the Logistic Regression Model

The discussion about the fit of the model is based on covariate patterns, which describe a single set of values for the covariates in the model. Since the logistic regression model contains age groups instead of age in years, the obtainable number of covariate patterns is limited. There are 64 possible patterns with observations for 39 of them.

### Pearson-$\chi^2$-Test and Deviance-Test

The Pearson-$\chi^2$-statistic $X^2$ and the deviance-statistic D test the nullhypothesis that the model is correct in every aspect. Under $H_0$ the teststatistics are supposed to be $\chi^2$-distributed with J-(p+1) degrees of freedom, with J denoting the number of observed covariate patterns and (p+1) the number of parameters in the model (p effects plus intercept). The model has 7 main effects and 4 inter-actions. For 39 covariate patterns there are observations, leading to 27 degrees of freedom:

| Test | Statistic | DF | p-value |
|---|---|---|---|
| **Pearson-$\chi^2$** | **$X^2$ = 25.95** | **27** | **0.521** |
| **Deviance** | **D = 31.60** | **27** | **0.247** |

The p-values differ notable. The value of the Pearson-statistic is satisfying, whilst the result for the Deviance is too small. It has to be stated that the assumptions for the $\chi^2$-distribution are violated, since the $m_j$ in some covariate patterns are very small. For 12 of the 39 patterns there is just one observation. Especially the small p-value for the deviance does not necessary result from a poor fit of the model. It has to be kept in mind that the model contains two variables which do not improve the model. The effect of bitumen is mainly modelled by the interaction younger than 65 × bitumen and age group 4 has no clear differences to the reference group in any model.

**The Hosmer-Lemeshow-Test**

Because of the high number of covariate patterns with very few observations, another approach shall be introduced here. The chosen form of the Hosmer-Lemeshow-test is based on a grouping of the data according to their estimated probabilities. In these groups the observed and the expected frequencies are compared.

If possible, SAS® divides the data into 10 groups of size n/10. Since the number of groups has to be higher than the number of parameters, an individual division into 13 groups is done. The data include many ties, for some patterns there are more than 33.8 (= n/13) observations, so that the huge covariate patterns with more than 50 observations limit the options for grouping, as seen in table 4. The 89 observations for covariate pattern 5 are randomly assigned to two groups, in other cases the frequent observed pattern build a group on their own. The 4 groups with these patterns include already 204 observations. The rest of 236 observations has to be divided into 9 groups. It can be arranged, that almost every group contains at least 20 observations, only group 3 has a size of 13 persons.

The resulting expected group frequencies are also given in table 4. The accordance is reckonable.

The statistic $\hat{C}$ is under the nullhypothesis $\chi^2$ - distributed with (G-2) degrees of freedom, where G denotes the number of groups. The distribution assumption is based on m-asymptotics, that means if J < n is fixed and n increases every $m_j$ will tend to become large. This is justified, when the expected frequencies are large enough. This condition is basically fulfilled, because only group 4 has a smaller number of cases and group 13 has a smaller number of controls.

| Test | Statistic | DF | p-value |
|---|---|---|---|

| | | | |
|---|---|---|---|
| **Hosmer-Lemeshow** | $\hat{C}$ = **7.143** | **11** | **0.787** |

The test provides a p-value of 0.787, stating a good fit of the model. Therefore all the covariate patterns with very few observations probably caused the deviations in the other statistics. Just this effect is controlled by grouping. A disadvantage of this variant of the Hosmer-Lemeshow-test is caused by the fact, that the probabilities are solely grouped with the aim of considerably large group

| Pattern No. | Estimated case-prob. | Obs. | Cases expected | Cases observed | Controls expected | Controls observed | Contrib. to $\hat{C}$ |
|---|---|---|---|---|---|---|---|
| 7 | 0.142 | 35 | 4.97 | 5 | 30.03 | 30 | |
| **Group 1** | **0.142** | **35** | **4.97** | **5** | **30.03** | **30** | **0.0003** |
| 5 | 0.166 | 89 | 14.75 | 16 | 74.25 | 73 | |
| **Group 2** | **0.166** | **45** | **7.46** | **7** | **37.54** | **38** | **0.033** |
| **Group 3** | **0.166** | **44** | **7.29** | **9** | **36.71** | **35** | **0.480** |
| 23 | 0.167 | 2 | 0.33 | 0 | 1.67 | 2 | |
| 39 | 0.182 | 10 | 1.82 | 1 | 8.18 | 9 | |
| 21 | 0.194 | 1 | 0.19 | 0 | 0.81 | 1 | |
| **Group 4** | **0.181** | **13** | **2.35** | **1** | **10.65** | **12** | **0.945** |
| 37 | 0.211 | 28 | 5.90 | 6 | 22.10 | 22 | |
| 55 | 0.213 | 1 | 0.21 | 0 | 0.79 | 1 | |
| 6 | 0.224 | 5 | 1.12 | 2 | 3.88 | 3 | |
| 53 | 0.245 | 2 | 0.49 | 0 | 1.51 | 2 | |
| **Group 5** | **0.215** | **36** | **7.73** | **8** | **28.27** | **28** | **0.012** |
| 9 | 0.246 | 59 | 14.51 | 14 | 44.49 | 45 | |
| **Group 6** | **0.246** | **59** | **14.51** | **14** | **44.49** | **45** | **0.024** |
| 38 | 0.280 | 5 | 1.40 | 1 | 3.60 | 4 | |
| 3 | 0.292 | 5 | 1.46 | 2 | 3.54 | 3 | |
| 13 | 0.293 | 10 | 2.93 | 3 | 7.07 | 7 | |
| **Group 7** | **0.289** | **20** | **5.79** | **6** | **14.21** | **14** | **0.011** |
| 41 | 0.305 | 27 | 8.23 | 11 | 18.77 | 16 | |
| 54 | 0.320 | 1 | 0.32 | 1 | 0.68 | 0 | |
| 10 | 0.321 | 5 | 1.61 | 2 | 3.39 | 3 | |
| **Group 8** | **0.308** | **33** | **10.16** | **14** | **22.84** | **19** | **2.095** |
| 1 | 0.331 | 21 | 6.96 | 5 | 14.04 | 16 | |
| 35 | 0.357 | 2 | 0.71 | 2 | 1.29 | 0 | |
| 42 | 0.389 | 1 | 0.39 | 0 | 0.61 | 1 | |
| 33 | 0.400 | 5 | 2.00 | 2 | 3.00 | 3 | |
| 2 | 0.419 | 1 | 0.42 | 0 | 0.58 | 1 | |
| **Group 9** | **0.349** | **30** | **10.48** | **9** | **19.52** | **21** | **0.322** |
| 11 | 0.420 | 56 | 23.53 | 24 | 32.47 | 32 | |
| **Group 10** | **0.420** | **56** | **23.53** | **24** | **32.47** | **32** | **0.016** |
| 49 | 0.448 | 1 | 0.45 | 1 | 0.55 | 0 | |
| 15 | 0.479 | 15 | 7.19 | 7 | 7.81 | 8 | |
| 43 | 0.494 | 12 | 5.92 | 3 | 6.08 | 9 | |
| **Group 11** | **0.484** | **28** | **13.56** | **11** | **14.44** | **17** | **0.938** |
| 25 | 0.531 | 3 | 1.59 | 1 | 1.41 | 2 | |
| 8 | 0.570 | 5 | 2.85 | 3 | 2.15 | 2 | |
| 57 | 0.604 | 4 | 2.41 | 2 | 1.59 | 2 | |
| 40 | 0.641 | 1 | 0.64 | 0 | 0.36 | 1 | |
| 45 | 0.671 | 7 | 4.70 | 4 | 2.30 | 3 | |
| **Group 12** | **0.610** | **20** | **12.20** | **10** | **7.80** | **10** | **1.016** |
| 27 | 0.715 | 4 | 2.86 | 3 | 1.14 | 1 | |
| 46 | 0.748 | 1 | 0.75 | 0 | 0.25 | 1 | |
| 59 | 0.772 | 3 | 2.32 | 3 | 0.68 | 0 | |
| 47 | 0.819 | 7 | 5.74 | 7 | 1.26 | 0 | |
| 12 | 0.853 | 1 | 0.85 | 1 | 0.15 | 0 | |
| 61 | 0.876 | 1 | 0.88 | 1 | 0.12 | 0 | |
| 16 | 0.881 | 1 | 0.88 | 1 | 0.12 | 0 | |
| 44 | 0.887 | 2 | 1.77 | 2 | 0.23 | 0 | |
| 63 | 0.940 | 1 | 0.94 | 1 | 0.06 | 0 | |
| **Group 13** | **0.809** | **21** | **16.98** | **19** | **4.02** | **2** | **1.251** |

Table 4: Grouping for the Hosmer-Lemeshow-test, groups consist of the covariate patterns listed directly above.

sizes. Since this study contains far more controls than cases, most observations have a $\hat{\pi}_j$ smaller than 0.5. Therefore the first 8 groups contain probabilities between 0.142 und 0.312, whilst group 13 includes all probabilities from 0.715 up to 0.940. On the other hand a grouping based on percentiles would have led to many groups of small size. It has to be stated that the properties of the Hosmer-Lemeshow-test in the given setting, where the number of covariate patterns is substantly smaller than n are hardly investigated in yet.

**Classification tables**

Classification tables examine the predictive power of a model. Therefore the observations are classified into cases and controls according to their estimated probabilities. Usually the division is made for $\hat{\pi}$ = 0.5. Since the number of observations differs that much for the two collectives, a division at $\hat{\pi}$ = 0.311 makes more sense, because the small fraction of 31.1% cases in the study is taken into account. Elsewise the observations would mainly be classified into the larger group.

Here the sensitivity, the specifity, the false positive and the false negative rate are of interest.

The sensitivity $\phi$ is the proportion of cases that are also predicted to be cases, whilst the specifity $\psi$ gives the proportion of controls that are predicted to be controls. The false positive rate describes the proportion of predicted cases that are observed as controls and the false negative rate states the proportion of predicted controls which are in reality cases.

| | Classified | | | Prob. of classification | |
|---|---|---|---|---|---|
| **Observed** | **Cases** | **Controls** | **Sum** | **Cases** | **Controls** |
| **Cases** | 68 | 69 | 137 | $\phi$ = 0.496 | f. neg. = 0.240 |
| **Controls** | 85 | 218 | 303 | f. pos. = 0.556 | $\psi$ = 0.719 |
| **Sum** | 153 | 287 | 440 | | |

Table 5: Classification table with classification at an estimated probability of 0.311.

Tables 5 and 6 show the results for $\hat{\pi}$ = 0.311 and $\hat{\pi}$ = 0.5. As expected, the controls are better predicted than the cases. The total rate of right predictions for $\hat{\pi}$ = 0.311 is 65%, for $\hat{\pi}$ = 0.5 a slightly higher proportion of 68.6% is achieved. The differences in the false rates are small. The poor sensitivity for $\hat{\pi}$ = 0.5 is striking, resulting from the low number of predicted cases, only 57 compared to 137 observed.

| | Classified | | | Prob. of classification | |
|---|---|---|---|---|---|
| **Observed** | **Cases** | **Controls** | **Sum** | **Cases** | **Controls** |
| **Cases** | 28 | 109 | 137 | $\phi$ = 0.204 | f. neg. = 0.285 |
| **Controls** | 29 | 274 | 303 | f. pos. = 0.509 | $\psi$ = 0.904 |
| **Sum** | 57 | 383 | 440 | | |

Table 6: Classification table with classification at an estimated probability of 0.5.

In conclusion the general fit of the model can be rated as good. Many covariate patterns with just one observation violate the conditions of the Pearson-$\chi^2$-test and the Deviance-test, resulting in p-values which are not very informative. The Hosmer-Lemeshow-test is based on a grouping of the data and gives a p-value of 0.79, which means that the model fits quite good. Since there are far more controls than cases in the study, this status was better modelled. The classification table for $\hat{\pi} = 0.311$ fulfilled a minimum requirement for a good model: the addition of sensitivity und specifity came out as 1.22, a value greater than one. Next local weaknesses of the model were examined by regression diagnostics leading to the following results:

- High leverage values were obtained for the covariate patterns without occupational exposure, which is closely related to the high number of observations for these patterns.

High Pearson- and Deviance-residuals were mainly reported for patterns with an exposure to paints, which all have small numbers of observation.

For further details about the fit of the model see Geller (1997).

## 6. Discussion

The higher odds ratios for an ever exposure to paints and for frequent exposure to the PAH-group is probably related to the role of these substances in cancerogenesis. The interactions with the age groups support the theses that:

- aromatic amines mainly initiate tumors very early and lead to quite young ages at first diagnosis (an ever exposure to paints has a positive interaction with an age younger than 55).
- polycyclic aromatic hydrocarbons mainly promote tumors and the age at first diagnosis is thereby lessened (a frequent exposure to bitumen has a positive interaction with an age younger than 65).

## 7. Outlook

The next step in investigating these occupation-related diseases is to search for individual susceptibility factors, which promote carcinogenesis and can interfere in many ways on the path from exposure to disease. Sen and Margolin (1995) combined aspects of genetic toxicology with epidemiologic research. The main ideas of this combination are shown in fig. 2.

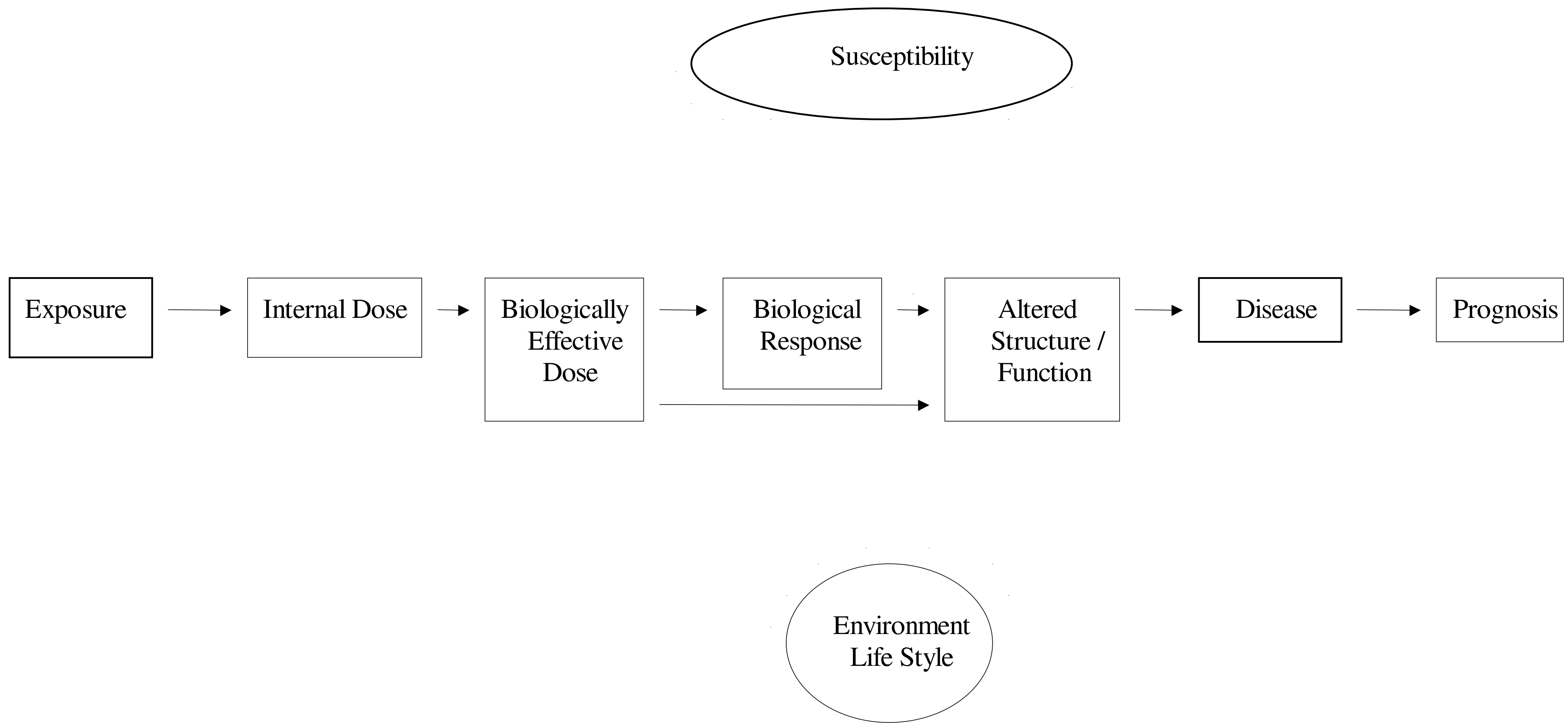


Fig. 2.: The way from exposure to disease (Sen and Margolin, 1992).

Interesting features of this topic are genetic predispositions which are related to certain exposures. In the development of bladder cancer the impacts of polymorphic enzymes involved in the metabolism of aromatic amines (N-acetyltransferase 2) and polycyclic aromatic hydrocarbons (glutathione transferase $\mu$), see for example Golka et al. (1997) have to be considered. Further investigation may examine if an association effects the latency period for the patients.

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