Carcinomas of the urinary bladder in a 4-chloro-o-toluidine cohort

Miroslaw Jan Stasik

Department of Occupational Medicine of Hoechst AG, D-6230 Frankfurt/Main, Federal Republic of Germany

Summary. In an historical mortality study [27], conducted on a cohort of 335 male employees in 4-chloro-o-toluidine (4-COT) production and processing plants, no deaths due to cancer of the urinary bladder had been identified. However, after completion of this study, urothelial carcinomas were recorded in eight of the employees, two of whom have died in the meantime (as of December 1986). All eight persons had been employed in the 4-COT production plant before improvements in industrial hygiene were introduced in 1970 (a subcohort of 116 men). This presumably higher level of exposure to monocyclic arylamines lasted for 14.0 years (median), and the total exposure time (before and after 1970) in the 4-COT plant was 25.5 years (median). The standardized incidence rate for urothelial carcinomas in the 4-COT subcohort was 73 times higher than expected and was comparable with the results obtained for polycyclic arylamines, which have been identified as human carcinogenic agents [5]. On the basis of our results an association may be postulated between occupational exposure to 4-COT and carcinomas of the urinary bladder observed among production workers.

Key words: Urothelial carcinomas – Monocyclic arylamines – Latency – N-Acetylation phenotypes – Acetylators

Introduction

4-Chloro-o-toluidine (4-COT), (4-chloro-2-methyl-aniline), was first synthesized in 1870 by Beilstein and Kuhlbert [14] and had been produced in Germany since 1927. 4-COT has been used as an intermediate for the manufacture of dyestuffs, pigments, and of chlordimeform, an acaricide and insecticide.

4-COT produces severe acute toxic effects in humans, such as hematuria owing to hemorrhagic cystitis [6, 9, 15, 26]. Studies in experimental animals with 4-COT have revealed the metabolites 5-chloroanthranilic acid and 4-chloro-2-methylacetyl-anilide [16]; in vitro, the microsomal metabolites 5-chloro-2-N-hydroxyl-amino-toluene and 4,4'-dichloro-2,2-dimethylazobenzene [12] are formed. Radioactivity from labelled 4-COT becomes extensively and irreversibly bound to protein, DNA and RNA of rat liver [12].

4-COT is mutagenic for various strains of salmonella typhimurium with and without metabolic activation. It was also positive in a DNA repair assay [23, 32]. In chronic feeding studies (mice of both sexes), 4-COT has induced hemangiosarcomas and hemangioendotheliomas [13, 21, 31].

No bladder cancer was found in two retrospective epidemiological reports of workers exposed to 4-COT [22, 30]. The significance of these results is limited due to the small number of subjects and to inadequate individual data.

To examine further the potential carcinogenicity of 4-COT, we carried out an historical cohort mortality study on 335 male employees who had been involved between 1929 and 1982 in the production and processing of 4-COT at Hoechst [27]. A subcohort of 116 subjects in the 4-COT cohort, employed in this plant before 1970, can be regarded as having had higher exposure to monocyclic arylamines. Our mortality study revealed a total of five cases of malignant neoplasms at various sites. All five malignant tumors occurred in the specified subcohort.
(exposure starting before 1970; see Table 1), but none of the causes of death was “urinary bladder carcinoma”.

The occurrence of urinary bladder carcinomas in two subjects in the 4-COT subcohort (still actively employed) prompted our present investigation, which was conducted in the last six months of 1986. The aim of the present work was to re-investigate subjects of the 4-COT-subcohort and to study the association between exposure to monocyclic arylamines and the occurrence of urinary bladder cancer in humans.

### Subjects and methods

All 116 subjects with exposure before 1970 were re-examined with respect to their vital status for the period from January 1, 1983 to June 30, 1986.

The clinical data on the morphological diagnoses of all cases of bladder carcinoma were obtained from several hospitals and institutes. If possible the histopathological diagnoses were made in accordance, with the WHO classification (as to grading and staging) of urinary bladder tumors [20].

The phenotype of N-acetylation was determined according to the method described by Evans [8], based on the “Bratton-Marshall assay”.

The expected incidence rate for bladder cancer during the follow-up period was calculated by multiplying the person-years at risk and the sex- and age-specific bladder cancer incidence of the Saarland for 1983 [28]. This reference was chosen in the absence of centralized records on cancer in the Federal Republic of Germany and under the assumption that the bladder cancer incidence in the Saarland is similar to that in Hessen. This assumption seems reasonable considering the cumulative mortality rates of 0.66 and 0.72 respectively [2].

### Results

Our investigation revealed eight subjects in whom bladder carcinomas were diagnosed between 1967 and 1985. Two of them had already died. Seven cases had papillary urothelial carcinomas. One tumor was partly solid and partly showed glandular growth. In two cases the tumor malignancy was confined to D 3 (carcinoma in situ) and G I. Malignancy G II-III was diagnosed in another six cases, three of whom showed recurrences of the carcinoma.

Of the six patients where the N-acetylation rate was determined, four were slow acetylators and two were fast.

Three subjects were non-smokers, one was an ex-smoker, two were smokers and the smoking habits of the remaining two were unknown.

The expected number of cases of bladder carcinoma calculated for the 4-COT subcohort is 0.11. Hence the eight cases of bladder carcinoma correspond to a standardized incidence rate that is 72.7 times higher (95% CI: 31.4–143.3) than expected [28].

### Discussion

The unexpected clustering of cases of bladder carcinoma in our 4-COT subcohort mainly between 1983 and 1985 is noteworthy. All eight patients with bladder tumors had worked in the old 4-COT production plant before 1970, i.e. in a period in which there was a higher level of exposure to the monocyclic arylamines, 4-chloro-o-toluidine and N-acetyl-o-toluidine.

Unfortunately, no quantitative measurements of the exposure are available. However, analysis of the production process indicates that the exposure to 4-COT in the plant was considerably higher than to N-acetyl-o-toluidine.

Our patients with bladder carcinoma were exposed to relatively high levels (before 1970) for a median of 14.0 years (Table 2). For two of the cases, the exposure period was only 1.5 and 4.0 years.