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Bladder cancer documentation of causes: multilingual questionnaire 'bladder cancer doc'

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1. ABSTRACT

There is a considerable discrepancy between the number of identified occupational-related bladder cancer cases and the estimated numbers particularly in emerging nations or less developed countries where suitable approaches are less or even not known. Thus, within a project of the World Health Organisation Collaborating Centres in Occupational Health, a questionnaire of the Dortmund group, applied in different studies, was translated into more than 30 languages (Afrikaans, Arabic, Bengali, Chinese, Czech, Dutch, English, Finnish, French, Georgian, German, Greek, Hindi, Hungarian, Indonesian, Italian, Japanese, Kannada, Kazakh, Kirghiz, Korean, Latvian, Malay, Persian (Farsi), Polish, Portuguese, Portuguese/Brazilian, Romanian, Russian, Serbo-Croatian, Slovak, Spanish, Spanish/Mexican, Tamil, Telugu, Thai, Turkish, Urdu, Vietnamese). The bipartite questionnaire asks for relevant medical information in the physician's part and for the occupational history since leaving school in the patient's part. Furthermore, this questionnaire is asking for intensity and frequency of certain occupational and non-occupational risk factors. The literature regarding occupations like painter, hairdresser or miner and exposures like carcinogenic aromatic amines, azo dyes, or combustion products is highlighted. The questionnaire is available on www.ifado.de/BladderCancerDoc.

2. INTRODUCTION

An estimated 386,300 new cases and 150,200 deaths from bladder cancer occurred in 2008 worldwide (1). Thus bladder cancer is one of the most important malignancies. In general, bladder cancer is more often observed in developed countries than in developing countries. An estimated 177,000 new cases occurred in males in developed countries and 119,500 in males in developing countries. The highest age-adjusted incidence rates (per 100.000 persons) are observed in Southern Europe (21.0 males, 3.3 females), followed by Northern America (20.1 males, 5.5 females) and Western Europe (18.2 males, 4.4 females), whereas the lowest incidence rates are observed in Eastern Africa (3.4 males, 1.8 females), Melanesia (2.7 males, 0.5 females) and Middle Africa (1.5 males, 0.3 females) (2), resulting in a 14-fold variation in incidence (1).

Bladder cancer is a model tumour of chemical carcinogenesis. In general, this cancer is more frequently diagnosed in industrialised and urban areas than in rural areas (3,4). This was most recently corroborated by an investigation on the association of population density and bladder cancer mortality in the United States (5). The most relevant factor is tobacco smoking. In some areas, up to 50% in males and up to 25% in females are caused by tobacco smoking (6). Tobacco smoke contains some 4000 different chemical compounds, of which 69 are carcinogens, including carcinogenic aromatic amines like 4-aminobiphenyl, 2-naphthylamine and o-toluidine, but not benzidine, and polycyclic aromatic hydrocarbons (6). The second most relevant cause of bladder cancer is exposure to bladder carcinogenic substances in the workplace, mostly carcinogenic aromatic amines and bioavailable (i.e. water soluble) azo dyes that can be cleaved in the body into the carcinogenic aromatic amine which was used as coupler during synthesis (7).

In 1981, Doll and Peto (8) estimated the portion of bladder cancer cases related to occupation in the United States at 10% in men and 5% in women. These figures were confirmed by the Harvard Report on Cancer Prevention (9). In 2010, Rushton *et al.* (10) estimated that for men the occupational attribution factor for bladder cancer in Britain is 7.1%. In Germany, in the period 1978 to 2003, a total of 1211 cases of bladder cancer were legally compensated as an occupational disease (11). From 2004-2009, another 705 cases were compensated (12). Otherwise, an estimated 27,450 persons were newly diagnosed in 2006 with bladder cancer (13). In Japan, 592 workers received compensation for benzidine-induced and 2-naphthylamine-induced cancers, as noted in 2005 (14,15). Nevertheless, there is a large discrepancy between the number of estimated and acknowledged cases (16-22). This was impressively shown by studies on bladder cancer cases in Italy (20) and in Denmark (18) and is in line with only 6 compensated bladder cancer cases in Spain in the period 2000-2008 (23).

It must be taken into account that exposure to bladder carcinogens, mostly carcinogenic aromatic amines, has changed over time. For decades, the main focus in bladder cancer was on workers highly exposed in aromatic amine production plants or in plants producing azo dyes on the basis of carcinogenic aromatic amines, mostly benzidine after the first report of occupational bladder cancer by Rehn (24,25) up to the reports on newly diseased persons many years after the plants were closed in the 1960s or early 1970s (e.g. 26-29). In Russia, benzidine production was reported at least up to 1988 (30).

However, it must be taken into account that in some countries benzidine production ended later for

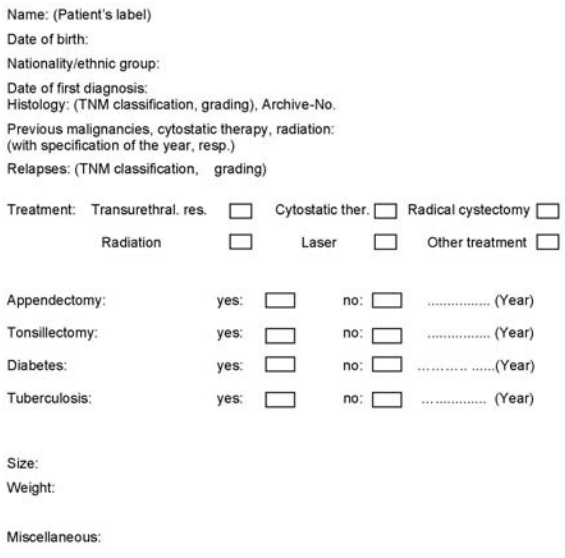
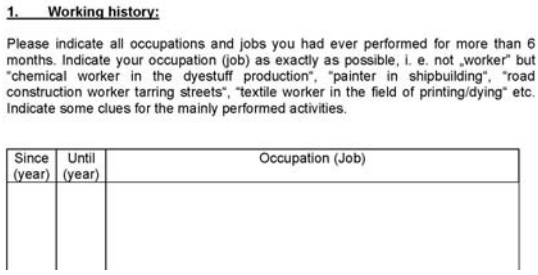

Name: (Patient's label)
Date of birth:
Nationality/ethnic group:
Date of first diagnosis:
Histology: (TNM classification, grading), Archive-No.
Previous malignancies, cytostatic therapy, radiation:
(with specification of the year, resp.)
Relapses: (TNM classification, grading)
Treatment: Transurethral. res. ☐ Cytostatic ther. ☐ Radical cystectomy ☐
Radiation ☐ Laser ☐ Other treatment ☐
Appendectomy: yes: ☐ no: ☐ ..... (Year)
Tonsillectomy: yes: ☐ no: ☐ ..... (Year)
Diabetes: yes: ☐ no: ☐ ....(Year)
Tuberculosis: yes: ☐ no: ☐ ..... (Year)
Size:
Weight:
Miscellaneous:

Figure 1. Items of physician's part of the questionnaire (examples).


1. Working history:

Please indicate all occupations and jobs you had ever performed for more than 6 months. Indicate your occupation (job) as exactly as possible, i. e. not „worker" but "chemical worker in the dyestuff production", "painter in shipbuilding", "road construction worker tarring streets", "textile worker in the field of printing/dying" etc. Indicate some clues for the mainly performed activities.

Since (year)	Until (year)	Occupation (Job)

Figure 2. Top of the first page of the patient's part of the questionnaire with examples for precise formulation of the working history.

economic reasons, e.g. in South Korea where benzidine production increased in the 1990s due to the importation of the technical equipment from Japan and was finally ended in 2000 (31,32). However, also details in the production process must be considered. The very few bladder cancer cases observed to date in Korea are reported, besides the shorter latency period, to be due to the fact that in Japan free benzidine base was used in contrast to Korea where benzidine hydrochloride was used. Benzidine base crumbles easily and can readily disperse in the air; however, if wet-caked as benzidine hydrochloride, its ability to disperse is markedly decreased. This difference may have reduced workers' exposure levels (31).

Nowadays, as almost all production facilities of highly carcinogenic aromatic amines like benzidine have been closed world-wide, and the occupational safety standards at aromatic amines production plants are not comparable to the working conditions decades ago, the focus has changed from the follow-up of the limited numbers of persons involved in the production process to the far greater number of applicants of colorants like painters and hairdressers.

To promote the identification of occupation-related bladder cancer world-wide, the Dortmund bladder cancer questionnaire, which was successfully applied to bladder cancer patients (and controls) in 3 published hospital-based studies (33-35), mostly with some help of the physician, and one study on after-care cancer patients mailing the questionnaire to the home address of the patients (36), was translated into currently more than 30 languages of the world.

3. STRUCTURE OF THE QUESTIONNAIRE

The questionnaire comprises two parts. The first part is to be completed by the physician and contains the standard questions regarding TNM classification and grading at first diagnosis, applied therapy like transurethral resection, intravesical instillation of the biological response modifier BCG (Bacillus Calmette-Guerin) or of the cytostatic agents mitomycin or adriablastin, and a documentation of relapses. Furthermore, some easily accessible factors, e.g. factors possibly influencing the immune status, like appendectomy, tonsillectomy or diabetes, are recorded (Figure 1).

The second part is to be completed by the patient. It begins with a listing of all occupations/jobs ever held for more than 6 months from the first employment on. For practical purposes, some examples for presenting relevant information on the performed occupation or job are given below (Figure 2). On the following pages, a number of suspected occupations or exposures at risk are presented. The aim of this procedure is the following. In the case of occupations or jobs, the patients will provide some more detailed information on the performed occupation or job of interest (Figure 3). For practical purposes very important are the questions aiming at exposures possibly relevant for bladder cancer risk (Figure 4). If the individual was exposed, the person is kindly asked to provide some relevant details like year of first and last exposure and the frequency of the exposure. These questions are dedicated to elucidate bladder cancer risks in occupations commonly not known for relevant bladder cancer risks, e.g. the teacher having given a course on synthesizing benzidine-based azo dyes, the welder applying carcinogenic aromatic amine-based azo dyes as constituents of crack test sprays used for quality control in the metal industry or the salesperson weighing and packing powdery colorants based on carcinogenic aromatic amines in a paint shop. Furthermore, some non-occupational bladder cancer risk factors like tobacco smoking or family history are also asked because in the future the interaction of different bladder cancer risk factors (occupational, life-style, genetic) will become more and more important. At the end, the questionnaire contains the declaration of consent.

4. TRANSLATION OF THE QUESTIONNAIRE

The aim was to translate the questionnaire into more than 30 languages, including the 10 most often spoken languages of the world, according to Lewis (37). Initially, some native speakers cooperating with us preferably in bladder cancer research were asked to

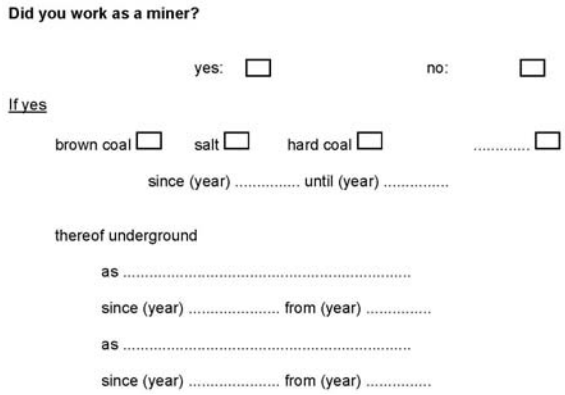


Figure 3. Query of more detailed information on an occupation of interest, using the example of the occupation of a miner.

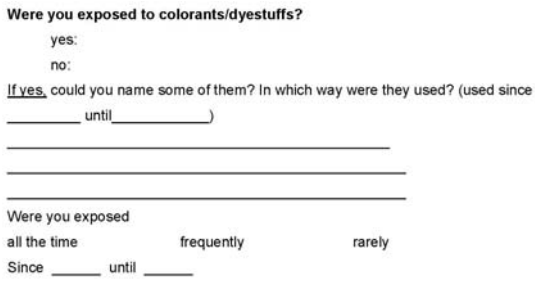


Figure 4. Query of more detailed information on an exposure of interest, using the example of exposure to colorants/dyestuffs.

participate and to provide a translation. Later, the questionnaire was offered to possibly interested physicians, natural scientists and other persons for translation. The colleagues were allowed to add questions not included in the original version of the questionnaire but of interest in their country. Furthermore, in a tight frame the colleagues were also allowed to omit some questions. For example, if there was no coal mining industry in the country a question regarding this exposure would possibly impede the cooperation of the patients and was therefore omitted.

5. OCCUPATIONAL EXPOSURES AND OCCUPATIONS/JOBS LISTED IN THE QUESTIONNAIRE

5.1. Chemicals

This is an open question. In general, no additional relevant information has been gained. However, by open questions like this the attention may be drawn to up to currently unknown risks. Furthermore, some patients may have the feeling that you are really interested in their individual situation which is not fully or even partially covered by the questionnaire.

5.2. Colorants/dyestuffs

Colorants based on carcinogenic aromatic amines are bladder carcinogens if they are bioavailable, i.e. water soluble (7). Pigments are not water soluble and therefore they are not carcinogenic to the bladder (7). For practical purposes it is important that in general spray paints contain pigments and may contain hardeners, the latter sometimes based on carcinogenic aromatic amines. This may explain the finding that in some smaller studies an elevated bladder cancer risk in spray painters was observed (38,39). The carcinogenicity of bioavailable azo dyes based on carcinogenic aromatic amines implies that applicants of those dyes may have an elevated risk. Due to the ban on carcinogenic aromatic amines for industrial purposes at different time points in different countries, the period when the exposure happened is very important and may vary considerably from country to country.

5.3. Aromatic amines

The carcinogenic potency of aromatic amines varies from highly carcinogenic to the human bladder to not carcinogenic to the human bladder and therefore aromatic amines are even allowed to be used as a coupler for synthesizing food colorants. Aromatic amines easily penetrate the skin. Therefore dermal exposure is an important risk factor. The most notorious bladder carcinogens classified by IARC as human carcinogens Group 1 ("carcinogenic to humans") are benzidine, 2-naphthylamine (synonym: ß-naphthylamine), 4-aminobiphenyl, 4-chloro-o-toluidine and o-toluidine. Benzidine is by far the most important aromatic amine regarding bladder cancer and was used mainly in the azo dye production. 2-Naphthylamine is the most important carcinogenic aromatic amine formerly used as antioxidant in the rubber industry. Due to the high bladder carcinogenicity and its ban in Germany in 1954, 2-naphthylamine was replaced by N-phenyl-2-naphthylamine. However, in some industrialized countries the production of 2-naphthylamine ended in the 1970s. As an impurity of N-phenyl-2-naphthylamine, it was identified in the rubber industry. Recently, 2-naphthylamine was also described as an impurity of N-phenyl-2-naphthylamine formerly used as an antioxidant in some technical fat, e.g. Stauffer fat (40). 2-Naphthylamine is also a constituent of the exhaust in aluminium reduction plants ("Soderberg electrolysis") (41-42). 1-Naphthylamine (synonym: α-naphthylamine) is not bladder carcinogenic but may contain small amounts (0.5% or less) of 2-naphthylamine as impurity (43). 4-Aminobiphenyl plays, to our best knowledge, a minor role in occupational bladder cancer but is, like 2-naphthylamine and o-toluidine, a constituent of tobacco smoke. 4-Chloro-o-toluidine was used in the production of the pesticide chlordimeform (44) only in a few production plants. o-Toluidine is the only Group 1 carcinogenic aromatic amine which is still used in the industry and in the workplace. It was classified as a Group 1 carcinogen recently. Exposure to aromatic amines classified as Group 2A ("probably carcinogenic to humans") may be also relevant for human bladder cancer. This is dependent on intensity and frequency of exposure. It is noteworthy that some of those aromatic amines are rarely used in the workplace and therefore only limited data on human carcinogenicity to the bladder may be available. Some benzidine derivatives and azo dyes based on it are classified as Group 2B ("possibly carcinogenic to humans"). An important example is 3,3'-dichlorobenzidine,

a basic compound for the production of 3,3'-dichlorobenzidine-based pigments. Biomonitoring data from a 3,3'-dichlorobenzidine producing plant provide evidence that workers may be exposed (45). However, data from such plants are scarce and epidemiological data are not available. For detailed information on aromatic amines and their carcinogenicity see Neumann (46) and the IARC Monographs Vol. 99 (47) and Vol. 100 A-F which will appear soon (48,49).

5.4. Tar or tar products, bitumen, combustion products

Polycyclic aromatic hydrocarbons may be generated by combustion processes, particularly under oxygen deprivation. An increased bladder cancer risk was reported for workers highly exposed to polycyclic aromatic hydrocarbons (PAH), e.g. for workers in aluminium reduction plants (50-53) and for coke oven workers in coking plants (36,54,55). In roofers, who have lower exposure to PAHs, also an increased bladder cancer risk was reported (56,57). The carcinogenic potency of tar was clearly shown in a tar chemical company where 13 bladder cancer cases and 7 bladder polyps (which would be classified today as G1Ta bladder cancer) were observed in 568 employees (58). However, the carcinogenic potency of tar and tar products has been controversial for many years. In a recent review, Bosetti and co-workers (59) concluded that, with the exception of town gas production, the bladder cancer risk in workers, exposed to PAHs is modest. We would like to add that we also see the workers in the aluminium reduction plants at a clearly increased risk. Exposure to bitumen in the past may be problematic. Bitumen itself does not contain PAHs or carcinogenic aromatic amines and is not carcinogenic to the bladder. However, it is important that the transition from tar (which contains PAH and traces of carcinogenic aromatic amines like 2-naphthylamine) to bitumen (which does not contain PAH or traces of carcinogenic aromatic amines) was made by using tar containing bitumen called coal tar bitumen or carbobitumen.

5.5. Solvents

Currently, the data on solvents regarding bladder carcinogenicity do not allow classification of solvents as relevant bladder carcinogens. However, painting and hairdressing are occupations with elevated bladder cancer risk and it remains unclear whether there is e.g. an interaction with solvents.

5.6. Trichloroethylene

Axelson *et al.* (60) did not observe an elevated bladder cancer risk in a large study in Sweden of persons exposed for short periods and/or to low concentrations of trichloroethylene. Currently, there are no data available which clearly show a bladder carcinogenic effect. However, as trichloroethylene differs from perchloroethylene only by one chlorine atom, this is an interesting substance. To date, studies on highly exposed individuals are not available.

5.7. Perchloroethylene

An elevated bladder cancer risk has been reported for dry cleaners in the United States in different studies (61-64). In a follow-up of the St. Louis cohort, the bladder cancer risk was still elevated, but no more statistically significant (65). A review (66) stated that there was an excess of bladder cancer in the study population mostly including laundry and dry cleaning workers. A recently published study on the morbidity of Swedish dry-cleaners and laundry workers did not show an elevated bladder cancer risk (67). However, the use of perchloroethylene in Swedish dry-cleaning shops was regulated very strictly and thus 8-hour average exposure levels rarely exceeded 50 ppm in the 1980s (67).

5.8. Non-chlorinated solvents

Currently, the data on non-chlorinated solvents regarding bladder carcinogenicity do not allow classifying non-chlorinated solvents as bladder carcinogens. However, painting and hairdressing are occupations with elevated bladder cancer risk and it remains unclear whether there is e.g. an interaction with non-chlorinated solvents.

5.9. Coking plant

Some early studies have described an elevated bladder cancer risk for coke oven workers (54,55). In the last years, only one study reported an elevated bladder cancer risk in coke oven workers (36). It is without doubt that coke oven workers are highly exposed to combustion products and to small amounts of the highly bladder carcinogenic aromatic amine 2-naphthylamine. In Germany, lung cancer in coke oven workers is an occupational disease (68) whereas bladder cancer in coke oven workers is not. However, due to the small amounts of 2-naphthylamine in coke oven fumes (69), bladder cancer in coke oven workers can also be compensated as an occupational disease, but this issue remains controversial. The evaluation of IARC (70) is as follows: Occupational exposures during coal gasification are carcinogenic to humans (Group 1). Occupational exposures during coke production are carcinogenic to humans (Group 1). It is noteworthy that producing coke, i.e. heating of coal under exclusion of air, is divided into two processes. Low-temperature coking up to 800°C produces fine coke and fairly large quantities of liquid and gaseous products, whereas high-temperature coking is used primarily for the production of high-temperature lump coke for blast furnaces and cupola ovens (71). High-temperature coking is associated with higher levels of exposure to PAHs than low-temperature processes (72).

5.10. Furnace

There are only a few reports of an elevated bladder cancer risk in furnace workers (73,74). However, due to the high concentrations of combustion products, this exposure may increase bladder cancer risk.

5.11. Hard coal mining

An elevated bladder cancer risk in hard coal miners was first described by Wynder *et al.* (75). Later, an elevated risk was observed in the French-Belgian hard coal mining area (76,77) and in a large study in the Ruhr area in Germany (78) also showing an increase of the risk with the duration of employment as a miner (79). A recent study

confirmed an elevated bladder cancer risk in hard coal miners in the Ruhr area (80). In 2008, Reulen and co-workers (81) reported in a review on occupational bladder cancer on the occasion of the World Health Organisation International Consultation Bladder Cancer - from Pathogenesis to Prevention 2007 in Stockholm that on the basis of 24 studies the bladder cancer risk in miners is clearly elevated. However, this was not the case in population-based studies. To date, the factor causing the elevated bladder cancer risk in miners remains unknown. However, hard coal does not contain aromatic amines (80) and the normal frequency of slow N-acetyltransferase 2 acetylators in hard coal miners with bladder cancer in two studies indicates that there is no hidden exposure to carcinogenic aromatic amines in hard coal mines (34,80). Most recently, elemental carbon (synonym: carbon black, ultrafine dust) has been observed in the lungs of coal miners (82).

5.12. Painter/varnisher

Painter and varnisher are occupations with an elevated bladder cancer risk (83,84). Several studies (e.g. 85,86), and all 4 studies performed in Germany (36,38,39; 87 (not adjusted for smoking) and 78 (adjusted for smoking)), but not all studies provided an elevated bladder cancer risk. This is most probably due to the exposure conditions which may considerably vary from country to country. Interestingly, also a recently published study by Dryson *et al.* (88) which was based on the New Zealand cancer registry provided an elevated bladder cancer risk. In that study the exposure to azo dyes based on carcinogenic aromatic amines should be estimated clearly lower compared to a study performed decades ago in this country (89). However, the bladder cancer risk was comparable and thus the question arises whether soluble azo dyes based on aromatic amines are the only bladder carcinogen painters are exposed to. Some paints also contain metal compounds containing chromium, cadmium or lead which are suspected to be carcinogenic. In the case of lead which was formerly extensively used as white lead in paints, a large biomonitoring-based study on lead-exposed workers pointed to an elevated cancer risk, also regarding the urinary bladder (90).

5.13. Rubber industry, with working areas

The rubber industry is related to an increased bladder cancer risk at least in some areas. In the largest study in the rubber industry ever performed an elevated mortality was observed for “storage and shipment” and for “general work” in this industry (91). In a study on workers from a factory manufacturing chemicals for the rubber industry, Sorahan *et al.* (92) investigated the standardized mortality ratio of workers which was higher in workers exposed before 1955 than in the entire cohort. In general it can be concluded that after the ban of 2-naphthylamine the bladder cancer incidence in the rubber industry clearly decreased but it is still higher than in the general population.

5.14. Asbestos

From the late 1970s to the early 1980s some papers reported the presence of asbestos fibres in animals fed with asbestos containing food (93-95) and in individuals with and without occupational exposure to asbestos (96,97). In 1989, Guillemin and co-workers (98) presented their own research work combined with a critical review of the literature. Monseur and colleagues (99) presented two cases of asbestosis of the bladder and the prostate, resp. However, since that no new publications on asbestos and urinary tract cancers appeared.

6. COMPETING NON-OCCUPATIONAL RISK FACTORS

6.1. Pain killers (quantification)

In the past, analgesics containing phenacetin were used in many countries and were well known for the carcinogenicity in the urinary tract. Combinations with other analgesics are suggested to exhibit a higher risk (100). It is remarkable that in a large study on more than 1500 bladder cancer patients all non-steroidal anti-inflammatory drugs except pyrazolone derivatives were associated with a lower bladder cancer risk. The protective effect was most pronounced in acetic acid ester-based drugs like indomethacin (101).

6.2. Smoking habits (quantification)

Smoking is the most important bladder cancer risk factor contributing up to 50% of cases in men and up to 25% in women. Of practical importance are the monographs of the International Agency for Research on Cancer (6,102). Furthermore, as representative of the numerous publications on bladder cancer risk, the multicenter studies of Brennan *et al.* for men and for women are cited (103,104). It is of utmost importance that Brennan *et al.* showed that the bladder cancer risk in smokers in both genders decreases immediately after cessation of smoking. The decrease was already more than 30% after 1-4 years of cessation, but did not reach the level of non-smokers even after 25 years.

6.3. Family history of bladder cancer

Bladder cancer risk increases 2-fold with one first-degree relative diagnosed with bladder cancer. Age at diagnosis in familial bladder cancer cases is not very different from cases without a family history. High-risk bladder cancer families are extremely rare (105). To date, only 16 case reports presenting 32 families and 86 affected individuals, 9 case-control studies and 4 cohort studies dealing with familial urinary tract cancer have been published (106).

6.4. Hobbies

As exposure to bladder carcinogens like colorants based on carcinogenic aromatic amines and/or to high levels of combustion products may also occur during leisure activities, this question was included. To date, only Sole and Sorahan (107) have reported an elevated bladder cancer risk due maggot baits stained with chrysoidine-based dyes. The intensive dermal contact was considered to be causal. However, in a larger study the risk factor “stained maggots” or “angling” could not be confirmed (108).

Table 1. Most frequently spoken languages (modified according to Lewis (37)) and available translations of the questionnaire „Bladder Cancer Doc“

Rank	Language	Primary Country	Total countries	Speakers (millions)
1	Chinese	China	31	1,213
2	Spanish	Spain	44	329
3	English	United Kingdom	112	328
4	Arabic	Egypt	57	221
5	Hindi	India	20	182
6	Bengali	Bangladesh	10	181
7	Portuguese	Portugal	37	178
8	Russian	Russian Federation	33	144
9	Japanese	Japan	25	122
10	German	Germany	43	90.3
11	Indonesian	Indonesia	5	84.6
12	*Lahnda*	*Pakistan*	*8*	*78.3*
	Panjabi, West.	*Pakistan*	*7*	*62.6*
	Seraiki	*Pakistan*	*3*	*13.8*
13	*Telugu*	*India*	*10*	*69.8*
14	Vietnamese	Viet Nam	23	68.6
15	*Marathi*	*India*	*5*	*68.1*
16	French	France	60	67.8
17	Korean	Korea, South	33	66.3
18	Tamil	India	17	65.7
19	Italian	Italy	34	61.7
20	Urdu	Pakistan	23	60.6
21	Turkish	Turkey	36	50.8
22	*Gujarati*	*India*	*20*	*46.5*
23	Polish	Poland	23	40.0
24	Malay	Malaysia	14	39.1
29	Kannada	India	3	35.3
34	Persian (Farsi)	Iran	29	31.4
40	Romanian	Romania	20	23.4
42	Dutch	Netherlands	12	21.7
44	Thai	Thailand	5	20.4
55	Serbo-Croatian		28	16.4
	Croatian	Croatia	14	5.5
	Serbian	*Serbia*	*22*	*7.0*
68	Greek	Greece	38	13.1
73	Hungarian	Hungary	14	12.5
81	Czech	Czech Republic	12	9.5
87	Kazakh	Kazakhstan	14	8.3
123	Slovak	Slovakia	12	5.0
124	Finnish	Finland	7	5.0
126	Afrikaans	South Africa	12	4.9
138	Georgian	Georgia	13	4.3
--	Kirghiz[+]	Kyrgyzstan	6	4.5
--	Latvian[+]	Latvia	1	1.55

Italic: translation currently not available

[+] according to Wikipedia (not included in Lewis (37))

7. TRANSLATIONS AVAILABLE AND FURTHER DEVELOPMENT

To date, translations into more than 30 languages are available (Table 1), among them the ten most often spoken languages of the world. The translations are available on the homepage of the Dortmund institute as text files and as pdf files: www.ifado.de/BladderCancerDoc . A wide use is highly appreciated by all authors. This questionnaire was developed as a project of the Global Plan of Action (GPA project 4.21c: Bladder Cancer Documentation of Causes: the multilingual questionnaire “Bladder Cancer Doc“) within the framework of the World Health Organisation Collaborating Centres in Occupational Health. For practical as well as for scientific purposes, a further development of the questionnaire regarding specific local problems is highly welcome. However, in publications based on the questionnaire or its modified version, this article should be cited. A feedback on applications not aiming at scientific publications to the corresponding author is also very welcome.

In a second step, publications for example in local medical journals will be encouraged to make this questionnaire and its numerous translations available to the people who have contact with bladder cancer patients. Translations into still not considered languages are very welcome and will be presented on the homepage of the Dortmund institute.

8. DISCUSSION

To date, numerous publications on occupational bladder cancer and some reviews on occupational bladder cancer causes have appeared (e.g. 81,109-113). However, too many occupational bladder cancer cases are not identified (16-22). This issue may vary considerably from one country to another and is mainly due to the fact that an occupational history is not taken. Compared to developed countries, the situation in developing countries seems to be even worse. To address this problem, we present an easily applicable questionnaire with translations into more than 30 languages. This questionnaire has several advantages. First of all, the German version of the questionnaire has been successfully completed by bladder cancer cases and controls who could ask their physician for assistance (33-35) and by those who could not (36). Additionally, the Hungarian, Urdu (official language of Pakistan) and the Spanish-Venezuelan versions have also been successfully applied under very different circumstances. As the questionnaire can be completed within a short time, the acceptance by physicians and patients is very good. On the other hand, not all occupational risks can be covered by such a questionnaire. To meet this inevitable shortcoming, the translations of the questionnaire, accessible at the homepage of the Dortmund institute (www.ifado.de/BladderCancerDoc) are offered as pdf files and as text files. The latter can be easily modified by the physicians considering specific local exposure conditions or possible causes of occupational bladder cancer or scientific topics not included or not adequately covered by this questionnaire.

First of all, persons who were occupationally exposed to bioavailable i.e. water soluble azo dyes based on carcinogenic aromatic amines, may be at risk. In recent years, hairdressers and people in related occupations like barbers or beauticians were subjects of scientific investigations (114,115). It is noteworthy that also investigations in developing countries aimed at the risk in this occupation (116). IARC (48) has classified the occupational exposure of a hairdresser as probably carcinogenic to humans (Group 2A) but it did not say what the cause of the elevated risk is. As hairdressers and people in related occupations are exposed to a broad spectrum of

Table 2. Items of patient's part of questionnaire

Occupational history
All occupations (jobs) performed for more than 6 months since leaving school with year specification
Detailed questions regarding occupational exposure, e.g.
Chemicals
Colorants/dyestuffs
Aromatic amines
Tar or tar products, combustion products
Solvents
Trichloroethylene
Perchloroethylene
Non-chlorinated solvents
Coking plant
Furnace
Hard coal mining
Painter/varnisher
Rubber industry, with working areas
Asbestos
Competing non-occupational risk factors
Pain killers (quantification)
Smoking habits (quantification)
Family history of bladder cancer
Hobbies
Consent form

chemical substances which may considerably vary from time to time and from country to country or even from area to area, this topic is also the subject of further research.

Unfortunately, only a limited number of publications on people occupationally exposed to azo dyes are available. In 2005, the global dyestuff production was an estimated 34 million tons, which was worth an estimated 23 billion USD. Consumption of dyestuffs is 40% printing inks, 30% paints, 20% plastics and others from segments like textile (117). As particularly the textile and the leather industry are also present in developing countries, this topic may inspire further studies in these industries. Most recently, our group described a series of bladder cancer cases in crack testers in the German metal industry who had applied this procedure for quality control (118). Surprisingly, some applied crack test sprays had contained azo dyes like p-phenylazo-anilin-N-ethyl-2-naphthylamine or Sudan red 7B and were available in Germany only for this very specific purpose at least up to the mid 1980s, although the industrial production of 2-naphthylamine was ended in Germany in 1954. These azo dye molecules may be cleaved into carcinogenic aromatic amines like 2-naphthylamine in the body.

Besides this, some occupations like foundry workers (119-121) are described at risk due to carcinogenic aromatic amines which may be released by pyrolysis from polyurethane-bonded sand cores used in the cold box procedure. Furthermore, people exposed to the explosive dinitrotoluene are described at risk due to reduction of the nitro group to an amino group (122-124). At least in Scandinavia a large study with two follow-ups has shown an elevated bladder cancer risk of chimney sweeps (125-127). In Germany, a large study showed that chimney sweeps had higher blood fat concentrations of polychlorinated dibenzodioxins (PCDD) and polychlorinated dibenzofurans (PCDF), applying the sum of PCDD and PCDF equivalents (128). However, the bladder cancer risk may considerably vary from one country to another due to the different fuels used.

Surprisingly, fire fighters do in general not have an increased bladder cancer risk (129). This may be explained by the personal protective equipment and the relatively short exposure scenarios, compared e.g. with aluminium reduction plant workers or coke oven workers. It is surprising that the bladder cancer risk in workers highly exposed to polycyclic aromatic amines in the workplace, e.g. aluminium electrolysis pot room workers or coke oven workers, is only moderately increased and lower than in long-term heavy smokers.

Furthermore, there are still some unanswered questions e.g. the cause of the elevated risk of professional bus, truck or taxi drivers which was observed in many studies. A recently published pooled analysis revealed a moderately increased risk which was lower in the more recently published studies (130). Although the risk is far too small to be compensated as an occupational disease, it is of scientific interest because many people are affected and the main cause is not clear. Currently discussed causes are for example the differences in drinking habits and urine voiding compared to the normal population, and inhalation of diesel exhaust, containing some nitroarenes that can be metabolized to aromatic amines in the body.

The same is the situation in motor mechanics who exhibited an elevated bladder cancer risk in a pooled analysis based on 17 studies (81). Discussed causes are exposure to diesel exhaust containing nitroarenes and, in former decades, carcinogenic aromatic amines like 2-naphthylamine which were observed as impurities in some fats and gasoline or technical fluids or mineral oils containing azo dyes like Sudan red 7B which were based on carcinogenic aromatic amines.

Bladder cancer risks in employees from petroleum industries were investigated in 8 different studies. An analysis of the 8 studies showed an association with an elevated bladder cancer risk (131).

It should be kept in mind that more occupations/jobs and occupational exposures have been reported to be associated with an elevated bladder cancer risk. As such exposures are rare, controversial or associated with a minor risk far too low to be acknowledged and/or compensated as an occupational disease, they are not listed in this article but available on the homepage of the Dortmund institute (www.ifado.de/BladderCancerDoc). They are taken from a CD-based tool, particularly designed for German urologists in practices and hospitals to screen for possible occupational risks in bladder cancer patients (132).

It is of utmost importance that bladder cancer risk in exposed persons may vary also between case-control studies which are at the state of the art level. An impressive example is the study on hair dye use and bladder cancer risk in the greater area of Los Angeles which showed a clearly elevated risk for the application of permanent hair dyes not only for professional but also for private use (133), which was corroborated by the observation of an elevated frequency of the slow acetylation genotype in the

affected persons (134). In 2007, it was stated that this study is state of the art but the findings cannot be transferred to other areas (114). To date, the results of this study have not been replicated by other studies.

Last but not least it should be mentioned that bladder cancer due to bilharziasis in farmers and agricultural workers in some developing countries is common (e.g. 135,136) and thus a very important issue which is unfortunately not termed as an occupational cancer.

9. SUMMARY

The authors believe that this questionnaire and the cited references highlighting the scientific background of the covered risk factors may help to elucidate still unidentified cases of occupational bladder cancer in developed and in undeveloped countries. To further promote the identification of occupational bladder cancer risks, a list of known and controversial occupations/jobs and exposures is presented on the homepage of the institute where the translated questionnaires can be downloaded. The authors disclaimed presenting these two tables in this article because they did not want to confuse readers who are looking for a questionnaire to screen for bladder cancer risks in daily routine work.

10. REFERENCES

1. A. Jemal, F. Bray, M.M. Center, J. Ferlay, E. Ward, D. Forman: Global cancer statistics. *CA Cancer J Clin* 61, 69-90 (2011)

2. Globocan: Cancer incidence and mortality worldwide in 2008. http://globocan.iarc.fr (2010) (accessed 2 September 2011)

3. G.M. Lower, Jr, T. Nilsson, C.E. Nelson, H. Wolf, T.E. Gamsky, G.T. Bryan: N-Acetyltransferase phenotype and risk in urinary bladder cancer: approaches in molecular epidemiology. Preliminary results in Sweden and Denmark. *Environ Health Perspect* 29, 71-79 (1979)

4. N. Rothman, M. Garcia-Closas, D.W. Hein: Commentary: Reflections on G.M. Lower and colleagues' 1979 study associating slow acetylator phenotype with urinary bladder cancer: meta-analysis, historical refinements of the hypothesis, and lessons learned. *Int J Epidemiol* 36, 23–28 (2007)

5. J. Colli, B.R. Lee, R. Thomas: Population densities in relation to bladder cancer mortality rates in America from 1950 to 1994. *Int Urol Nephrol* 2011 Jun 24 [Epub ahead of print]

6. International Agency for Research on Cancer (IARC): Tobacco smoke and involuntary smoking. (IARC Monographs on the Evaluation of the Carcinogenetic Risk of Chemicals to Humans, Vol 83) Lyon, France 2004. http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php (accessed 2 September 2011)

7. K. Golka, S. Kopps, Z.W. Myslak: Carcinogenicity of azo colorants: influence of solubility and bioavailability. *Toxicol Lett* 151, 203-210 (2004)

8. R. Doll, R. Peto: The causes of cancer: Quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst* 66, 1191-1308 (1981)

9. G. Colditz, W. DeJong, D. Hunter, D. Trichopoulos, W. Willet (eds.): Harvard report on cancer prevention Vol 1: Causes of human cancer. *Cancer Causes Control* 7 Suppl, 3-59 (1996)

10. L. Rushton, S. Bagga, R. Bevan, T.P. Brown, J.W. Cherrie, P. Holmes, L. Fortunato, R. Slack, M. Van Tongeren, C. Young, S.J. Hutchings: Occupation and cancer in Britain. *Br J Cancer* 102, 1428-1437 (2010)

11. Hauptverband der gewerblichen Berufsgenossenschaften (HVBG) (ed.): Beruflich verursachte Krebserkrankungen. Eine Darstellung der im Zeitraum 1978 bis 2003 anerkannten Berufskrankheiten, 8. uberarbeitete und erganzte Aufl. HVBG, Sankt Augustin, Germany (2005)

12. Deutsche Gesetzliche Unfallversicherung (DGUV): BK-Report 2/2011 Aromatische Amine. Eine Arbeitshilfe in Berufskrankheiten-Ermittlungsverfahren. 2. aktualisierte Auflage des BK-Reports 1/2009, Sankt Augustin

13. Robert Koch Institute and the Association of Population-based Cancer Registries in Germany: Cancer in Germany 2005/2006 incidence and trends. Seventh edition, Germany (2010)

14. Japan Occupational Safety and Health Resource Center (JOSHRC): *JOSHRC Newsletter* Aug 19 (2005)

15. J. Park, N. Hisanaga, Y. Kim: Transfer of occupational health problems from a developed to a developing country: lessons from the Japan-South Korea experience. *Am J Ind Med* 52, 625-632 (2009)

16. K. Golka, W. Schops, G. Kierfeld, H.M. Bolt: Urothelial diseases as an occupational disease. *Versicherungsmedizin* 46, 158-161 (German) (1994)

17. K. Golka: Occupational and nonoccupational causes of bladder cancer. *South Med J* 99, 1203 (2006)

18. M. Thomsen, K.J. Mikines: Occupationally conditioned bladder cancer - are the patients identified? *Ugeskr Laeger* 168, 4095-4098 (Danish) (2006)

19. M. Zellner, W. Schops, K. Golka, J. Zumbe: Berufsbedingtes Blasenkarzinom Dunkelziffer weiterhin hoch. *URO-NEWS* 11, 36-43 (2007)

20. R. Borchini, M. Bonzini, G. Veronesi, C. Fava, M.C. Carenzi, S. Mombelli, A. Marconi, A.V. Bono, M.M. Ferrario: Validation of a screening method for occupational bladder cancer. *Med Lav* 100, 438-447 (Italian) (2009)

21. A. Scarselli, P. Scano, A. Marinaccio, S. Iavicoli: Occupational cancer in Italy: evaluating the extent of compensated cases in the period 1994-2006. *Am J Ind Med* 52, 859-867 (2009)

22. W. Schops, O. Jungmann, J. Zumbe, M. Zellner, J.G. Hengstler, K. Golka: Compensation of occupational bladder cancer patients. *Front Biosci* –submitted-

23. Eurogip Survey report August 2010 Work-related cancers: what recognition in Europe? (2010) http://www.eurogip.fr/en/docs/EUROGIP_RecoCancerspro_49E.pdf (accessed 2 September 2011)

24. L. Rehn: Blasengeschwulste bei Fuchsinarbeitern. *Arch Klin Chir* 50, 588-600 (1895)

25. H.G. Dietrich, K. Golka: Bladder tumors and aromatic amines – Historical milestones from Ludwig Rehn to Wilhelm Hueper. *Front Biosci* –in press-

26. R.A. Cartwright, H.J. Rogers, D. Barham-Hall, R.W. Glashan, R.A. Ahmad, E. Higgins, M.A. Kahn: Role of N-acetyltransferase in bladder carcinogenesis: a pharmacogenetic epidemiological approach to bladder cancer. *Lancet* 2, 842-846 (1982)

27. X.Y. You, J.G. Chen, Y.N. Hu: Studies on the relation between bladder cancer and benzidine or its derived dyes in Shanghai. *Br J Ind Med* 47, 544-552 (1990)

28. K. Golka, V. Prior, M. Blaszkewicz, H.M. Bolt: The enhanced bladder cancer susceptibility of NAT2 slow acetylators towards aromatic amines: a review considering ethnic differences. *Toxicol Lett* 128, 229-241 (2002)

29. Q.W. Ma, G.F. Lin, Y.Q. Quin, D.R. Lu, K. Golka, F. Geller, J. Chen, J. Shen: GSTP1 A1578G (Ile105Val) polymorphism in benzidine-exposed workers: an association with cytological grading of exfoliated urothelial cells. *Pharmacogenetics* 13, 409-415 (2003)

30. M.A. Bulbulyan, L.W. Figgs, S.H. Zahm, T. Savitskaya, A. Goldfarb, S. Astashevsky, D. Zaridzee: Cancer incidence and mortality among beta-naphthylamine and benzidine dye workers in Moscow. *Int J Epidemiol* 24, 266-275 (1995)

31. Y. Kim, J. Park, Y.C. Shin: Dye-manufacturing workers and bladder cancer in South Korea. *Arch Toxicol* 81, 381-384 (2007)

32. J. Park, K.S. Shin, Y. Kim: Occupational reproductive function abnormalities and bladder cancer in Korea. *J Korean Med Sci* 25(Suppl), S41-45 (2010)

33. K. Golka, V. Prior, M. Blaszkewicz, I. Cascorbi, W. Schops, G. Kierfeld, I. Roots, H.M. Bolt: Occupational history and genetic N-acetyltransferase polymorphism in urothelial cancer patients of Leverkusen, Germany. *Scand J Work Environ Health* 22, 332-338 (1996)

34. K. Golka, T. Reckwitz, M. Kempkes, I. Cascorbi, M. Blaskewicz, S.E. Reich, I. Roots, J. Soekeland, H. Schulze, H.M. Bolt: N-Acetyltransferase 2 (NAT2) and glutathione S-transferase μ (GSTM1) in bladder-cancer patients in a highly industrialized area. *Int J Occup Environ Health* 3, 105-110 (1997)

35. K. Golka, T. Seidel, H. Dietrich, G. Roth, C. Rotzel, R. Thier, F. Geller, T. Reckwitz, H. Schulze: Occupational and non-occupational risk factors in bladder cancer patients in an industrialized area located in former East-Germany. *Aktuelle Urol* 36, 417-422 (in German) (2005)

36. K. Golka, P. Heitmann, F. Gieseler, J. Hodzic, N. Masche, H.M. Bolt, F. Geller: Elevated bladder cancer risk due to colorants - a statewide case-control study in North Rhine-Westphalia, Germany. *J Toxicol Environ Health A* 71, 851-855 (2008)

37. M.P. Lewis (ed.): Ethnologue: Languages of the world, Sixteenth edition. Dallas, Tex.: SIL International. Online version: http://www.ethnologue.com/ (2009) (accessed 2 September 2011)

38. J.C. Claude, R.R. Frentzel-Beyme, E. Kunze: Occupation and risk of cancer of the lower urinary tract among men. A case-control study. *Int J Cancer* 41, 371-379 (1988)

39. U. Bolm-Audorff, K.H. Jockel, B. Kilguss, H. Pohlabeln, T. Siepenkothen: Bosartige Tumoren der ableitenden Harnwege und Risiken am Arbeitsplatz. Wirtschaftsverlag NW, Bremerhaven (Schriftenreihe der Bundesanstalt fur Arbeitsschutz, Dortmund, Forschung; Fb 697) Germany (1993)

40. T. Weiss, R. Merget, J. Henry, T. Bruning: Harnblasenkrebs durch Staufferfett? Dermale Aufnahme aromatischer Amine bei einem Kraftwerkmeister. *IPA-Journal* 2, 6-9 (2010)

41. R. Roussel, A. Gaboury, C. Lariviere: Aromatic amines in the workplace atmosphere of an aluminium smelter. In: Light metals (ed.): E.L. Rooy, The Minerals, Metals & Materials Society (1991)

42. J.P. Farant, D. Ogilvie: Investigation of the presence of amino and nitro polycyclic aromatic hydrocarbons in a Soderberg primary aluminum smelter. *AIHA J* (Fairfax, Va). 63, 721-725 (2002)

43. National Toxicology Program (NTP): 2-Naphthylamine. *Rep Carcinog* 12, 278-280 (2011)

44. M.J. Stasik: Carcinomas of the urinary bladder in a 4-chloro-o-toluidine cohort. *Int Arch Occup Environ Health* 60, 21-24 (1988)

45. K.F. Knoell, N. Will, G. Leng, S. Selinski, J.G. Hengstler, K. Golka, H.M. Bolt: Development of a strategy for biological monitoring in a chemical plant producing

3,3'-dichlorobenzidine dihydrochloride. *J Toxicol Environ Health A* –submitted-

46. H.G. Neumann: Aromatic amines: mechanisms of carcinogenesis and implications for risk assessment. *Front Biosci* 15, 1119-1130 (2010)

47. International Agency for Research on Cancer (IARC): Some aromatic amines, organic dyes, and related exposures. (IARC Monographs on the Evaluation of the Carcinogenetic Risk to Humans, Vol 99) Lyon, 2010 http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php (accessed 2 September 2011)

48. International Agency for Research on Cancer (IARC): Agents classified by the IARC Monographs, Volumes 1-102. (IARC Monographs on the Evaluation of the Carcinogenetic Risk to Humans) Lyon, 2011 http://monographs.iarc.fr/ENG/Classification/ClassificationsAlphaOrder.pdf (accessed 2 September 2011)

49. International Agency for Research on Cancer (IARC): A review of human carcinogens, Part F. (IARC Monographs on the Evaluation of the Carcinogenetic Risk to Humans, Vol 100F) Lyon, in preparation http://monographs.iarc.fr/ENG/Classification/ClassificationsAlphaOrder.pdf (accessed 2 September 2011)

50. A. Ronneberg, F. Langmark: Epidemiologic evidence of cancer in aluminium reduction plant workers. *Am J Ind Med* 22, 573-590 (1992)

51. J.J. Moulin, T. Clavel, B. Buclez, G. Laffitte-Rigaud: A mortality study among workers in a French aluminium reduction plant. *Int Arch Occup Environ Health* 73, 323-330 (2000)

52. P. Romundstad, A. Andersen, T. Haldorsen: Cancer incidence among workers in six Norwegian aluminum plants. *Scand J Work Environ Health* 26, 461-469 (2000)

53. G.W. Gibbs, M. Sevigny: Mortality and cancer experience of Quebec aluminum reduction plant workers, part 4: cancer incidence. *J Occup Environ Med* 49, 1351-1366 (2007)

54. R. Doll, M.P. Vessey, R.W.R. Beasley, A.R. Buckley, E.C. Fear, R.E.W. Fisher, E.J. Gammon, W. Gunn, G.O. Hughes, K. Lee, B. Norman-Smith: Mortality of gasworkers - final report of a prospective study. *Br J Ind Med* 29, 394-406 (1972)

55. A. Manz: Harnwegskarzinome bei Beschaftigten der Gasindustrie. *Munch Med Wschr* 118, 65-68 (1976)

56. E.C. Hammond, I.J. Selikoff, P.L. Lawther, H. Seidman: Inhalation of benzpyrene and cancer in man. *Ann NY Acad Sci* 271, 116-124 (1976)

57. F.B. Stern, A.M. Ruder, G. Chen: Proportionate mortality among unionized roofers and waterproofers. *Am J Ind Med* 37, 478-492 (2000)

58. S. Letzel, H. Letzel, E. Blumner, A. Hendrichs, C. Sommerburg: Haut-, Bronchial-, Kehlkopf-, und Harnwegskarzinommorbiditat bei Patienten mit berufsbedingter Teerhaut. Schriftenreihe des Hauptverbandes der gewerblichen Berufsgenossenschaften, Sankt Augustin, Germany (1992)

59. C. Bosetti, P. Boffetta, C. La Vecchia: Occupational exposures to polycyclic aromatic hydrocarbons, and respiratory and urinary tract cancers: a quantitative review to 2005. *Ann Oncol* 18, 431-446 (2007)

60. O. Axelson, A. Selden, K. Andersson, C. Hogstedt: Updated and expanded Swedish cohort study on trichloroethylene and cancer risk. *J Occup Med* 36, 556-562 (1994)

61. R.M. Katz, D. Jowett: Female laundry and dry cleaning workers in Wisconsin: a mortality analysis. *Am J Public Health* 71, 305-307 (1981)

62. D.T. Silverman, R.H. Hoover, S. Albert, K.M. Graff: Occupation and cancer of the lower urinary tract in Detroit. *J Natl Cancer Inst* 70, 237-245 (1983)

63. D.P. Brown, S.D. Kaplan: Retrospective cohort mortality study of dry cleaner workers using perchlororethylene. *J Occup Med* 29, 535-541 (1987)

64. A. Blair, P.A. Stewart, P.E. Tolbert, D. Grauman, F.X. Moran, J. Vaught, J. Rayner: Cancer and other causes of death among a cohort of dry cleaners. *Br J Ind Med* 47, 162-168 (1990)

65. A. Blair, S.A. Petralia, P.A. Stewart: Extended mortality follow-up of a cohort of dry cleaners. *Ann Epidemiol* 13, 50-56 (2003)

66. K.A. Mundt, T. Birk, M.T. Burch: Critical review of the epidemiological literature on occupational exposure to perchloroethylene and cancer. *Int Arch Occup Environ Health* 76, 473-491 (2003)

67. A.I. Selden, G. Ahlborg Jr: Cancer morbidity in Swedish dry-cleaners and laundry workers: historically prospective cohort study. *Int Arch Occup Environ Health* 84, 435-443 (2011)

68. Bundesministerium fur Arbeit (BMA): Lungenkrebs durch polyzyklische aromatische Kohlenwasserstoffe bei Nachweis der Einwirkung einer kumulativen Dosis von mindestens 100 Benzo[a]pyren-Jahren [(µg/m3)xJahre] Bek. des BMA vom 5. Februar 1998 - IVa 4-45206-4110 in: *BArbBl* 4/1998, 54-61 (1998)

69. G. Grimmer, K. W. Naujack, G. Dettbarn: Beitrag zur Ursachenforschung exogen bedingter Blasencarcinome - Profilanalyse aromatischer Amine am Arbeitsplatz. Schriftenreihe der Bundesanstalt fur Arbeitsschutz: Forschung; Fb 511 Wirtschaftsverl. NW, Verl. fur Neue Wiss. Bremerhaven, Germany (1987)

70. International Agency for Research on Cancer (IARC): Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures. (IARC Monographs on the Evaluation of the Carcinogenetic Risk to Humans, Vol 92) Lyon, France (2010) http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php (accessed 2 September 2011)

71. J.C. Crelling, H.W. Hagemann, D.H. Sauter, R.V. Ramani, W. Vogt, D. Leininger, S. Krzack, B. Meyer, F. Orywal, R. Reimert, B. Bonn, U. Bertmann, W. Klose, W. Gatzka: Coal. In: Ullmann's Encyclopedia of Industrial Chemistry, 5th Ed., Wiley-VCH Verlag GmbH & Co. KGaA [online version] (2005)

72. I. Price: Survey of occupational exposure to polycyclic aromatic hydrocarbons. Environmental Measurement Group, Health and Safety Laboratory, an agency of the Health and Safety Executive. Issued 04/09/2000, job number JS200329, Registry file 12CR/393/03.1977, document filename hchamber\pah\finrep5.lwp

73. K. Steenland, C. Burnett, A.M. Osorio: A case-control study of bladder cancer using city directories as a source of occupational data. *Am J Epidemiol* 126, 247-257 (1987)

74. K.A. Mallin: Nested case-control study of bladder cancer incidence in a steel manufacturing plant. *Am J Ind Med* 34, 393-398 (1998)

75. E.L. Wynder, J. Onderdonk, N. Mantel: An epidemiological investigation of cancer of the bladder cancer. *Cancer* 16, 1388-1407 (1963)

76. E. Schifflers, J. Jamart, V. Renard: Tobacco and occupation as risk factors in bladder cancer: a case-control study in southern Belgium. *Int J Cancer* 39, 287-292 (1987)

77. S. Cordier, J. Clavel, J.C. Limasset, L. Boccon-Gibod, N. Le Moual, L. Mandereau, D. Hemon: Occupational risks of bladder cancer in France: a multicentre case-control study. *Int J Epidemiol* 22, 403–411 (1993)

78. K. Golka, T. Bandel, S. Schlaefke, S.E. Reich, T. Reckwitz, W. Urfer, K.D. Bremicker, W. Neugebauer, J. Soekeland, H.M. Bolt: Urothelial cancer of the bladder in an area of former coal, iron, and steel industries in Germany: a case-control study. *Int J Occup Environ Health* 4, 79-84 (1998)

79. K. Golka, T. Bandel, T. Reckwitz, W. Urfer, H.M. Bolt, K.D. Bremicker, W. Neugebauer, H. Schulze: Occupational risk factors for bladder carcinoma. A case control study. *Urologe A* 38, 358-363 (in German) (1999)

80. D. Ovsiannikov, S. Selinski, M.L. Lehmann, M. Blaszkewicz, O. Moormann, J.G. Hengstler, K. Golka: Polymorphic enzymes, urinary bladder cancer risk, and structural change in the local industry. *J Toxicol Environ Health A* –submitted-

81. R.C. Reulen, E. Kellen, F. Buntinx, M. Brinkman, M.P. Zeegers: A meta-analysis on the association between bladder cancer and occupation. *Scand J Urol Nephrol* (Suppl 218), 64-78 (2008)

82. R.K. Saxena, M.E. McClure, M.D. Hays, F.H. Green, L.J. McPhee, V. Vallyathan, M.I. Gilmour: Quantitative assessment of elemental carbon in the lungs of never smokers, cigarette smokers, and coal miners. *J Toxicol Environ Health A* 74, 706-715 (2011)

83. International Agency for Research on Cancer (IARC): Painting, firefighting, and shiftwork. (IARC Monographs on the Evaluation of the Carcinogenetic Risk to Humans, Vol 98) Lyon, France (2010) http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php (accessed 2 September 2011)

84. N. Guha, N.K. Steenland, F. Merletti, A. Altieri, V. Cogliano, K. Straif: Bladder cancer risk in painters: a meta-analysis. *Occup Environ Med* 67, 568-573 (2010)

85. R. Chen, A. Seaton: A meta-analysis of painting exposure and cancer mortality. *Cancer Detect Prev* 22, 533-539 (1998)

86. K. Steenland, S. Palu: Cohort mortality study of 57 000 painters and other union members: a 15 year update. *Occup Environ Med* 56, 315-321 (1999)

87. Z.W. Myslak, H.M. Bolt, W. Brockmann: Tumors of the urinary bladder in painters: a case-control study. *Am J Ind Med* 19, 705-713 (1991)

88. E. Dryson, A. 't Mannetje, C. Walls, D. McLean, F. McKenzie, M. Maule, S. Cheng, C. Cunningham, H. Kromhout, P. Boffetta, A. Blair, N. Pearce: Case-control study of high risk occupations for bladder cancer in New Zealand. *Int J Cancer* 122, 1340-1346 (2008)

89. P.B. Bethwaite, N. Pearce, J. Fraser: Cancer risks in painters: study based on the New Zealand Cancer Registry. *Br J Ind Med* 47, 742-746 (1990)

90. A. Anttila, P. Heikkila, E. Pukkala, E. Nykyri, T. Kauppinen, S. Hernberg, K. Hemminki: Excess lung cancer among workers exposed to lead. *Scand J Work Environ Health* 21, 460-469 (1995)

91. K. Straif, S.K. Weiland, B. Werner, L. Chambless, K.A. Mundt, U. Keil: Workplace risk factors for cancer in the German rubber industry: Part 2 Mortality from non-respiratory cancers. *Occup Environ Med* 55, 325-332 (1998)

92. T. Sorahan, L. Hamilton, J.R. Jackson: A further cohort study of workers employed at a factory manufacturing chemicals for the rubber industry, with special reference to the chemicals 2-mercaptobenzothiazole (MBT), aniline, phenyl-beta-naphthylamine and o-toluidine. *Occup Environ Med* 57, 106-115 (2000)

93. W.H. Hallenbeck, K.J. Patel-Mandlik: Presence of fibers in the urine of a baboon gavaged with chrysotile asbestos. *Environ Res* 20, 335-340 (1979)

94. W.H. Hallenbeck, D.R. Markey, D.G. Dolan: Analyses of tissue, blood, and urine samples from a baboon gavaged with chrysotile and crocidolite asbestos. *Environ Res* 25, 349-360 (1981)

95. K.J. Patel-Mandlik, J.R. Millette: Chrysotile asbestos in kidney cortex of chronically gavaged rats. *Arch Environ Contam Toxicol* 12, 247-255 (1983)

96. P.M. Cook, G.F. Olson: Ingested mineral fibers: elimination in human urine. *Science* 204, 195-198 (1979)

97. M.B. Finn, W.H. Hallenbeck: Detection of chrysotile asbestos in workers' urine. *Am Ind Hyg Assoc J* 46, 162-169 (1985)

98. M.P. Guillemin, G. Litzistorf, P.A. Buffat: Urinary fibres in occupational exposure to asbestos. *Ann Occup Hyg* 33, 219-233 (1989)

99. J. Monseur, B. Leguene, L. Lebouffant, G. Tichoux: Asbestosis of the bladder neck and prostate. Reflections on 2 cases. *J Urol* (Paris) 92, 17-21 (French) (1986)

100. International Agency for Research on Cancer (IARC): Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Suppl. 7) Lyon, France (1987) http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php (accessed 2 September 2011)

101. J.E. Castelao, J.M. Yuan, M. Gago-Dominguez, M.C. Yu, R.K. Ross: Non-steroidal anti-inflammatory drugs and bladder cancer prevention. *Br J Cancer* 82, 1364-1369 (2000)

102. International Agency for Research on Cancer (IARC): Tobacco smoking. (IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol 38) Lyon, France (1986)

103. P. Brennan, O. Bogillot, S. Cordier, E. Greiser, W. Schill, P. Vineis, G. Lopez-Abente, A. Tzonou, J. Chang-Claude, U. Bolm-Audorff, K.H. Jockel, F. Donato, C. Serra, J. Wahrendorf, M. Hours, A. T'Mannetje, M. Kogevinas, P. Boffetta: Cigarette smoking and bladder cancer in men: a pooled analysis of 11 case-control studies. *Int J Cancer* 86, 289-294 (2000)

104. P. Brennan, O. Bogillot, E. Greiser, J. Chang-Claude, J. Wahrendorf, S. Cordier, K.H. Jockel, G. Lopez-Abente, A. Tzonou, P. Vineis, F. Donato, M. Hours, C. Serra, U. Bolm-Audorff, W. Schill, M. Kogevinas, P. Boffetta: The contribution of cigarette smoking to bladder cancer in women (pooled European data). *Cancer Causes Control* 12, 411-417 (2001)

105. L.A. Kiemeney: Heriditary bladder cancer. *Scand J Urol Nephrol* 42 (Suppl 218), 110-115 (2008)

106. C.M. Mueller, N. Caporaso, M.H. Greene: Familial and genetic risk of transitional cell carcinoma of the urinary tract. *Urol Oncol* 26, 451-464 (2008)

107. G. Sole, T. Sorahan: Coarse fishing and risk of urothelial cancer. *Lancet* 1, 1477-1479 (1985)

108. T. Sorahan, G. Sole: Coarse fishing and urothelial cancer: a regional case-control study. *Br J Cancer* 62, 138-141 (1990)

109. G. Steineck, N. Plato, S.E. Norell, Ch. Hogstedt: Urothelial cancer and some industry-related chemicals: An evaluation on the epidemiologic literature. *Am J Ind Med* 17, 371-391 (1990)

110. K. Golka, A. Wiese, G. Assennato, H.M. Bolt: Occupational exposure and urological cancer. *World J Urol* 21, 382-391 (2004)

111. S.M. Olfert, S.A. Felknor, G.L. Delclos: An updated review of the literature: risk factors for bladder cancer with focus on occupational exposures. *South Med J* 99, 1256-1263 (2006)

112. K. Golka, P.J. Goebell, A.W. Rettenmeier: Bladder cancer: Etiology and prevention. *Dtsch Arztebl* 104, 719-723 (2007) (http://www.aerzteblatt.de/int/article.asp?src=search&id=58090&p=Golka) (accessed 2 September 2011)

113. G.L. Delclos, S.P. Lerner: Occupational risk factors. *Scand J Urol Nephrol* Suppl 218, 58-63 (2008)

114. H.M. Bolt, K. Golka: The debate on carcinogenicity of permanent hair dyes: new insights. *Crit Rev Toxicol* 37, 521-536 (2007)

115. B. Takkouche, C. Regueira-Mendez, A. Montes-Martinez: Risk of cancer among hairdressers and related workers: a meta-analysis. *Int J Epidemiol* 38, 1512-1531 (2009)

116. M.P. Galiotte, P. Kohler, G. Mussi, G.J. Gattas: Assessment of occupational genotoxic risk among Brazilian hairdressers. *Ann Occup Hyg* 52, 645-651 (2008)

117. Federation of Indian Chambers of Commerce & Industry (FICCI): Indian dyestuff industry and global opportunities - white paper. FICCI, New Delhi, India (2006) http://www.cygnusindia.com/articles/Indian Dyestuff Industry-FICCI Whitepaper-180906.pdf (accessed 2 September 2011)

118. K. Golka, S. Kopps, H.-M. Prager, S. v. Mende, R. Thiel, O. Jungmann, J. Zumbe, H.M. Bolt, M. Blaszkewicz, J.G. Hengstler, S. Selinski: Bladder cancer in crack testers applying azo dye-based sprays to metal bodies. *J Toxicol Environ Health A* –submitted-

119. E.S. Hansen: Cancer mortality among Danish molders. *Am J Ind Med* 20, 401-409 (1991)

120. D. Sherson, O. Svane, E. Lynge: Cancer incidence among foundry workers in Denmark. *Arch Environ Health* 46, 75-81 (1991)

121. J. Clavel, L. Mandereau, J.C. Limasset, D. Hemon, S. Cordier: Occupational exposure to polycyclic aromatic hydrocarbons and the risk of bladder cancer: a French case-control study. *Int J Epidemiol* 23, 1145-1153 (1994)

122. T. Bruning, C. Chronz, R. Thier, J. Havelka, Y. Ko, H.M. Bolt: Occurrence of urinary tract tumors in miners highly exposed to dinitrotoluene. *J Occup Environ Med* 41, 144-149 (1999)

123. H.C. Roemer, K. Golka, H. Schulze, D. Loehlein: Two extrapulmonary neoplasms in a uranium miner. *J R Soc Med* 95, 302 (2002)

124. V. Harth, H.M. Bolt, T. Bruning: Cancer of the urinary bladder in highly exposed workers in the production of dinitrotoluenes: a case report. *Int Arch Occup Environ Health* 78, 677-680 (2005)

125. P. Gustavsson, A. Gustavsson, C. Hogstedt: Excess of cancer in Swedish chimney sweeps. *Br J Ind Med* 45, 777-781 (1988)

126. B.A. Evanoff, P. Gustavsson, C. Hogstedt: Mortality and incidence of cancer in a cohort of Swedish chimney sweeps: an extended follow up study. *Br J Ind Med* 50, 450-459 (1993)

127. C. Jansson, M. Alderling, C. Hogstedt, P. Gustavsson: Mortality among Swedish chimney sweeps (1952-2006): an extended cohort study. Occup Environ Med 2011 Jun 24. [Epub ahead of print]

128. R. Wrbitzky, B. Beyer, H. Thoma, B. Flatau, M. Hennig, A. Weber, J. Angerer, G. Lehnert: Internal exposure to polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans (PCDDs/PCDFs) of Bavarian chimney sweeps. *Arch Environ Contam Toxicol* 40, 136-140 (2001)

129. K. Golka, W. Weistenhofer: Fire fighters, combustion products, and urothelial cancer. *J Toxicol Environ Health B Crit Rev* 11, 32-44 (2008)

130. L. Manju, P.S. George, A. Mathew: Urinary bladder cancer risk among motor vehicle drivers: a meta-analysis of the evidence, 1977-2008. *Asian Pac J Cancer Prev* 10, 287-294 (2009)

131. A.V. Baena, M.F. Allam, C. Diaz-Molina, A.S. Del Castillo, A.G. Abdel-Rahman, R.F. Navajas: Urinary bladder cancer and the petroleum industry: a quantitative review. *Eur J Cancer Prev* 15, 493-497 (2006)

132. J. Zumbe, K. Golka, W. Schops, M. Zellner: Berufsbedingte Urothelkarzinome UROTOP 17, 2. uberarbeitete Auflage medac (2008)

133. M. Gago-Dominguez, J.E. Castelao, J.M. Yuan, M.C. Yu, R.K. Ross: Use of permanent hair dyes and bladder-cancer risk. *Int J Cancer* 91, 575-579 (2001)

134. M. Gago-Dominguez, D.A. Bell, M.A. Watson, J.M. Yuan, J.E. Castelao, D.W. Hein, K.K. Chan, G.A. Coetzee, R.K. Ross, M.C. Yu: Permanent hair dyes and bladder cancer: risk modification by cytochrome P450 1A2 and N-acetyltransferases 1 and 2. *Carcinogenesis* 24, 483-489 (2003)

135. S. Khurana, M. L. Dubey, N. Malla: Association of parasitic infections and cancers. *Indian J Med Microbiol* 23, 74-79 (2005)

136. R. Bedwani, E. Renganathan, F. El Kwhsky, C. Braga, H.H. Abu Seif, T. Abul Azm, S. Franceschi, P. Boffetta, C. La Vecchia: Schistosomiasis and the risk of bladder cancer in Alexandria, Egypt. *Br J Cancer* 77, 1186-1189 (1998)

Abbreviations: PCDD polychlorinated dibenzodioxins; PCDF polychlorinated dibenzofurans; IARC International Agency for Research on Cancer; TNM tumor node metastasis; PAH polycyclic aromatic hydrocarbons; USD US dollars; BCG Bacillus Calmette-Guerin

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