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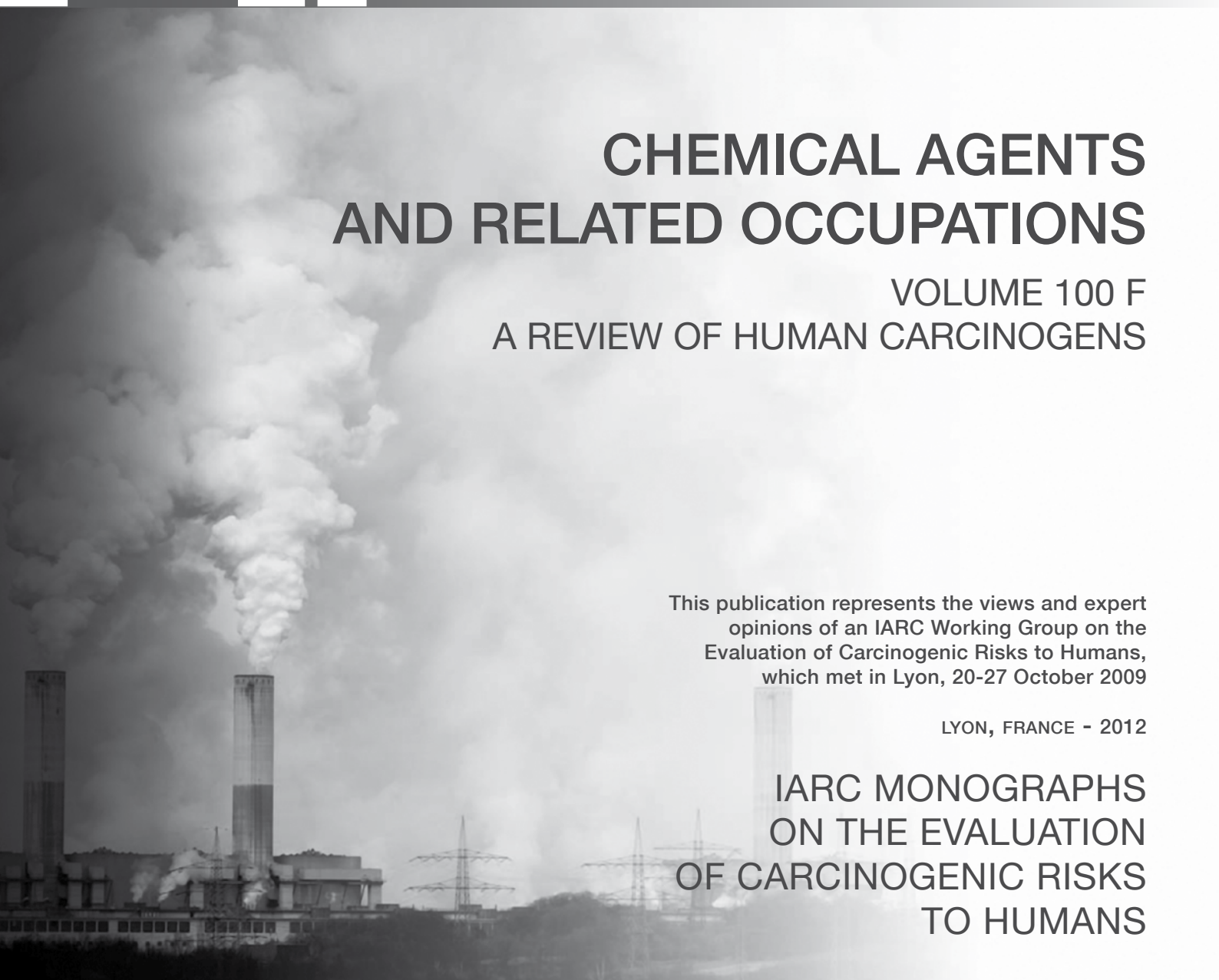

CHEMICAL AGENTS AND RELATED OCCUPATIONS

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A REVIEW OF HUMAN CARCINOGENS

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IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer
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OCCUPATIONAL EXPOSURES DURING COAL-TAR DISTILLATION

Occupational exposures during coal-tar distillation were considered by a previous Working Group in 2005 (IARC, 2010). Since that time new data have become available, which have been incorporated in this *Monograph,* and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Manufacturing process

Coal tar is obtained by cooling the gas that is formed during the destructive distillation of coal to approximately ambient temperature. It is a black, viscous liquid composed primarily of a complex mixture of condensed-ring aromatic hydrocarbons. It may contain phenolic compounds, aromatic nitrogen bases and their alkyl derivatives, and paraffinic and olefinic hydrocarbons. Coal-tar pitch is the residue from the distillation of coal tar (Betts, 1997).

The largest source of tar and pitch is the pyrolysis or carbonization of coal. Until the end of the Second World War, coal tar was the main source of benzene, toluene, xylenes, phenol, cresols and cresylic acids, pyridine and methylpyridines, naphthalene, anthracene, creosote, tar paints, road tars and pitch binders (Betts, 1997). However, by the 1990s, over 90% of the world production of these aromatic chemicals was derived from the petrochemical industry, and coal tar became chiefly a source of anti-corrosion coatings, wood preservatives, feed-stocks for the manufacture of carbon black and binders for electrodes (Betts, 1997).

Coal-tar distillation products comprise essentially the distillate (primarily a complex mixture of mono- and polycyclic aromatic hydrocarbons) and the residue from the distillation (pitch) (Betts, 1997).

The part of coke-oven tar that is normally distillable at atmospheric pressure boils at up to ~400 °C and contains principally aromatic hydrocarbons. These include (in order of the distillation fraction): benzene, toluene and the xylene isomers, tri- and tetra-methylbenzenes, indene, hydrindene (indane), and coumarone; polar compounds, including tar acids (phenol and cresols) and tar bases (pyridine, picolines (methylpyridines) and lutidines (dimethylpyridines)); naphthalene, contaminated with small but significant amounts of thionaphthene, indene and other compounds; methylnaphthalene isomers; biphenyl, acenaphthene and fluorene; anthracene and phenanthrene; pyrene and fluoranthene (Betts, 1997).

Much less is known about the composition of pitch, the residue from coal-tar distillation. Studies of coke-oven pitch indicate that it contains: four-membered aromatic hydrocarbon

Table 1.1 Concentrations of PAHs in the air and urine of workers in coal-tar distillation

Reference Country Year of study	Job/task	No. of subjects	No. of samples	No. of smokers	PAH	Air (µg/m³)		Urinary 1-hydroxypyrene (µmol/mol creatinine)	
						Mean	Range	Mean	Range
van de Ven & Nossent (1984) the Netherlands NR	Coal-tar distillation Operators, cleaners, maintenance	NR	49	NR	Sum of 11 PAHs	31	< 1–277		
Jongeneelen *et al.* (1986) the Netherlands NR	Coal-tar distillation		*Air; urine*		Sum of 11 PAHs; pyrene 1-Hydroxypyrene				
	Operator pitch unit	1	8; 2	0		26; 8.5	< 2–280;	3.7	NR
	Operator batch distillery	1	6; 2	1		14; 5.1	< 2–96	11.8	NR
	Operator pump station	1	5; 4	0		4.7; 1.4		4.0	NR
	Cleaner	1	4; 4	1		16; 5.2		4.6	NR
Price *et al.* (2000) United Kingdom 1998	Tar distillation								
	Low-temperature	8	8	1	Total 19 PAHs	12.17	3.99–38.59		
					HSE 11[a]	0.008	< 0.004–0.008		
					Benzo[*a*]pyrene	ND	ND		
					Pyrene	0.037	0.013–0.068		
					1-Hydroxypyrene			0.36	0.21–1.05
	High-temperature	12	12	4	Total 19 PAHs	279.04	51.9–1130.5		
					HSE 11[a]	0.95	0.15–4.87		
					Benzo[*a*]pyrene	0.283	0.019–0.642		
					Pyrene	1.24	0.14–6.73		
					1-Hydroxypyrene			2.60	0.78–5.69
Preuss *et al.* (2003) Germany 1999–2001	Tar distillation	18	NR	NR		*Median*	*90%*	*Median*	*90%*
					Sum of 16 PAHs	63.62	455.17	0.78	2.28
					1-Hydroxypyrene			3.65	12.36
					Sum of hydroxy-phenanthrene				

[a] Benz[*a*]anthracene, chrysene, benzo[*b*]fluoranthene, benzo[*j*]fluoranthene, benzo[*a*]pyrene, benzo[*ghi*]perylene, indeno[1,2,3-*cd*]pyrene, dibenzo[*a,h*]anthracene, anthanthrene, cyclopenta[*cd*]pyrene

ND, not detected; NR, not reported; PAHs, polycyclic aromatic hydrocarbons

Conversions used for 1-hydroxypyrene: 1 µmol/mol creatinine = 1.93 µg/g creatinine = 0.013 µmol/L = 2.84 µg/L = 2.84 ng/mL

ring systems (e.g. chrysene, fluoranthene, pyrene, triphenylene, naphthacene and benzanthracene); five-membered ring systems (picene, benzo[*a*]pyrene and benzo[*e*]pyrene, benzofluoranthenes and perylene); six-membered ring systems (dibenzopyrenes, dibenzofluoranthenes and benzoperylenes); and seven-ring systems (coronene). Other aromatic chemicals present in pitch include methyl- and polymethyl-derivatives, mono- and polyhydroxy-derivatives, and heterocyclic compounds (Betts, 1997).

For a more detailed description of the coal-tar distillation process, see the previous *IARC Monograph* (IARC, 2010).

1.2 Occupational exposure

Concentrations of PAHs in the ambient air and in urine of workers in coal-tar distillation have been measured in several studies. The results are summarized in Table 1.1. The levels of PAH exposures overall were similar in installations that used the high-temperature process and much lower in the low-temperature distillation facility. A study from Germany (Preuss *et al.*, 2003) showed high air concentrations of total PAHs as well as urinary 1-hydroxypyrene levels.

2. Cancer in Humans

A previous Working Group (IARC, 2010) concluded that there was *sufficient evidence* in humans for the carcinogenicity of occupational exposures during coal-tar distillation. Two large surveillance programmes provided evidence of an increased risk for skin cancer among coal-tar distillers. Notifications of skin cancer in England during 1911–38 were analysed in relation to occupation and more than 700 skin cancers attributed to exposure to coal tar among coal-tar distillers had been recorded; crude mortality rates of scrotal cancer were very high among coal-tar distillers (Henry, 1946). Occupational health surveillance in a German coal-tar distillation plant identified 606 individuals with skin lesions during 1946–96, a third of whom had also malignant skin tumours (squamous-cell and basal-cell carcinoma); 20 cases of scrotal cancer (squamous-cell) were observed (Letzel & Drexler, 1998). No indication of an increased risk for skin cancer was found in more recent cohort-mortality studies, but mortality studies are not sufficiently sensitive to identify potential risks for skin cancer. The findings for other cancer sites were inconsistent. A modest, non-significant increase in mortality was reported for lung cancer in one British and one Dutch study (Maclaren & Hurley, 1987; Swaen & Slangen, 1997), and a significant excess in the incidence of buccal cavity and pharyngeal cancers was reported in a French study (Moulin *et al.*, 1988).

Since the previous evaluation (IARC, 2010) there have been no further relevant studies of cancer risk associated with occupational exposures during coal-tar distillation.

3. Cancer in Experimental Animals

Three high-temperature tars – one undiluted and two as benzene extracts – produced skin tumours, including carcinomas, when applied to the skin of mice. Each one of five blast-furnace tars and two extracts of blast-furnace tars produced skin tumours, including carcinomas, after topical application to mice (IARC, 1985). Likewise, each one of five pharmaceutical coal-tar preparations caused skin tumours, including carcinomas, when applied to the skin of mice (IARC, 1985).

Two unspecified coal tars caused skin tumours, including carcinomas, after application to the skin of mice. Lung tumours but not skin tumours were produced in rats after application of coal tar to the skin. In one study, an

unspecified coal tar produced tumours when applied to the ears of rabbits (IARC, 1985).

No data were available to the Working Group on the carcinogenicity of distillation fractions of low-temperature tars or of products derived from these tars (IARC, 1985).

In addition, several individual polynuclear aromatic compounds for which there is *sufficient evidence* of carcinogenicity in experimental animals have been measured at high concentrations in air samples taken from certain areas in coal-tar distillation plants (IARC, 2010).

4. Other Relevant Data

4.1 Mechanistic considerations relevant to the carcinogenic hazards of exposures during coal-tar distillation

4.1.1 Experimental systems

In previous *IARC Monographs* (IARC, 1985, 1987, 2010) coal-tar pitch and roofing-tar emissions were found to be mutagenic in *Salmonella typhimurium* (in the presence of an exogenous metabolic activation system) and in two mammalian cell systems (in the presence and absence of an exogenous metabolic activation system). Coal-tar pitch and roofing-tar emissions induced sister chromatid exchange in Chinese hamster ovary cells and enhanced viral transformation in Syrian hamster embryo cells (both in the absence and presence of an exogenous metabolic activation system). Samples of therapeutic coal-tars, extracts of coal-tar shampoos, an industrial coal-tar-pitch and vapours escaping from a coal-tar sample at 37 °C were all mutagenic in *Salmonella typhimurium* in the presence of an exogenous metabolic activation system.

Coal tar applied topically to the skin of male Parkes mice produced a complex pattern of DNA adducts in skin and lung tissues when analysed by means of ^{32}P-postlabelling (Schoket *et al.*, 1988), with one adduct spot tentatively identified as benzo[*ghi*]perylene (Hughes *et al.*, 1993).

Benzo[*ghi*]perylene was shown to be photomutagenic in *Salmonella typhimurium* strains. It induced DNA strand-breaks (comet assay) in V79 Chinese hamster lung fibroblasts with photo-activation (Yan *et al.*, 2004; Platt & Grupe, 2005; Platt *et al.*, 2008a; IARC, 2010). The major metabolic intermediate of benzo[*ghi*]perylene is the K-region oxide, 3,4-epoxy-3,4-dihydrobenzo[*ghi*]perylene (Platt *et al.*, 2008b).

Male B6C3F1 mice fed a diet containing coal tar from manufactured gas plant residue produced a complex pattern of aromatic adducts in DNA of the liver, lung, and fore-stomach, which increased with dose and time of treatment; one of the adducts was identified as the *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide-deoxyguanosine-adduct (Culp & Beland, 1994; Culp *et al.*, 2000). In a similarly designed feeding study, a complex pattern of aromatic DNA adducts was produced in the lung, fore-stomach, and spleen tissues of mice; it was demonstrated that the benzo[*a*]pyrene content alone in the coal tar could not account for the aromatic DNA-adduct levels (Weyand *et al.*, 1991). In the lung of female A/J mice fed a diet containing coal tar from manufactured gas plant residue, three major aromatic DNA adducts were identified as being derived from benzo[*b*]fluoranthene, benzo[*a*]pyrene, and *7H*-benzo[*c*]fluorene (Weyand & Wu, 1995; Koganti *et al.*, 2000). The *7H*-benzo[*c*]fluorene-DNA adduct was also observed in mice who received topical application of manufactured gas plant residue (Cizmas *et al.*, 2004); the structure of this adduct is unknown, although a diol epoxide structure has been proposed (Wang *et al.*, 2002).

In the previous *IARC Monograph* (IARC, 2010) benzo[*b*]fluoranthene was found to be both genotoxic and carcinogenic in experimental studies. *7H*-benzo[*c*]fluorene gave inconclusive results when tested for mutagenicity in *Salmonella*

typhimurium strains TA98 and TA100 in the presence of rat liver S9 (IARC, 1983), but it was found to be carcinogenic to mice (IARC, 2010).

Coal tar applied topically to *lambda-lacZ* transgenic mice (MutaMouse®) strongly increased the mutation frequency in epidermal cells. Isolated epidermal cells from C3H/Tif/hr hairless mice that had been given coal tar had higher levels of DNA strand-breaks (as analysed in the comet assay) (Thein *et al.*, 2000). In female B6C3F1 mice fed diets containing coal tar, cell proliferation was increased in the small intestine. *K-ras*, *H-ras*, and *p53* mutations were observed in the coal tar-induced tumours, the most abundant being *K-ras* mutations in fore-stomach and lung tumours (Culp *et al.*, 2000).

Chemical analyses of high-temperature coal tars have identified a series of polycyclic aromatic hydrocarbons that are both genotoxic and carcinogenic in experimental studies. Among these compounds are benz[*a*]anthracene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, benzo[*a*]pyrene, dibenz[*a,h*]anthracene, chrysene, and indeno[1,2,3-*cd*]pyrene (IARC, 1983, 1985, 2010). These polycyclic aromatic hydrocarbons may contribute in part to the genotoxic and tumorigenic activities of coal tars.

Both naphthalene and benzene are constituents of coal tars produced by various processes (IARC, 1985). Both chemicals are genotoxic and induce tumours in experimental animals (IARC, 1982, 2002). Benzene is considered to be carcinogenic to humans (IARC, 2002).

4.1.2 Humans

In previous *Monographs* (IARC, 1985, 2010) short-term assays were reviewed to assess the genotoxic effects of coal-tar exposure in humans. Patients treated with coal-tar ointments produced urine that was mutagenic in *Salmonella typhimurium* strains TA98 and YG1024 in the presence of an Aroclor–1254-induced rat-liver metabolic activation system. In the *S. typhimurium* strain YG1024, *GSTM1*-null patients had higher levels of mutagens in their urine than *GSTM1*-positive patients.

DNA-adduct measurements that involved coal-tar workers or patients undergoing coal-tar therapy have focused solely on detection of benzo[*a*]pyrene-7,8-diol-9,10-oxide-DNA adducts. In the skin and white blood cells (monocytes, lymphocytes, and granulocytes) of a group of eczema patients topically treated with coal-tar ointments the presence of aromatic DNA adducts was demonstrated by means of ^{32}P-postlabelling analysis. One of the adducts co-migrated with the benzo[*a*]pyrene-7,8-diol-9,10-oxide-DNA adduct (Godschalk *et al.*, 1998). Analysis of the same adduct by use of an HPLC/ fluorescence method in a group of 26 psoriasis patients showed that the percentage of subjects with adducts did not exceed the 95 percentile control-subject value (Pavanello *et al.*, 1999). The white blood cells of 23 psoriasis patients undergoing clinical coal-tar therapy were examined for the presence of benzo[*a*]pyrene-7,8-diol-9,10-oxide-DNA adducts with an enzyme-linked immunosorbent assay (ELISA). These adducts were detected and the adduct levels decreased with time after treatment, but no relationship could be ascertained between the level of exposure and the number of adducts and no difference in DNA-adduct formation was found between smoking and non-smoking patients (Paleologo *et al.*, 1992). PAH diolepoxide-DNA adducts and *GSTM1* genotype were determined in white blood cells of 57 psoriasis patients and 53 controls by use of ELISA and polymerase chain reaction (PCR), respectively. These DNA adducts were slightly elevated in patients compared with controls. There was no relationship between the presence of the *GSTM1* gene and the number of adducts (Santella *et al.*, 1995). Skin-biopsy samples from 12 psoriasis patients receiving coal-tar ointments contained aromatic DNA adducts, measured by ^{32}P-postlabelling analysis (Schoket *et al.*, 1990). In another ^{32}P-postlabelling study no significant

effects were reported of a similar treatment of psoriasis patients on the levels of benzo[*a*]pyrene-7,8-diol-9,10-oxide-DNA adducts in peripheral blood lymphocytes (Pavanello & Levis, 1994). In a study of 111 Korean painters using coal-tar-based paint, the levels of aromatic DNA adducts measured by ^{32}P-postlabelling analysis were slightly higher compared with 17 on-site control workers (Lee *et al.*, 2003).

In lymphocytes of 49 coal-tar workers a significant increase of chromosomal aberrations, sister chromatid exchange, and satellite associations was observed, compared with values in non-exposed controls (Yadav & Seth, 1998).

Increased levels of p53 peotein were found in skin biopsies of atopic eczema patients treated topically with coal-tar; a correlation was observed between p53 and aromatic DNA-adduct levels measured in the same tissue by ^{32}P-postlabelling analysis (Godschalk *et al.*, 2001).

4.2 Synthesis

In experimental systems, coal tars were mutagenic in bacteria and mammalian cells, and induced sister chromatid exchange and morphological cell transformation in cultured mammalian cells. Coal tar was also mutagenic *in vivo*, in transgenic mice. Mouse-lung tumours induced by coal-tar treatment had mutations in the K-*ras* proto-oncogene.

Epidemiological studies in humans and studies in experimental animals were consistent with respect to coal-tar exposures being carcinogenic to the lung. Coal tars produced lung and skin tumours in mice and rats after exposure by inhalation, lung tumours in rats after dermal treatment, and skin tumours in mice after dermal treatment. Coal tar was a mouse skin-tumour initiator (see Section 3).

Indications on the role of PAH in the mechanism of action of exposure to coal tar are based on the detection of DNA adducts of several PAHs, e.g. benzo[*ghi*]perylene, benzo[*b*]fluoranthene, *7H*-benzo[*c*]fluorene and benzo[*a*]pyrene in *in vitro* studies, with DNA adducts of benzo[*b*]fluoranthene, benzo[*c*]fluorene and benzo[*a*]pyrene being detected in lung tissues of exposed animals. The benzo[*a*]pyrene DNA adduct was identified as an *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide-deoxyguanosine-adduct.

In studies in humans, the urine from patients undergoing coal-tar treatments was mutagenic in bacteria. Peripheral blood lymphocytes of workers occupationally exposed to coal tars had increased chromosomal damage. Measurements of PAH-DNA adducts in human studies are based exclusively on detection of benzo[*a*]pyrene-DNA adducts, in particular *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide-deoxyguanosine.

In conclusion, studies in experimental systems and in surrogate tissues of humans provide strong evidence for a genotoxic/mutagenic mechanism underlying the effects of occupational exposures during coal-tar distillation.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of occupational exposures during coal-tar distillation. Occupational exposures during coal-tar distillation cause cancer of the skin (including, but not limited to, cancer of the scrotum).

There is *sufficient evidence* in experimental animals for the carcinogenicity of coal tars.

Studies in experimental systems and in tissues of humans provide strong evidence for a genotoxic mechanism underlying the effects of occupational exposures during coal-tar distillation in humans. The detection of *anti*-benzo[*a*]pyrene-7,8-diol-9,10-epoxide-DNA adducts in the peripheral blood lymphocytes of exposed humans suggests the participation of benzo[*a*]pyrene in the genotoxic mechanism of this exposure in humans.

Occupational exposures during coal-tar distillation are *carcinogenic to humans (Group 1).*

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