

Review

Skin disease after occupational dermal exposure to coal tar: a review of the scientific literature

Giannis-Aimant Moustafa¹, MD, Eleni Xanthopoulou¹, MD, Elena Riza², MPH, MSc, PhD, and Athena Linos², MD, MPH

¹Faculty of Medicine, National and Kapodistrian University of Athens, Athens, Greece, and ²Department of Hygiene, Epidemiology and Medical Statistics, Medical School, University of Athens, Athens, Greece

Correspondence

Giannis-Aimant Moustafa, MD
75 Hiou Street, 153 43, Agia Paraskevi
(Athens), Attica, Greece
E-mail: giannis.a.moustafa@gmail.com

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Abstract

For about a century, coal tar has been used in industry and has been applied in the therapeutic management of several skin diseases. However, in the last decades the benefits of coal tar exploitation for humans could not outweigh its harmful effects on health. The aim of this study is to present the main adverse effects of coal tar on skin, with the emphasis on occupational exposure. The scientific literature indicates that dermal exposure to coal tar and coal tar pitches can be the cause of phototoxic reactions, irritation and burn, allergic dermatitis, folliculitis, occupational acne, atrophy of the epidermis, and hyperpigmentation. Moreover coal tar has been implicated in tumorigenesis, a relationship shown in numerous studies but not confirmed yet as the mechanism has not been fully clarified. A common finding in most studies is that exposure over a long period is the main risk factor for malignancy development, even in low exposure levels. Additional prospective, well-designed studies need to be performed to confirm the validity of the carcinogenic, mutagenic, and cytotoxic potential of coal tar on skin.

Introduction**Historical overview**

The correlation between skin cancer and occupation dates back to the eighteenth century. The English surgeon Sir Percival Pott of St. Bartholomew's Hospital of London was the first to notice the high incidence of squamous cell carcinoma of the scrotum in chimney sweeps. Soon after the industrial revolution and the subsequent increased exposure to coal tar, von Volkman noted the increased incidence of skin cancer in exposed workers (Berlin, Germany, 1873).

Coal tar definition

Coal tar is among the by-products of the destructive distillation of coal. It is an oily, dark brown-colored liquid. Among the estimated 10,000 components of coal tar, only about 400 have been identified. The composition and properties of coal tar depend on the type of coal distilling, mainly though on the temperature of the distillation, and therefore high-temperature tars (1000–1300 °C) have higher levels of polycyclic aromatic hydrocarbons (PAHs), coal tar's primary component, than those at low temperature (400–700 °C).^{1,2}

Coal tar should not be confused with asphalt/bitumen, which is a semisolid, dark material, either found as a natural deposit or produced as a residue of petroleum

distillation. Similarly to coal tar, bitumen also contains PAHs but in far less quantities.

Use of coal tar and related hazards

Coal tar has anti-inflammatory, antimicrobial, antipruritic, and cytostatic effects. Thus, for many decades it has been used as a therapeutic agent in skin diseases, such as psoriasis, eczema, dermatitis, etc. While the general population comes into contact with coal tar through its therapeutic application or the environmental contamination, occupational exposure is much higher. Coal tar is currently used in many industries, particularly in manufacturing and primary production. Therefore, workers in aluminum production, steel and iron foundries, tar refineries, road paving, roof insulation, pavement sealcoat, and wood surfaces painting^{3–6} experience high exposure to coal tar and its components. The exposure is mainly through inhalation and dermal contact.² Coal tar's main components, PAHs, such as benzo[a]pyrene (BaP), benzo[a]anthracene, and dibenz[a,b]anthracene, consist of cytotoxic, oncogenic, and mutagenic agents.¹ Moreover, additional harmful effects on skin have been attributed to coal tar.

Despite the fact that many investigators have studied the effect of coal tar exposure to the skin, a structured presentation of its adverse effects on human health is lacking. This review aims to provide a concise report on

the adverse effects of coal tar on skin, which are due to occupational exposure in various working settings.

Materials and Methods

We performed an exhaustive electronic search in PubMed, ScienceDirect, and several medical journals published during the period from 1995 to 2012. The main keywords used were “coal tar”, “polycyclic aromatic hydrocarbons”, “skin”, “dermal”, “occupational”, “workers”, “cancer”, “malignant”, and combinations. We focused mainly on the more recent articles, the majority dating from 2004 to 2012, selected according to the following criteria: published in the English language and involving coal tar occupational exposure, aiming at covering a variety of occupational environments. Additional sources for epidemiological and contemporary legislative data were the following:

<http://www.fda.gov/> (U.S. Food and Drug Administration)
<http://www.iarc.fr/> (International Agency for Research on Cancer)
<http://www.cancer.gov/> (National Cancer Institute)
<http://eur-lex.europa.eu/JOIndex.do?ihmlang=en> (Official Journal of the European Union)
<http://www.pca.state.mn.us/> (Minnesota Pollution Control Agency)
<http://www.hse.gov.uk/index.htm> (Health and Safety Executive)
<http://www.asphaltinstitute.org/> (Asphalt Institute)
<http://echa.europa.eu/> (European Chemicals Agency)
<http://ec.europa.eu/social/main.jsp?catId=148&langId=en&intPageId=684> (The Scientific Committee on Occupational Exposure Limits).

The electronic search in PubMed, ScienceDirect, and Google Scholar yielded 234 articles based on the applied key words. After reviewing those articles' abstracts, 173 studies were excluded, as they did not precisely match thematically with the concept of our work. In the 61 remaining articles, we checked the compatibility with our review by the abstract, and we further cross-checked all references in each article. Another study was added to our pool by this method. Owing to important information, we also decided to include two articles in Italian and one in German. We retrieved the full text of the 62 articles, and we rejected 16 because the full text did not offer information that contributed to the scopes of our review as they mostly referred to animal studies with results having little relevance to humans. This procedure led to the inclusion of 46 records for our paper consisting of 12 review articles and 34 studies. In addition, we included six legislative, political, and epidemiologic references retrieved after searching databases of major research institutes (National Cancer Institute; National Institutes of Health; NCI; International Agency for Research on Cancer, IARC). In total, we based this review on 52 full text records contributing

information relevant to the topic of dermal occupational exposure to coal tar.

It must be noted that despite our thorough search that spanned over quite a long period of time (15 years), the majority of work relevant to the occupational exposure to coal tar was published after 2004. We critically appraised all records reviewed and identified some methodological weaknesses, which resulted in interpretation flaws; however, these did not substantially alter the conclusions of the studies we finally included.

A schematic presentation of the record selection flow is outlined in Figure 1.

Elaborating on the study characteristics, we included six background and legislation documents, 20 non-PICOS documents (12 reviews, two reports, three case reports, and two laboratory studies, and one animal study) and 26 PICOS documents (17 cohort and nine case-control studies) involving a great variety of populations, interventions, comparison groups, lengths of follow-up, and outcomes (Table 1).

Results

Fifty-two records consisting of field study results, reviews, and research institute publications were used in this review. As already mentioned, the number of published studies in the English language focusing on the topic of occupational dermal exposure to coal tar is moderate.

Critical appraisal of the reviewed publications

A critical point is the fact that some studies use ambiguous criteria for confirming occupational exposure and rely on the results from other studies to confirm the magnitude of work-related cancers. This is a common problem in occupational epidemiology, as it is often difficult to ascertain occupational exposure and separate it from general exposure to several risk factors, particularly in cases such as skin cancer where there is inevitable exposure to many other factors from the general environment.

The low representation of women in the studies included is a weak point and a general remark in occupational studies in areas such as coal tar production. In our review, which can be explained by the fact that probably the number of women employed in jobs with high exposure to coal tar is relatively low, it is important to bear in mind that the reported study results may be applied to women with caution.

Few studies reported possible loss of data due to the long follow-up period of the study, but this loss is estimated to have resulted in an underestimation of the reported positive association of occupational coal tar exposure to skin cancer.

A problem noted in one paper⁷ was the fact that it did not directly refer to the correlation of exposure to PAHs

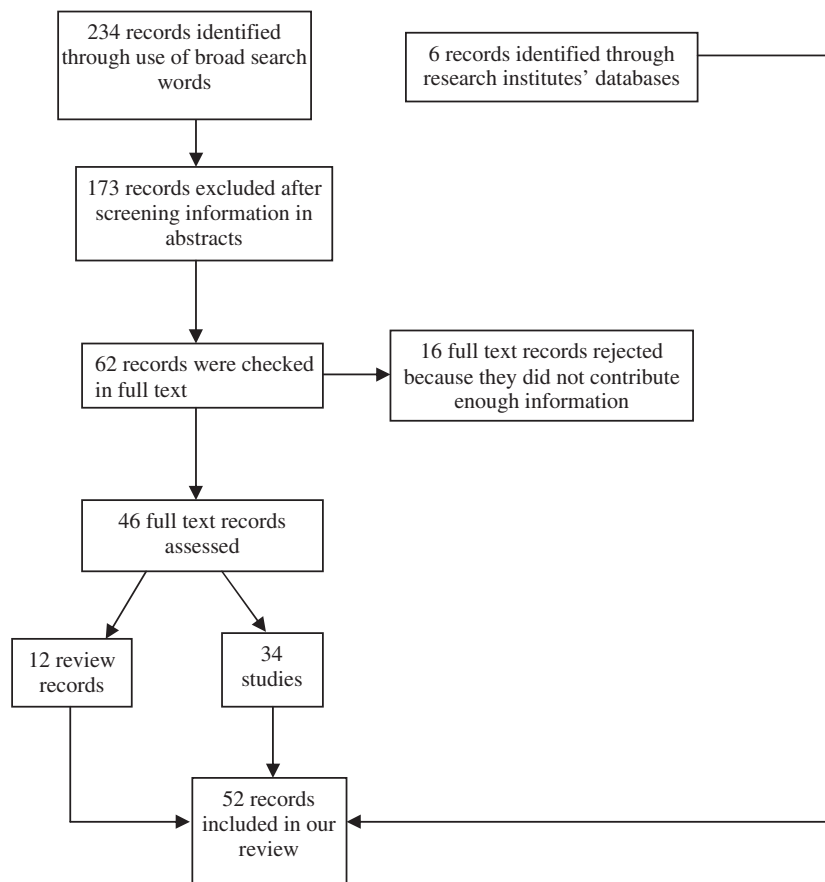


Figure 1 Flow of record selection for the review

solely with skin cancer but with other cancer sites including skin cancer that comprised 61% of the reported cancer sites. This study was used in our review to discuss the carcinogenicity of coal tar in general and not specifically the carcinogenicity on the skin.

Some studies report, particularly those relying on cancer registry data, that few potential pathogenic factors such as skin type of the workers, may have not been taken into account. This is an issue in all studies using registry data, but it does not introduce systematic error to bias the reported associations.

Finally, some pure methodological issues such as lack of comparable control group, small sample size, and skin cancer diagnostic definitions were identified in few studies, but the statistical analyses have indicated that the reported associations are not greatly affected.

Cancer

Cancer is the most extensively studied adverse effect of coal tar on skin. Both coal tar as a mixture of PAHs and some PAHs themselves, such as BaP, are known carcinogens as recognized by the IARC, (Table 2) which classifies these substances as group 1 carcinogens (carcinogenic to

humans). The mechanism after dermal contact includes penetration of PAHs into the cells of the epidermis, absorption, and metabolic activation into benzo[a]pyrene diol-epoxides (BPDE), i.e., bioactive molecules, by the enzymes of the superfamily of cytochrome P-450^{2,8} in the liver, skin, and blood. These molecules then react with the DNA macromolecule, forming the BPDE DNA-adducts, which seem to be associated with carcinogenesis.

Cancer in humans

Whether coal tar is able to cause cancer in humans or not has preoccupied many researchers of the twentieth century. Inhalation, skin contact, and ingestion of therapeutic agents (for psoriasis, eczema, dandruff, seborrheic dermatitis, etc.) or environmental contamination are the main ways that the general population comes in contact with coal tar; however, those who are the most affected by the carcinogenic properties of coal tar are the occupationally exposed individuals,¹ and consequently many epidemiological studies have been conducted in the workplace, to clarify the issue, along with many case reports.

A French study⁷ estimating the proportions of cancer in workers exposed to carcinogens came to the conclusion

Table 1 Study characteristics: PICOS

Population	Intervention	Comparison	Outcome	Study design duration (ref. no.)
Asphalt roofing workers	Dermal patch sampling	Roof-tear-off workers	PAH absorption determinants	Cohort 90 d ²
Newly diagnosed cancer patients	Occupational history	–	Estimates of work-related cancers	Cohort 3 years ⁸
Male tar refinery workers	Questionnaire, occupational records, dermatological reports	General population	Determination of histological findings	Cohort 56 years ¹⁰
Male tar refinery workers	Questionnaire, historical dermatological records	General population	Determination of histological findings	Cohort 50 years ¹
Male coke oven workers	Urinary 1-OHP questionnaire occupational history	Male workers in non-ferrous metals company	1-OHP levels comparison	Case-control 7 months ¹⁶
Male coal-handling workers	Pre- and post-urinary 1-OHP before and after treatment	Levels pre- and post-1-OHP	National Institute for Occupational Safety and Health (NIOSH) for hazard evaluation	Cohort ¹⁸
Coal tar-treated patients	Urinary 1-OHP before and after treatment	Levels before and after treatment	PAH urinary secretion	Cohort ¹⁷
Workers in 217 asphalt companies	Questionnaire, expert judge analysis	–	Data matrix for carcinogen in asphalt workers	Cohort ²⁰
Roofing workers	Semistructured interviews	–	Confounding carcinogens in workers	Cohort 55 years ²¹
Patients with psoriasis and eczema treated with tar	Statistical analysis	Patients treated with corticosteroids	Increased cancer risks	Cohort 6 months ³⁰
Female mice	Application of chemicals on epidermis	Groups of mice	Metabolism of PAH-DNA binding	Cohort 25 weeks ³⁸
Roofers and road pavers	Questionnaire, dermatological symptoms	–	Evaluate health risks	Cohort ⁴²
Patients with chemical burns	Recording of detailed data	–	Explore epidemiology and mechanisms of burns	Cohort 5 years ⁴³
Patients with psoriatic lesions	Cream 3% coal tar	IgE response before and after application	Dermal exposure to PAHs	Cohort 8 d ⁴⁴
Patients with allergic dermatitis	Retrospective review of medical records	–	Occupational allergens	Cohort 8 d
Healthy adult males	Topical applications of coal tar	–	Atrophogenic effects of coal tar on skin	Cohort 40 d ⁴⁸
Patients with chronic psoriasis	Coal tar ointment	Healthy volunteers	Levels of 1-OHP pre and post application	Case-control 96 h ⁹
Asphalt workers	Urinary sampling of 1-OHP	General population, workers in other areas	PAH exposure levels	Case-control 1 year ¹³
Nursing staff	Coal tar ointments	Coal tar ointment application on skin using vinyl gloves	Differences in 1-OHP levels	Cohort ¹⁴
Mastic asphalt workers	Measurement of 1-OHP and Hydroxyphenanthrene (OHPH)	Non-exposed construction workers	1-OHP levels as biological monitoring	Cohort ¹⁵
Patients with squamous cell carcinoma of the skin	Statistical analysis	Healthy individuals	Risk factors for squamous cell carcinoma	Case-control 4 years ²⁴
Patients with basal cell carcinoma of the skin	Statistical analysis	Healthy individuals	Risk factors for basal cell carcinoma	Case-control ²⁵
Asian coal tar workers	Genotyping and statistical analysis	Non-exposed Asian workers	Chromosomal aberrations	Case-control ³⁴
Indian coal tar workers exposed to PAHs	Genomic DNA and genotyping	Indian healthy non-exposed workers	Genotype assessment	Case-control ³⁵
Patients with a topic dermatitis	Treatment with coal tar	Patients with atopic dermatitis with MPO-463GG polymorphism	Determine BPDE-DNA adduct levels in skin	Case-control ³⁷
Coal tar workers	DNA damage analysis genotyping	Healthy non-exposed volunteers	Associations of genetic variants	Case-control ³⁹

BPDE, benzo[*a*]pyrene diol-epoxides; MPO, myeloperoxidase; 1-OHP, 1-hydroxypyrene; PAH, polycyclic aromatic hydrocarbon.

Table 2 Coal tar and its components in International Agency for Research on Cancer classification

Agent	CAS no.	Group	Cancer sites
Benzene	000071-43-2	1	Lung, skin, bladder
Benzo[a]pyrene	000050-32-8	1	Lung, skin, bladder
Coal tar	008007-45-2 <i>plus</i>	1	Lung, skin, bladder
Coal tar pitch	065996-93-2	1	Lung, skin, bladder

Source: International Agency for Research on Cancer.

that PAHs (contained in coal tar) constitute the most frequent cause of carcinogenesis in the workplace together with asbestos (Table 3), while two-thirds of the work-related cancers occur in the sectors of construction, fabricated metal products, and manufacturing machinery.

The advantage of this research is the satisfying approximation (3.18%) of the global estimated proportion of cancers attributable to work, according to Doll and Peto, who calculated the rate at about 2–4%.⁵

A similar, more targeted study by Voelter-Mahlknecht *et al.*⁹ studied prospectively (from 1946 to 2002) 618 male workers in a tar refinery with normal age distribution and ranging 78 years (from 1882 to 1960, median 1922, mean 1920). After long-term exposure (large latency period up to manifestation, Table 4) 393 squamous cell carcinomas, 298 basal cell carcinomas, 194 keratoacanthomas, and six melanomas were diagnosed. Compared to the general population, the study findings show that keratoacanthomas are diagnosed at younger ages in the occupational group (median age 55 years as opposed to 64 years in the general population) pointing towards a possible occupational adverse effect. Regarding other non-melanoma skin cancers, differences were noted in the areas affected between the occupational group (the less sun-exposed forearms) and the general population (the back of the hands), also indicating tar exposure as a causal factor.

Table 3 Frequency of carcinogenic agents in occupation

Substance	No. of carcinogen exposures <i>n</i> = 68 ^a (%)
Asbestos	43 ^b (63)
PAHs	17 ^b (25)
Iron oxides	4 (6)
Wood	3 (4.5)
Benzene	1 (1.5)

PAH, polycyclic aromatic hydrocarbon.

Adapted from Deschamps *et al.*⁷

^a68 is the number of cancers considered to be related to occupation from the number of people examined.

^bFour cases with double exposure.

It is estimated that in the general population the lifetime risk for developing melanoma is 2.1% among men and women,¹⁰ for squamous cell carcinomas 9–14% among men, 4–9% among women,¹¹ and for basal cell carcinomas 33–39% among men and 23–28% among women.¹¹

Some workers were diagnosed with multiple malignancies on their skin, a fact in which the occupational nature of the disease may have played a role. Another feature of possible occupational disease effect observed was the recurrence of the lesions. Moreover, the divergence in the localization and distribution of the lesions noted when compared to the general population (for example, more cases detected in the upper lip than the lower lip and in the less sun-exposed forearm compared to the back of the hand) points to occupational exposure. Remarkable is the discrepancy between the number of tumors developed in the nostrils (which are not exposed to the sun) and those on the part of the nose that is exposed to the sun, which is probably caused by the inhalation of tar. The occupational origin is also supported by the high incidence of the lesions in that subset of the population compared to the general population. However, the majority of the lesions appear to have been developed more intensely in parts of the body exposed to the sun, and thus the additive causal effect of solar radiation in their pathogenesis should be considered. For the full chart in Figure 2, see Voelter-Mahlknecht *et al.* (Fig. 2).¹⁰

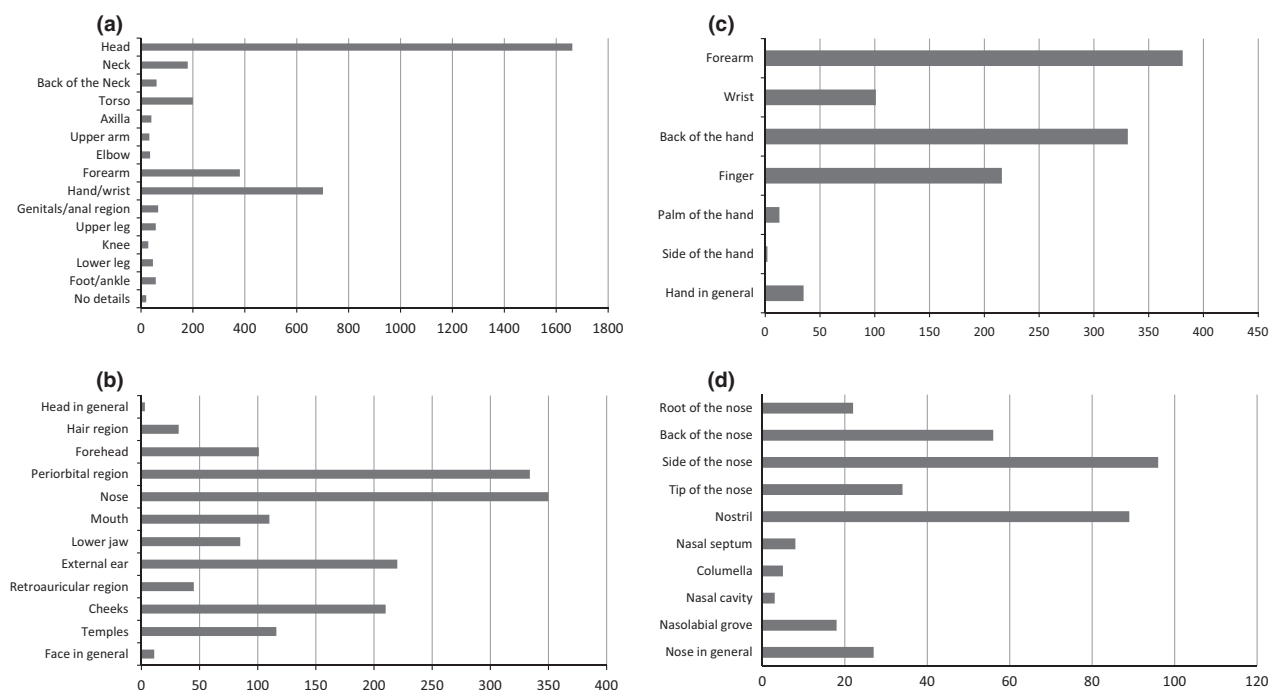
The same research team¹² presented similar results in an earlier publication verified by the above analysis.

Other occupations affected by the adverse effects of tar and its components are employees in coke production, coal gasification, aluminum, iron and steel production, coke oven industry, asphalt workers, railway workers, miners, roofers, painters, those involved in cosmetics, etc. A handy biomarker to evaluate the exposure of these individuals to PAHs, which are contained in coal tar, is 1-hydroxypyrene (1-OHP) which, excreted in the urine, indicates the relative degree of exposure.^{3,13–18}

It is worth mentioning that, apart from the kind of occupation, there are additional factors that determine the extent of exposure to PAHs. For instance, the exposure is significantly higher in workers exposed to tar and its fractions rather than asphalt, substances that often coexist in the workplace. This fact is due to the greater amount of PAHs contained in tar compared to asphalt, and this becomes obvious in studies in which greater amounts of 1-OHP are found in workers even in the same workplace with others, only because they work in a different location within the factory or have undertaken a different post.^{3,15,16} It has been shown that these workers came in contact with tar in their workplace or during the work they had undertaken. More specifically, in a study in which 73 exposed asphalt workers were

Table 4 Temporal course of squamous cell carcinomas, basal cell carcinomas, and keratoacanthomas within employees of a tar refinery

Time variables (years)	Mean	Min.	1st Quartile	Median	3rd Quartile	Max.
Age at time of first diagnosis of a squamous cell carcinoma	54.9	25	47	55.0	64	79
Latency period between first employment in the tar refinery to first diagnosis of a squamous cell carcinoma	29.1	2	19.0	28.0	39.0	61
Age at time of first diagnosis of a basal cell carcinoma	62.7	35	57.0	63.0	69.8	86
Latency period between first employment in the tar refinery to first diagnosis of a basal cell carcinoma	36	<1	26.0	38.0	45.0	69
Age at time of first diagnosis of a keratoacanthoma	56.3	21	47.8	56.0	64	81
Latency period between first employment in the tar refinery to first diagnosis of a keratoacanthoma	30.2	3	19	29.5	40.3	63

Adapted from Voelter-Mahlknecht *et al.*⁹**Figure 2** Number of skin lesions (squamous cell carcinomas, basal cell carcinomas, keratoacanthomas, precancerous lesions) on the whole body (a), on the head (b), on the hands and forearms (c), on the nose (d). Adapted from Voelter-Mahlknecht *et al.*⁹

compared to 49 non-exposed workers in the construction sector, larger amounts of PAH metabolites were found in seven of the 73, compared to both the control group and the other 66 exposed.¹⁵ Furthermore, a more than 12-fold increase of metabolites was found in those seven workers before and after work, while the increase in the other 66 was only twofold. Upon closer examination, it was found that the seven workers were unwittingly exposed to tar

(co-exposure with asphalt, Fig. 3), which justifies the significantly increased excretion of PAH metabolites (Table 5). The results were statistically significant despite the small sample and even after adjustment for smoking habits and the respiratory function of the participating workers.

A study with a larger sample size reached the same conclusions concerning the importance of the employees'

Table 5 Urinary metabolites of workers with and without exposure to tar or bitumen (median values)

Urine variable	Reference (n = 49)		Exposure to fumes of bitumen			
			Bitumen only (n = 66)		Bitumen and tar (n = 7)	
	Pre-shift	Post-shift	Pre-shift	Post-shift	Pre-shift	Post-shift
Creatinine (g/l)	1.2	1.2	1.3	1.6	1.2	1.8
1-OHP (ng/g creatinine)	175	182	252	455	442*	6605*
OH-phenanthrenes (ng/g creatinine)	948	992	954	1770	1494*	12774*

1-OHP, 1-hydroxypyrene.

*Significant differences.

Adapted from Raulf-Heimsoth *et al.*¹⁵

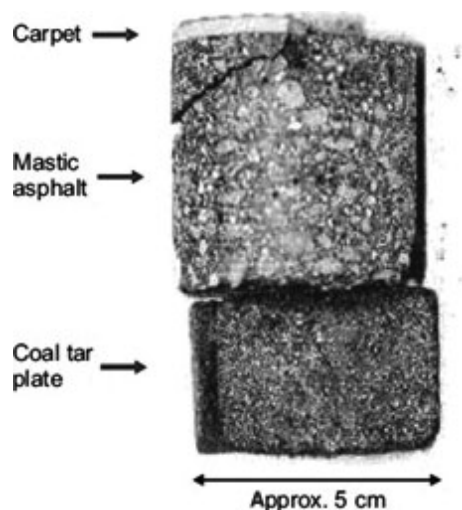


Figure 3 Withdrawal of a drilling core from the ground in the workplace of seven workers, in which a coal tar plaque is seen under the mastic asphalt layer¹⁵

post in the workplace.¹⁶ Furthermore, additional factors, such as smoking habits, age, body mass index, level of education, respirator usage, which seem to be involved in the degree of the exposure, have been taken into account. Alcohol consumption did not appear to be particularly important.

Moreover, roofers seem to be more affected compared to other laborers working with bitumen,¹⁹ and this is justified by the fact that many old asphalt roofs also contain coal tar in large amounts. This technique tends to be reduced or eliminated in some countries (such as Denmark, the Netherlands, and other countries in northern Europe, where it was systematically applied), but the removal of the old roofs to apply the new bitumen eventually has the highest risk for health, and these workers experience high exposures to PAHs.^{3,20} The same is true for some old streets, pavements, and other applications of coal tar.^{21–23}

Yet, the problem becomes more serious when health-care personnel who provide treatment and care are themselves exposed to coal tar, as demonstrated in a notable study, in which nurses who smeared pharmaceutical coal tar on patients were examined.¹⁴ It was shown that those nurses were exposed to coal tar, as their skin was found contaminated with pyrene and BaP, and the 1-OHP excretion in their urine was increased. It was also found that the main source of contamination were the coal tar ointments applied on patients. Thus, a new protocol was introduced, according to which the nurses would use vinyl gloves and special Tyvek® sleeves when applying the ointments, which led to a 97% decrease of skin contamination with pyrene and BaP (Table 6) and a 57% decrease of 1-OHP excretion in urine (Table 7).

Coal tar is currently considered a mixture of substances with mutagenic potential after dermal exposure.^{1,2,4,25} However, even PAH fumes are able to penetrate the epidermis, perhaps even more rapidly, a fact that cannot rule out the health hazards from PAHs in gas form.²⁶ Despite

Table 6 Skin contamination before and after the introduction of the new protocol (median values)

Subgroup	PAH contamination before introduction of skin protection protocol (ng/pad)	PAH contamination after introduction of skin protection protocol (ng/pad)
Same nurses (paired observations, n = 6)		
PYR	349	0.9*
BaP	184	4.6**
Different nurses (unpaired observations, n = 10–12)		
PYR	173	3.7**
BaP	107	3.2**

BaP, benzo[a]pyrene, ND, not detected; PAH, polycyclic aromatic hydrocarbon; PYR, pyrene.

* $P < 0.001$, ** $P < 0.05$.

Adapted from Scheepers *et al.*¹⁴

Table 7 Urinary 1-OHP excretion before and after the establishment of the new protocol (median values)

Subgroup	Before introduction of skin protection protocol	After introduction of skin protection protocol
Paired observations (<i>n</i> = 6)		
Total urinary excretion of 1-OHP (nmol in 24 h)	1.6	0.69*
Unpaired observations (<i>n</i> = 10–12)		
Total urinary excretion of 1-OHP (nmol in 24 h)	1.5	0.64**

1-OHP, 1-hydroxypyrene.

P* < 0.005, *P* < 0.05.Adapted from Scheepers *et al.*¹⁴

the fact that exposure to coal tar can be in various ways and various doses, not every kind of exposure is considered equally dangerous. The majority of research concludes that those at highest risk from the oncogenic properties of coal tar are those who undergo long-term exposure, even in small doses.^{2,12,17} The exposure does not have to be constant, but at least recurrent. Similar are the results of case reports of people who came in to long-term contact with coal tar.^{27–29} Additionally, some studies suggest that patients with psoriasis are at lower risk for malignancy development,^{8,30,31} but this is yet to be confirmed. Another remarkable point is that, even after removal of the employee working with coal tar from the workplace, the risk for cancer and the development of the corresponding lesions remains unaffected.⁹

Cancer on experimental level

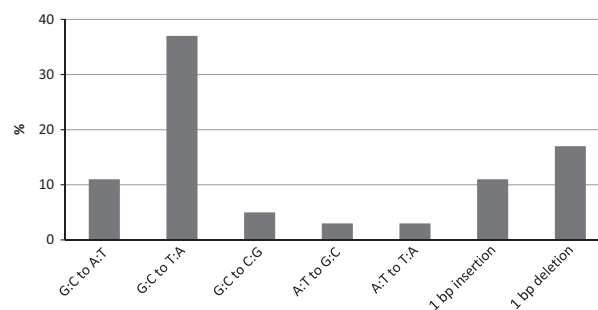
Dermal exposure to coal tar and its fractions caused tumors in mice and rabbits in laboratory studies. Intramuscular injections of an extract coal tar fume condensate in mice also caused sarcomas at the injection site.¹ Other laboratory protocols caused perianal skin cancers in mice,³² while application of tar on the back of guinea pigs increased the thickness of the epidermis.³² PAHs have been linked to the mutation of the tumor suppressor gene p53 in lung cancer, but the mechanisms of tumorigenesis on skin have not been fully elucidated.²³ Vogel *et al.*³³ noticed that after skin contact with coal tar, mice (MutaTM Mice, TNO Institute for Experimental Gerontology, Rijswijk, The Netherlands) showed frequently (about half of the mutations) transversion of G:C pairs to T:A, less frequently G:C to A:T and G:C to C:G, quite frequently insertions and deletions of base pairs, while about half of the mutations were at CpG sites, i.e. frequently methylated positions for suppression of gene expression (Fig. 4).

In recent years, particular attention has been paid to the search of genetic polymorphisms, which may reflect an idiosyncratic susceptibility or, on the other hand, protection and resistance to the genotoxic effects of coal tar. Such polymorphisms are those of glutathione *S*-transferase (GSTM1, GSTT1), where GSTM1(+) and GSTT1(+) genotypes have a protective role compared to the GSTM1 and GSTT1 null genotypes,^{2,8,34–36} and of myeloperoxidase (MPO), where MPO-463AA/AG genotype, which is characterized by reduced MPO activity, also acts in a protective way concerning the development of skin lesions due to coal tar.³⁷ Marston *et al.*³⁸ observed that induction of cytochrome P-450 enzymes (CYP1A1, CYP1B1), which, as mentioned above, are those that convert BaP to bioactive molecules that bind to the DNA and induce the genetic lesions, reduced the number of BPDE DNA-adducts. However, another study showed that coal tar workers with genetic polymorphisms of CYP1A1 m1 and m2, which are associated with enhanced enzymatic activity, seem to be susceptible to genetic damage from PAHs.³⁹ More studies are necessary to describe the exact molecular mechanisms behind coal tar and the latest research data to be interpreted with certainty.

Cancer is the most extensively studied effect of coal tar on skin. The rest of its complications, though not rare at all, are less mentioned in contemporary references, perhaps due to the reduced research interest in them, because of their minor impact on health in most of the times and their effective treatment. Finally, they occur more acutely than cancer.

Photosensitivity

Coal tar has a photosensitizing effect on skin (increased skin reactivity to sunlight or other stressors) expressed in the form of a phototoxic reaction (a type of skin reaction from overexposure to certain wavelengths of light and phototoxic substances). This reaction mainly occurs in the ultraviolet A spectrum and the lowest wavelengths of the visible light.² Its action is accomplished through two

**Figure 4** Types of skin mutations from coal tar in MutaTM mouse. Adapted from Vogel *et al.*³³

independent pathways. The first of the two involves an oxygen-independent reaction with DNA (type I reaction), and the second one involves cellular damage through an oxygen-dependent mechanism (type II reaction).^{32,40} It has been shown that the phototoxic damage is attributed to PAHs.⁴¹ This damage has also been observed in other organisms, such as plants and microorganisms.⁴¹

What is remarkable about phototoxicity is that co-exposure to PAHs and ultraviolet radiation is not uncommon. One of the therapeutic options for psoriasis is the combination of coal tar and ultraviolet radiation (Goeckerman therapy/regimen), a fact that makes reasonable the follow-up of those patients to diagnose possible early complications from photosensitivity. Additionally, workers that are exposed to coal tar are usually exposed to solar radiation as well. Roofers, road-surfacing workers, and several employees in industry constitute such examples. The follow-up of those high-risk groups is therefore necessary to prevent complications of photosensitivity, such as sunburn and cancer.

Skin irritation and burn

Irritation of the exposed skin is a common effect of coal tar and is often observed in patients treated for psoriasis, eczema, and other skin diseases. However, it is very often observed in occupation as well.⁴² The arms, legs, and face seem to be the most commonly affected areas in coal tar operators.^{42,43} In some cases, severe burns can occur, making the case more urgent. In a study from Iran examining 121 separate cases of chemical burns in the East Azerbaijan province in a period of about five years, 60.3% of the burns were due to coal tar, making coal tar the main cause of the chemical burns (Table 8) with 78.5% of the burns occurred in the workplace.

Protection of the workers, such as using special uniforms and avoiding staining of clothes and tools with coal tar, is of utmost importance.

Hypersensitivity

Another side effect of coal tar on skin is the allergic reaction.^{2,31,44,45} It has been shown that PAHs in coal tar increase total IgE after dermal contact.⁴⁴ Additionally, in a retrospective study conducted in a region of Bosnia and Herzegovina, it was found that coal tar was the most frequent cause of allergic dermatitis in metal workers.⁴⁵

Folliculitis

Folliculitis is a very common complication after dermal exposure to coal tar,² particularly when the concentration of the mixture is high in tar, such as in the case of workers, although treated patients very often develop follicular irritation as well. Folliculitis requires medication discontinuation for 3–5 days.

Table 8 Frequency of chemical agents in chemical burns according to a study in Iran

Chemical agent	Frequency <i>n</i> = 121 (%)
Tar	73 (60.3)
Cement	1 (0.8)
Acid	27 (22.3)
Alkali	5 (4.1)
Tyner	3 (2.5)
Unknown	12 (9.9)

Adapted from Maghsoudi and Gabraely.⁴³

Occupational acne

Coal tar is responsible for causing the so-called coal tar acne,⁴⁶ due to obstruction of the sebaceous glands by the mixture and subsequent keratin production, resulting in accumulation of the oily liquid of the glands and formation of black plugs, which are indicative of occupational coal tar acne.

Dermal atrophy

Owing to its cytostatic action, coal tar may cause atrophy of the epidermis.^{47,48} Atrophy is usually preceded by thickening of the epidermis on the contact site, which is characterized by intense proliferation of the epidermal cells.²

Hyperpigmentation

Coal tar can also cause increased skin pigmentation.

Discussion

Nowadays, it is known that dermal exposure to coal tar is associated with certain complications. Some of them are considered indisputable; these are mainly the acute side effects of coal tar, which include photosensitivity, burn, skin irritation, folliculitis, allergic reactions, occupational acne, atrophy of the epidermis, and hyperpigmentation.

As for the long-term consequences, cancer is the most important. Many are the studies that support the tumorigenic potential of coal tar. However, as far as the development of malignancies is concerned, the majority of studies indicate the necessity for chronic exposure,^{2,12,17} which means that not every kind of exposure is equally dangerous. The US Food and Drug Administration has monographed coal tar as Category I OTC drug (safe and effective) for psoriasis, dandruff, and seborrheic dermatitis, and indeed the severe side effects do not appear to affect those patients to the same extent.^{8,30,31} The IARC, however, classifies coal tar and its components as group 1

carcinogens and warns against regular contact. The last decade's campaigns for raising public awareness were fruitful. As a result, many older applications of coal tar have been reduced or eliminated (road surfacing, pavement and roof coating, wood preservation, etc.), while in many countries new laws were introduced, according to which the use of coal tar and its fractions is illegal, contributing in this way to prevention of exposure.^{49,50} Even in industrialized countries, the percentage of malignancies attributed to occupation has decreased notably, mainly due to the strict regulations on known carcinogens.^{2,3} Nevertheless, significant sources of exposure still exist, and prevention of exposure to these sources should be the focus at the federal, administrative, and personal level. First, it is up to the state to impose stricter measures and, in particular, guarantee the implementation of existing laws. Similarly, industry administrations should adopt alternative practices where possible. Finally, individuals themselves should be well informed and avoid hazardous exposures. Coal tar operators should avoid contact as much as possible, keep their clothes and tools clean, change clothing regularly, and be systematically checked for possible complications. The aforementioned suggestions constitute realistic measures that can be implemented. Furthermore, no uniform occupational exposure limits exist in the European Union, and establishment of a European occupational exposure limit should be considered.^{51,52} This would probably have a direct impact on a specific workplace's risk assessment and, consequently, on the measures that should be taken in this workplace for eliminating or minimizing possible health effects on workers. It is worth noting that prevention of the consequences would probably have a positive impact on the cost-benefit scale with fewer hospitalizations and more healthy individuals, a fact that should make governing bodies focus more on preventing the adverse effects of coal tar exposure.

Questions (see answers after references)

- 1 Which of the following individuals is most likely to develop malignant lesions due to coal tar?
 - a A roofer that was recently hired but has high coal tar exposure
 - b A roofer working about 20 years but having controllable (low) coal tar exposure
 - c A psoriatic patient treated with coal tar for about 5 years
 - d A patient with eczema treated with coal tar for about 5 years
- 2 Which of the following consequences is NOT a result of coal tar exposure?
 - a Hypersensitivity
 - b Acne
 - c Atrophy of the epidermis
 - d Hypopigmentation of the skin
- 3 Which skin malignancy is LESS associated with coal tar?
 - a Basal cell carcinoma
 - b Squamous cell carcinoma
 - c Melanoma
 - d Keratoacanthoma
- 4 IARC considers coal tar to be
 - a Probably not carcinogenic to humans
 - b Not classifiable as to its carcinogenicity to humans
 - c Possibly carcinogenic to humans
 - d Carcinogenic to humans
- 5 Coal tar exposure entails
 - a Lower risk for malignancy development compared to bitumen exposure
 - b The same risk for malignancy development with bitumen exposure
 - c Higher risk for malignancy development compared to bitumen exposure
 - d Coal tar and bitumen cannot be compared concerning their carcinogenic potential
- 6 Which of the following circumstances entails the highest risk for skin cancer development in coal tar workers?
 - a Often switching to posts that include exposure only to bitumen
 - b Working with personal protective equipment
 - c Working indoors
 - d Working under the sun
- 7 Nowadays, which task most likely entails the highest risk for cancer development on skin?
 - a The removal of old roads or pavements
 - b The building of new roads or pavements
 - c The combination of the above-mentioned tasks (a and b)
 - d The above mentioned tasks (a and b) entail the same risk
- 8 Which of the following is true?
 - a Coal tar is one of the main causes of occupational cancer and chemical burning
 - b Coal tar is one of the main causes of occupational cancer but not of chemical burning
 - c Coal tar is one of the main causes of occupational chemical burning but not of cancer
 - d Coal tar is not one of the main causes of occupational cancer nor of chemical burning
- 9 Which type of skin mutation was most frequently observed in experimental animals?
 - a Transversion of G:C to T:A pairs
 - b Transversion of G:C to A:T pairs
 - c One base pair deletion
 - d One base pair insertion

10 The use of vinyl gloves in nurses who applied coal tar ointments on a patient's skin decreased skin contamination by

- a 15%
- b 57%
- c 80%
- d 97%

References

- 1 National Toxicology Program. Coal tars and coal-tar pitches. *Rep Carcinog* 2011; 12: 111–113.
- 2 Roelofzen JH, Aben KK, van der Valk PG, et al. Coal tar in dermatology. *J Dermatolog Treat* 2007; 18: 329–334.
- 3 McClean MD, Rinehart RD, Sapkota A, et al. Dermal exposure and urinary 1-hydroxypyrene among asphalt roofing workers. *J Occup Environ Hyg* 2007; 4: 118–126.
- 4 Hugener M, Emmenegger L, Mattrel P. Emissions of tar-containing binders: a laboratory study. *J Environ Sci Health A Tox Hazard Subst Environ Eng* 2007; 42: 241–247.
- 5 Boffetta P. Epidemiology of environmental and occupational cancer. *Oncogene* 2004; 23: 6392–6403.
- 6 Porru S, Assennato G, Bergamaschi E, et al. The toxicology and prevention of the risks of occupational exposure to aromatic polycyclic hydrocarbons. III. The effects: epidemiological evidence, early effects. Individual hypersusceptibility. Health surveillance. *G Ital Med Lav Ergon* 1997; 19: 152–163.
- 7 Deschamps F, Barouh M, Deslee G, et al. Estimates of work-related cancers in workers exposed to carcinogens. *Occup Med (Lond)* 2006; 56: 204–209.
- 8 Roelofzen JH, van der Valk PG, Godschalk R, et al. DNA adducts in skin biopsies and 1-hydroxypyrene in urine of psoriasis patients and healthy volunteers following treatment with coal tar. *Toxicol Lett* 2012; 213: 39–44.
- 9 Voelter-Mahlknecht S, Scheriau R, Zwahr G, et al. Skin tumors among employees of a tar refinery: the current data and their implications. *Int Arch Occup Environ Health* 2007; 80: 485–495.
- 10 National Cancer Institute (2011) SEER Cancer Stat Fact Sheets. [WWW document] <http://seer.cancer.gov/statfacts/html/melan.html> [accessed on 2 December 2014].
- 11 Miller DL, Weinstock MA. Nonmelanoma skin cancer in the United States: incidence. *J Am Acad Dermatol* 1994; 30: 774–778.
- 12 Letzel S, Drexler H. Occupationally related tumors in tar refinery workers. *J Am Acad Dermatol* 1998; 39: 712–720.
- 13 Garattini S, Sarnico M, Benvenuti A, et al. [PAH exposure in asphalt workers]. *Med Lav* 2010; 101: 110–117.
- 14 Scheepers PT, van Houtum J, Anzion RB, et al. The occupational exposure of dermatology nurses to polycyclic aromatic hydrocarbons – evaluating the effectiveness of better skin protection. *Scand J Work Environ Health* 2009; 35: 212–221.
- 15 Raulf-Heimsoth M, Angerer J, Pesch B, et al. Biological monitoring as a useful tool for the detection of a coal-tar contamination in bitumen-exposed workers. *J Toxicol Environ Health A* 2008; 71: 746–750.
- 16 Chen B, Hu Y, Zheng L, et al. Urinary 1-hydroxypyrene concentrations in Chinese coke oven workers relative to job category, respirator usage, and cigarette smoking. *Am J Ind Med* 2007; 50: 657–663.
- 17 Nenoff P, Richter B, Will W, et al. [Longitudinal study of the excretion of 1-hydroxypyrene in urine after external treatment with coal tar]. *Hautarzt* 1997; 48: 240–245.
- 18 Malkin R, Kiefer M, Tolos W. 1-Hydroxypyrene levels in coal-handling workers at a coke oven. *J Occup Environ Med* 1996; 38: 1141–1144.
- 19 Boffetta P, Jourenkova N, Gustavsson P. Cancer risk from occupational and environmental exposure to polycyclic aromatic hydrocarbons. *Cancer Causes Control* 1997; 8: 444–472.
- 20 Burstyn I, Boffetta P, Kauppinen T, et al. Estimating exposures in the asphalt industry for an international epidemiological cohort study of cancer risk. *Am J Ind Med* 2003; 43: 3–17.
- 21 Anttila P, Heikkilä P, Mäkelä M, et al. Retrospective exposure assessment for carcinogenic agents in bitumen waterproofing industry in Finland and Denmark. *Ann Occup Hyg* 2009; 53: 139–151.
- 22 Asphalt Institute - Executive Offices and Research Center. Detection of coal tar materials in asphalt pavements using chemical and biological methods. [WWW document]. URL http://www.asphaltinstitute.org/wp-content/uploads/public/engineering/pdfs/environmental/Detection_Coal_Tar_Materials_Aspphalt_Pavements_Using_Chem_Bio_Methods.pdf [accessed on 2 December 2014].
- 23 Gawkrödger DJ. Occupational skin cancers. *Occup Med (Lond)* 2004; 54: 458–463.
- 24 Mitropoulos P, Norman R. Occupational nonsolar risk factors of squamous cell carcinoma of the skin: a population-based case-controlled study. *Dermatol Online J* 2005; 11: 5.
- 25 Vlajinac HD, Adanja BJ, Lazar ZF, et al. Risk factors for basal cell carcinoma. *Acta Oncol* 2000; 39: 611–616.
- 26 Binet S, Pfohl-Leszkowicz A, Brandt H, et al. Bitumen fumes: review of work on the potential risk to workers and the present knowledge on its origin. *Sci Total Environ* 2002; 300: 37–49.
- 27 Carlsten C, Hunt SC, Kaufman JD. Squamous cell carcinoma of the skin and coal tar creosote exposure in a railroad worker. *Environ Health Perspect* 2005; 113: 96–97.
- 28 Izikson L, Vanderpool J, Brodsky G, et al. Combined basal cell carcinoma and Langerhans cell histiocytosis of the scrotum in a patient with occupational exposure to coal tar and dust. *Int J Dermatol* 2004; 43: 678–680.

- 29 Shimauchi T, Rikihisa W, Yasuda H, *et al.* [A case of squamous cell carcinoma that developed on chronic tar dermatosis]. *J UOEH* 2000; 22: 183–187.
- 30 Roelofzen JH, Aben KK, Oldenhof UT, *et al.* No increased risk of cancer after coal tar treatment in patients with psoriasis or eczema. *J Invest Dermatol* 2010; 130: 953–961.
- 31 Thami GP, Sarkar R. Coal tar: past, present and future. *Clin Exp Dermatol* 2002; 27: 99–103.
- 32 Cosmetic Ingredient Review Expert Panel. Final safety assessment of coal tar as used in cosmetics. *Int J Toxicol* 2008; 27: 1–24.
- 33 Vogel U, Thein N, M $\ddot{u}$ ller P, *et al.* Pharmacological coal tar induces G:C to T:A transversion mutations in the skin of muta mouse. *Pharmacol Toxicol* 2001; 89: 30–34.
- 34 Kumar A, Yadav A, Giri SK, *et al.* Effect of genetic polymorphism of GSTM1 and GSTT1 genotypes on cytogenetic biomarkers among coaltar workers. *Environ Toxicol Pharmacol* 2011; 32: 128–135.
- 35 Giri SK, Yadav A, Kumar A, *et al.* Association of GSTM1 and GSTT1 polymorphisms with DNA damage in coal-tar workers. *Sci Total Environ* 2011; 409: 4465–4469.
- 36 Godschalk RW, Ostertag JU, Zandsteeg AM, *et al.* Impact of GSTM1 on aromatic-DNA adducts and p53 accumulation in human skin and lymphocytes. *Pharmacogenetics* 2001; 11: 537–543.
- 37 Rojas M, Godschalk R, Alexandrov K, *et al.* Myeloperoxidase-463A variant reduces benzo[a]pyrene diol epoxide DNA adducts in skin of coal tar treated patients. *Carcinogenesis* 2001; 22: 1015–1018.
- 38 Marston CP, Pereira C, Ferguson J, *et al.* Effect of a complex environmental mixture from coal tar containing polycyclic aromatic hydrocarbons (PAH) on the tumor initiation, PAH-DNA binding and metabolic activation of carcinogenic PAH in mouse epidermis. *Carcinogenesis* 2001; 22: 1077–1086.
- 39 Giri SK, Yadav A, Kumar A, *et al.* CYP1A1 gene polymorphisms: modulator of genetic damage in coal-tar workers. *Asian Pac J Cancer Prev* 2012; 13: 3409–3416.
- 40 Pathak MA, Joshi PC. The nature and molecular basis of cutaneous photosensitivity reactions to psoralens and coal tar. *J Invest Dermatol* 1983; 80: 66s–74s.
- 41 Dong S, Fu PP, Shirsat RN, *et al.* UVA light-induced DNA cleavage by isomeric methylbenz[a]anthracenes. *Chem Res Toxicol* 2002; 15: 400–407.
- 42 Riala R, Heikkilä P, Kanerva L. A questionnaire study of road pavers and roofers work-related skin symptoms and bitumen exposure. *Int J Dermatol* 1998; 37: 27–30.
- 43 Maghsoudi H, Gabraely N. Epidemiology and outcome of 121 cases of chemical burn in East Azarbaijan province, Iran. *Injury* 2008; 39: 1042–1046.
- 44 Mastrangelo G, Veller Fornasa C, Pavanello S, *et al.* Polyaromatic hydrocarbons administered in humans by dermal route increase total IgE. *Int J Immunopathol Pharmacol* 2003; 16: 145–150.
- 45 Sijerčić N, Hadzigrabić N, Kamberović S, *et al.* Frequency of standard and occupational contact allergens in Tuzla area, Bosnia and Herzegovina: retrospective study. *Acta Dermatovenerol Croat* 2003; 11: 75–79.
- 46 Ancona AA. Occupational acne. *Occup Med* 1986; 1: 229–243.
- 47 Dodd WA. TARS. Their role in the treatment of psoriasis. *Dermatol Clin* 1993; 11: 131–135.
- 48 Lavker RM, Grove GL, Kligman AM. The atrophogenic effect of crude coal tar on human epidermis. *Br J Dermatol* 1981; 105: 77–82.
- 49 Minnesota Pollution Control Agency (2014) Actions to restrict or discontinue the use of coal tar-based sealants in the United States. [WWW document] URL <http://www.pca.state.mn.us/index.php/view-document.html?gid=16180> [accessed on 2 December 2014].
- 50 Commission Regulation (EC) No. 552/2009 of 22 June 2009 amending Regulation (EC) No. 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards Annex XVII. Official Journal of the European Union 2009.
- 51 European Chemicals Agency. Coal Tar Pitch, High Temperature. CAS No: 65996-93-2 EINECS No: 266-028-2. 2007.
- 52 Scientific Committee on Occupational Exposure Limits (2013) SCOEL Recommendations (List). [WWW document]. URL <http://ec.europa.eu/social/search.jsp?advSearchKey=recommendations&x=0&y=0&mode=advancedSubmit&langId=en> [accessed on 2 December 2014].

Answers

1, b; 6, d; 2, d; 7, a; 3, c; 8, a; 4, d; 9, a; 5, c; 10, d.