Safety Assessment of Coal Tar

March 16, 2004
Final Safety Assessment of Coal Tar

Abstract: Coal Tar is a semisolid byproduct obtained in the destructive distillation of bituminous coal which functions in cosmetic products as a cosmetic biocide and denaturant — antidaandruff agent is also listed as a function, but this is considered an over-the-counter (OTC) drug use. Coal Tar is a nearly black, viscous liquid, heavier than water, with a naphthalene-like odor and a sharp burning taste, produced in coking ovens as a byproduct in the manufacture of coke. Crude Coal Tar is composed of 48% hydrocarbons, 42% carbon, and 10% water. In 2002, Coal Tar was reported to FDA to be used in four formulations, all of which appear to be OTC drug products. Coal Tar is monographed by the Food and Drug Administration as Category I (safe and effective) for over-the-counter drug ingredient for use in the treatment of dandruff, seborrhea, and psoriasis. Coal Tar is absorbed through the skin of animals and humans and is systemically distributed. In short term studies, mice fed Coal Tar in their diet found their diet unpalatable, but no adverse effects were reported other than weight loss; rats injected with Coal Tar residue experienced eating avoidance, respiratory difficulty, sneezing, and weight loss. In a subchronic neurotoxicity study using mice, a mixture of phenols, cresols, and xylene at concentrations approximately equal to those expected in Coal Tar extracts produced regionally selective effects, with a rank order of striatum > cerebellum > cerebral cortex. Coal Tar applied to the backs of guinea pigs increases epidermal thickness. Painting female rabbits with tar decreases the absolute and relative weights of the ovaries and decreased the number of interstitial cells in the ovary. Four therapeutic Coal Tar preparations used in the treatment of psoriasis screened using the Ames test were mutagenic. Urine and blood from patients treated with Coal Tar were genotoxic in bacterial assays. Coal Tar was genotoxic in a mammalian genotoxicity assay and induced DNA adducts in various tissue types. Chronic exposure of mice significantly decreased survival and liver neoplasms were seen in a significant dose-related trend; in other studies using mice lung tumors and perianal skin cancers were found. Coal Tar was comedogenic in three small clinical studies. Folliculitis is associated with the prolonged use of some tars. Several published reports describe cases of contact sensitivity to Coal Tar. Polycyclic aromatic hydrocarbons which make up Coal Tar are photosensitizers and cause phototoxicity by an oxygen dependent mechanism. A retrospective study of the reproductive toxicity of Coal Tar in humans compared exposed women to controls and found little difference in spontaneous abortion and congenital disorders. Cancer epidemiology studies of patients who have received Coal Tar therapy of one form or other have failed to link treatment with an increase in the risk of cancer. While the CIR Expert Panel believes that Coal Tar use as an antidaandruff ingredient in OTC drug preparations is adequately addressed by the FDA regulations, the Panel also believes that the appropriate concentration of use of Coal Tar in cosmetic formulations should be that level that does not have a biological effect. Additional data needed to make a safety assessment include product types in which Coal Tar is used (other than as an OTC drug ingredient), use concentrations, and the maximum concentration that does not induce a biological effect.

INTRODUCTION

Coal Tar (CAS No. 8007-45-2) is a thick liquid or semi-solid obtained as a byproduct in the destructive distillation of bituminous coal. In the United States, Coal Tar may be used as an active ingredient (treatment of dandruff, seborrhea, and psoriasis) in OTC drug products. Coal Tar is listed as an antidaandruff agent, cosmetic biocide, and denaturant in cosmetics in the International Cosmetic Ingredient Dictionary and Handbook (Gottschalck and McEwen, 2004).

CHEMISTRY

DEFINITION AND STRUCTURE

According to International Agency for Research on Cancer (IARC, 1985) and the Environmental Protection Agency (EPA, 1994), crude Coal Tar is composed of 48% hydrocarbons, 42% carbon, and 10% water. It is composed of approximately 10,000 compounds, of which about 400 have been identified. One hundred of these 400 compounds are polycyclic aromatic hydrocarbons (PAHs) only 17 of which have been chemically and toxicologically characterized.
Synonyms for Coal Tar include Picis Carbonis and Pix Carbonis, (Budavari, 1989; Lewis, 1993; RTECS, 2001).

Jackson (2003) stated that Crude Coal Tar is refined or processed for use in over-the-counter drug products by alcohol extraction (USP coal tar) or vegetable oil solubilization. There are also coal tars refined by patented and proprietary filtration and solubilization processes which are also used in over-the-counter drug products.

The USP does not resolve whether products labeled as Coal Tar are refined or crude, stating only that such material may be processed further, while products labeled as Coal Tar topical solution are clearly refined (Committee on Revision of the United States Pharmacopeial Convention, 1995).

**PHYSICAL AND CHEMICAL PROPERTIES**

Coal Tar is a nearly black, viscous liquid, heavier than water, with a naphthalene-like odor and a sharp burning taste (Gennaro, 1990). The composition of Coal Tar is variable, but generally it consists of 2 to 8% light oils (benzene, toluene, xylene); 8 to 10% middle oils (phenols, cresols, and naphthalene); 8 to 10% heavy oils (naphthalene and derivatives); 16 to 20% anthracene oils (mostly anthracene); and about 50% pitch (Gosselin et al., 1984). Coal Tar is “practically insoluble” in water; however “all or almost all” dissolves in benzene or nitrobenzene (Budavari, 1989).

**METHOD OF MANUFACTURE**

Coal Tar is produced in coking ovens as a byproduct in the manufacture of coke (see Figure 1). In this process, coal is subjected to destructive distillation and is transformed into an amorphous mass of coke, which in turn is used in the manufacture of steel. The gases produced are condensed, forming a liquid. Upon removal of ammonia, a black viscous product, crude Coal Tar, is left. Crude Coal Tar may be heated at various temperatures to yield fractional distillates as shown in Figure 2 (Lin and Moses, 1985).

Lerner and Lerner (1960) noted that the term “crude coal tar” was not very specific. For example, when crude Coal Tar is ordered without further specification in the eastern part of the United states, it is prepared from bituminous (soft) coal, whereas when it is ordered on the west coast, it comes from the oils of natural gas. Some commercial dermatologic tars are derived from anthracite (hard) coal.

According to the Code of Federal Regulations (21CFR358.703), the Coal Tar used for medicinal purposes is “obtained as a byproduct during the destructive distillation of bituminous coal at temperatures in the range of 900 deg. C to 1,100 deg. C. It may be further processed using either extraction with alcohol and suitable dispersing agents and maceration times or fractional distillation with or without the use of suitable organic solvents”.

**ANALYTICAL METHODS**

Crude Coal Tar, refined Coal Tar, and over-the-counter drug products containing Coal Tar are analyzed by one of two methods: high pressure liquid chromatography with either UV or fluorescence detection (HPLC/UV, HPLC/FD), and gas chromatography/mass spectroscopy (GC/MS) (EPA, 1994; Litofsky, 1999).
USE

COSMETIC

As noted earlier, the International Cosmetic Ingredient Dictionary and Handbook (Gottschalk and McEwen, 2004) gives the functions of Coal Tar in cosmetic products as a cosmetic biocide and denaturant — antidan druff agent is also listed as a function, but this is considered an over-the-counter (OTC) drug use. For more information on the OTC drug use, see the NON-COSMETIC use section.

Industry reports to the Food and Drug Administration (FDA) give current categories with products containing Coal Tar (FDA, 2002), but as noted above and in Table 1, these uses are over-the-counter (OTC) drug uses in which coal tar functions as an antidan druff ingredient.

According to the Bureau of Alcohol, Tobacco, and Firearms regulations in the Code of Federal Regulations (CFR), 10 pounds of Coal Tar may be added as a denaturant to 100 gallons of ethanol to make SD Alcohol 38-B, which has uses listed as hair and scalp preparations; lotions and creams; deodorants; perfumes and perfume tinctures; toilet waters and colognes; dentifrices; mouthwashes; shampoos; and soap and bath preparations (27CFR21.65). As 1 gallon of ethanol = 6.59 pounds, the approximate maximum concentration of use for Coal Tar used as a denaturant is 10 pounds Coal Tar/659 pounds of ethanol = 1.5% (CTFA 2002).

Currently, there appear to be no uses of Coal Tar as a denaturant or as a cosmetic biocide.

In Europe, Coal Tar is in the list of substances which must not form part of the composition of cosmetic products (EEC Cosmetics Directive, 1999). Coal Tar is not included on the list of prohibited ingredients that are marketed in Japan (Ministry of Health, Labor, and Welfare [MHLW], 2001a) or on the list of restricted ingredients for cosmetic products that are marketed in Japan (MHLW, 2001b).

Coal Tar is used in shampoos as a keratolytic or exfoliative in the treatment of dandruff (Wilkinson and Moore, 1982). According to the International Cosmetic Ingredient Dictionary and Handbook, Coal Tar functions as an antidan druff agent, cosmetic biocide, and denaturant in cosmetics (Gottschalk and McEwen, 2004).

NON-COSMETIC

Coal Tar is monographed by the FDA as a Category I (safe and effective) for over-the-counter drug ingredient for use in the treatment of dandruff, seborrhoea, and psoriasis (FDA, 1982; 1986; 1991). FDA regulations specify the concentration for Coal Tar for external drug products in the control of dandruff at 0.5 to 5 percent (21CFR358.710). FDA re-reviewed Coal Tar in 2001 in response to a citizens petition. This review, including more recent epidemiology studies, confirmed Coal Tar as a Category I (Safe and Effective) OTC drug ingredient (FDA, 2001a; FDA, 2001b).

Therefore, while the International Cosmetic Ingredient Dictionary and Handbook (Gottschalk and McEwen, 2004) gives a function of Coal Tar in cosmetics as an antidan druff agent, industry reports of Coal Tar use in cosmetics are actually in OTC preparations (as an antidan druff agent) at concentrations from 0.06 - 7% (CTFA, 2002).

Coal Tar is used in the treatment of chronic skin diseases, such as psoriasis, often with ultraviolet radiation. It reportedly suppresses hyperplasia by decreasing epidermal synthesis of DNA (Gennaro, 1990).

Coal Tar is also used for waterproof coatings, wood impregnation, road surfaces, and as a chemical feedstock for the production of benzene, toluene, xylene, phenol, etc. (L’Epee et al., 1983).

Table 1. Coal Tar Product Formulation and Concentration of Use Data

<table>
<thead>
<tr>
<th>Product Category (Total number of Formulations in Category, FDA, 2002)</th>
<th>Formulations containing Coal Tar (FDA 2002)</th>
<th>Current concentration of use (CTFA 2002)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bath preparations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bath Oils, Tablets, and Salts (143)</td>
<td>-</td>
<td>.06 - 5%*</td>
</tr>
<tr>
<td><strong>Hair preparations (non-coloring)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shampoos (884)</td>
<td>3*</td>
<td>1 - 7%*</td>
</tr>
<tr>
<td>Tonics, Dressings, etc. (598)</td>
<td>1*</td>
<td>5%*</td>
</tr>
<tr>
<td><strong>Total uses/ranges for Coal Tar</strong></td>
<td>4*</td>
<td>0.06 - 7%*</td>
</tr>
</tbody>
</table>

* Over-the-counter (OTC) drug uses (treatment of dandruff, seborrhoea, and psoriasis); There are no reported cosmetic uses of coal tar as a cosmetic biocide or denaturant.
**GENERAL BIOLOGY**

**ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION**

The information on absorption, distribution, metabolism, and excretion of Coal Tar is gleaned from studies for which gathering these data were not the purpose of the study. Studies involving various animal species and humans are described. In many cases penetration of Coal Tar through the stratum corneum was detected by measuring enzyme induction rather than Coal Tar or one of its constituents, e.g. aryl hydrocarbon hydroxylase (AHH) induction.

**Mice**

Das et al. (1985) irradiated SKH hairless mice with UVB to induce squamous cell carcinoma (SCC). Mice were given a single topical application of USP Coal Tar solution (1 ml/100g) 24 hours before being killed. Coal Tar treatment resulted in a 14-fold induction of AHH and 7-ethoxycoumarin O-deethylase (ECD) activities.

Das et al. (1986) divided twenty four male athymic nude mice with skin grafted from one human specimen into three groups of eight animals. Group 1 mice were treated topically with 0.1 ml of Crude Coal Tar to the human grafted skin. Group 2 received 0.1 ml of Crude Coal Tar at a site opposite to the grafted skin. Group 3 received 0.1 ml of acetone on both the grafted human and mouse skin. All animals were killed 24 hours after the application of Crude Coal Tar. The skin was scraped, then minced and homogenized. AHH and ECD levels were measured with a spectrophotofluorimeter and ethoxyresorufin deethylase (ERD) levels were measured with a spectrofluorometer.

Group 1 mice showed 3.9 and 3.5; 3.2 and 2.9; and 1.1 and 1.2 fold increases in mouse and human epidermal AHH, ERD and ECD activities respectively. Group 2 mice showed 27.8 and 6.4; 12.8 and 3.3; and 1.7 and 2.6 fold increases in mouse and human epidermal AHH, ERD and ECD activities, respectively. Topical application of Coal Tar either onto human transplanted skin or to mouse skin also resulted in substantial induction of hepatic and pulmonary AHH and ERD activities (Das et al., 1986).

Weyand et al. (1991) maintained B6C3F1 mice on 0.25% Coal Tar adulterated diets for 15 days. PAH metabolites excreted in the urine of animals ingesting a control or adulterated gel diet were determined by using HPLC with fluorescence detection. 1-Hydroxypyrrene (1-OH-P) was the major fluorescent metabolite excreted by all groups of animals maintained on a Coal Tar diet. The amount of 1-OH-P excreted in urine paralleled the pyrene content of Coal Tar samples.

**Rats**

Bickers and Kappas (1978) applied 1% Coal Tar solution (0.05 ml) to the skin of six neonatal rats. Twenty-four hours later, AHH activity (production of 3-OH benzo[a]pyrene (BP)/min/mg protein) was measured in the skin and liver. After topical application, there was a greater than 10-fold induction of skin AHH activity compared to the controls. Hepatic AHH activity also increased “markedly” indicating substantial percutaneous absorption had occurred.

Bickers et al. (1982) applied 100 ml of a Coal Tar solution (USP) to 6-8 neonatal rats. In another experiment in which they studied maternal and prenatal enzymes 48 hours prior to the expected date of delivery, the backs of pregnant animals were shaved and Coal Tar solution (USP) was applied to the shaved area. Treatment and other details are given in Tables 2 and 3. After 24 hours, animals were killed. In each experiment, tissues for 6 animals were pooled for single determinations. Skin and liver were removed. The epidermis and dermis were separated and AHH activity was assayed spectrophotofluorometrically.

Application of Coal Tar solution to neonatal rats induced skin and liver AHH 15- and 8-fold, respectively. AHH induction in isolated epidermis and dermis was 10 and 18-fold over the corresponding control values (Table 2). The authors also tested whether the vapors from the Coal Tar solution applied on the experimental animals might be inducing cutaneous AHH activity in the controls. Data supporting this hypothesis are shown in Table 4. When pregnant rats were treated with Coal Tar, the skin and liver AHH activity of the mothers was induced to a higher extent (3.8 and 4.8-fold for skin and liver respectively) than that achieved in the fetuses (2.0 and 1.9-fold for skin and liver respectively). In further studies, several constituents of Coal Tar were analyzed for their ability to induce AHH, with acridine, anthracene, and benzo[a]pyrene reaching statistical significance as shown in Table 4 (Bickers et al., 1982).

Mukhtar and Bickers (1982) treated neonatal rats (type unspecified) with skin applications of 100 ml of Coal Tar (USP) solution. Control rats were treated with acetone. Twenty-four hours after treatment, rats were killed. AHH activity was determined spectrophotofluorometrically. Following topical application of Coal Tar, there was an approximately 10-fold induction of AHH and ECD activities in the skin. Hepatic AHH and ECD activities were induced 6.2 and 2.9 fold, respectively. Coal Tar application also resulted in the induction of hepatic cytosolic glutathione-S-transferase activities in neonatal rats.

Mukhtar et al. (1986b) divided neonatal Sprague-Dawley rats into 6 groups of 20 each. Group 1 rats, the control group, received a single topical treatment of acetone. Group 2 received UVB alone.
**Table 2.** Effect of cutaneously applied Coal Tar on AHH in neonatal rats (Bickers et al., 1982).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Whole skin</th>
<th>Epidermis</th>
<th>Dermis</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control‡</td>
<td>0.24±0.03</td>
<td>0.35±0.02</td>
<td>0.42±0.03</td>
<td>23.22±1.41</td>
</tr>
<tr>
<td>Coal Tar</td>
<td>3.69±0.42*</td>
<td>3.58±0.51*</td>
<td>7.82±0.81*</td>
<td>192.73±5.82*</td>
</tr>
<tr>
<td>Coal Tar fumes</td>
<td>0.51±0.06*</td>
<td>0.62±0.04*</td>
<td>0.86±0.06*</td>
<td>39.47±1.57*</td>
</tr>
</tbody>
</table>

*Four-day old neonatal rats were treated with topically applied acetone (100 μl) and kept in a separate room from other experimental animals.

*Animals were treated with 100 μl Coal Tar solution (USP) 24 hours prior to sacrifice.

*Animals were treated with 100 μl acetone and housed in cages adjacent to Coal Tar treated animals 24 hours prior to sacrifice. Data represents mean±SD of 3 experiments.

*Results are significantly different from respective controls (p<0.05)

**Table 3.** Effect of cutaneously applied Coal Tar on maternal and fetal AHH in pregnant rats (Bickers et al., 1982)

<table>
<thead>
<tr>
<th>AHH (p mole 3-OH BP/min/mg protein)</th>
<th>Skin</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Treatment</td>
</tr>
<tr>
<td>Maternal ‡</td>
<td>1.01±0.11</td>
<td>3.82±0.26*</td>
</tr>
<tr>
<td>Fetal ‡</td>
<td>0.24±0.01</td>
<td>0.47±0.03*</td>
</tr>
</tbody>
</table>

*Sperm positive pregnant rats at 19 days of gestation (2 days before expected delivery) were shaved and treated with 500 μl Coal Tar solution (USP). Twenty-four hours later (16 Hours before expected delivery), mothers were killed by decapitation. Unborn rats from control and Coal Tar-treated mothers were removed and washed. Skin and liver supernatant fractions were prepared and used as the enzyme source. Data represent mean±SD of 3 experiments in each of which one mother and a minimum of 8 neonates was used.

*Results statistically different from controls (p<0.05)

**Table 4.** Effect of cutaneously applied Coal Tar constituents on AHH activity in neonatal rats (Bickers et al., 1982)

<table>
<thead>
<tr>
<th>Constituent†</th>
<th>AHH (p mole 3-OH BP/min/mg protein)</th>
<th>Skin</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Treated</td>
<td>Control</td>
</tr>
<tr>
<td>Benzene</td>
<td>0.51±0.03</td>
<td>0.54±0.04</td>
<td>22.15±4.12</td>
</tr>
<tr>
<td>Naphthalene</td>
<td>0.53±0.05</td>
<td>0.57±0.07</td>
<td>23.12±3.12</td>
</tr>
<tr>
<td>Acridine</td>
<td>0.57±0.05</td>
<td>1.23±0.02*</td>
<td>23.17±3.33</td>
</tr>
<tr>
<td>Anthracene</td>
<td>0.53±0.04</td>
<td>1.43±0.11*</td>
<td>21.16±1.67</td>
</tr>
<tr>
<td>Benzo[a]pyrene</td>
<td>0.59±0.04</td>
<td>5.23±0.40*</td>
<td>27.83±8.33</td>
</tr>
</tbody>
</table>

*Each was dissolved in acetone or benzene and administered topically to 4-day old rats in a single dose (100 mg/kg body weight). Animals were killed 24 hours later. Data represent mean±SD of 3-4 experiments in each of which a minimum of 6 neonates was studied.

*Results are significantly different from respective controls (p<0.05).
Group 3 received a single topical application of Crude Coal Tar alone (10 ml/kg). Group 4 received UVB followed immediately by Crude Coal Tar. Group 5 received UVB followed by acetone. Group 6 received Crude Coal Tar followed by UVB. AHH, ERD and ECD were determined as in Das et al. 1986. The quantitation of phenolic BP metabolites was based on comparison with the fluorescence of a standard solution of 3-hydroxybenzo[a]pyrene. The effect of exposure of animals to UVB and Crude Coal Tar, alone and combined, on cutaneous AHH, ERD, and ECD activities is given in Table 5. A single topical application of Coal Tar resulted in significant induction of AHH, ERD, and ECD. When UVB exposure was added, the result was additive and synergistic.

Treatment of animals with Crude Coal Tar alone resulted in 352% increased formation of benzo[a]pyrene (BP) metabolites. Topical application of Crude Coal Tar followed by exposure to UVB resulted in the highest enhancement of BP metabolite formation. BP metabolite formation increase was 834%, 322%, and 373%, respectively, as compared with the control group, and groups treated with UVB alone, and with UVB followed by acetone (Mukhtar et al., 1986b).

**Pigs**

VanRooij et al. (1995) killed healthy domestic pigs (75-100 kg) and retrieved the ears. Five ears were used. Each ear was cut transversely, distal from the bifurcation of the vena auricularis lateralis. Cannulas were inserted into the vena auricularis intermediums and arteria auricularis.

The preparation was perfused with phosphate-buffered saline until the perfusate was clear. After 30 minutes of perfusion, industrial Coal Tar was applied on a square area of 6 x 4 cm² with an average dose of 11 mg/cm². The range in absorbed amounts of 10 PAHs through pig ear skin during 200 minutes after Coal Tar application is given in Table 6 (VanRooij et al., 1995).

**Humans**

Bickers and Kappas (1978) studied the induction of AHH by Coal Tar. Nine patients with psoriasis or atopic dermatitis applied 100 µl of a 20% Coal Tar solution to clinically unaffected skin in the lower lumbar region. A second skin area left untreated or treated with the vehicle only served as a control. Twenty-four hours later, a 6 mm punch biopsy was obtained from both sites. The skin samples were homogenized and AHH activity was measured via a spectrophotometer. A two- to fivefold increase in AHH activity was seen in the treated areas compared to the control sites.

Černíková et al. (1983) selected 28 patients (2 females, 26 males) who required Coal Tar treatment on an area larger than two-thirds of the body surface. Approximately 1–6 g of Coal Tar in a paste was spread on the skin in one application. Urine analysis was carried out before and after the treatment, and in some cases during the treatment. The presence of acridine, which is present in Coal Tar, in the urine was demonstrated by mass spectrographic analysis. The authors concluded that the presence of acridine demonstrated absorption of a Coal Tar component through the skin.

**Table 5. Effect of UVB and Crude Coal Tar (CCT), Alone and Combined in Neonatal Rats (Mukhtar et al., 1986b)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AHH Activity</th>
<th>ERD Activity</th>
<th>ECD Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pmol 3-OHPB/min/mg Protein</td>
<td>Percent Increase over Control</td>
<td>pmol RF/min/mg Protein</td>
</tr>
<tr>
<td>Control</td>
<td>1.75±0.12</td>
<td></td>
<td>1.92 ± 0.14</td>
</tr>
<tr>
<td>UVB alone</td>
<td>3.97±0.34a</td>
<td>127</td>
<td>4.64±0.27a</td>
</tr>
<tr>
<td>CCT alone</td>
<td>7.85±0.66</td>
<td>350</td>
<td>17.20±2.41a</td>
</tr>
<tr>
<td>UVB+CCT</td>
<td>8.00±0.64a</td>
<td>358</td>
<td>17.89±2.84a</td>
</tr>
<tr>
<td>UVB+acetone</td>
<td>3.27±0.21a</td>
<td>87</td>
<td>3.59±0.31a</td>
</tr>
<tr>
<td>CCT+UVB</td>
<td>16.74±1.06a</td>
<td>858</td>
<td>24.30±2.97a</td>
</tr>
</tbody>
</table>

* Statistically significant from control (p<0.01)

* Statistically significant from control and from UVB (p<0.01)

* Statistically significant from control, from UVB and from UVB + CCT (p<0.01)
Table 6. Absorbed amounts of PAHs through pig ear skin (VanRooij et al., 1995)

<table>
<thead>
<tr>
<th>PAH</th>
<th>Amount Absorbed (pmole/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorene</td>
<td>222-2377</td>
</tr>
<tr>
<td>Phenanthrene</td>
<td>334-1623</td>
</tr>
<tr>
<td>Anthracene</td>
<td>47-302</td>
</tr>
<tr>
<td>Fluoranthene</td>
<td>23-193</td>
</tr>
<tr>
<td>Pyrene</td>
<td>26-193</td>
</tr>
<tr>
<td>Benzo[b]fluoranthene</td>
<td>&lt;0.1-13</td>
</tr>
<tr>
<td>Benzo[k]fluoranthene</td>
<td>&lt;0.1-1</td>
</tr>
<tr>
<td>Benzo[a]pyrene</td>
<td>&lt;0.1-13</td>
</tr>
<tr>
<td>Indeno[123-cd]pyrene</td>
<td>&lt;0.1-1</td>
</tr>
<tr>
<td>Dibenzo[ah]anthracene</td>
<td>&lt;0.1-2</td>
</tr>
</tbody>
</table>

To study the inducibility of AHH, Hukkelhoven et al. (1984) conducted a study using human volunteers. A circled area of about 3 cm diameter of the scalp of each volunteer (number not given) was marked with ink. This area received 5 applications of Coal Tar (0.5 ml) with an interval of 12 hours. During this period, volunteers did not wash their hair. The first application was at about 2300 h. In the morning, volunteers were asked to wash their hair thoroughly to remove exogenously absorbed Coal Tar. Hair follicles were then plucked from the study site while control follicles were plucked from the other side of the scalp. For the measurement of AHH activity, hair follicles were incubated for 1 hour. Fluorescence was determined with a Perkin-Elmer 650-40 fluorometer.

Even after extensive washing of the hair after the last Coal Tar application, some Coal Tar remained associated with the hair. When the hair follicles plucked from the Coal Tar region were incubated, a relatively high background fluorescence was obtained. No fluorescence was extracted from the control hair follicles. It was also studied whether the effect of Coal Tar on AHH activity was limited to the treated scalp region. AHH activity was measured outside the marked area in 3 persons before and after application of Coal Tar.

The results showed similar enzyme activities before and after treatment indicating the effect of Coal Tar on AHH activity is restricted to the treated skin surface (Hukkelhoven et al., 1984).

Storer et al. (1984) gave five volunteers 85 g of a 2%-Crude Coal Tar in petrolatum preparation and instructed them to apply the medication to the trunk and extremities. The application was to be done at night and removed 8 hours later on each of 2 successive days. Blood samples were taken before the study and after completion of the second 8 hour application. Blood samples were analyzed by gas chromatography and mass spectrometry. Values obtained from the first blood sample were subtracted from those for the final blood samples. PAHs found in the volunteers’ blood include naphthalene, biphenyl, acenaphthene, fluorene, phenanthrene, anthracene, fluoranthene, pyrene, and benzo[b]thiophene. Absorption of PAHs in Crude Coal Tar occurred in a variable manner. PAH levels in blood ranged from undetectable amounts to 100.0 parts per billion.

Van Cantfort et al. (1986) studied BP metabolism by the incubation of epidermal blisters from 19 volunteers with 0.35 μCi [14C]BP at 32°C for 24 or 48 hours. The survey found large variations in basal epidermal activity. Next, 11 volunteers were treated with Coal Tar (one or three applications at 24 hour intervals). This resulted in a 2 to 8-fold increase in BP metabolism. This induction was not increased with repeated Coal Tar application.

Merk et al. (1987) evaluated the effect of human exposure to a Crude Coal Tar. AHH activity was measured as well as the metabolism of BP and benzo[a]pyrene-7,8-diol (BP 7,8-diol). Twelve healthy volunteers were studied before and after shampooing their hair daily for 4 days with the Crude Coal Tar-containing shampoo. Hair follicles were plucked and incubated in the appropriate solutions for each assay. For the AHH study, specific basal enzyme activity ranged from 0.6 to 8.9 fmol/h/hair follicle.
Coal tar application caused a 50-148% increase in AHH activity in 10 of the 12 individuals. The remaining 2 individuals, who manifested the highest basal levels of enzyme activities, showed a decrease in enzyme activity after use of the shampoo. For the BP study, 628 fmol of BP derivatives were detected after a 90 minute incubation. The metabolites formed were as follows: BP 9,10-diol, 91 fmol; BP 4,5-diol, 64 fmol; BP 7,8-diol, 55 fmol; BP 1,6-quinone, 171 fmol; BP 3,6-quinone, 174 fmol; 9-hydroxy-BP, 18 fmol; and 3-hydroxy-BP, 55 fmol. The authors concluded that the BP 7,8-diol study showed that human hair follicle enzymes are capable of converting BP 7,8-diol to tetroils (Merk et al., 1987).

Jongeneelen et al. (1988) treated five female patients suffering from eczematous dermatitis on the arms and legs for several days with an ointment containing 10% Coal Tar. During the treatment, the ointment was removed daily with arachis oil, and a fresh dose of approximately 40 g of ointment was applied for the next 24 hours. The patients collected spot urine samples, one before the start of the application and two samples per day (morning and evening) during the first 3 days of treatment. After the treatment was started, the concentration of 1-OH-P rapidly increased to about 100-1000 times the background level.

Arnold et al. (1993) investigated the effects of topical application of isoquinoline (a component of Coal Tar) on human skin. Of interest was the level of induction of ornithine decarboxylase (ODC) following tape stripping as an indicator for potential PKC inhibition in vivo. The subjects included 18 volunteers with no history of skin diseases and 17 psoriasis patients who had received no therapy for 2 and/or 4 weeks prior to the study. In each patient, two symmetrical comparable lesions designated left and right were selected. For the volunteers, Crude Coal Tar containing 0.2% isoquinoline was applied in an area of 3 cm² and covered with gauze. The treated site and a contralateral site were tape stripped after 16 hours followed by a second application of the Coal Tar to the treated site. A biopsy was taken from both sites after 8 hours.

For psoriasis patients, 2 jars, one with Vaseline® album/lanette wax cream (50%/50%) with 0.2% isoquinoline and one with basecream only were randomly assigned to the left or right lesion. Patients were asked to use the creams twice daily. In their last trial week, the patients applied the creams on 2 uninvolved areas. On day 21, the different areas were tape stripped, followed by application of the assiged cream, and biopsied after 8 hours. Biopsies were homogenized, and ODC measurements were taken via scintillation counting. The authors concluded that application of 0.2% isoquinoline or even Crude Coal Tar did not have any significant influence on ODC induction (Arnold et al., 1993).

Hansen et al. (1993) studied the urinary excretion patterns of 1-OH-P and α-naphthol in urine in 2 patients. Each subject was treated once a day with Coal Tar pitch covering >50% of the skin. After 1 week, the urinary concentration of 1-OH-P and α-naphthol increased approximately 100 times. However, after 3 weeks, the urinary concentration decreased to approximately the pre-experiment levels, even though the treatment remained unchanged.

VanRooij et al. (1993) applied a dose of 2.5 mg/cm² Coal Tar ointment on 24 cm² skin to the forehead, shoulder, volar forearm, palmar site of hand, groin, and ankle of 4 male volunteers. After 45 minutes, the remaining ointment was removed using tissues with 1 ml TIV-plus cleaner (DEB Nederland NV), followed by washing with warm water and soap. The disappearance of the remaining compounds was monitored up to 55 hours, taking 8-18 measurements per skin site in triplicate, using a fiberoptic luminoscope, that enables the measurement of the fluorescence of chemical substances on and in the upper layers of the skin. HPLC separation of the Coal Tar combined with fluorescence detection was applied to estimate the contribution of 11 polycyclic aromatic hydrocarbons (PAHs) to the luminescence signal as measured by the luminoscope. The percentage of each PAH is listed in Table 7.

Table 7. Levels of PAH in Pharmaceutical Coal Tar (VanRooij et al. 1993).

<table>
<thead>
<tr>
<th>PAH</th>
<th>Level (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naphthalene</td>
<td>0.13</td>
</tr>
<tr>
<td>Fluorene</td>
<td>0.28</td>
</tr>
<tr>
<td>Phenanthrene</td>
<td>0.91</td>
</tr>
<tr>
<td>Anthracene</td>
<td>0.24</td>
</tr>
<tr>
<td>Fluoranthene</td>
<td>1.07</td>
</tr>
<tr>
<td>Pyrene</td>
<td>0.81</td>
</tr>
<tr>
<td>Benzo[b]fluoranthene</td>
<td>0.60</td>
</tr>
<tr>
<td>Benzo[k]fluoranthene</td>
<td>0.31</td>
</tr>
<tr>
<td>Benzo[a]pyrene</td>
<td>0.72</td>
</tr>
<tr>
<td>Dibenzo[ah]anthracene</td>
<td>0.16</td>
</tr>
<tr>
<td>Idenol[123-cd]pyrene</td>
<td>0.38</td>
</tr>
</tbody>
</table>

* Mean value of two measurements

These authors also applied 2.5 mg/cm² Coal Tar ointment for three 6 h periods to either the volar forearm, hand (both palmar and dorsum), neck, trunk, or calf of eight male volunteers. Sites were covered with plastic and cotton. After 6 hours, TIV-plus cleaner was used in combination with soap to clean the surface. All urine voided 24 hours before the application to 3 days after application was sampled.
The total 1-OH-P excreted ranged from 5.0 to 23.8 nmol. There were significant differences in the total excreted amount of 1-OH-P between individuals, but no significant differences in the extent of urinary 1-OH-P excretion after Coal Tar application between the various skin sites. The time in which half the total 1-OH-P was excreted differed significantly between the volunteers ranging from 8.2 to 18.9 hours (VanRooij et al., 1993).

Santella et al. (1994) used Coal Tar treated psoriasis patients as a model population to test a newly developed ELISA for the urinary excretion of BP and related PAHs. Urine samples were collected from 57 patients and 53 untreated volunteers. Patients applied either an ointment or gel-based Coal Tar product, or both, to the entire body surface at least once a day, followed by UVB treatment. Precise dosages were not possible because treatments were self applied with variable efficiency. The estimated exposure was 20-100 g of tars/day. Twenty-four hour urine samples were collected from all subjects and frozen. 1-Hydroxypyrene (1-OH-P) was analyzed by HPLC with a fluorometer. PAH metabolites were analyzed by competitive ELISA.

Urinary PAH metabolites were elevated in patients (mean 730 ± 1370 μmol equivalents of BP/mmol creatinine) compared with untreated volunteers (110 ± 90 μmol/mol, P<0.0001). Urinary levels of 1-OH-P were also elevated in treated patients (mean 547 ± 928 μmol/mmol creatinine) compared with volunteers (mean 0.14 ± 0.17 μmol/mol, P<0.0001). The authors indicated there was a good correlation (r=0.717, n=96, P<0.0001) between the PAH-ELISA data and the 1-OH-P levels in all subjects (Santella et al. 1994).

van Schooten et al. (1994) assessed the urinary excretion of 1-OH-P to assess the internal dose of polycyclic aromatic hydrocarbons after acute dermal application of a Coal Tar shampoo. A single use of the shampoo resulted in increased 1-OH-P excretion in all 11 volunteers on day 1 compared to pre-experiment samples. The mean increase was 10 times pre-experiment values. On day 2, the concentration was still raised; the mean increase was 5 times pre-experiment values.

Viaud and Vyskočil (1995) had one male volunteer suffering from psoriasis of the scalp and undergoing treatment with a Coal Tar shampoo provide all his micturitions between two applications (interval of 4 days). A single treatment with the Coal Tar shampoo resulted in at least a 10-fold increase in the excretion of 1-OH-P. The excretion reached its maximum approximately 12 hours after the treatment and corresponds to 3.45 μmol/mol creatinine.

The use of 1-OHP as a marker for PAH exposure has been criticized because: 1-Hydroxypyrene levels fluctuate and decline after initial exposure which prevents constant monitoring of PAH exposure from coal tar (Hansen, 1993); 1-Hydroxypyrene is not a suitable marker for low urinary excretion rates which would result from topical applications (Jacob, 1989; Grimmer, 1990); and 1-Hydroxypyrene levels vary dramatically among exposed individuals, especially those who smoke, even when the exposure rate is constant (Jacob, 1989; Grimmer 1990).

**HAIR GROWTH**

Ritschel et al. (1975) studied the influence of Coal Tar on hair growth in New Zealand rabbits. White and black rabbits with two rectangular patches shaved on their backs were used. In the first experiment, the left side was kept as a control and on the right side 5% Coal Tar was applied once a day for three days. On the fourth day, the tar was removed and hairs were epilated and measured for length. The rate of hair growth for the white rabbit with Coal Tar was significantly increased but not for the black rabbit.

For the second experiment the black rabbits were shaved and killed. A lipid extract and an aqueous extract using a 0.9% sodium chloride solution were prepared from the skin and hair, respectively. On the shaved backs of white rabbits 8 areas were marked on each side, the left side the test without tar, the right side for the test with tar. Two rabbits each were used for the lipid extracts and the aqueous extracts. The following areas were used: control, solvent blank, skin extract, and hair extract. The solvent blanks and extracts were injected intracutaneously (0.5 ml dose) into the designated areas. Tar application was done once a day for three days. The intracutaneous administration of a 0.9% sodium chloride solution with and without Coal Tar had a stimulatory effect on hair growth. A slight positive effect occurred when aqueous skin and hair extracts were used together with Coal Tar.

In the third experiment, the influence of intracutaneous administration of 0.9% sodium chloride solution and aqueous extract of skin with and without application of tar on the rate of hair growth was studied. The extracts were the same as described for the second experiment. Again, a highly significant difference occurred with the Coal Tar treatment. A significant increase was also observed for the intracutaneous administration of 0.9% sodium chloride solution, which was further increased when followed by Coal Tar application (Ritschel et al., 1975).

**INFECTION**

Stone and Willis (1969) reported the effect of tar on bacterial infection. The hair was clipped from the backs of 12 adult, white, male rabbits. Two grams of Coal Tar U.S.P. mixed with hydrophilic ointment was applied to one side and an equal amount of base was applied to the opposite side. Sites were covered with plastic film, covered by gauze, and removed after 24 hours. A micrococcus suspension (0.2 ml) was injected into the superficial dermis at both sites. The areas were again covered by tar and the base. After 24 hours, the
sites were uncovered and induration was measured. Yellow staining and a mild erythema were present on the tar site. The average diameters of the indurations were 12.7 mm at the tar sites and 4.3 mm at the control sites.

**ANIMAL TOXICOLOGY**

**SHORT-TERM ORAL TOXICITY**

Weyand et al. (1991) conducted palatability experiments using B6C3F1 mice. Eight groups of 5 male mice were maintained on a control basal gel diet for 14 days after which seven of the groups were switched to an adulterated diet containing 0.1, 0.2, 0.5, 1, 2, 5, or 10% Coal Tar. Animals were maintained on either control or adulterated diets for another 15 days. A ninth group of mice received a pellet diet during the 29 day study. Animals on the control and 0.1, 0.2, 0.5, and 1% diets were killed on day 29.

No difference in body weight was detected between animals fed a control gel diet or a standard pellet diet. Animals given 2, 5, or 10% Coal Tar adulterated diets refused to eat and rapidly lost weight. Animals receiving the 0.5 or 1% adulterated diets initially refused to eat the diets but eventually tolerated the diets. Animals on the 0.5% diet regained lost body weight; however, those on the 1% diet continued their weight loss. In contrast, animals fed the 0.1 or 0.2% adulterated diets readily consumed the diet and had weight gains similar to the controls (Weyand et al., 1991).

Culp and Beland (1994) fed male B6C3F1 mice (8 per dose group) NIH-31 meal containing 0.0, 0.1, 0.25, 0.50, 1.0, or 2.0 g Coal Tar per 100 g meal (or % Coal Tar) for 28 days. A dose-related decrease in food consumption and body weight was found. The average body weights and food consumption over the 28 day period for the 1 and 2% dose groups were significantly less than the controls (p<0.05). Significant differences were not found for the remaining dose groups.

**SUBCHRONIC ORAL TOXICITY**

Pinsky and Bose (1988) conducted a study to determine if chronic exposure to the principal constituents of the aqueous fraction of Coal Tar extracts could lead to neurological damage. Forty-two pigmented mice of the Belknap strain were divided into groups of 6. Six experimental groups received mixtures of artificial Coal Tar extracts in their drinking water, a seventh (control) group received tap water. The solutions were composed as follows: pyridine at 0.2 µl/ml; pyridine at 2.0 µl/ml; a mixture of phenols, cresols, and xylenols at concentrations approximately equal to those expected in Coal Tar extracts with the pyridine amounts used above (designated MXT,LO and MXT,HI); and mixtures of pyridine, phenol, cresols, and xylenol at concentrations proportional to those found by Perov (1972) in Coal Tar extracts and again containing pyridine in the above amounts (designated MXT,LO and MXT,HI). After 3 months of exposure, the mice were decapitated and their brains and livers removed and dissected.

There were no significant differences in water consumption between any of the groups, including the controls. Weight gain, general health, and behavior were also similar in all groups. There was no difference in vertical climbing ability between any of the groups. The MXT,HI mixture produced a significant increase in lipid peroxidation, relative to that seen with tap-water, in the striatum, cerebellum, and liver. The 2.0 µl/ml pyridine mixture induced statistically significant increases in the levels of lipid peroxidation in the striatum and cerebellum. The striatum was less sensitive to the 2.0 µl/ml pyridine mixture than to the MXT,HI mixture while the reverse was true for the cerebellum. The authors concluded that artificial mixtures of the aqueous fraction of Coal Tar could exert a distinct regionally selective neurotoxicity in pigmented mice, with a rank order of regional sensitivity being striatum > cerebellum > cerebral cortex (Pinsky and Bose, 1988).

**SHORT-TERM PARENTERAL TOXICITY**

Jorstad (1925) injected 12 male and 10 female rats with 1 cc of Coal Tar subcutaneously at the same place (location not given) every seventh day. After the third injection, the rats had definite signs of malaise. They lost weight, their coats became yellow and ruffled.

Watson (1935) injected two groups of 12 rats with 0.375 cc of Coal Tar mixed with 50% rat tissue extract or 50% paraffin wax over a period of 12 weeks. For the rat tissue extract group, the numbers of animals alive on the 200, 300, and 400th day were 7, 7, and 3 respectively. For the paraffin wax group, the numbers of animals alive on the 200, 300, and 400th day were 11, 10, and 7, respectively.

Simonds and Curtis (1935) injected 5% Tar residue (in heavy liquid petrolatum) into 32 healthy rabbits of both sexes, chiefly rufous reds, into a vein of the ear usually once a week. Their weights ranged from 2.5 to 5 kg. Depending on the constitution and local reactions to the first injection, each animal was given an injection of 0.2 or 0.4 cc of the Tar-oil mixture. If an animal became undernourished and appeared sick, the injections were stopped. One animal received one injection of 1 cc anthrancene intravenously.

All the animals refused to eat for a day or two following the injections. The majority of the rabbits had signs of respiratory difficulty and sneezing. All animals died at times ranging from 8 days to over a year after the first injection. A few days before death, a serosanguineous fluid escaped from the nose and sometimes the mouth. There was marked weight loss in all animals that lived less than 9 months (average of 0.8 kg).
The decrease was proportionally greatest following the first injection. Of the 32 rabbits, 15 had no proliferation of either the bronchial or alveolar epithelium, 4 had very slight epithelial proliferations, and 13 had marked epithelial proliferation with metaplasia (Simonds and Curtis, 1935).

Evelo et al. (1989) divided nine one month old male Wistar rats into three groups. Two groups were injected with 5 or 25 mg/day of a Coal Tar suspension in olive oil for eight days. After this period, animals were killed and the livers were isolated. The animals were observed daily. No visible changes in appearance or behavior were noted; however when the animals treated with 25 mg/day were handled, contact with the belly appeared to be painful. The intake of water was significantly decreased for both treated groups (30.5±6.1 and 22.6±3.1 ml/day for the 5 and 25 mg Coal Tar treated rats respectively) compared to that of the control animals (17.5±2.9 ml/day).

When the livers were isolated, macroscopic observation of the abdomen revealed the black residue of the injected Coal Tar. Small fat particles on the liver were similarly blackened. On the liver of one animal from the 5 mg group, a hollow 7 mm cyst was present. The mean liver weights were 13.2±0.6, 15.4±2.5, and 16.6±1.7 mg for the control, 5, and 25 mg for the treated groups respectively. The increased liver weight for the 25 mg treated groups was statistically significant (p<0.05) (Evelo et al., 1989).

**CHRONIC ORAL TOXICITY**

Culp et al. (1998) compared the effects in mice of two Coal Tar mixtures to that of benzo[a]pyrene (BP) after 2 years of feeding. Mixture 1 was a composite from seven manufactured gas plant waste sites. Mixture 2 was a composite from two of the seven waste sites plus a third site having a very high BP content. Coal Tar diets were prepared by freezing the mixtures in liquid nitrogen and blending with the appropriate amount of NIH-31 meal. BP diets were prepared by dissolving the appropriate amount of BP in acetone and mixing the solution with the NIH-31 meal. Female B6C3F1 mice were divided into 14 dose groups of 48 mice each. The dose groups consisted of 0.01, 0.03, 0.1, 0.3, 0.6, and 1.0% Mixture 1; 0.03, 0.1, and 0.3% Mixture 2; and 5, 25, and 100 ppm BP. An additional group was fed untreated meal to serve as a control. All mice, including those that died during the experiment, were examined. The results of the gross examinations are given in the Carcinogenicity section.

Mice fed 0.6 or 1.0% Mixture 1 ate significantly less than the control mice. Similarly, a significant decrease in food consumption was seen in mice fed 0.3% Mixture 2. None of the mice fed 0.6 or 1.0% Mixture 1 survived the treatment period. Only 21% of the mice in the 0.3% Mixture 1 group survived the 2-year period, a difference that was significantly different from the control group (p<0.0001). The survival for the mice in the 0.0, 0.01, 0.03, and 0.1% Mixture 1 groups ranged from 63 to 71%. In mice fed Mixture 2, there was significantly decreased survival in the 0.3% dose group compared to the control. All the mice fed 100 ppm BP were removed from the study due to morbidity or death. A significant number of mice in the 25 ppm BP group also died early (Culp et al., 1998).

**DERMAL IRRITATION**

Sarkany and Gaylarde (1976) applied preparations of Coal Tar (5-10%) and its components to 2-8 regions on the clipped backs of albino male guinea pigs. Applications were made daily for 3 or 4 days. Animals were killed 24 hours after the final application and biopsies were taken. Increases in epidermal thickness between 12.4 and 180% were observed.

Foreman et al. (1979) applied 45-55 mg of crude Coal Tar to the dorsal flanks of hairless hamsters daily for 9 days. In another study the intervals were 1, 2, 4, and 6 day periods. After the specified length of treatment, animals were killed and the skin from the test and control sites were excised. The measurement of epidermal thickness was performed using a Quantimet 720 Image Analyzing Computer. Epidermal thickness increased significantly (p<0.05) by Day 2, reaching an almost two-fold increase by Day 9. Comedo formation was also noted in many of the sections studied.

**REPRODUCTIVE AND DEVELOPMENTAL TOXICITY**

Bacelar (1932) painted 11 female rabbits with tar and compared them to 2 controls. The absolute and relative weights of the ovaries were increased among the control rabbits than among those painted with tar. The author speculated that painting with tar decreased the number of interstitial cells in the ovary.

**GENOTOXICITY**

**BACTERIAL SYSTEMS**

**Coal Tar**

Koppers Company, Inc. (no date) examined seven Coal Tar distillate fractions for mutagenic activity using the Ames Salmonella/mammalian microsome reverse mutation assay. S. typhimurium strains TA98 and TA1537 were used with and without S9. The doses ranged from 0.00001 to 6.0 mg/plate and differed for each distillate fraction under study. Also, the number of experiments performed using each distillate fraction differed. Only two of the seven Coal Tar distillate fractions tested were mutagenic to TA98 in the presence of S9. The other five caused slight increases in the number of
TA98 revertants when S9 was present, but these were not dose-related or reproducible. Likewise, only one Coal Tar fraction showed an increase in the number of revertants in TA1537, but the increase was neither dose related nor reproducible.

Saperstein and Wheeler (1979) evaluated four therapeutic Coal Tar preparations used in the treatment of psoriasis (Zetar ® Emulsion, Extar ®, Lavatar, and Coal Tar Solution USP) using the Ames Salmonella/microsome mutagenicity test. The products were screened in strains TA98, TA100, and TA1538 with S9 fraction. Tar preparations were tested at doses ranging between 10 and 200 μg tar/plate. All of the Coal Tar preparations were mutagenic within the dose range tested. Strain TA98 was the most sensitive to the mutagenic effects of the tar, but a significant increase in his+ revertants was seen in all three strains.

Fysh et al. (1980) tested the mutagenicity of four commercial shampoos (Zetar Emulsion®, Tersa Tar ®, Pentrax ®, and Polytar ®) using S. typhimurium strain TA100 in the presence and absence of S9. Each sample was extracted with hexane, and dissolved in dimethylsulfoxide for the mutagenesis assay. It was decided that 5 μl of each shampoo extract gave close to optimal results (maximal mutagenicity and minimal toxicity). If the background rates are subtracted (85-118 revertants/plate), the revertant rates ranged between approximately 200 and 400/plate.

Santella et al. (1994) analyzed urinary mutagens from healthy volunteers and from psoriatic patients who applied an ointment or a gel-based Coal Tar product (or both) to their entire body surface at least once a day, followed by UBV treatment. Analysis was carried out on S. typhimurium strain TA100 in the presence of S9 and β-glucuronidase. Induced revertants/25 ml of urine for controls ranged from 0 to 480 (mean, 134±99 revertants/25 ml) while in patients the range was 0-670 (mean, 153±134 revertants/25 ml).

**Coal Tar Metabolites**

Wheeler et al. (1981) collected urine samples from 12 nonsmoking and 2 smoking psoriasis patients and from 4 non smoking volunteers (controls). Patients were treated with 1% Crude Coal Tar U.S.P. or 1 to 10% Crude Coal Tar in petrolatum in the evening. The following morning, patients received Coal Tar baths followed by UV light (mainly 290-320 nm UVB). Urine samples were extracted by adsorption and assayed in the Ames Salmonella/Microsome test using strain TA98 with S9. Ten of the 12 nonsmoking psoriatics had at least one mutagenic urine that was 3 to 10-fold higher than control urines. Typical values for nonsmoking psoriatics treated with Crude Coal Tar ranged from 42 to 496 his+/20 ml of urine after the subtraction of spontaneous his+ counts. Two nonsmoking normal volunteers were found to excrete mutagenic urines. The values for smoking psoriatic patients ranged from 213 to 1100 his+/20 ml urine.

These authors also applied Crude Coal Tar for 3 consecutive days to 3 male psoriatic patients, followed by exposure to UV rays for 2 minutes on the first day, 3 minutes on the second, and 4 minutes on the third. Urine was collected by each patient starting from 6 hours after the first therapeutic application of Coal Tar up to 36-48 hours after the last application. Urinary extracts were tested for mutagenicity in the Ames plate incorporation assay using S. typhimurium strains TA98 and TA100 in the presence of S9 both in the presence and absence of β-glucuronidase. Mutagenicity of the urinary extracts was detectable at 6-7 hours after the first application of Coal Tar. In all patients, elevated peak values, ranging from 37,600 to 129,300 induced revertants/g creatinine were reached after approximately 50 hours from the start of the therapy.

Clonfero et al. (1986) also tested the Coal Tar preparation in the Ames plate incorporation assay using the following dose levels: 500 μg, 100 μg, 10 μg, and 1 μg of Coal Tar in 100 μl of DMSO per plate in the presence or absence of S9. Salmonella typhimurium strains TA98 and TA100 were used. No direct mutagenic activity was found, while after addition of S9 mix, the Coal Tar was mutagenic on strain TA100 and TA98 of S. typhimurium. A 2-fold increase over the spontaneous revertant level was obtained with the following doses of Coal Tar/plate: 10 μg/plate on TA98 and 16 μg/plate on TA100 (Clonfero et al., 1986).

Jongeneelen et al. (1986) conducted the Ames mutagenicity test using urine from 5 female eczema patients treated with an ointment containing 10% Coal Tar for several days. Salmonella typhimurium strain TA98 was used in the presence of S9 and β-glucuronidase. The mutagenicity of the urine samples could not be assayed because of the toxic properties of the urine extract, even after dilution. However, the authors also used rats receiving topical Coal Tar treatment. The 24 hour urine samples from 3 rats were pooled for the mutagenicity study using S. typhimurium strain TA98 in the presence of S9 and β-glucuronidase. There was evidence of a dose-dependent uptake through the skin. The results are shown in Table 8.

Clonfero et al. (1987) monitored three male psoriatic patients during their therapy which consisted of a daily application of Crude Coal Tar for 3 consecutive days followed by exposure to UV rays. Urine samples were collected starting from 6 hours after the first Coal Tar application up to 36-48 hours after the last. Various doses of urine extracts were tested in the Ames plate incorporation assay using strains TA98 and TA100 of S. typhimurium in the presence of S9 and β-glucuronidase. The psoriatic patients had 64,462 induced revertants/g of creatinine compared to 279 for a group of 5 control subjects. In addition, there was a correlation found between the total urine PAH levels and mutagenic activity of
the urine extracts of the psoriatic patients.

Clonfero et al. (1989) collected a single sample of urine from a male psoriatic patient, following a 3 day therapeutical exposure to pure Coal Tar. The sample was serially diluted (dilutions ranging from 1:2 to 1:256), using a pool of urine from subjects not exposed to PAHs. Samples were assayed in the Ames plate incorporation assay on S. typhimurium strain TA98 in the presence of S9 and β-glucuronidase. The mutagenic activity ranged from 563 to 7034 induced revertants/g creatinine. Clear mutagenic activity was evident in the dilutions from 1:2 to 1:16.

Sarto et al. (1989) tested the mutagenicity of undiluted Coal Tar and an ointment containing 4% Coal Tar in the Ames plate incorporation assay. Dose levels corresponding to 500 μg, 100 μg, 10 μg, and 1 μg/plate (in 100 μl of DMSO) either of the pure Coal Tar or the ointment were assayed on S. typhimurium strains TA98 and TA100 in the presence or absence of S9. The mutagenicity of the 4% Coal Tar ointment, in the presence of S9, was five times less on S. typhimurium strain TA100 (0.3 net induced revertants/μg) and 10 times less on strain TA98 (0.9 net induced revertants/μg) than the corresponding mutagenicity of the pure Coal Tar. Neither the pure nor the diluted Coal Tar were mutagenic in the absence of S9.

In addition, Sarto et al. (1989) collected blood samples from 6 psoriatic patients using either undiluted Coal Tar or the ointment containing 4% Coal Tar for the evaluation of sister chromatid exchanges (SCEs). In 5 of 6 patients, chromatid type breaks and SCEs were significantly increased from historical averages; however, in comparison to pretreatment samples, only 2 were significantly increased.

Clonfero et al. (1990) analyzed urine samples from psoriatic patients treated topically with Coal Tar based ointments using the Ames plate incorporation test and the fluctuation test. Assays were done using S. typhimurium strain TA98 in the presence of S9 and β-glucuronidase. Mutagenicity of the extracts was detectable down to a dilution corresponding to a 1-OH-P content of about 50 μg/g creatinine and 7 μg/g creatinine of total PAHs. In the second part of the study, the minimum mutagenic dose, defined as the minimum concentration of 1-OH-P which could be hypothesized to correspond to a positive mutagenic response in each of the mutagenic assays was calculated. The mean level of 1-OH-P which could be estimated to correspond to a positive mutagenic response was 71.5±55.9 μg/g creatinine for the plate incorporation assay and 33.6±22.5 μg/g creatinine for the fluctuation test.

**MAMMALIAN ASSAYS**

**Coal Tar**

Thein et al. (2000) painted 6-10 week old Muta™Mice females (CD2-LacZ80/HazBR) with 10 mg/cm² of Coal Tar or corn oil on the dorsal skin, on an area of about 1 x 3 cm. Concentrations of 25% and 50% Coal Tar were made in corn oil. The controls were treated with corn oil only. Muta™Mice were shaved at the lower dorsal area 24 hours prior to painting. After 32 days, the animals were killed.

The epidermal cells were isolated and DNA was extracted for in vitro phage packaging. The DNA was added to the packaging extract and incubated. An overnight culture of E. coli C lac Z rec A gal E harboring a gal K gal T multicopy plasmid was inoculated in LB medium, MgSO₄, ampicillin, and kanomycin and grown. The host bacteria were used for infection after they reached an OD₆₀₀=1.7-1.9. X-gal is metabolized by β-galactosidase to yield blue plaques. Phages were allowed to infect an overnight culture of E. coli C lac Z rec A gal E. Only phages with an inactivated lac Z gene would be able to form plaques; bacteria infected with wild type phages would lyse. Light blue plaques with a partially inactivated lac Z gene were considered as mutants.

The mutation frequency in epidermal cells of treated mice was 2735±281 x 10⁻⁶ (n=3) and in control mice 171±97 x 10⁻⁶ (n=5). The authors concluded that that a single painting induced a 16-fold increase in the number of mutations above

<table>
<thead>
<tr>
<th>Applied Coal Tar</th>
<th>Time of excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-24 h</td>
</tr>
<tr>
<td>0 (mg/rat)</td>
<td>47</td>
</tr>
<tr>
<td>2.5 (mg/rat)</td>
<td>90</td>
</tr>
<tr>
<td>12.6 (mg/rat)</td>
<td>135</td>
</tr>
<tr>
<td>53.0 (mg/rat)</td>
<td>146</td>
</tr>
</tbody>
</table>

Table 8. Revertants/plate in an Ames assay of urine of rats treated with Coal Tar (Jongeneelen et al., 1986).
the background level (p<0.002) in epidermal cells (Thein et al., 2000).

**Coal Tar Metabolites**

Granella and Clonfero (1992) compared the sensitivity of the plate incorporation, macro-scale fluctuation, and microsuspension tests in detecting mutagens in urine of 3 male psoriatic patients who applied Coal Tar ointments for 4 consecutive days. Urine samples were filtered, eluted, and dried to obtain a 250 X concentrate for the plate and fluctuation tests and a 100 X concentrate for the microsuspension assay. S. typhimurium strain TA98 with S9 and β-glucuronidase was used. A urine extract was considered positive if it produced at least a doubling of the number of spontaneous revertants, or in the case of the fluctuation assay, a $X^2$ statistical significance with p<0.05.

All samples were mutagenic. Minimum mutagenic doses of extracts were 1.5-12.5, 0.4-3.1, and 0.5-2.5 ml of urine for the plate, fluctuation, and microsuspension tests respectively (Granella and Clonfero, 1992).

Giles et al. (1996) investigated the metabolic activation of benzo[g]chrysene (B[g]C), a moderately carcinogenic PAH present in Coal Tar, in mouse skin. B[g]C (0.5 μmol) was applied to the dorsal skin of male Parkes mice. Control mice received acetone only. Groups of four animals were killed 6 hours and 1, 2, 4, 7, or 21 days after treatment and the treated areas of skin were removed and frozen. DNA was isolated for 32P-postlabelling. Resolution of 32P-labelled adducts was performed on TLC sheets and visualized by autoradiography.

Seven principal adduct spots were consistently detected. Maximum levels of 6.55 fmol adducts/μg of DNA were detected 24 hours after treatment. There was a loss of 58% of the damage by day 4, followed by a slower removal of adducts over subsequent days (Giles et al., 1996).

**DNA ADDUCTS**

The formation of DNA adducts as a result of Coal Tar exposure is well recognized --- Table 9 summarizes the available data.

**CARCINOGENICITY**

The carcinogenicity of Coal Tar was first reported when a variety of metastasizing skin cancers occurred in mice painted with Coal Tar (Yamagiwa and Itchikawa, 1917). The ability of tar to cause cancer is generally attributed to its PAH content. According to Lin and Moses (1985), inducible microsomal enzymes, such as aryl hydrocarbon hydroxylase, convert these compounds into active forms which then bind to DNA and RNA, thus exerting their carcinogenic influences of DNA and RNA.

**RAT - SUBCUTANEOUS**

Jorstad (1923) injected Coal Tar beneath the epidermis of an embryonic rat and described how the epithelial cells migrated towards the drop to form a collar. When injected into subcutaneous tissue, Coal Tar caused dense masses of connective tissue cells to develop. These masses became larger when more tar was added until they were sarcomatous.

**MOUSE - ORAL**

In the study by Culp et al. (1998) (see Chronic Oral Toxicity section for details), the tumorigenicity of two Coal Tar mixtures was compared to benzo[a]pyrene (BP) after 2 years of feeding in mice. Liver neoplasms occurred in all dose groups fed Mixtures 1 and 2, but not in the control group. A significant dose-related trend was observed. Alveolar/bronchiolar adenomas, carcinomas, or both were present in the control group and in all groups of mice fed Mixtures 1 and 2. With Mixture 1, the incidence in the 0.3, 0.6, and 1.0% dose groups was significantly increased compared to the control group and a significant dose-related trend was observed. A significant dose-related trend was also found with Mixture 2 and the frequency was significantly increased in the 0.1 and 0.3% dose groups. The predominant lung lesions were adenomas, with only 15 carcinomas detected. Papillomas and/or carcinomas of the forestomach squamous epithelium were observed in all groups of mice treated with Mixtures 1 and 2 but no neoplasms were detected in the control group.

**MOUSE - DERMAL**

Murphy and Sturm (1925) studied the influence of external application of Coal Tar on the incidence of lung tumors in mice. The tar product used had for its base the residue from a coke oven in which the crude tar had been distilled at a temperature of approximately 377°C. The mice came from a stock with an extremely low cancer incidence. For each experiment, each mouse received Coal Tar on 12 areas, each less than a centimeter in diameter, painted in rotation such that 36 applications were distributed over 83 days. Each site was painted three times with a month in between. In the first experiment, 20 mice were painted according to the above scheme. As a control, 22 mice from the same stock were kept under the same laboratory conditions.

The lung tumor rate for the treated group in this experiment was 66.6%. None of the control animals showed developed tumors. In the second experiment, an unspecified number of mice were subjected to the same system of applications as that in the first experiment. The lung tumor rate was 60%; however, 1 mouse had a tumor of the uterus. In the third experiment, 40 mice were painted in the same fashion as in the
### Table 9. Studies on Coal Tar and DNA adducts

<table>
<thead>
<tr>
<th>Reference</th>
<th>Test system</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mukhtar et al. 1986c</td>
<td>male SENCAR mice</td>
<td>Topical application of 0.5 ml of Crude Coal Tar resulted in the formation of 278 fmol and 410 fmol BPDE-I-dG adducts per mg DNA in the epidermis and lung, respectively.</td>
</tr>
<tr>
<td>Schoket et al. 1988a</td>
<td>male Parkes mice</td>
<td>The application of 150 μl of 20% pharmaceutical grade Coal Tar solution resulted in ~0.4 fmol total adducts/μg DNA 24 hours after treatment. When given multiple treatments, a steady accumulation of adducts was seen in skin DNA.</td>
</tr>
<tr>
<td>Schoket et al. 1988b</td>
<td>Adult and fetal human skin samples</td>
<td>A single dose of pharmaceutical grade Coal Tar (equivalent to 30 mg Crude Coal Tar) resulted in 0.2 to &gt;0.6 fmol adducts/μg DNA.</td>
</tr>
<tr>
<td>Schoket et al. 1990</td>
<td>male Parkes mice skin</td>
<td>Application of 45 mg of Coal Tar ointment resulted in 0.5 fmol/μg DNA in the skin 1 day after the five treatments. Biopsies taken 24 hours after 5 treatments with Coal Tar ointment contained adducts ranging from 0.1 to 0.39 fmol/μg DNA.</td>
</tr>
<tr>
<td>Zhang et al. 1990</td>
<td>Human skin biopsy samples</td>
<td>Topical application of 10-50 mg/kg/day of Coal Tar for at least 7 days produced adduct levels ranging from 0.18 to 9.4 adducts/10⁸ nucleotides.</td>
</tr>
<tr>
<td>Weyand et al. 1991</td>
<td>B6C3F1 mice</td>
<td>A dose related increase in DNA adduct levels was observed in the lung tissue of mice fed 0.1, 0.2, 0.5, and 1% Coal Tar diets. Adduct levels were 4 times greater in mice fed a 0.5 or 1% diet relative to those fed a 0.1 or 0.2% diet.</td>
</tr>
<tr>
<td>Paleologo et al. 1992</td>
<td>Human lymphocytes</td>
<td>Psoriatic patients treated with Coal Tar products had mean adduct levels of 0.257±0.162 fmol BPDE/μg DNA in their white blood cells during treatment.</td>
</tr>
<tr>
<td>Pavanello and Levis 1992</td>
<td>Human lymphocytes</td>
<td>No significant differences were found in the amounts of total DNA adducts between psoriatic patients treated with Coal Tar and controls or between psoriatic patients before and after Coal Tar treatment.</td>
</tr>
<tr>
<td>Hughes et al. 1993</td>
<td>Male Parkes mice</td>
<td>When a group of PAHs were applied to mouse skin, the pattern of adducts formed in the skin resembled that elicited by the application of Coal Tar solution</td>
</tr>
<tr>
<td>Pfau et al. 1993</td>
<td>Male Parkes mice</td>
<td>A major DNA adduct formed in the skin of mice treated with pharmaceutical grade coal tar was found to be derived from benzo[a]pyrene rather than benzo[b]fluoranthene</td>
</tr>
<tr>
<td>Pavanello and Levis 1994</td>
<td>Human lymphocytes</td>
<td>In psoriatic patients treated with crude Coal Tar, there was no correlation between the levels of PAH-DNA adducts and the exposure to Coal Tar. According to the authors, Coal Tar treatment should not be considered a potential genetic and carcinogenic risk for psoriatic patients.</td>
</tr>
<tr>
<td>Culp and Beland 1994</td>
<td>Male B6C3F1 mice</td>
<td>Adduct levels were greater in Coal Tar fed mice compared to those fed benzo[a]pyrene. In Coal Tar fed mice, adduct levels were in the order of lung&gt;liver&gt;forestomach.</td>
</tr>
<tr>
<td>Santella et al. 1995</td>
<td>Human lymphocytes</td>
<td>PAH-DNA adducts were elevated in Coal Tar treated psoriasis patients compared to controls (6.77±12.05 adducts.10⁹ nucleotides).</td>
</tr>
<tr>
<td>Giles et al. 1997</td>
<td>Male Parkes mice</td>
<td>When 0.5 μmol of benzo[c]chrysene, a component of Coal Tar was applied to the skin of mice, a maximum adduct level of 0.89 fmol adducts/μg of DNA was detected in the skin.</td>
</tr>
<tr>
<td>Godschalk et al. 1998</td>
<td>Human skin</td>
<td>When eczema patients were topically treated with Coal Tar, median aromatic DNA adduct levels significantly increased in the skin from 2.9 to 63.3 adducts/10⁸ nucleotides.</td>
</tr>
<tr>
<td>Pavanello et al. 1999</td>
<td>Human lymphocytes</td>
<td>Median aromatic DNA adduct levels were significantly increased in lymphocytes from 0.33 to 0.89 adducts/10⁸ nucleotides.</td>
</tr>
<tr>
<td>Koganti et al. 2000</td>
<td>Female CD-1 mice</td>
<td>In animal feeding studies, 7H-benzo[c]fluorene, a PAH in Coal Tar, is a potent lung adductor.</td>
</tr>
</tbody>
</table>

a BPDE-I-dG = benzo[a]pyrene diol epoxide-I-deoxyguanosine

b Concentrations of benzo[a]pyrene, benzo[b]fluoranthene, benzo[j]fluoranthene, benzo[k]fluoranthene, benzo[ghi]perylene, dibenz[a,h]-anthracene, indeno[1,2,3-cd]pyrene, benz[a]anthracene, and cyclopental[cd]pyrene equivalent to those present in 30 mg of Coal Tar were used
first experiment. For controls, a group of 16 untreated mice from the same stock were kept under the same conditions. While none of the control mice had any tumors, the tumor incidence for the painted animals was 78.3% (Murphy and Sturm, 1925).

Watson and Mellanby (1930) studied the effects of pretreatment of the skin and diet on Coal Tar induced carcinogenesis, but much experimental detail is lacking in the report.

Pretreatment with tannic acid (saturated aqueous solution) or by application of homologous fat (ether extracted from mouse carcasses) followed by Coal Tar application was done for 120 days in 70 animals for each group. The animals were followed for one year. The authors concluded that the rate of growth of tumors was unaffected by tannic acid pretreatment, but accelerated by fat pretreatment, compared to controls.

Pretreatment with olive oil was done in another group of 70 animals for 90 days. According to the authors, animals in the olive oil + Coal Tar group showed a greater tendency to develop tumors than the control group. This is a different measure than above, where rate of growth was determined.

Pretreatment with ether (to remove fatty substances in the skin) prior to Coal Tar treatment was done in another group of 60 mice for 120 days. Animals were followed for 360 days. The authors interpreted the results to suggest that the rate of tumor growth was inhibited by ether pretreatment. Lung nodules in tumor-bearing animals were reduced in the ether pretreatment group, as well.

In another experiment, a diet rich in butter was compared to control diet. Animals (70 in each group) were treated with Coal Tar daily for 120 days and followed for 360 days. More animals in the butter diet group had tumors than the controls, and those in the butter diet had a higher proportion with lung nodules than the control group (Watson and Mellanby, 1930).

Seelig and Cooper (1933) tested the effect of light on cancer in mice. Three sets of mice were used in this experiment: (1) 125 male mice for tarring in the dark; (2) a similar group of 125 mice for tarring in the light; and (3) a similar group of 50 mice which were kept as untarred controls in the dark. Coal Tar (distillate at 370°-440°C was collected) was applied to the interscapular region at the root of the neck, over an area about 1.5 cm in diameter. The time intervals between applications were varied to meet the problem of high death rates in the mice. Applications continued until the death of the last tarred mouse. A necropsy was performed on all mice that died. Only growths that infiltrated the subcutaneous muscle layers were considered carcinomas. The last mouse in Group 1 died 23 weeks after the first application and the number of carcinomas in the group was 11. In contrast, the last mouse in Group 2 died 32 weeks into the experiment and there were only 5 cases of carcinomas in the group. When the last tarred mouse died, only 58% of the control mice had died and none of the Group 3 mice had carcinomas. The authors concluded that the absence of light did not compromise the health of mice and that white light was not a necessary factor in the development of tar cancer in mice.

Berenblum (1948) painted 12 white mice twice weekly for 41 weeks with undiluted Coal Tar on a small area of the skin in the interscapular region. Papillomas appeared in the treated areas in seven of the mice. Of these seven, four subsequently developed squamous malignant growths, which were found to be squamous cell carcinomas. There were no metastases.

Christie and McCallum (1958) studied the carcinogenicity of brown Coal Tar. Included in their experiments were two treatments (8 mice each, C3H strain) where (1) brown Coal Tar ointment, identical with black Coal Tar ointment APF, but substituting brown Coal Tar for black and (2) black Coal Tar ointment were applied on the back and flank of the mice once per day, six days per week. In the brown Coal Tar ointment group, no papillomata, warts or deranged keratinisation occurred in 8 months of painting. In the black Coal Tar ointment group, five animals developed warty papillary growths from 6-8 months, but no malignant tumors were obtained.

Wright et al. (1985) performed painting assays on Charles River CD-1 mice (numbers not given). Industrial Coal Tar from the National Bureau of Standards (NBS) and the Coal Tar portion of a pharmaceutical stock material were diluted 1:1 by weight in methylene chloride and applied to the shaved backs of the mice in 50 μl volumes. Two weeks after initiation, 50 μl of phorbol myristate acetate were applied to the treated area twice weekly for 6 months. Both the NBS Coal Tar and the Coal Tar isolate from the pharmaceutical stock produced tumors in all the mice after 169 days.

Mukhtar et al. (1986a) applied a single dose of 200 μl of crude Coal Tar in 0.2 ml of acetone to 20 female SENCAR mice. The mice were shaved and depilated before the experiment. Skin tumor formation was recorded weekly and tumors greater than 1 mm in diameter were included in the cumulative total only if they persisted for 2 weeks or more. The first appearance of tumors occurred at 6 weeks. After 8 weeks, there were 46 cumulative tumors in the group of mice. At the termination of the experiment after 11 weeks, 100% of the mice had tumors and the average number of tumors/mouse was 3.3.

Warshawsky et al. (1993) painted Coal Tar (in toluene such that it contained 0.0006% benzo[a]pyrene) on the clipped backs of male C3H/HEJ mice twice weekly for up to 66 weeks. Observations of the skin were recorded. Lesions persisting for at least one week which were a minimum of 1 mm² in size were considered papillomas. The times and
appearance of tumors and time for their progression to malignancy were noted. A necropsy was conducted on all animals. Tumors were present in 51% of the mice. The latent period was 73 weeks.

Phillips and Alldrick (1994) attempted to determine whether treatment with Coal Tar followed by dithranol was tumorigenic. Female CD-1 mice were treated topically 5 times a week with 1.5% Coal Tar ointment (50 mg per treatment) for 2 weeks and then with 0.1% dithranol cream (50 mg per treatment) three times weekly for 40 weeks. Other groups received either Coal Tar or dithranol alone. Hair on the mice was shaved and the material was applied to the whole of the shaved area. Tumors >1 mm were scored. The animals were killed by cervical dislocation and subjected to post-mortem examination. None of the mice treated with Coal Tar or dithranol alone developed tumors during the experiment. However, four mice that had received Coal Tar followed by dithranol developed papillomas and 12 mice had enlarged cervical lymph nodes. Five mice that received dithranol only also had enlarged lymph nodes, though this condition was not seen in any of the mice treated with Coal Tar only.

**MOUSE - MUCOSAL**

Shabad (1927) applied Coal Tar to the rectum of 78 juvenile white mice 2-3 times a week. A thin smooth round wooden stick with a blunt tip was dipped in Coal Tar and carefully inserted 1.5-2 cm into the rectum. Of the 37 animals that survived the first 6 months of the test, cancer of the perianal skin developed in 21 (56.7%).

**RABBIT - DERMAL**

Itchikawa and Baum (1925) conducted three experiments using rabbits (strain unspecified). In the first experiment 6 rabbits had Coal Tar painted on their ears in addition to being fed 10 grams of anhydrous lanolin mixed in the food. In the second experiment, 6 rabbits had Coal Tar painted on their ears in addition to being fed 0.5 cc of a 2% watery solution of potassium arsenite mixed in the food. In the third experiment, 6 rabbits had Coal Tar painted on their ears. The painting covered the entire inner surface of rabbits’ ears and was performed usually twice a week for 10 weeks. After the painted area dried, the coal tar was easily removed with tweezers, and the ears were repainted. The appearance of folliculo-epithelioma and its transformation into the early stage of carcinoma appeared around the same time in all the animals, but the alteration of the early stage into advanced carcinoma took place sooner in the animals that were fed on arsenic and lanolin than in those that were painted with Coal Tar alone.

Kligman and Kligman (1994) applied ~10 mg of crude Coal Tar on albino rabbit ears at 0.001, 0.01, 0.1 and 1.0% with 5 weekday applications for 3 weeks and at 10, 25, and 100% three times weekly for up to 15 weeks. Crude Coal Tar, whether applied at 10, 25, or 100% was carcinogenic. With 10% Coal Tar, tumors developed as early as 1-2 weeks following 3 weeks of treatment. With longer term treatment, the number of tumors increased. No results were reported for Coal Tar concentrations at 1.0% or less.

These authors also applied ~10 mg of crude Coal Tar on albino rabbit ears at 0.001, 0.01, 0.1 and 1.0% with 5 weekday applications for 3 weeks and at 10, 25, and 100% three times weekly for up to 15 weeks. The vehicle was petrolatum. Crude Coal Tar, whether applied at 10, 25, or 100% was comedogenic. The threshold for comedogenicity was less than 0.1% with 3 weeks application (Kligman and Kligman, 1994).

**CLINICAL ASSESSMENT OF SAFETY**

**DERMAL IRRITATION**

Burden et al. (1994) patch tested 74 psoriasis patients with Coal Tar 3% pet. A positive reaction was followed by dilution series testing down to a concentration of 0.1%. Of the 74 patients, 13 reported that they were allergic to coal tar; however, in actuality only 2 had a positive patch test reaction confirmed by serial dilutions.

**PHOTOSENSITIZATION AND PHOTOTOXICITY**

Several of the polycyclic aromatic hydrocarbons which make up coal tar are photosensitizers and cause phototoxity by an oxygen dependent mechanism (Gould et al. 1995). Ultraviolet-A (UVA) light contains the part of the light spectrum that activates coal tar (Arnold 1997). Studies on photosensitization and phototoxicity of Coal Tar are summarized in Table 11.

**FOLLICULITIS**

Folliculitis is associated with the prolonged use of some tars (Lerner and Lerner, 1960).

**COMEDOGENICITY**

Kaidbey and Kligman (1974) applied 25% crude Coal Tar to the backs of adult males for 3 times a week for 3 weeks. Biopsy specimens were obtained at 7, 14, and 21 days and sporadically thereafter. Caucasians and African Americans differed in their responses. In Caucasians, the response was primarily inflammatory. In African Americans, the inflammatory phase was largely absent. Instead, small open comedones began to appear after 14 days and were obvious by the end of the treatment period.
Table 11. Studies on Coal Tar photosensitization and phototoxicity.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starke and Jillson 1961</td>
<td>Case Report - A 37 year old male had eczema and weeping to patch tests of Coal Tar. A photopatch developed an even more eczematous reaction.</td>
</tr>
<tr>
<td>Everett et al. 1961</td>
<td>When Coal Tar solution and ultraviolet light were applied to the skin of 21 persons, erythema and tanning were more prominent at the control sites in all patients</td>
</tr>
<tr>
<td>Everett and Miller 1961</td>
<td>When Coal Tar solution (USP) and ultraviolet light were applied to the skin of five adult males, erythema was greater in the tar-free areas than the tar-exposed areas</td>
</tr>
<tr>
<td>Kaidbey and Kligman 1974b</td>
<td>The intensity of the phototoxic response to Coal Tar was strongly influenced by the vehicle, with vanishing cream producing the greatest reaction (erythema and minimal edema)</td>
</tr>
<tr>
<td>Kaidbey and Kligman 1975</td>
<td>When 40 µl of a 25% Coal Tar distillate was applied to the skin of adult males irradiated with UVA alone, the epidermis was largely unaffected except for occasional intercellular edema</td>
</tr>
<tr>
<td>Kaidbey and Kligman 1977</td>
<td>Volunteers who applied a 5% concentration of four different crude Coal Tars followed by UVA exposure experienced whealing followed by raised lesions.</td>
</tr>
<tr>
<td>Kroon 1983</td>
<td>40 out of 194 patients photopatch tested with Waxtar (Coal Tar 5%) had phototoxic reactions. 4 patients developed pigmentation 7 days after irradiation.</td>
</tr>
<tr>
<td>Diette et al. 1983, 1985</td>
<td>The time between tar removal and UVA irradiation was important in determining the minimal phototoxic dose and the minimal smarting dose in human volunteers.</td>
</tr>
<tr>
<td>Berne and Fischer 1987</td>
<td>Compared to Balnetar® and Spiritus carbonis detergents, 5% crude Coal Tar gave the strongest erythema phototoxicity. Its action spectra ranged from 330 to 400 nm.</td>
</tr>
</tbody>
</table>

* Minimal phototoxic dose: the minimal UVA dose required to induced delayed erythema

* Minimal smarting dose: the minimal UVA dose required to induce an immediate smarting reaction

Mills et al. (1978) applied 15% crude Coal Tar in Hydrophilic Ointment USP to the upper backs of 5 adult males. The agent was applied to 8 cm squares of skin thrice weekly. Before renewing the applications, one-half of each square was subjected to UVA radiation. A combination of open and closed comedones was present in each of the 5 subjects receiving Coal Tar without radiation. Comedones and papules increased in size and number when irradiated.

CASE REPORTS

Table 12 summarizes case reports involving Coal Tar.

CLINICAL TESTING

Wright et al. (1992) divided 15 healthy volunteers (11 women, 4 men) into 3 groups of 5, subjecting them to different modes of application of Berniter®, a 0.5% coal tar preparation for the scalp. In application mode 1, Berniter® was applied twice a week over a period of 8 weeks; in mode 2, it was applied on a daily basis for 8 weeks. The preparation was administered by wetting the scalp with water, spreading and massaging the preparation into the scalp, rinsing the hair and scalp with water, spreading and massaging the preparation into the scalp again, and allowing the preparation to work for 5 minutes. In application mode 3, Berniter® was applied every other day over a period of 4 weeks. Here the preparation was applied under occlusion (a plastic cap) and allowed to work for 15 minutes. The test subjects’ 24-hour urines were tested for low-molecular phenol bodies before and after treatment. In addition, multiple chemical analyses were undertaken (GOT, GPT, Gamma-GT, AP, LDH, cholinesterase, total bilirubin, etc.) as well as creatinine clearance, gel-electrophoresis protein excretion pattern, and alanine aminopeptidase activity.

No pathological findings were noted in any of the test subjects. The results of the blood and urine studies, as well as of the multiple chemical analyses, were all within normal limits (Wright et al., 1992)

CLINICAL TESTING FOLLOW-UP

Kaaber (1976) reported on 326 patients treated with Coal Tar for atopic dermatitis. Patients were followed for 42 years to determine if they had developed cancer. These 326 patients had been treated in the Department of Dermatology, Finsen Institute, Copenhagen, Denmark from 1930 to 1939 for atopic dermatitis. The follow up period for each patient was calculated from the first examination until the date of death or
Table 12. Coal Tar case reports.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgson, 1948</td>
<td>A 62 year old male using Coal Tar to treat pruritus developed epithelioma.</td>
</tr>
<tr>
<td>Simon and Brandt, 1953</td>
<td>A 60 year old female with a history of psoriasis had a positive reaction to a patch test with 2% crude Coal Tar in an oxycholisterol-petroleum ointment base.</td>
</tr>
<tr>
<td></td>
<td>A 64 year old female had a positive reaction to a patch test with 3% crude Coal Tar in petrolatum with erythema and edema occurring within 48 hours.</td>
</tr>
<tr>
<td>Alexander and Macrosson, 1954</td>
<td>A 31 year old male using a 20% Coal Tar in emulsifying base ointment to treat psoriasis developed squamous epithelioma.</td>
</tr>
<tr>
<td>Person and Rogers III, 1976</td>
<td>A 53 year old male using the Goeckerman regimen to treat psoriasis developed bullous pemphigoid.</td>
</tr>
<tr>
<td></td>
<td>A 53 year old male using 2% crude Coal Tar to treat psoriasis developed bullae.</td>
</tr>
<tr>
<td></td>
<td>A 66 year old male using the Goeckerman regimen to treat psoriasis developed a bulla.</td>
</tr>
<tr>
<td>Durkin et al., 1978</td>
<td>A 32 year old male psoriatic developed melanoma after 16 years of treatment with UV light and Coal Tar.</td>
</tr>
<tr>
<td>Koerber et al., 1978</td>
<td>A 53 year old female using Coal Tar creams to treat psoriasis developed bullous pemphigoid.</td>
</tr>
<tr>
<td>Gonçalo et al., 1984</td>
<td>A 25 year old female with psoriasis had a positive reaction to a patch test with Coal Tar.</td>
</tr>
<tr>
<td></td>
<td>A 17 year old female with psoriasis had a positive reaction to a patch test with Coal Tar.</td>
</tr>
<tr>
<td>Kokkini and Giotaki, 1984</td>
<td>A 45 year old female psoriatic developed pancytopenia due to hypoplastic and ineffective bone marrow following 5% Coal Tar cream application for 6 months.</td>
</tr>
<tr>
<td>Riboldi et al., 1986</td>
<td>A 54 year old female with psoriasis had a positive reaction to a patch test with Coal Tar (blistering).</td>
</tr>
<tr>
<td>Illchyshyn et al., 1987</td>
<td>A 31 year old female with eczema had a positive reaction to patch tests with 1% and 5% Coal Tar in petrolatum.</td>
</tr>
<tr>
<td>McGarry and Robertson, 1989</td>
<td>A 67 year old male with scrotal psoriasis developed squamous cell carcinoma after using a 10% crude Coal Tar ointment.</td>
</tr>
<tr>
<td>Cusano et al., 1992</td>
<td>A 57 year old male had a positive reaction to a patch test with Coal Tar (5% pet).</td>
</tr>
<tr>
<td>Landro et al., 1992</td>
<td>A 29 year old male with psoriasis had a positive reaction to a patch test with 0.05% Coal Tar.</td>
</tr>
<tr>
<td>Ibbotson et al., 1995</td>
<td>A 29 year old female asthmatic had severe symptomatic bronchoconstriction which was likely due to inhalation of Coal Tar vapor from the application of Coal Tar bandages. An inhalation challenge test with vapor from the Coal Tar bandages produced a 28% reduction in forced expiratory volume.</td>
</tr>
<tr>
<td>Clark and Sheretz, 1998</td>
<td>A psoriasis patient had positive allergic reactions to Coal Tar diluted to 1% and 5% when given patch tests.</td>
</tr>
</tbody>
</table>

until cancer was diagnosed. The expected cancer rated was calculated based on the cancer registry data on the incidence of cancer in Denmark. The values were then compared to the results of the follow up of the 326 patients. There was no sufficient deviation in the expected values versus the observed values for the 326 patients treated for atopy.

Maughan et al. (1980) performed a 25 year follow-up study on 305 patients with atopic dermatitis or neurodermatitis who received Coal Tar and UV treatment (Goeckerman therapy) from 1950 through 1954. These patients were located and contacted by either a follow-up questionnaire or telephone in order to determine if any malignancy of the skin or other cancer had developed since the initial treatment. The numbers of persons in whom skin cancers were expected to develop were calculated using data from the Third National Cancer Survey. Of the 305 patients, 13 reported skin cancer had developed after the initial Goeckerman therapy. Eight patients had basal cell carcinomas, one had a squamous cell carcinoma, two had an unknown skin malignancy, and two had malignant melanomas. The maximum number of people in the study who would have been expected to have developed non-melanoma skin cancers if they had lived in any of the regions reported in the Third National Cancer Survey was 18.8 for the
Worth are since 11 patients developed non-melanoma skin cancer, no significant increase in the incidence of skin cancer was seen in the population of patients when compared to the expected occurrence of skin cancer if the population were to have resided in the Dallas-Fort Worth area.

In a later study, Pittlekow et al. (1981) performed another 25 year follow-up analysis of patients receiving Coal Tar and UVB treatment from 1950-1954. Patients were instructed to report any cancerous lesions of the skin that had been removed since the initial Goeckerman treatment. Of 260 patients, 20 (7.7%) had one or more reported carcinomas of the skin. One patient reported the development of a malignant melanoma; the remaining 19 reported either basal cell or squamous cell carcinomas or unknown varieties of cutaneous malignant neoplasms. Comparing the group of patients in which skin cancer subsequently developed with the group in which it did not, there was no appreciable difference in the median number of days of Coal Tar treatment.

The Pittlekow study also contains the results from a review by the National Psoriasis Foundation on the medical histories of 15,000 of its members. The results from that review found no suggestion of an increased risk to skin cancer. The results of this survey also showed no increase in skin cancer from patients who had been treated with Coal Tar.

Larko (1982) conducted a study in Sweden on 85 psoriasis patients extensively treated with UVB light and topical Coal Tar. The results were compared to 385 individuals in a control group. The incidence of premalignant/malignant skin lesions was only 5.96% in the 85 treated psoriasis patients, but was 10.1% in the 385 control individuals. The authors conclude that it is unlikely that treated psoriatic patients will have an increased incidence of malignant skin lesions from their treatment with topically applied Coal Tar and UVB light.

Jones et al. (1985) compared the observed incidence of carcinoma in 719 psoriasis treated with Tar with that expected in the general population. The 719 patients (305 males and 414 females) had received topical Tar therapy intermittently over a 10 year period between 1953 and 1973. There were 19 cases of cancer in the male patients which was very similar to that expected from the general population. In the case of female patients, the 12 cases found was less than expected. Of particular interest were the rates of cancer in the skin and bladder, neither of which showed a significant increase in the patient population. The authors concluded that long-term Tar therapy was not associated with an increase in cutaneous or non-cutaneous malignancy in patients with psoriasis.

Bhate (1993) published the results of an epidemiology study on the use of Coal Tar in the treatment of psoriasis. Between 1977 and 1983, 2,247 patients were treated with Coal Tar at the Department of Dermatology, Royal Victoria Infirmary, UK where they were examined for the prevalence of both skin and internal malignancies. These results were compared against 4,494 matched control individuals. The results of this extensive epidemiological study were that there was no difference in the age of onset of skin cancers between psoriasis and controls. There was also no evidence of a cumulative therapeutic risk. Finally, there was no difference in the prevalence of non-skin cancers between psoriatics and controls.

Jemec (1994) published results from 88 patients treated extensively with Coal Tar in Denmark from 1917 to 1937. Cancers were identified through the Danish Cancer Registry and relative risk of cancer was calculated. No overall risk of cancer for the treated patients was found in the 88 patients compared to the incidence of cancer in the general population. The authors go on to state that these data provide further support for the safety of Coal Tar in the management of dermatological disease.

**Epidemiology**

Franssen et al. (1999) performed a retrospective study on the reproductive toxicity of Coal Tar in humans. Women were chosen based on past history of psoriasis or dermatitis. Out of 103 pregnancies there were 59 in which no Coal Tar had been used, 21 in which it was uncertain whether or not Coal Tar had been used, and 23 in which Coal Tar was definitely used. Of the 59 in which no Coal Tar had been used, 19% of the pregnancies ended in spontaneous abortion and 5% in a congenital disorder. In the 23 cases in which Coal Tar was used during pregnancy, 26% resulted in spontaneous abortion and 4% in a congenital disorder. The authors note the small sample size of patients exposed to Coal Tar and the lack of uniformity regarding the time and duration of exposure.

In a study completed in Yugoslavia, Vlajinac et al. (2000) found that the use of tar for cosmetic purposes was a risk factor for basal cell carcinoma. Participants (200 confirmed cases of basal cell carcinoma and 399 control subjects) were interviewed by physicians and given questionnaires regarding various risk factors. The use of tar was found to be a significant risk factor (p=0.0064). However, the authors also used oral methotrexate and photochemotherapy (PUVA) and the effects from Coal Tar cannot be separated out as the sole cause.

**Risk Assessments**

The International Agency for Research on Cancer (IARC) reviewed PAHs as well as Coal Tars in 1984 (IARC 1985). IARC concluded: “There is sufficient evidence for the carcinogenicity in experimental animals of coal-tars, creosotes, creosote oils, anthracene oils and coal-tar pitches.” IARC evaluated the limited epidemiological studies generated
on the therapeutic use of Coal Tar up to that point in time, but could not draw any conclusions. The therapies were mixed in most studies and therefore effects from Coal Tar alone could not be evaluated.

In a review of the use of dermatologic drugs during pregnancy, Bologa et al. (1992) suggested limiting the use of Coal Tar to the second and third trimesters, once organogenesis is complete. In a review of the use of OTC drugs during pregnancy, Conover and Rayburn (1992), however, believe the risk of congenital anomalies in children of women treated with Coal Tar during pregnancy is unlikely.

Pion (1995) examined the question of whether the use of Coal Tar in dermatological practice was a cause of concern. From his extensive review of both animal and human data, he stated that “conclusive evidence for the carcinogenicity of coal tar used in dermatologic practice is lacking.”

Hess (1999) used BP data as a surrogate to perform a quantitative risk assessment on Coal Tar as an ingredient. Rinse-off hair care products contain 1% refined Coal Tar that were stated to include a maximum level of 50 mg/kg BP. After a typical application of 12 g, it was estimated that 1% of the product remains after rinsing. The lifelong exposure to BP was estimated to be not higher than 0.001 ng/cm² of exposed skin surface area per day, which was below the BP no-effect level. The author concluded that the safety of cosmetic usage of coal tar was further confirmed by extensive epidemiological data showing that no carcinogenic consequences have emerged from its well-established and intense use in dermatological therapy.

Fehling (2000) stated that an absorbed dose of 52.12 mg/day was the no significant risk level (NSRL) for Coal Tar containing products.

Jackson (2003) generated a quantitative risk assessment for 8 Coal Tar containing products, one soap bar, two ointments, and 5 shampoos by chemically analyzing the PAH content of these products. The lifetime averaged absorbed dose for each of these Coal Tar containing products was significantly below the 0.0600 µg/day NSRL for benzo[a]pyrene, a known genotoxic chemical.

Coal Tar itself is on California’s Proposition 65 list of substances known to be carcinogenic; soots, tars, and mineral oils (untreated and mildly treated oils and used engine oils) are also listed (OEHHA 2003).

**SUMMARY**

Coal Tar is a semisolid byproduct obtained in the destructive distillation of bituminous coal, produced in coking ovens as a byproduct in the manufacture of coke. Coal Tar is a nearly black, viscous liquid, heavier than water, with a naphthalene-like odor and a sharp burning taste. Crude Coal Tar is composed of 48% hydrocarbons, 42% carbon, and 10% water.

Coal Tar is an active ingredient in OTC drug products and is described as an antidiandruff agents, cosmetic biocides, and denaturant in cosmetics. Coal Tar is monographed by the Food and Drug Administration (FDA 1991) as a Category I (safe and effective) for OTC drug ingredient for use in the treatment of dandruff, seborrhoea, and psoriasis. While Coal Tar was reported in 2002 to FDA to be used in four formulations, these uses are OTC. No uses of Coal Tar as a cosmetic biocide or denaturant have been reported. The concentration of use of Coal Tar was reported as follows: Shampoos (OTC) (1-7%), Bath soaps and detergents (OTC) (0.06-5%), and Lotions (OTC)(5%).

Mice, rats, and humans given a single dose of Coal Tar solution orally resulted in the induction of one or more of aryl hydrocarbon hydroxylase (AHH), ethoxyresoru fin deethy lase (ERD), and 7-ethoxy coumarin O-deethylase (ECD) activities in the skin and liver (liver studies not performed on humans). The absorption of Coal Tar through skin and its systemic distribution is confirmed by these AHH, ERD, and ECD induction studies. The absorption of specific Coal Tar polycyclic aromatic hydrocarbons (PAHs) was demonstrated in a pig ear skin penetration study. The presence of acridine, and other Coal Tar PAHs, in urine of patients or healthy volunteers treated with Coal Tar demonstrated absorption of Coal Tar.

In short term animal studies mice fed Coal Tar at concentrations over 2% in their diet found their diet unpalatable, but no adverse effects were reported other than weight loss.

Injection of 1 ml Coal Tar 3x over 21 days produced malaise in rats. Injection of a 5% Tar residue in rabbits produced eating avoidance, respiratory difficulty, sneezing, and weight loss. Injection of 5 mg/kg day⁻¹ of a Coal Tar suspension for 8 days in rats decreased water intake, resulted in black residues in the liver, and increased liver weights.

In a subchronic neurotoxicity study using mice using 2.0 µl/ml of a mixture of phenols, cresols, and xyleneols at concentrations approximately equal to those expected in Coal Tar extracts, regionally selective toxicity was found, with a rank order of striatum > cerebellum > cerebral cortex.

Mice given a chronic exposure to 0.3% Coal Tar in the diet had a significantly decreased survival. Liver neoplasms were seen in a significant dose-related trend.

When Coal Tar was applied to the backs of guinea pigs, increases in epidermal thickness were seen.
Painting female rabbits with tar decreases the absolute and relative weights of the ovaries and decreased the number of interstitial cells in the ovary. A retrospective study of the reproductive toxicity of Coal Tar in humans compared 23 exposed women to 59 controls and found little difference in spontaneous abortion and congenital disorders. Conflicting advice has been given to pregnant women — one suggestion was to avoid use of Coal Tar to the 2nd or 3rd trimester, after major organogenesis; another opined that the risk of congenital abnormalities in children of women treated with Coal Tar during pregnancy is unlikely.

When four therapeutic Coal Tar preparations (Zetar® Emulsion, Estar®, Lavatar, and Coal Tar Solution USP) used in the treatment of psoriasis were screened using the Ames S. typhimurium/microsome mutagenicity test, all of the Coal Tar preparations were mutagenic within the dose range tested. Strain TA98 was the most sensitive to the mutagenic effects of the tar. Urine and blood from patients treated with Coal Tar were genotoxic in bacterial assays. Coal Tar was genotoxic in plate incorporation, macro-scale fluctuation, and microsuspension assays.

In a mammalian genotoxicity assay (Mutagenicity Mice), the mutation frequency in treated animals was 2735±281x10^{-6} (n=3) and in control mice 171±97x10^{-6} (n=5), a 16 fold increase in the number of mutations above the background level in epidermal cells.

Coal Tar induces DNA adducts in various tissue types. A lowest observed effect level of 0.1% Coal Tar (oral) produced DNA adducts in mouse lung tissue.

In a carcinogenicity experiment, five groups of 95 mice were painted with Coal Tar for four months. The percentage of animals with tumors in the lungs was 45.1, 53.7, 50.0, 55.6, and 57.1, respectively. After being treated with 200 μl Crude Coal Tar in 0.2 ml acetone for 11 weeks, 100% of the 20 female SENCAR mice had tumors. After Coal Tar was applied to the rectum of 78 juvenile white mice for 6 months, of the 37 animals that survived, cancer of the peri-anal skin developed in 21 (56.7%).

Out of 74 psoriasis patients, 13 reported that they were allergic to Coal Tar; but only 2 had a positive patch test. Several of the polycyclic aromatic hydrocarbons which make up Coal Tar are photosensitizers and cause phototoxicity by an oxygen dependent mechanism. Coal Tar was comedogenic in three small clinical studies. Several published reports describe cases of contact sensitivity to Coal Tar. Folliculitis is associated with the prolonged use of some tars.

Follow-up studies have been performed on patients who have received Coal Tar therapy of one form or other: 326 patients with atopic dermatitis or neurodermatitis treated with Coal Tar were followed for 42 years; 305 patients who received Coal Tar and UV treatment were followed for 25 years; 206 patients receiving Coal Tar and UV treatment were followed for 25 years; 85 psoriatic patients treated with Coal Tar and UV treatment were compared to 385 matched controls; 719 psoriatics who received Coal Tar therapy intermittently were studied 10 - 25 years later; 2,247 psoriatics treated with Coal Tar were compared to 4,494 matched controls; cancers identified from a cancer registry in 88 patients treated extensively with Coal Tar from 1917 to 1937 were compared to the general population. In none of these follow-up studies was an increase in the risk of cancer found.

One retrospective study of women who used Coal Tar at the time of their pregnancies. It was unclear if the percentage with spontaneous abortions or births with congenital disorders was higher in the Coal Tar group compared to controls. A case-control study of 200 individuals with basal cell carcinoma compared to 399 controls identified use of tar for cosmetic purposes as a risk factor, but it was not clear how oral methotrexate and phototherapy may have confounded the results.

DISCUSSION

The data presented in this report indicate that Coal Tar can produce adverse biological effects. While the CIR Expert Panel believes that Coal Tar use as an antifungal ingredient in OTC drug preparations is adequately addressed by FDA regulations, the Panel also believes that the appropriate concentration of use of Coal Tar in cosmetic formulations should be that level that does not have a biological effect. The Panel was concerned that information on the maximum concentration that could be used in cosmetic formulations that would not have a biological effect was not available.

Section I, paragraph (p) of the CIR Procedures states that “A lack of information about an ingredient shall not be sufficient to justify a determination of safety.” In accordance with Section 30(j)(2)(A) of the Procedures, the Expert Panel informed the public of its decision that the data on this ingredient were not sufficient for determination whether the ingredient, under relevant condition of use, was either safe or unsafe. Additional data needed to make a safety assessment are product types in which Coal Tar is used (other than as an OTC drug ingredient), use concentrations, and the maximum concentration that does not induce a biological effect.

CONCLUSION

The available data are insufficient to support the safety of Coal Tar for use in cosmetic products as described in this safety assessment.
REFERENCES


Cosmetic, Toiletry, and Fragrance Association (CTFA). 2002. Concentration of use of Coal Tar. Unpublished data submitted by the CTFA. 1


Environmental Protection Agency (EPA). 1994. *Toxicological Profile for Polycyclic Hydrocarbons (PAHs)*. Washington, DC: Environmental Protection Agency:

1 Available for review from the Director, CIR, 1101 17th Street, NW, Suite 310, Washington, DC 20036


