III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Tars and pitches are black or brown, liquid or semisolid products derived from coal, petroleum, wood, shale oil, or other organic materials. Pitches are the residues from heated and distilled tars; they can have a variety of properties but are generally solid cementlike materials that liquefy when heated. Tars derived from a variety of organic materials are similar in properties [1], but only those biologic effects associated with exposure to coal tar, coal tar pitch, and creosote, are considered in this document. Coal tar pitch and creosote are derived from coal tar; another product of coal tar, so-called chemical oil, is not considered here.

The coke-oven plant is the principal source of coal tar [2]. The hot gases and vapors produced during the conversion of coal to coke are collected by means of a scrubber, which condenses the effluent into ammonia, water, crude tar, and other byproducts. Crude tar is separated from the remainder of the condensate for refining and may undergo further processing.

Distillation of coal tar produces a variety of compounds, which are generally characterized as coal tar pitch, creosote, and other chemicals or oils. Typical fractions collected during continuous tar distillation are shown in Table XII-1. Hot vapor enters the fractionating column, where the volatile components are separated into chemical oils and creosote oil (referred to as creosote). The chemical oil can be further refined.

Figure III-1, adapted from Wilson and Wells [2], shows a schematic diagram for the production of coal tar products.

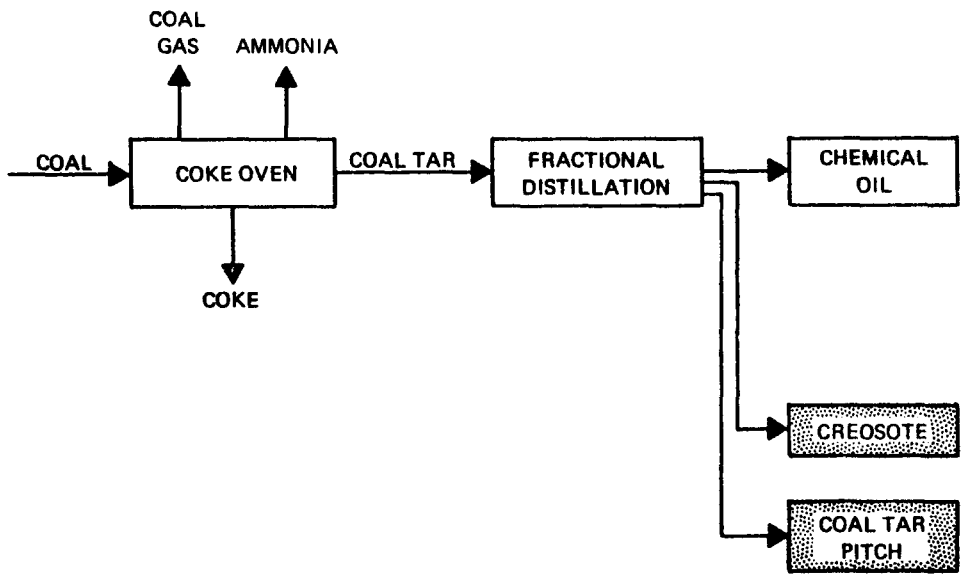


FIGURE III-1

PRODUCTION SCHEMATIC FOR COAL TAR PRODUCTS

Coal tar pitch accumulates in the tar still and is removed as a residual product. The rates of feeding and firing of the still are regulated to produce a pitch residue with the desired industrial characteristics. The grade of coal tar pitch produced depends on the retention time and temperature in the fractionating column [1].

Employees may be exposed to pitch and creosote in metal and foundry operations, when installing electrical equipment, and in construction, railway, utility, and briquette manufacturing. A list of primary employment in which the various types of pitch and creosote are encountered

is presented in Table XII-2. An estimated 145,000 employees are engaged in operations that involve coal tar products either directly or indirectly [3,4]. Examples of such processes and products are indicated in Figure XII-1. Table XII-3 lists a wide range of occupations that include potential exposure to coal tar products in the occupational environment.

Coal tar pitch is used as a binder for electrodes in the aluminum reduction process, and about 16% of the total estimated number of workers handling coal tar residues or distillate products are exposed in potrooms [5]. The pitch is used to bind the carbon electrodes used in the reduction pots. In prebaked electrodes, the pitch volatiles are driven off prior to installation in the pots, whereas in the Soderberg process, the volatiles are emitted during the reduction process. Thus, there is normally greater worker exposure in the Soderberg process. Horizontal and vertical Soderberg processes vary in the positioning of current-conducting pins. Because of the difficulty in producing adequate ventilation in the vertical process, worker exposure is likely to be greater.

The railway, utility, and construction industries employ a smaller percentage of workers (2.8%) in handling, packaging, and distributing creosote. More than 99% of the creosote produced is sold to wood preservation plants. Only about 0.1-0.2% of the total amount of creosote produced is sold to individual consumers. Creosote is transported from storage facilities to the wood-processing plants mostly by tank cars, but it may also be loaded directly into barges, tank cars, or tank trucks at the production facility [6]. In 1972, more than 275 million cubic feet of wood were treated with preservative or fire-retardant materials, including almost 1,000 million pounds of creosote [6]. Railroad ties and marine

pilings were treated almost exclusively with creosote and creosote-containing materials, and more than one-third of all wood telephone and telegraph poles were treated with creosote. In addition, a portion of the creosote produced is consumed as fuel by steel producers. Over 180 million gallons of tar was used as fuel in steel production in 1974, which represented about 26% of the total consumed, according to production and sales figures for coal tar and derived products [7].

Crude coal tar is widely used in the clinical treatment of acute and chronic dermatoses, eg, infantile and varicose eczema, occupational and contact dermatitis, and psoriasis [8]. For several centuries, tar preparations have been used in dermatologic treatments. According to a review by Everett et al [9], Dioscorides described the use of asphaltic tar as a remedy for cutaneous disorders. Since then, coal tar has been used to treat many types of cutaneous lesions. The exposure of the US population to dermatologic coal tar preparations may be extensive, since psoriasis alone is estimated to affect about 2% of the population [10].

Coal tar pitch volatiles (CTPV's), particulate polycyclic organic material (PPOM), and polynuclear aromatic hydrocarbons (PNA's) are terms frequently encountered in dealing with coal tar and its products. CTPV refers to the volatile matter emitted into the air when coal tar, coal tar pitch, or their products are heated, and may contain several PNA's (also referred to in the literature as PAH's). PPOM refers to condensed ring aromatic hydrocarbons normally arising from pyrolysis of organic matter [11]. PNA's in the occupational environment can result from coal tar, heavy petroleum fractions, PPOM, and other materials [11].

Some of the polynuclear hydrocarbons that have been identified [5,12,13] in coal tar, coal tar pitch, or creosote include anthracene, benz(a)anthracene, benzo(b)chrysene, benzo(j)fluoranthene, benzo(k)fluoranthene, benzo(g,h,i)perylene, benzo(a)pyrene (BaP), benzo(e)pyrene (BeP), carbazole, chrysene, dibenz(a,h)anthracene, fluoranthene, perylene, phenanthrene, and pyrene. The BaP and dibenz(a)anthracene analogs have been the subject of much carcinogenicity research. Because of the widespread use of coal, petroleum, and their derivatives, the carcinogenic potential of these PNA's has been extensively investigated and reviewed [1,11,12,14-19].

In general, the composition of various coal tars and coal tar pitches and, thus, probably their carcinogenic potential depends on the source of the tar and the methods of processing, which determine the relative amounts of tarry matter as well as the chemical characteristics of the products. Over 300 compounds have been positively identified in coal tar, and it is estimated that as many as 10,000 compounds may exist, although many are present only in trace amounts [1].

From July 1972 to May 1976, the Occupational Safety and Health Administration conducted 335 investigations of workplaces in which samples were collected to determine CTPV; 172 workplaces had concentrations exceeding the CTPV limit of 0.2 mg/cu m. Approximately 60 of these were in coke or steel operations, with the remainder in wood-treating, aluminum reduction, coating plants operations, construction, and other operations [20,21].

Historical Reports

In 1775, Pott [22] reported scrotal cancer in chimney sweeps in England. Since then, numerous investigators have confirmed his observations.

In 1885, Ball [23] reported skin cancer in two male tar workers, 41 and 80 years old, who had worked in a tar distillation factory for 9 and 15 years, respectively, and had handled crude naphtha, creosote, and residual pitch. The younger man noticed a wart on the front of his scrotum, and examination by the author showed it to be an epithelioma. This term was used to characterize what is now referred to as squamous-cell carcinoma. The wart was removed by surgery, and, ignoring medical advice, the worker returned to the tar factory. Two years later, he returned to Ball, who removed a second epithelioma from the side of the scrotum. The older patient developed warts on his forearms, hands, and face after 7-8 years of exposure to tar. On his left hand, the warts became ulcerated and invaded the underlying tendon and bone, necessitating amputation of the forearm 15 years after his first exposure to tar. After microscopic examination of the warts from both patients, Ball [23] emphasized that they were epitheliomas and were "feebly malignant."

In 1908, Oliver [24] described epitheliomas in six or seven men who had worked for unspecified periods with coal tar. Each epithelioma began as a small wart or as an inflammation of a sebaceous gland on an exposed part of the body. The small warts either existed for many years without becoming malignant tumors, or they disappeared. The initial sign of malignancy was ulceration, with or without bleeding. Later, the inflammation penetrated into the deeper tissue, possibly reaching the bone.

Oliver noted that crude coal tar could cause irritation of the skin, inflammation of the hair follicles, and inflammation of the sebaceous glands, forming small red nodules. He suggested that plugged skin pores seen as black spots on the skin, accompanied by mechanical irritation, including that from coal tar, resulted in an overgrowth of cells around the hair follicles. This led to development of a wartlike condition that might ultimately become a malignant epithelioma.

Birdwood [25], in 1938, cited two cases of keratitis from creosote exposure. Two male gardeners, one 49 and the other 67 years old, had complained of nonpainful hazy vision about 12 days after creosoting garden fences. Ophthalmologic examination revealed gray spots on the cornea adjacent to the pupil, and hazy keratitis in the left eye of each patient. According to the author, these conditions must have been caused by creosote droplets having splashed into their eyes. Vision in the affected eyes was expected to be permanently impaired.

In 1923, Kimura [26] found lung cancer following intrabronchial administration of coal tar to animals. Three rabbits and 10 guinea pigs were used for the experiment, but information on age, sex, or experimental strain was not provided. One rabbit and three guinea pigs survived. The surviving rabbit was killed on the 80th day, and the surviving guinea pigs on the 140th day. Details of the deaths of the other animals were not given. A small adenoma-like growth, with brown granules in the stroma of the tumor, was found in the rabbit lung. Multiple adenocarcinomas, with unspecified numbers of brown or black coal tar spots in the stroma of the tumors and in the surrounding pulmonary tissue, were found in one of the guinea pigs. Kimura concluded that the coal tar alone produced lung cancer

in the experimental animals by chemical action. This was one of the earliest reports to recognize that an experimental cancer was caused by the chemical action of coal tar and not by mechanical irritation.

Effects on Humans

Exposure to coal tar products has been reported to produce phototoxic effects, such as skin erythema and burning and itching of skin, photophobia, conjunctivitis, and skin and lung cancer, in humans.

(a) Skin Effects

Tanenbaum et al [27] described in 1975 how they measured the phototoxicity of several tar preparations and investigated the action spectrum after producing a physiologic response. The preparations were 5, 2, and 1% crude coal tar in petrolatum; a 20% solution of coal tar in 80% ethanol; Zetar emulsion, a 50% colloidal emulsion of washed crude coal tar in water; and Lasan's Pomade, 0.4% anthralin in a base containing cetyl alcohol, mineral oil, and sodium lauryl sulfate, with salicylic acid as a preservative. The phototoxicity of each of the tar preparations was determined by using two light sources, UVB (290-320 nm) and UVA (320-400 nm). Production of erythema was regarded as the endpoint of the phototoxic reaction, and the phototoxic index (PI) for each preparation was calculated. The phototoxic index is the ratio of the minimal phototoxic dose (MPD, minimum energy required to produce the same degree of erythema at treated sites) to the minimal erythemal dose (MED, minimum energy required to produce the same degree of erythema at an untreated site).

An unspecified amount of each tar solution was painted on the upper and middle part of the back of each of five to nine white volunteers [27]. Ninety minutes later, the tar preparations were removed with 70% ethanol followed by water. The backs were then irradiated by the light sources for graduated periods, and the PI was calculated with UVA light. The PI's of 5, 2, and 1% crude oil tar solution in petrolatum with UVA light were 4.16, 3.15, and 1.84, respectively, and the PI of 20% coal tar in ethanol was 4.92. The PI's of all the tar preparations in response to UVB were about 1. The results showed that all six tar preparations tested were phototoxic with UVA and not with UVB. The PI values, determined with UVA, of Zetar and anthralin preparations were 2.65 and 2.05, respectively. The action spectrum, the light energy required to produce minimal erythmatous response on untreated skin, was determined in 15 subjects. Burning and smarting sensations were felt by 10 of the 15 subjects 5 minutes after the treated sites were exposed to UVA light. The action spectra of the two light sources were 29.98 joules/sq cm for UVA and 29.87 millijoules/sq cm for UVB. From these results, Tanenbaum et al concluded that a high-energy UVA light is required to produce tar-phototoxicity, or erythema, in humans. The phototoxic effects of coal tar observed in these subjects agree with those observed by Crow et al [28], who also tested for spectral reactivity of acridine and anthracene in three subjects. Only one subject showed an erythematous reaction to acridine. With anthracene, striking urticarial responses with smarting were observed in all three subjects when tested at wavelengths from 340 to 380 nm.

Fisher and Maibach [29] applied crude coal tar alone or in combination with UVA or sunlight to the backs of groups of four men to

determine the effects on the mitotic division of human epidermal cells. In one experiment, unspecified amounts of 2, 6, or 10% crude coal tar solutions in a water-washable cream base were applied to the backs of the subjects once a day for 4-21 days. On the morning of the final day, the medication was removed, and 0.5% demecolcin (a form of colchicine) cream was applied under an occlusive patch test plaster to arrest the epidermal cell division. Six hours later, the skin was cleaned, a biopsy was taken, and the specimen was stained by the Feulgen method to detect mitotic figures by a light microscope. The rate of mitotic cell division was expressed as the number of mitoses/1,000 viable cells. Each reported value was an average of eight specimens, two taken from each subject, and was compared with values from tissues from an untreated site of the same subject. In a second experiment, coal tar solutions were similarly applied, but, after 3 days, the test sites were temporarily cleaned and exposed for 60 minutes to either natural sunlight or UVA (wavelength 366 nm) light, at a distance of 8 inches. The tissue was prepared and examined as described above. In a third experiment, 10% coal tar solution was applied for 21 days.

In the first experiment the mitotic rates on the 4th day following applications of 2, 6, and 10% tar solutions were 0.51, 0.60, and 0.62, respectively; the control rate was 0.63 [29]. In the second experiment, the mitotic rate for tissues treated with 6% tar was reduced to 0.37 when the treated areas were exposed to sunlight for 60 minutes on day 3 of the 4-day experiment. In the third experiment, the mitotic rates on the 21st day in coal tar-treated and untreated skin were 1.50 and 1.36, respectively. Fisher and Maibach concluded that crude coal tar alone, at

concentrations of 2-10%, did not alter the mitotic division of epidermal cells in humans, but that crude coal tar in combination with sunlight produced a small but highly significant ($P<0.005$) decrease in mitotic activity.

NIOSH conducted a health hazard evaluation [30] to determine exposure to coal tar pitch fumes during a roofing operation. Thirty-four 18- to 60-year-old men (median age, 33) were involved in laying a roof over a 46-acre area on a sunny day, at an air temperature of 72 F and relative humidity of 75%. Twenty-nine of the 34 workers were white, of whom 4 were Spanish-Americans, and 5 were black. Thirty of the men were roofers, with work experience of 6 weeks to 25 years (median 6 years), two were managers, and two were maintenance workers. The less experienced roofers worked as insulation layers, felt machine helpers, hot pitch carriers, and miscellaneous helpers. Coal tar pitch, characterized by workers as "no burn" quality, was used at 375 to 400 F. Before the roofing operation began, detailed occupational and medical histories of the workers were collected. Roofers had not worked at the same job from one place of employment to another. At the beginning and at the end of the workday, each worker's skin and eyes were examined and the responses recorded. Photographs of skin lesions in a small number of workers were also obtained. Workers were required to wear personal samplers, and an unspecified number of them were asked to wear two to three personal samplers, to collect coal tar pitch volatiles for 7-8 hours on glass fiber-silver membrane filters. In all, 38 personal samples from 26 workers and general air samples from samplers located on the handles of felt-pitch machines and near the driver's seats were analyzed for PPOM as cyclohexane

solubles, which include PNA's, by the NIOSH method involving UV spectrophotometry [31]. Each sample was also analyzed for BaP, BeP, and alpha- and beta-naphthylamines.

Twenty-three of 34 workers (68%) complained of skin reactions, including burning or tingling sensations, to coal tar pitch fumes [30]. None of the four management personnel reported any skin effects. Six workers had localized erythema or desquamation, one had hyperpigmentation, one had papular dermatitis on the hands and knees, and others had localized thermal burns. One roofer had multiple actinic keratoses on his hands and neck. In five workers, skin irritation and burning sensations were attributed to fibrous glass, one of the components used in the roofing material. Skin symptoms occurred on the nose in seven workers, the forehead in four workers, and the creases around the eyes and nose in four workers. Two workers from unspecified job categories experienced burning sensations, one through the shirt and the other through the gloves. In general, the burning sensations began within an hour of the start of exposure and diminished in the evening. Skin peeling without erythema occurred in some workers. Burning and itching of unexposed skin on the gloved hand was enhanced when the gloves were removed and the hands exposed to sunlight. Protective measures, such as wearing gloves, long-sleeved shirts, and hats, using emollient creams or protective lipsticks, and taking hot showers after work, were somewhat effective in reducing the effects of coal tar pitch fumes on the skin. Sunscreens were not effective in reducing the skin effects.

Seventeen of the 34 workers had complaints pertaining to the eyes; 8 of these described slight burning, 5 had burning and slight conjuctival

erythema, and 4 had burning conjuctival erythema, lacrimation, and swelling of the lids [30]. The symptoms in these last four workers were sometimes associated with conjuctival discharge, inability to close the eyes, or interference with vision. Some of these workers wore eye protection, such as sunglasses, and some did not. The roofers had indicated that they often experienced eye symptoms when they were tearing off old roofs where ventilation was poor, when working with old-style pitch (instead of "no burn" pitch used in the present operation), or when using pitch at temperatures higher than 400 F.

The NIOSH report [30] further indicated that severe eye symptoms usually began as burning and lacrimation 3-4 hours after beginning work and led to conjunctivitis on exposure to sunlight. Conjunctival erythema, increased tearing, and swelling of eyelids also occurred. Instillation of eye drops or local anesthetic drops usually provided temporary relief. Some workers complained of matted eyelashes in the morning and a purulent discharge. Normally, these conditions disappeared within 72 hours after the first exposure. Although the report indicated that no workers complained of such eye symptoms when they worked with asphalt fumes, it is not clear from this report how the investigators distinguished the effects of pitch fumes. Of six workers showing clinical evidence of conjunctivitis, four were exposed to PPOM at 0.21-0.49 mg/cu m, higher than the ACGIH-recommended TLV of 0.2 mg/cu m, and two were exposed at concentrations less than 0.2 mg/cu m. In addition to conjunctivitis, four roofers had pterygia (lesions of superficial vascular tissue folding onto the cornea), which sometimes occurs as a result of continued or long-term exposure to warmer climate, wind, dust, and sunlight or reflected solar

radiation.

When chemically analyzed, bulk pitch samples were said to have 4.89% PPOM by weight as cyclohexane solubles, 1.9-13% of which was PNA [30]. The bulk pitch contained BaP and BeP, which cannot be separated by the method used, at concentrations of 270 ppm. Total particulate matter concentrations in the air were less than 2 mg/cu m; the authors did not define respirable particulate or its measurement. The PPOM of personal samples varied from less than 0.02 to 0.49 mg/cu m and averaged 0.1 mg/cu m. Six roofers (hoisting engineer, two gravel-pitch machine operators, felt-pitch operator, broom operator, and support operator) were exposed to PPOM at concentrations of 0.21 to 0.49 mg/cu m. A separate analysis of seven personal samples collected 2 weeks later showed concentrations of PPOM varying from 0.03 to 0.53 mg/cu m. Three of these seven workers (gravel pitch machine operator and two broom operators) were exposed to PPOM at concentrations in excess of 0.2 mg/cu m. The concentrations of PPOM in the area samples ranged between 0.04 and 2.38 mg/cu m. An unspecified number of glass fiber-silver membrane filters plus backup pads were analyzed, and it was found that 10-80% of the PPOM passed through the filters and was absorbed on the backup pad. None of the samples analyzed contained BaP or BeP at the detection levels of 0.03 mg/sample. By comparison, the limit recommended by the Coke Oven Advisory Committee for BaP is 0.2 μg/cu m (29 CFR 1910.1029).

Analysis of 11 personal samples using glass fiber-silver membrane filters showed that concentrations of alpha-and beta-naphthylamines were less than 0.05 mg/cu m. Analysis of bulk samples of pitch showed no detectable concentrations of alpha- or beta-naphthylamines.

The NIOSH investigators [30] concluded that exposure to coal tar pitch fumes during a roofing operation caused acute (short-lived) eye and skin disorders in roofers, some of whom were exposed to concentrations of PPOM greater than 0.2 mg/cu m of air [30]. They further stated that the incidence and severity of eye and skin effects depend on the concentration of airborne PPOM which, in turn, depends on the type of operation, the type of pitch used, the temperature to which the pitch is heated, and on environmental factors, such as wind. NIOSH recommended that roofers minimize the effects of coal tar pitch fumes by using protective measures, such as wearing gloves, respirators, and goggles. NIOSH also advised that they should work upwind of pitch fumes and wash thoroughly at the end of the working day.

In 1943, Jonas [32] described creosote burns in 450 of approximately 2,700 fair-skinned, dark-skinned, and black carpenters, roofers, and wood-treaters. Mild creosote burns were characterized by erythema, which was most marked on the face and the back of the neck. According to the author, mild burns resembling sunburn were accompanied by itching and burning and were followed by more intense pigmentation within 1-3 days. Severe creosote burns were characterized by intense burning, itching, subsequent intense bronze pigmentation, and desquamation. Jonas observed that seven black workers had mild burns and none had severe burns, but the total number of black workers in the group was not given. In contrast, fair-skinned and dark-skinned workers had 216 and 101 mild burns and 96 and 30 severe burns, respectively. Fifteen percent of those workers who had burns also experienced conjunctivitis, and 3% had corneal lesions. Weakness, depression, headaches, vertigo, transitory confusion, or nausea were

reported by about 0.4% of the workers. The urine of 11 workers was allowed to stand for an unspecified time, to see if it turned black due to phenolic constituents of creosote, but this test was negative in those workers who had systemic effects.

Shambaugh [33], in 1935, investigated the incidence of coal tar cancer in fishermen who had handled tar-treated nets. He began this study after finding an epidermoid cancer of the skin that had metastasized to the local lymph nodes on the neck of a 41-year-old fisherman, who had worked for 6 years mending coal tar-treated nets. During this period, the fisherman had developed a habit of holding a tar-smeared needle between his lips on the right side of the mouth; this resulted in a small, hard, nontender growth on the lower lip, commonly known as "fisherman's sore." He received some unspecified treatment, and the lesion disappeared within 2 weeks. The patient received X-ray therapy for the lymph-node metastasis on the neck, but it soon recurred, and he died 5 months later with a fistula of the esophagus.

Shambaugh then conducted a survey to determine the frequency of skin or lip cancer in fishermen. Four fishermen responded to a questionnaire sent to 141 lip-cancer patients from one hospital, and three more fishermen were identified from other sources. These seven patients were 56-77 years old and had been fishermen or had mended tarred nets for 5-60 years. Of the eight patients with tar cancer of the lip, two used no tobacco at all and six smoked pipes. Of these six, four held the pipe on the side opposite from that on which the lesion developed. In the eight fishermen, including the 41-year-old who precipitated the study, there were four squamous-cell carcinomas confirmed microscopically and four carcinomas

diagnosed by gross observation of the lower lip. Three of the carcinomas were on the right side of the lip, two on the left side, and three on the middle half of the lower lip. Shambaugh also visited two net-tarring or net-repairing establishments, each employing three or four men. An unspecified number of older workers, employed in these plants for many years, had developed tar warts on their forearms and hands, but none had cancer.

Spitzer et al [34] found an excess of lip cancer among Newfoundland fishermen. However, they did not provide details on exposure to coal tar among these fishermen, except for evidence that fishermen holding tar-treated nets in their mouths as a "third hand" had a lower incidence of lip cancer than did age-matched controls.

In 1951, Mauro [35] examined 32 workers in a tar distillation plant for skin lesions. Twenty workers, of which 4 were distillers, 14 were laborers, and 2 were stokers, had constant exposure to tar or pitch. The remaining workers included four mechanics, three apprentices, three janitors, a messenger, and a domestic worker. Mauro found that six workers had simple folliculitis, three had erythema plus folliculitis, two had papular dermatitis plus folliculitis, one had acne, two had warts and perifolliculitis, and four had skin cancer. Skin cancers were found in two distillers, aged 61 and 50 years with 30 and 25 years of work experience, respectively, and in two laborers, 64 and 53 years old with 30 and 22 years of experience, respectively. In both tar distillers, painful or burning nodules had developed on the scrotum. The nodules were surgically removed, and biopsy revealed them to be squamous-cell carcinomas. The 61-year-old distiller had a recurrence of the scrotal cancer. He was operated on

again, but he died of septicemia. The younger distiller had developed a painful hardening with exudate on the forearm. The lesion was found to be spinocellular, or prickle-cell, epithelioma with inflammation. A biopsy was done on the older of the two laborers with skin cancer on the groin, and the lesion was found to be cancroid, or moderately malignant. The patient apparently was cured with X-ray treatment. The second laborer developed a painful swelling on the left side of the lip. Biopsy of the lesion revealed it to be a squamous-cell carcinoma, which was apparently successfully treated with X-radiation.

Rosmanith [36] described a case of skin cancer in a 52-year-old woman. She had worked in a tar distillation factory for 10 years, filling vessels with hot tar from a large container. She wore no protective aids except cloth gloves, and her face was exposed to hot tar vapor. After 10 years, she was declared unfit for work when a physician found scars on both cheeks, extending to the ear on the left and nearly covering the cheek on the right. Apparently, the scars were mainly residues from lupus erythematosus, but with spinocellular (prickle-cell) cancer superimposed. The physician also noted a fist-sized swelling on her nose, which left the nasal passages free but produced a red malodorous secretion on its surface. Rosmanith believed that the cancerous scars and the cancerous growth on the nose were caused by hot tar vapor and were thus occupationally related.

Hodgson and Whiteley [37] observed skin effects from coal tar pitch exposure in workers at a patent-fuel works in Wales, where pitch and coal dust were fused into blocks by steam. A detailed survey was initiated by the authors after they had seen, from 1957 to 1963, 59 workers from the plant who had hyperplastic, squamous skin lesions. Of the lesions on the

59 workers, there were 35 pitch acanthomas, or pitch warts, 3 squamous-cell carcinomas, and 29 squamous keratoses or combinations of these lesions. The authors stated that 48% of the patients with pitch warts had a history of multiple warts, and that 23% had five or more pitch warts. The latent period in about half the workers was less than 10 years. In the rest, it was 10-20 years. In their survey, the authors examined workers exposed to pitch in the plant, a total of 144 men, aged 20-69 years; 263 men from a dermatologic outpatient department were examined as a control group. Of the 144 pitch workers, 87.5% were white, 5.5% were Indian, and 7.0% were black. The control group consisted of 98.4% white, 0.8% Indian, and 0.4% each black and Chinese.

According to Hodgson and Whiteley, the age distribution by 10-year intervals was similar in the exposed and control groups. Full dermatologic examination of each employee was conducted, including notation of the color of hair and eyes. The workers were first examined in 1963 and reexamined 2 years later. Biopsies from suspicious proliferative lesions were examined microscopically. Occupational histories were recorded in terms of heavy, medium, and light exposure to pitch. Pitch feeders (off-loading pitch) and pressmen (cobble makers) had high exposure; maintenance men, such as electricians, had medium exposure; and crane drivers, boilermen, and office personnel had light exposure to pitch. The clinical findings were classified as (1) benign proliferative lesions (papillomas), (2) premalignant and malignant epidermoid lesions, (3) pitch acanthomas (pitch warts), (4) photosensitivity, (5) acneiform lesions, (6) scrotal changes, and (7) antecedent or incidental skin lesions. There was little difference between the incidence of benign proliferative lesions in the exposed and

that in the control groups [37]. However, the difference might have been greater if the controls had been drawn from a normal population. The incidence was 4.8% in exposed workers versus 4.1% in controls in the 20- to 29-year-old group, 36.2% versus 29% in the 50- to 59-year old group, and 14% versus 25.7% in the 60- to 69-year-old group.

Premalignant squamous keratoses were present in 12% of the pitch workers, compared to 10% of the controls [37]. Chronic tar dermatoses had developed in seven pitch workers after an average exposure of 43 years (range 30-50 years). In some of these cases, the skin had thickened with hyperkeratosis, atrophy, scarring, altered pigmentation, persistent erythema, and telangiectasia with either hyperplastic proliferative or acneiform lesions. None of the controls showed such lesions. About 3% of the pitch workers had squamous-cell carcinomas, compared to 0.4% of the control group. These lesions were found on the scrotum, face, and hands.

Pitch warts less than 2 cm in diameter were present on the face, around the eyes and nose, on the ears, and on the hands of 3.4-15.7% of the pitch workers in several age groups. Histologically, all the pitch warts were true keratoacanthomas. The highest numbers of pitch warts were found in workers 60 years of age or older who had 40-49 years of exposure. However, one pitch worker who was exposed for 50 years never had a wart, and one worker developed a wart after only 3 years of exposure. The occurrence of acanthomas was also influenced by the degree of coal tar pitch exposure. Workers who were exposed to coal tar pitch at a combination of high, medium, and low levels had the highest incidence of acanthomas (24%), while the population of workers with only low exposure had the lowest incidence of acanthomas (3.2%). Seventy percent of the

warts developed during spring and summer. About 58% of the pitch workers reported photosensitivity reactions, or smarting of skin resembling sunburn. No such reactions were reported by blacks or Indians.

Ninety-three percent of the pitch workers had acneiform lesions, including comedones, acne, sebaceous retention cysts, and folliculitis, compared to 31% of the controls [37]. Pitch workers had four times the incidence of comedones, two times the incidence of acne, and nine times the incidence of folliculitis that the control group had. The incidence of all lesions in the exposed group was 9.7% in the 20- to 29-year-old group, reached a peak of 27.8% in the 40- to 49-year-old group, and then declined to an unspecified degree. In the control group, the incidence remained between 6.5 and 6.9% during the same period and thereafter declined to an unspecified degree.

About 13% of all pitch workers had scrotal proliferative changes, about 5% of these with "velvety plaque" lesions of apparently thickened skin. The scrota of the controls were not examined. All the pitch workers with velvety plaques had high exposure to pitch and a total exposure duration of 12-50 years. According to Hodgson and Whiteley [37], the velvety thickened areas on the scrotum may have resulted from inflammatory reactions produced either by friction from pitch-contaminated clothing or by an irritant chemical effect of pitch on the skin, but this was not confirmed histologically.

In addition to the above-described lesions, Hodgson and Whiteley [37] found that 11.1% of pitch workers had virus-induced warts, 15.2% had eczema, 1.4% had rosacea, and 2.1% had acne keloid; incidences of these lesions in controls were 4.2, 21, 1.5, and 1.3%, respectively.

Hodgson and Whiteley [37] concluded that pitch workers had an increased susceptibility to proliferative lesions, either premalignant or malignant, compared to controls. Only 10.7% of the pitch workers were affected with pitch acanthomas (warts), and 50% of these had multiple warts. Even though the incidence of pitch warts increased with increased exposure, the authors' findings suggested that there was also a personal susceptibility to pitch. Hodgson and Whiteley therefore suggested that exposure to pitch be reduced. They also suggested that susceptible persons or those prone to develop pitch warts or other lesions should be removed from excessive exposure, but they did not indicate how such people could be detected. They further suggested that all persons working with pitch should have clean industrial protective clothing and that adequate washing facilities should be provided.

Sladden [38] reported several cases of skin cancer in patent-fuel workers. He examined 200 patent-fuel workers, of whom 150 were selected randomly and 50 were specifically selected because they had skin lesions or industrial diseases. He found a total of 235 lesions in 125 persons, affecting mainly the arms, the face, the eyelids and orbits, and the scrotum; 33 of these lesions were malignant. The neck, trunk, hands, and thighs were also affected to some degree. The prevalence of warts and epitheliomas was found to be related to both age and duration of exposure. None of the nine workers aged 15-25 years had any warts or epitheliomas, but six of the thirty-three 25- to 35-year-old workers had such lesions. Their prevalence increased with the age of the workers, with warts and epitheliomas occurring in 65% of the 55- to 60-year-old workers and in 72% of the workers aged 60 or more. The frequency of warts and epithelimoas

also increased with duration of exposure, from 17% after 1-5 years of exposure to 36% after 10-15 years and to 100% after more than 40 years of exposure. De Vries [39] also reported similar cases of pitch cancer in briquette factory workers.

In a 1965 study, Pierre et al [40] found skin tumors in 10 of 103 workers in a briquette factory where coal tar pitch was used as an ingredient in briquettes. A semiannual medical examination revealed that the 10 workers had a total of 22 skin tumors on the ears, eyelids, nose, lips, chin, corners of mouths, and temples. The authors did not specify the areas in which the employees worked, other than stating that 35 of the 103 had worked either in manufacturing or in maintenance areas. Tumors were examined microscopically, and the patients' work histories were studied. The study revealed that one 36-year-old worker had been exposed to coal tar pitch for 1 year, one worker of unspecified age for 1.5 years, a 21-year old for 3 years, four 42- to 51-year olds for 10-16 years, and three 61- to 65-year-olds for 10-43 years. Five of the 10 workers had developed skin tumors within the first 10 years of exposure, but their coal tar pitch exposure levels were not given. Two other workers, drivers of an unspecified machine or vehicle, developed tumors on the upper lip and corner of the mouth after 36 and 43 years of exposure, respectively. Microscopic examination of the tumors revealed that, of the 22 tumors, 9 were papillomas, 3 were keratoacanthomas, and 10 were spinocellular epitheliomas. The tumors in all 10 patients were removed by surgery or treated with electrocoagulation or contact radiotherapy. Although Pierre et al did not provide the results of the various treatments, they suggested that regular medical examinations would detect early signs of skin tumors

and that tumors could be treated effectively with electrocoagulation or contact radiotherapy.

In 1947, Henry [41] surveyed the chemical industry to find workers who had handled various chemicals, including coal tar, coal tar pitch, and creosote, and who had developed skin cancer. He examined the Chief Inspector's Annual Reports from 1920 through 1945 and found 2,975 persons with 3,753 skin cancers. Coal tar products were considered to be causative agents in 2,229 cancers (59%), while 1,515 cancers (40%) were attributed to shale oil, mineral oil, or bitumen, but he did not describe the basis for his conclusions. The remaining 9 cancers were ascribed to mixed exposure to mineral oil and tar. Of the 3,753 skin cancers, 93 (2.4%) were basal-cell carcinomas; 21 of these were in pitch or tar workers. The sites affected were mainly the head, neck, arms, and scrotum. Some cases of cancer of the groin, trunk, or penis were also reported in persons who worked with tar, mineral oil, or both.

In the coal gas industry, there were 324 skin cancers in 309 workers, including managers, retort stokers, retort setters and repairers, main and pipe workers, fitters, pipelaggers, carpenters, maintenance men, and yard-laborers [41]. There were 54 skin cancers in 36 pitch loaders employed at wharves. One epithelioma had developed in a worker who mixed melted pitch with chalk in manufacturing clay pigeons. After 3 years of this work, he developed growths on the upper lip and nose. Henry also reported 939 cases of cutaneous epitheliomas in 538 men who worked as pitch getters, pitch breakers, fitters, drain cleaners, plate layers, boiler-makers, and boatmen.

In 1956, Lenson [42] reported a case of multiple skin carcinomas in a 64-year-old patient who had painted creosote on planks and scows for 3 years without wearing gloves. One year after beginning employment, the patient noticed several ulcerations on his cheeks and forehead, and his hands "broke out." Five years later, the ulcerations began to itch and bleed on slight trauma. A physician learned that the patient had worked as a painter for 41 years, working with oils and lead paints and using turpentine and gasoline as paint removers. There was no previous history of skin disease or X-ray therapy. A thorough physical examination showed a 3- x 3-cm, superficial ulcerated lesion on the right supraorbital ridge and ulcerations measuring 1.0 x 1.2 and 1.0 x 0.6 cm on the right and left cheeks, respectively. Hyperpigmentation and hyperkeratotic papillomas were present on the face, neck, hands, and fingers. There were no lesions on the scrotum. Results of eye examination, X-ray studies of the chest, and analyses of the blood and urine were within the normal ranges. The lesions on the forehead and cheeks were surgically removed, and the healing was normal. Microscopic examination of the excised lesions showed that they were basal-cell carcinomas with signs of marked inflammation consisting of lymphocytes, plasma cells, and polymorphonuclear leukocytes. Eight months after surgery, the patient returned for a followup examination. Two additional 2-month-old lesions were surgically removed. Microscopic examination revealed that one was basal-cell carcinoma and the other a mixed-type basal-cell and epidermal carcinoma. It is not clear from the report whether the skin cancer was caused by creosote or any of the many materials he worked with.

Cookson [43] reported a case of squamous-cell carcinoma on the right hand of a 66-year-old creosote factory worker. For 33 years, his job was to carry creosoted wood. During the last 8 years, a small growth had grown into a large tumor covering the entire back of his right hand. His right arm was amputated above the elbow, but the patient died 7-8 weeks later. Post-mortem examination found tumors in the lungs, liver, kidneys, and heart.

A similar skin tumor was observed by Haldin-Davis [44] on the hand, forearms, and thigh of a 52-year-old creosote worker, whose job for several years was to impregnate wood logs with gas-tar-derived creosote and then hand carry them, still dripping, outside for drying. Microscopic examination of the biopsied tissues revealed squamous-cell papillomas.

(b) Eye Effects

In 1968, Leb et al [45] described effects observed in six coal tar pitch workers. After loading or unloading coal briquettes from a railroad car for 4-5 hours on a sunny day, all six workers reported burning and watering of the eyes, photophobia, burning sensations on the face, stuffiness in the nose, dry cough, pressure in the chest, and hoarseness. Medical examination showed that all the workers had conjunctivitis, hyperemia and edema of the eyelids, and mild photophobia. The nasal mucosa and sinuses were swollen and infiltrated with serous secretions. Laryngoscopic examination showed that the vocal cords were thickened, the mucosa of the throat was hyperemic, and there were unidentified white deposits in the trachea. Blood pressure and heart rate were within the normal range. An unspecified number of workers had dry wheezing in the lungs. The heart and spleen were not enlarged in any of the workers.

However, the left lobe of the liver was enlarged in all six workers and could be palpated by the examining physician. Examination of blood from some workers showed eosinophilia (10-14%), but serum protein concentrations were within the normal range. The patients were treated with albucid (a sulfanilamide), alkaline nose drops and rinses, levomycetin (an antibiotic), multivitamins, and oxygen [45]. Inflammation of the eyes disappeared within 3-5 days, and the upper respiratory problems disappeared by the 8th or 9th day. Leb et al concluded that coal tar pitch causes short-lived conjunctivitis and affects the upper respiratory tract. They further suggested that all workers handling coal tar pitch should wear protective clothing, goggles, and respirators and should work at night to avoid the photosensitizing effects of coal tar pitch. However, later exposure to sunlight would probably initiate the photodynamic reaction.

In 1970, Susorov [46] reported the effects of coal tar pitch on the eyes of 36 workers, 19-23 years old. Half of these men, wearing no protective clothing or equipment, unloaded coal tar pitch from a railroad car at night. The other half, wearing ordinary sunglasses and two-layered gauze masks, performed the same task during the day for 4 hours. No data on environmental dust concentrations were reported. The nightworkers spent 5 hours at their task, which they completed at sunrise. Thirty minutes later, they complained of photophobia, watering and sharp pain in the eyes, reduced vision, burning sensations on the face and neck, head-cold symptoms, and sneezing. Dayworkers reported similar symptoms 3 hours after they began work. A physician found that all 36 workers had edema, hyperemia of the face and neck, conjunctivitis, and constriction of the pupils. All the patients had numerous pits in the corneal epithelium. In

men who had worked inside a railroad car, where dust concentrations were assumed to be highest, visual acuity (in undefined units determined by an undescribed method) was reduced to 8-20% of normal in 11, to 30-70% of normal in 20, and to 80-90% of normal in the remaining 5 workers. The patients' eyes were treated with a 1% solution of quinine, a 30% solution of a sulfanilamide, and an antibiotic and were washed periodically with drops of a 0.25% solution of dicaine, a local anesthetic. Most of the reported symptoms disappeared within 1 day, and visual acuity returned to normal by the 5th day.

Susorov [46] suggested that these effects of coal tar pitch exposure were temporary and that workers should wear protective equipment, such as goggles, respirators, and canvas clothing, should work at night, and should wet the coal tar pitch with water to reduce the pitch dust in the air. These observations of Susorov [46] agree with those of Leb et al [45].

Lane [47], in 1937, presented a study of cancer of the eye and surrounding structures in workers from several occupational groups. One thousand case histories were obtained from several sources, including eye clinics in the United States and Canada, cancer research institutions, and records of ophthalmologists, industrial plants, and the US Army Medical Museum. A microscopic examination of each tumor and a detailed followup of each patient were made. On the basis of the case histories, the workers were divided into seven occupational groups. One group of nine workers who had been exposed to coal and coal tar pitch included five coal miners, a fireman, two stonepavers, and a company official. A second group of 12 workers, including fishermen, a diver, a dock worker, and 6 sailors, had been exposed to sunlight, unspecified elements, and tar and pitch. Another

group of 37 workers included 5 bricklayers, 21 carpenters, and 11 painters who had been exposed to sunlight, unspecified trauma, and undescribed chemicals. In all occupational groups, the average age of workers with eye carcinomas was 57 years, and the average of those with sarcomas was 48 years. In the workers exposed to coal and coal tar pitch, there were four carcinomas in coal miners, two in stonepavers, and one each in a fireman and a coal company official, and one sarcoma in a coal miner. In the 12 workers exposed to sunlight and tar and pitch, there were six carcinomas in sailors, two in fishermen, one in a diver, and one in a dock worker, and two sarcomas in fishermen. Other than the statement that these tumors were in the eye and surrounding tissue, details were not provided. In the workers exposed to sunlight, trauma, and unspecified chemicals, there were 3 carcinomas in bricklayers, 11 in carpenters, and 4 in painters. There were 2 sarcomas in bricklayers, 10 in carpenters, and 7 in painters. According to Lane, there was an increased prevalence of skin cancer as well as eye cancer in the carpenters because they handled roofing, other building materials, and creosote-treated shingles. A fine sawdust or resinous material from these products fell on their hands and arms, which were exposed to sunlight. Of the 11 carpenters with carcinomas, 7 had basal-cell tumors of the eyelid and 4 had squamous-cell lesions of the eyelids and conjunctiva. Of the 10 sarcomas found in the carpenters, 7 were in the choroid, 1 in the iris, and 2 in the conjunctiva. Lane, however, did not provide any normal control values to allow comparison.

(c) Effects on the Oral Cavity

In 1967, Pekker [48], investigated the oral health of 962 workers, 79.4% of whom were 24- to 45-year-old men, who worked in coal tar

processing industries. The study included 100 workers from coal tar processing plants, 293 from pitch-coke plants, 415 from coking plants, and 154 from other industries, such as benzene-naphtha, nitrobenzene, and benzene distilleries. The length of employment, smoking histories, and conditions of exposure were not described. One hundred performers, age and sex not matched or described, from a nearby theater served as a control group. The author examined the oral cavity of each worker or performer for condition of teeth in terms of decay, condition of oral mucosa and gums, and oxygen tension of oral mucosa, determined by an undescribed method. The data were analyzed by an unspecified statistical test.

Pekker [48] found that 82-94% of all workers had decayed teeth. The author did not provide the corresponding values for the controls. Only 1.7% of the benzene distillers had gum disease, significantly less ($P<0.05$) than the 25% of coal tar processors with the same condition; 9-20% of the workers in other plants had gum disease. Gingivitis, white patches on the oral mucosa diagnosed as leukoplakia, and edema of the oral mucosa were found in 7, 8, and 4% of the coal tar workers and in 4.7, 6.1, and 3.7% of the pitch-coke workers, respectively. The prevalence of leukoplakia in workers not exposed to coal tar was 1.8%. The control values for other conditions were not given. The patients with mucosal edema were reexamined 3-5 months after their first medical examination. Edema of the cheek mucosa had disappeared, but keratosis had developed. The author suggested that coal tar exposure causes an increased rate of oral cavity disease, specifically leukoplakia, in humans. Leukoplakia is often considered to be premalignant change. It should be mentioned that other possible causes of gingival changes, such as smoking, were not mentioned by the author.

Epidemiologic Studies

Those case histories and limited epidemiological studies concerned with morbidity from coal tar exposure were considered in Effects on Humans to facilitate a balanced description of toxic effects from exposure to coal tar products. Those epidemiologic studies that are largely concerned with mortality associated with coal tar products are considered in this section.

In 1976, Hammond et al [49] described an epidemiologic study of death rates and cancer occurrence in pitch workers. They first measured the exposure of workers at a roofing site and found that workers inhaled as much as an average of 53 μg of BaP in 7 hours, with concentrations ranging from undetectable to 135 μg. The concentrations of other airborne coal tar components were not determined. Thereafter, they examined a total of 5,939 records of pitch workers who were union members between January 1, 1960, and December 31, 1971. The workers, aged 39-80 or more years, had 9-40 or more years of work experience. The authors were able to trace 5,788 men (97.5%) for 12 years. The remaining 151 men were traced for an average of 5.5 years. The ratio of lung cancer deaths in pitch workers to the number of such deaths expected on the basis of US mortality data was 0.92 for workers exposed less than 20 years, 1.5 for those exposed 30-39 years, and 2.47 for those exposed 40 years or longer. The authors concluded that work exposure to BaP was associated with increased mortality from lung cancer. However, they also pointed out that one or more other agents to which the pitch workers were exposed, or a combination of these agents and BaP, could have contributed to the increased lung cancer mortality. The authors failed to determine smoking histories of the workers, but their observations showed that many of the workers did smoke cigarettes.

Therefore, Hammond et al suggested that cigarette smoke and pitch fumes may have been concomitant causes of lung cancer in pitch workers.

Redmond et al [50] reported an epidemiologic study initiated by Lloyd and Ciocco to determine the risk of mortality from cancers of several organs in steel workers, including coke-plant workers. Employment records from a large, longitudinal study of 58,828 men working in 1953 were collected from seven steel plants located in Allegheny County, Pennsylvania. Men who had left the plants before January 1, 1967, were followed up to ascertain their vital status. Less than 0.1% (54) of the total workers were lost to followup. For the 8,628 men who had died, the cause of death was determined from death certificates. Mortality data on the 2,543 men working in the coke plants during 1953 were compared with those on steelworkers who had never worked in coke plants, through 1966. Because of inconsistent job-title terminology in different plants, and because certain job titles, such as "laborers, coke plant," could not be classified precisely by work area, Redmond et al [50] classified jobs in two categories, "coke oven" and "non-oven" workers, rather than in the three more generally used categories of coal handling, coke-oven, and byproducts workers. The coke-oven group of 1,316 workers included all jobs requiring that part of the workday be spent at the top or side of the ovens; all other jobs, involving 1,227 workers were classified as non-oven. For analyses involving duration of exposure, workers who had held jobs in both oven and non-oven areas, were considered coke-oven workers. Non-oven workers who worked in byproduct areas were considered, without a stated reason, to have been more highly exposed to polycyclic hydrocarbons than were the workers in the coal-handling group. To analyze the data, the

expected number of deaths was calculated for subgroups on the basis of race, age, and years of observation. Steelworkers with no known exposure to coke ovens were used as the control group. The estimated risk for coke-plant workers was a weighted average of the ratio of observed to expected deaths summed across all subgroups. A Mantel-Haenszel Summary Chi Square test was used to determine whether the relative risk differed significantly from 1.

Redmond et al [50] found that the 2,543 coke-plant workers had a relative risk of 1.93 ($P<0.01$) for all cancers of the respiratory system; 2.01 ($P<0.01$) for cancers of the lungs, bronchi, and trachea; 1.82 ($P<0.05$) for cancer of the genitourinary system, and 5.00 ($P<0.01$) for kidney cancer.

For the 1,852 coke-plant workers with 5 or more years of work experience, the standard mortality ratios (SMR, number of observed deaths/number of expected deaths x 100) for all causes (1.12) and for cancers of the respiratory system (2.05); lungs, bronchi and trachea (2.09); genitourinary system (1.76); and kidney (4.5) were significantly high. The SMR for cancers of the digestive system and peritoneum was not significantly high. There was also a significant excess, 1.62 ($P<0.05$) of nonmalignant respiratory disease. In the 783 non-oven workers who had worked for 5 or more years, the relative risk of dying from cancer of the digestive organs and peritoneum was 1.62 ($P<0.05$).

Data of Redmond et al [50], summarized in Table III-1, showed that coke-oven workers (1,316) had high risks from cancer of the respiratory system (3.19) and lungs, bronchi, and trachea (3.31). When the data were analyzed for length of exposure, it was found that the 965 coke-oven

workers with 5 or more years of exposure had a higher risk from all cancers of the respiratory system (3.53), and from cancer of the lungs, bronchi and trachea (3.67). Length of employment significantly increased the risk in non-oven workers, but only in 111 coal-handling workers (2.74, $P<0.05$). When the data of the 783 non-oven workers were further analyzed, a

TABLE III-1

MORTALITY AMONG COKING PLANT WORKERS IN ALLEGHENY COUNTY EMPLOYED 1953-1966 (DEATHS/1,000)

Cause of Death	Workers Employed Through 1953						Workers Employed 5 or More Years					
	Coke Plant (n=2,543)		Coke Oven (n=1,316)		Non-oven (n=1,227)		Coke Plant (n=1,852)		Coke Oven (n=965)		Non-oven (n=783)	
	O	E	O	E	O	E	O	E	O	E	O	E
All causes	397	367.1	199	178.1	198	185.2	402	36.65*	214	192.4	178	163.5
Cancer of respiratory system	45	25.9**	34	12**	11	11.6	48	26.5**	41	14.8**	6	10.3
Cancer of lungs, bronchi, trachea	44	24.5**	33	11.3**	11	10.9	46	25	40	14.1**	5	9.7
Other respiratory disease	22	15.6	9	8.2	13	7.1*	21	16.1	11	9.3	10	6.4
Cancer of genitourinary system	16	9.3**	8	4.6	8	4.4	17	10.3*	10	5.8	20	12.6*
Cancer of kidney	6	1.4**	4	0.6	2	0.7	6	1.6**	4	0.8	2	0.7

*Significant difference ($P<0.05$)
**Significant difference ($P<0.01$)
O=observed, E=expected

Adapted from reference 50

significant excess in mortality from cancer of the digestive organs and peritoneum (1.62, $P<0.05$), specifically cancer of the large intestine (2.93) and pancreas (4.55), was found. An increased risk of dying from any of the cancers was not demonstrated in 353 byproduct workers.

Redmond et al [50] concluded that coke-oven workers who had worked for 5 years or more had a high risk of lung and kidney cancer, while non-oven workers had a high risk of cancer of the colon and pancreas. Cancer of the buccal cavity and of the pharynx also appeared at a higher rate in the non-oven workers.

Konstantinov and Kuzminykh [51] investigated mortality from malignant neoplasms in electrolytic furnace operators, anode operators, and crane operators in two USSR aluminum works studied. These two works were equipped with electrolytic furnaces with self-burning (works 1, Soderberg process) and preburned or prebaked (works 2) anodes. The authors did not describe in detail how mortality data were collected and analyzed, but they indicated that the mortality index observed in these workers was compared with the mortality of the city or district population where the workers lived. The study included an undisclosed number of men, divided into workers 18-39 years old and those 40 years and older.

Total cancer mortality was found to be higher in works 1 than in the local population by a factor of 1.85 [51]. For 18- to 39-year-old workers, cancer mortality was 7.15 times as high in works 1 as in that age group in the general population, and, for workers 40 and over, it was 1.57 times as high. Mortality from cancer of the lungs, bronchi, and pleura was increased by a factor of 1.7 for the entire group from works 1, 8.3 for those under 40, and 1.6 for the aged 40 and older workers, when compared to

that of the entire city. Mortality from skin cancer was not calculated for any of the groups, although the incidence of skin cancer was noted to be higher in workers by a factor of 38.8 for younger workers, 6.6 for older workers, and 10.5 for all workers. Cancer mortality in works 2 was not significantly different from that of the city population, and there were no deaths from primary cancer of the respiratory system in workers from works 2.

To determine the cause of this increase in mortality, Konstantinov and Kuzminykh [51] measured concentrations of airborne tarry substances and BaP at several locations where the operators replaced anodes and operated cranes. The four USSR plants selected for the study had anodes equipped with overhead (vertical Soderberg process) or lateral (horizontal Soderberg process) supplies of current. Three of the four aluminum works studied were equipped with self-burning electrodes (one with vertical and two with horizontal process), and the fourth works was equipped with prebaked anodes. The concentrations of airborne tarry substances in the aisles were 8-15 mg/cu m in the vertical Soderberg process and 12-23 mg/cu m in the horizontal Soderberg process with cooled and uncooled anodes. The corresponding levels of BaP were 0.6-9.4 and 29-56 μg/cu m. No airborne tars or BaP were detected in the aisles of the plant with prebaked anodes. The concentrations of tarry substances above the surface of the anodes in the three plants with self-burning electrodes were 27.1-43.5, 534-2,130 and 69.5-97.0 mg/cu m, while the corresponding BaP concentrations were 7.8-12.8, 370-1,385, and 383-602 μg/cu m, respectively.

Based on these data, the authors [51] concluded that tarry substances and BaP were chiefly responsible for the high cancer risk involved in

working in electrolytic shops with self-burning anodes. This type of anode is a source of high concentrations of airborne tarry substances and BaP in the occupational environment of electrolytic works.

Gibbs and Horowitz [52] conducted an epidemiologic study to determine whether an excess of lung cancer deaths had occurred at three aluminum plants in Canada, which have used the Soderberg process predominantly, and to evaluate the relationship of lung cancer mortality to length and extent of tar exposure. The study population of 5,891 workers included all men working at the aluminum plants, except those who had worked in the railroad and power station sections, as of January 1, 1950 (5,406 workers from plants A and B), or January 1, 1951 (485 from plant C). Based on the work histories obtained from the company records, the tar exposure of the employees was classified as (A) no exposure, (B) some tar exposure, or (C) definite tar exposure. Mortality data were collected for 1950-1973 (1951-1973 for plant C), with the cause of death determined from death certificates, insurance company records, and the medical department records of the plants. Mortality data calculated for each year for men exposed and unexposed to tar were compared with age-adjusted death rates from lung cancer and from all causes for men in Quebec province. The expected numbers of deaths from lung cancer in each year were added to provide a total for the expected number of lung cancer deaths for the 24-year study period. A standard mortality ratio (SMR) for each year was calculated from the ratio of observed lung cancer deaths to expected lung cancer deaths multiplied by 100. Workers were grouped by years of exposure, viz, 0, 10 or less, 11-20, and 21 or more years. For each man, a tar-year exposure index was calculated by multiplying the total number of years in the tar-

exposed occupation by the "tar factor" (0.25 for occupations with some exposure and 1.0 for occupations with definite exposure). For example, if a worker had worked in a potroom, where the tar factor was 1.0, for 1 year, the tar-year exposure index was 1; if he had worked for 1 year as a maintenance man in the potroom and carbon room, an occupation with a tar-factor of 0.25, the tar-year exposure index was 0.25. SMR's for lung cancer and for all causes were calculated for the men with various tar-years of exposure, for each year.

Data analysis showed that in plants A and B, the SMR's for lung cancer in both the exposed and unexposed groups were 128.9 and 118.8, significantly higher ($P<0.05$) than expected [52]. However, the SMR for the exposed group did not differ significantly from that for the unexposed group [52]. In plant C, the number of lung cancer deaths (11 observed, 4.4 expected) was too small for statistical comparison of the exposed and unexposed groups. However, the SMR for all persons at plant C was 247, significantly higher than that for the province. When the results for exposed and unexposed workers of all three plants were combined, the SMR for lung cancer was 133.4 (95 observed, 71.2 expected), but again the difference between exposed and unexposed groups was insignificant (135.6 versus 128.3). When the mortality from lung cancer was analyzed for four cities where the employees of the three aluminum plants lived, a similar trend, ie, an increased SMR (112-134.6), was found. The SMR for all causes in combined exposed and unexposed workers in all three plants was considerably less than 100, the expected ratio for Quebec males [52].

Since the number of expected deaths from lung cancer at plant C was so small, only the data from plants A and B were analyzed in terms of

length of exposure [52]. The SMR's for the groups with 0, 10 or less, 11-20, and 21 or more years of exposure were 118.8, 84.2, 166.7, and 279.7, respectively. This demonstrates an exposure-response relationship. The SMR in the group with 21 or more years of exposure was 2.4 times that in the 0 tar-years group ($P<0.05$). An increase in the "tar-years" resulted in an increased mortality from all causes in the combined groups from all the aluminum plants. Gibbs and Horowitz [52] concluded that the increased lung cancer mortality of men employed at plants A and B was probably accounted for by the slightly increased lung cancer mortality in the communities serving the industry. However, it should be noted that there was an increase in the lung cancer rate proportional to an increase in exposure, and this increase was statistically significant in those exposed over 21 years. This suggests a causal relationship between tar exposure and lung cancer in these workers.

A study performed by Equitable Environmental Health, Inc. for the Aluminum Association, Inc. [53] compared mortality of workers in aluminum reduction plants with a standard US population adjusted for birth dates and for various calendar years. Mortality data for various jobs and processes in the plants were also compared. The study population consisted of 23,033 men from 15 US aluminum reduction plants, with 625-4,385 workers from each plant. The plants chosen were among the major US producers of aluminum and represented a mix of geographic areas and methods of processing. The occupational history of each worker employed at one of the plants at some time during 1946-1973 and who had worked there for 5 or more years was obtained from company records. For deceased workers, the cause of death was obtained from death certificates and classified according to the 7th

revision of the WHO International Classification of Diseases. The workers were classified by plant process and by job location within the plant. Numbers of workers from each process were 11,205 prebake workers, 5,719 horizontal Soderberg process workers, 2,048 vertical Soderberg process workers, and 3,038 mixed workers. As discussed earlier in Extent of Exposure, these potroom processes involve the heating of coal tar pitch, and, consequently, the potroom and other workers are exposed to CTPV. However, in this study, the authors gave no environmental data. The "mixed" category for process classification was for men who had spent a majority of time in more than one process. The number of workers in each job location was 8,602 in the potroom, 1,909 in the paste/carbon area, 2,108 in the casting area, 4,786 maintenance workers, 4,122 "other" workers, and 483 "mixed" workers. The "mixed" category in this case was for men whose job specification could not be identified from the records. A majority of workers had worked in one process or job location category for more than 50% of their careers.

Overall, 95.6% of the original study population was traced, and data from analysis of a total of 22,010 successfully traced workers were analyzed. Of the 3,320 deceased workers, death certificates for 3,173 (95.6%) were obtained. For the data analysis, the number of deaths from each of 35 causes was calculated and compared with that of the age-adjusted US male population. The SMR's were calculated for each cause from the ratio of observed to expected numbers of deaths multiplied by 100. Categories in which more than five deaths occurred were tested for statistical significance [53].

There were 3,320 deaths observed compared to 3,810.57 expected, giving an SMR of 87 for all causes in the combined total study population. The corresponding SMR's for all causes in prebake, horizontal Soderberg, vertical Soderberg, and "mixed" processes were 94, 82, 62, and 73, respectively, all significantly lower ($P<0.01$) than expected. The SMR for workers in the vertical Soderberg process was particularly low, the authors noted, because this recently introduced process employed a younger work force [53]. There was less variation among the major job locations; the SMR's for all causes in potroom, paste/carbon, casting, maintenance, "other," and "mixed" workers were 90, 93, 97, 92, 79, and 87, respectively. A detailed analysis in terms of cause-specific mortality showed that there was no excess mortality from cancer of the digestive tract; the SMR of the total study population was 81 for this cancer. Of the 165 deaths, 37 were due to primary pancreatic malignancy, compared to the expected 35.7 or 36.0 from 1962 or 1972, respectively. In potroom workers, deaths from cancer of the pancreas were distributed among the major processes approximately in proportion to the person-years observed for workers in each process.

The SMR for malignant neoplasms of the respiratory tract in the total population was 98, ie, no overall excess was observed [53]. However, there were 91 deaths in potroom workers versus the expected 77.8 (SMR 121). There was no strong association with duration or recency of exposure [53]. While the SMR for cancer of the respiratory tract of potroom workers in prebake areas was 132 without any association with the length of exposure; the SMR of potroom workers in the horizontal Soderberg process was 162, with mortality increasing with duration of employment and time since employment began. Other location groups such as paste/carbon, casting, and

casting-prebake also had SMR's above 100. For example, paste/carbon workers who had been exposed for 5-9, 10-19, 20-29, and 30+ years had SMR's of 63, 104, 160, and 128, respectively, indicating a lack of association of mortality with exposure. A similar trend was observed for other job locations. The report [53] indicated that although SMR's were not significantly different from 100, it was clear that there was a slight positive association of lung cancer with the potroom occupation.

The SMR for leukemia in the total population was 140 (37 deaths), and that for potroom workers was 170 (16 deaths). None of the SMR's were statistically significant, and no relationship between mortality and duration of exposure was demonstrated, conceivably, because of the small populations.

From malignant lymphomas, there were 18 deaths in potroom workers (SMR 125), and 38 deaths in the total population (SMR 97). Horizontal Soderberg process workers had an SMR of 156 (11 observed; 7.35 expected). None of these SMR's was significantly different from the control value of 100 (36.8 and 38.9 deaths in the age-adjusted male population of the US in 1962 and 1972, respectively).

There was also an excess of mortality from "other hypertensive diseases" and from motor vehicle accidents in potroom workers. The authors attributed the higher mortality from hypertensive diseases to higher rates normally found in the southern US. The significance of excess automobile accidents is difficult to assess.

There were no excess deaths from cancer of the esophagus, pancreas, or respiratory tract. Neither was there any excess of mortality from "other causes," such as emphysema or bronchitis, or from cancers of other

organs, such as testes, kidneys, and bladder. There was a slightly high, but nonsignificant, number of deaths from cancer of the central nervous system. A limited mortality analysis was also performed on the study population by comparing the distribution of cause-specific deaths in the study population with that of the age-adjusted male population for 1962. A proportional mortality ratio (PMR) of 134 was found for tumors of the central nervous system. Four of the 24 observed brain tumors were astrocytomas, a rare type of tumor. An elevated PMR, corresponding to an SMR of 156, was also found for deaths from leukemia, consistent with the elevated SMR found for leukemia in the main part of the study. This study, like other studies that compare workers with the general population, points out that workers are healthy. This could obscure other possible effects that would be observed if workers were compared with other workers.

Doll et al [54], in 1965, reported the results of a prospective mortality study of gas-industry workers in Britain, with particular reference to cancer of the lungs and bladder, chronic bronchitis, and pneumoconiosis. The subjects were employees and pensioners from four British associations of gas companies (gas boards), who had worked in the industry for at least 5 years. A total of 26,856 men, 40-65 years old at the beginning of the study (1953), were grouped into three classes. Class A consisted of workers with high exposure to coal tar products, eg, coal-carbonizing process workers in the retort houses. Class B consisted of maintenance workers who had intermittent exposure to products in the gasworks, and class C included workers exposed only to byproducts (C1) and workers with minimal or no exposure (C2). On the basis of 3 years of annual followup, the authors decided to limit the study to men in the three

classes who had worked regularly in carbonization plants, since occupational differences in cancer prevalence would otherwise be slow to develop. As a result of this selection of occupations, 11,499 men were studied for 8 years, and only 50 of these (0.4%) were not traced until the end of the study. Causes of death, identified from death certificates, were classified according to the WHO list of causes of death and compared with mortality figures for all men in England and Wales during the same period.

Class A workers had the highest total death rate, 17.2/1,000, class B had a rate of 14.6/1,000, and class C had a rate of 13.3/1,000 [54]. The corresponding mortality for all men in England and Wales was 16.4/1,000. The death rate from lung cancer in class A was 3.06/1,000, 69% higher than in class C or the national rate, and the death rate from bronchitis was 2.89/1,000 in class A, 126% higher than in class C and 112% higher than the national rates. Death rates in class B and class C were similar for both diseases.

Deaths from bladder cancer, scrotal cancer, and pneumoconiosis were more common in class A (heavy exposure) workers than in class B (moderate exposure) and class C workers (minimal or no exposure) or the population at large [54]. However, the number of deaths in each class was very small. For other causes of death, the differences between the classes were small and the death rates were similar to or less than the corresponding national rates.

Doll et al [54] then compared death rates from the various causes in each of the four gas boards with regional, rather than national, death rates. Lung cancer mortality and bronchitis mortality in class A workers

were both higher than the regional rates in workers from all four gas boards, with the increases varying from 9 to 74% for lung cancer and from 7 to 144% for bronchitis. Mortality from other causes in other classes did not show consistent differences.

Adjusting for age and regional mortality differences, the authors [54] performed "trend" Chi-square significance tests on mortality versus occupational classes. Significant trends were found for lung cancer and bronchitis, indicating the highest rates in class A and the lowest rates in class C.

Class A workers were then subdivided according to the type of retort house in which they were working at the time of the study [54]. Although the results were not statistically significant, it was found that the workers in horizontal retort houses had higher lung cancer mortality, whereas workers in vertical retort houses had a higher mortality from bronchitis, compared to the national rates. Ventilation in horizontal retort houses would be more difficult, so workers there probably had higher exposure. No differences in smoking habits were found between any groups of workers, nor were there differences between the smoking habits of the workers and those of the national population. Thus, smoking habits do not help explain the different incidences of lung cancer and bronchitis.

From the data of Doll et al [54], it is evident that exposure to products of coal carbonization produced increased death rates from lung cancer and bronchitis, and that these rates increased with intensity of exposure in the three occupational classes.

In a followup study, Doll et al [55] followed 3,028 workers from the same four gas boards studied earlier [54] for 4 additional years (1961-

1965). They divided these workers into two groups, class A (2,449 coal carbonizing workers) and class C1 (579 byproducts and chemical plant workers). They also added 4,687 workers from four additional area gas boards not previously studied. The workers were 40- to 65-year old men who had been employed for at least 5 years. The added group included 1,176 coal carbonizing workers (class A), 1,430 workers who had intermediate exposure (class B), and 2,081 men who had minimal or no exposure (class C2). The cause of death of the workers was ascertained from death certificates, and the death rates were compared with age-adjusted rates for England and Wales.

Lung cancer death rates (deaths/1,000) in class A and class C1 workers of the four original boards were 4.08 and 1.78, respectively, compared to a national rate of 2.24 [55]. Death rates from bladder cancer in classes A and C1 were 0.42 and 0.29, compared to 0.17 nationally. Death rates from bronchitis were 2.42 in class A, 3.12 in class C1, and 1.64 nationally. Total death rates for class A, class C1, and for the nation were 21.69, 14.50, and 18.69, respectively. There were slight, insignificant differences from national death rates from other causes, such as all other cancers, pneumoconiosis, respiratory disease, arteriosclerosis, and degenerative heart disease. Mortality in byproducts workers (class C1) from any of the causes except bladder cancer and bronchitis was lower than that observed in the general population.

Doll et al [55] also analyzed the cumulative data of 12 years, including those already reported [54], and found that bladder and scrotal cancer death rates were significantly higher in class A workers than the national averages (P=0.03 and P=0.02, respectively). In addition, change

in the occupational status of class A workers did not change mortality from lung cancer except in those who left the industry without pension or transferred to occupations involving minimal or no exposure in carbonizing plants. In these workers, there was no excess of lung cancer deaths. There were no increases in death from bladder and scrotal cancer in class C1 workers.

The data from the four additional gas boards showed that the death rate from lung cancer in class A workers was 34% higher than that for England and Wales (2.72 versus 2.03) [55]. In class B workers, who had intermediate exposure, the rate was 72% higher than the national rate (3.50 versus 2.03, $P<0.01$). There was no significant difference between classes A and B, but the death rates in classes A and B were significantly higher ($P<0.01$ and $P<0.001$, respectively, than those in class C2. The death rate from bronchitis was 1.06 for all classes of gas workers and did not differ significantly in any class from the national rate of 1.41. Deaths from bladder cancer in class A workers were slightly higher than the national standard (0.23 versus 0.15); according to the authors, heavy exposure in the gas industry created an increased risk of bladder cancer. The mortality data of class C2 workers, summarized in Table III-2, revealed that death rates from lung cancer, bladder cancer, and skin or scrotal cancer did not differ from national rates. Furthermore, the report indicated that men who worked near or in the vertical retort houses had a slightly, but not significantly, higher risk of dying from bronchitis than those who worked in horizontal or mixed-type retort houses. Mortality data were analyzed by occupation within retort houses and compared with data from retort house workers who died of causes other than scrotal, bladder,

or lung cancer or bronchitis. These controls were matched for age at death and board of employment with the men who died of occupational cancer. It was found that 3 men who died of scrotal cancer and 12 who died of bladder cancer had worked for longer periods as retort house workers, primarily as topmen and hydraulic-main attendants, than had the control workers [55]. Although occupational titles vary among plants, topmen and hydraulic-main attendants are common to most and are the jobs with the heaviest exposure to coal tar products.

Doll et al [55] also determined mortality from leukemia and multiple myeloma. There were 9 deaths from leukemia out of 16,186 workers surveyed in all plants, versus 11.3 expected, and 1 of these was from erythremic myelosis, a type of leukemia characteristic of benzene workers, according to the authors. The gasworker with this leukemia died at the age of 56 years, after 33 years of employment as a pipefitter. There were also nine deaths from myeloma versus 4.15 expected, none of which were in class C1 workers. However, three of these deaths from myeloma were in class C2 workers. The authors [55] stated that normally the incidence of myeloma is one-third that of leukemia, but that the occurrence of an equal number of myelomas and leukemias in the present study could be a chance finding.

Doll et al [55] confirmed their earlier finding [54] that exposure to the products of coal carbonization can lead to cancer of the lungs. They were unable to explain why the mortality from lung cancer was higher in class B (intermittently exposed) workers than in Class A workers in two of the four additional gas boards [55]. Work in the retort house also increased the risk of death from bladder cancer and, to some extent, from scrotal cancer. The data, contrary to their earlier findings [54],

TABLE III-2

CANCER MORTALITY (DEATHS/1,000) IN COAL TAR PRODUCTS WORKERS*

Cause of Death	1953-1961		1961-1965		1953-1965	
	Observed	National	Observed	National	Observed	National
Lung cancer	1.16	2.05	1.78	2.24	1.59	2.13
Bladder cancer	0	0.17	0.29	0.17	0.13	0.17
Bronchitis	2.10	1.61	3.12	1.64	2.57	1.63
Skin and scrotum cancer	0	0.02	0	0.02	0	0.02
All causes**	15.00	18.66	14.50	18.69	14.91	18.67

*Low exposure (class C1) group from two studies by Doll et al [54,55] of coking plant workers, 45-50 years old, employed at least 5 years, in Great Britain; the first study [54] included 11,499 men, of whom 579 were by-products workers; the followup study [55] included 7,715 workers, of whom 2,560 were either byproducts or maintenance workers or had minimal or no exposure to coal tar products.
** All cancer and noncancer deaths, including bronchitis, pneumoconiosis, accidents, and other causes

provided very limited support to the view that bronchitis is a specific occupational hazard for gas workers. These contrary findings are possibly explained, according to Doll et al [55], by changes in the production methods or by long latency periods following the poor working conditions

during the war years. Data from the four additional gas boards provide no support whatsoever. There was no evidence that byproducts workers experience any increased risk of death as a result of their occupation.

In 1956, Reid and Buck [56] conducted an epidemiologic study to determine the risk of death from cancer in coking plant workers in Great Britain. An average of 8,000 men were employed between 1949 and 1954 in the coking plants. In 1952, at random, 800 detailed histories of the nature and duration of jobs were collected, and this sample was used to estimate the total number of workers in each of four job categories. The categories were (a) coke-oven workers, (b) byproducts (coal tar, benzol, and ammonia) plant workers, (c) laborers, and (d) maintenance crew, foremen, and craftsmen. Occupational histories of the workers that had died between 1949 and 1954 were collected from the files. The cause of death in each case was obtained from death certificates, which were obtained either from claims to the funeral fund or from a special search at the General Registrar's office. The data were analyzed by dividing the number of deaths according to the age and job, and the rates were compared with the expected age-specific death rates in a large unspecified industrial organization from 1950 to 1954. Reid and Buck did not specify the number of workers in any of the groups.

Analysis of the data revealed that the number of deaths from lung cancer, and from other causes in byproducts workers, were not different from the expected number [56]. The data, as presented by Reid and Buck are summarized in Table III-3. (It is noted that entries under "Total, excluding respiratory cancer" are in error. Perhaps entry "All cancers" should be "All other cancers"). For each occupational group, an estimate

was made of the number of workers employed at some time either as coke-oven workers or as byproducts workers, based on data from the 10% sample of detailed occupational histories. The calculations showed higher than expected numbers of deaths from respiratory and other cancers in men who had been employed at any time as coke-oven workers. Deaths from these causes in workers never employed as coke-oven workers were lower than the expected values. Men who had been employed at some time as byproducts workers had 4 deaths from respiratory cancer, 16 from other cancers, and 46 from causes other than cancer, compared to expected values of 6, 18, and 53, respectively.

TABLE III-3

MORTALITY IN COKING PLANT WORKERS*

Cause of Death	Mortality by Last Job Held						Mortality by Work History							
	Oven Workers		Byproducts Workers		Maintenance Workers		Workers at Some Time		Oven Workers At No Time		Byproducts Workers at Some Time		Byproduct Workers At No Time	
	O**	E	O	E	O	E	O	E	O	E	O	E	O	E
Respiratory cancer	4	5	3	3	14	14	14	10	7	13	4	6	17	17
All cancers	24	16	9	9	38	48	40	32	31	41	16	18	55	55
Other causes	50	49	29	26	166	141	71	95	174	121	46	53	199	163
Total, excluding respiratory cancer	74	65	38	35	204	189	111	127	205	162	62	71	254	218

*Study included 800 randomly selected case histories from approximately 8,000 men employed in coking plants in 1952 in England.
**O = observed, E = expected deaths (adjusted for age) based on an unspecified industry for the period 1949-1954

Adapted from reference 56

Because of the increased death rate from respiratory cancer in coke-oven workers, the duration of exposure was studied [56]. The occupational histories of 20 workers who died of lung cancer while still on the company records showed they had spent an average of 23.0 years in the coking plants, 16.3 of these as coke-oven workers. These figures did not differ appreciably from the average duration of employment for men of the same age included in the random sample, ie, 5.3 years in the coking plant and 16.7 years as oven workers [56].

Reid and Buck [56] concluded that there was no great excess either in cancer mortality in general or in respiratory cancer mortality in byproducts workers. These conclusions agreed with those of Doll et al [55].

Animal Toxicity

(a) General Toxicologic Effects

Coal tar products have been reported to produce toxic effects in the liver [57,58] and the lungs [59,60]. When fed to ducks [57] or made available to pigs in the diet [58], coal tar pitch produced liver damage in both species. Carlton [57] fed ducks diets containing 0.5%, 0.75%, or 1% ground clay pigeons for up to 4 weeks and found hydropericardium, ascites, anemia, and extensive liver damage. Perov [59,60] reported cytotoxic effects, such as decreased membrane detoxification processes, karyotropic disturbances and some disorganization in the ground substance, after exposure to aerosolized anthracene oil (a distillation fraction of coal tar) on the rat lung.

In 1940, Graham et al [58] investigated the effects of coal tar pitch on young pigs. The studies were undertaken to determine the cause of four

outbreaks of disease in pigs with free access to remnants of clay pigeons, composed chiefly of coal tar pitch, which were used in shooting practice. The disease was characterized by weakness, loss of appetite, and death, with gross degenerative lesions of the liver. To study the effects of ingestion of clay pigeons, groups of five healthy 9-week-old pigs were provided diets containing either powdered target remnants from a farm where pigs were affected or commercial coal tar of an unspecified type. A control group was given only grain for 60 days. Necropsy was performed on all pigs, and the tissues from internal organs were examined by light microscopy.

The first group of pigs received 15 g of powdered target remnants daily mixed with their food for 3 days; after 3 days they refused the feed mixture and were given 6 g daily for 2 days in capsules [58]. The total dose of powdered remnants was 57 g/pig, containing an unspecified amount of coal tar. All pigs died 8-20 days after the start of the experiment, and necropsy revealed jaundice, excessive serous abdominal fluid, and edema of the visceral lymph nodes in all animals. Four of the five pigs had marked degenerative liver changes, including central necrosis of the liver lobule and red blood cell engorgement of the sinusoids near the central veins. This lesion was similar to that found in the livers of pigs dying of spontaneous toxicity of unknown origin.

To confirm the role of coal tar pitch in the production of liver damage, Graham et al [58] administered liquid coal tar in capsules to a group of pigs. Three pigs received daily 3-g doses for 5 days, and two pigs received daily 3-g doses for 2 days. Pigs given coal tar for 5 days died in 10-18 days, and all showed marked gross hepatic degeneration at

autopsy. One of the two pigs receiving coal tar for 2 days died in 38 days, but no gross evidence of hepatic change was found in either pig. The authors noted, however, that a pseudomelanosis of the colon was present in the pig that died and that the survivor had an extensive moist dermatitis of unknown origin. Control pigs remained healthy and showed no evidence of liver damage at necropsy.

Graham et al [58] concluded that ingestion of clay target remnants composed of coal tar pitch was responsible for the reported outbreaks of illness in pigs, and that coal tar pitch may cause liver degeneration in swine.

(b) Carcinogenic Effects

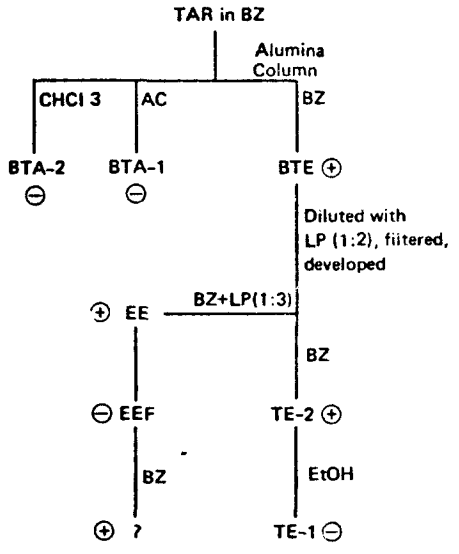
(1) Skin Effects

Berenblum and Schoental [61] conducted several experiments to determine whether unknown carcinogens, in addition to BaP, were present in coal tar, and, if so, whether their properties differed from those of known carcinogens. The experiments are described separately. A horizontal-retort tar was extracted into benzene, light petroleum ether with a boiling point of 60-80 C, dilute hydrochloric acid (to remove bases), or dilute sodium hydroxide (to remove phenols), and chromatographed on alumina columns, which were then eluted with benzene, light petroleum ether, ethanol, chloroform, acetone, or mixtures of light petroleum ether and benzene containing progressively higher proportions of benzene. At each stage of elution, the collected fraction was concentrated and applied to the skin of 10-20 mice once weekly and 5-6 rabbits twice weekly for 11-28 weeks. The animals were observed for tumor development. The sex and age of the animal and the amount of each fraction applied were not reported.

Each fraction was also examined for fluorescence, chromatographic behavior, and tendency to crystallize; these criteria were used to separate the fractions for biologic testing. The amount of BaP in some fractions was estimated spectrometrically. The method of fractional extraction and chromatography is shown in Figure III-2.

The results of these experiments, in terms of tumor incidence and latent period in mice and rabbits, are shown in Table XII-4. Benzene eluates (EE, BTE) from the alumina column were carcinogenic in both species, while light petroleum ether eluate (EEF), acetone (AC), ethanol (EtOH), or chloroform (CHC13) eluates were not [61]. In a separate fractionation, tar extracted with light petroleum ether was shaken with dilute HCl to remove basic constituents, and then with dilute alkali to remove phenolic and other acidic constituents, and separated into several fractions, I-V, for testing. Fraction II was carcinogenic to rabbits (5/5), but not to mice (0/11), fractions III and IV were carcinogenic to both rabbits (5 5 and 4/5) and mice (7/10 and 3/10). Fraction V did not produce tumors in mice or rabbits. The results of fraction I were not reported. None of the crystals obtained from any of the fractions were carcinogenic to mice or rabbits, which suggested that the carcinogenicity of the fraction remained in the mother liquor. All the fractions except 1, 2, and 3 collected during distillation in vacuo were carcinogenic to mice and rabbits, regardless of whether they contained BaP or not. Fractions collected at 145-160 C and 170-180 C were retested only on rabbits and produced tumors in 2 of 6 and 5 of 6 rabbits, respectively. The fractions collected at 160-180 C were rechromatographed with light petroleum ether. Two of the four fractions collected, one (PF) that contained chrysene,

A



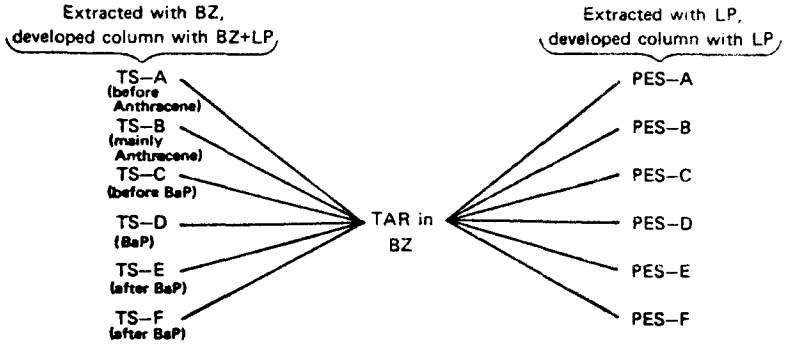
C

TAR DISTILLED

(in Vacuo)

Fractions	Temp. range (C)	Vacuum (mmHg)	BaP (9)
1	—140	30	–
2	80-120	0.1	–
3	120-140	0.1	–
4	140-160	0.1	–
5	160-180	0.1	<0.05
6	180-225	0.1	0.80
7	225-260	0.1	2.0
8	Residue (Pitch)		>0.70
Fractions 6&7 combined and redistilled:			
9a	180-200	0.1	0.24
9b	200-220	0.1	1.10
9c	220-240	0.1	1.30
9d	Residue (Pitch)	0.1	0.03

B



AC = Acetone, BZ = Benzene, CHCl 3 = Chloroform, EtOH = Ethyl alcohol, LP = Light Petroleum Ether

FIGURE III-2

FRACTIONATION OF COAL TAR

Coal tar was dissolved in benzene and chromatographed on alumina columns, eluted with several solvents, and appropriate fractions were collected; a separate lot of tar was also distilled in vacuo and several fractions collected, all of which were separately tested for carcinogenicity. A positive sign denotes that the fraction was found to be carcinogenic; absence of carcinogenic action is denoted by a negative sign.

Adapted from reference 61

anthracene, fluoranthene, and some chrysene homologues, and another (PH) that contained BaP and some chrysene, were highly carcinogenic, producing tumors in five of six and four of six rabbits, respectively. Crystals obtained from one of these fractions were noncarcinogenic to rabbits.

Berenblum and Schoental [61] concluded that horizontal-retort tar contained potent carcinogens other than BaP, and that these carcinogens were soluble in both benzene, in which the bulk of the tar constituents are readily soluble, and in light petroleum ether in which many of the tar constituents are insoluble. Several fractions that contained no BaP were carcinogenic; one of these (fraction II), which appeared before BaP on the alumina column, was carcinogenic to rabbits but not to mice. The authors pointed out that, because the objective of the experiments required only small numbers of animals and short-term exposure, the failure to produce tumors did not necessarily mean complete absence of carcinogenic activity.

In 1960, Grigoriev [62] tested the carcinogenicity of unprocessed tar from the Pechora coal mines in mice and rabbits. This tar, widely used in the USSR, was obtained from a coke-gas works. The solidified black tar contained 0.57% phenols, 8.5% pyridine bases, and 5.8% naphthalene. Fluorometric analysis revealed a BaP content of 0.57%.

The carcinogenicity of the tar was tested on 31 mice and 15 rabbits by skin painting [62]. The interscapular skin was painted in mice, and one-third of the external side of the ear was painted in rabbits. The tar was applied three times weekly for 6 months, for a total of 80 applications. The unprocessed tar softened with benzene (14%) was tested on 13 Strain A mice and on 5 rabbits. The unprocessed tar softened with 25% refined sunflower oil was applied to 18 C3HA mice and to 10 rabbits.

Thirty mice were used as controls; 10 were painted with pure benzene, 10 were painted with sunflower oil, and 10 were untreated. The dosage was not specified for any of the groups, and neither were the sex and weight of any experimental animals. Throughout the experiment, all the animals were observed for the appearance of skin tumors. The animals that died were necropsied and examined microscopically.

Among the animals treated with tar softened with 14% benzene, there were seven mice with papillomas, four of which also had skin carcinomas, and five rabbits with papillomas, four of which also had skin carcinomas. The group treated with tar softened with 25% sunflower oil had 2 mice with papillomas, 1 mouse with a skin carcinoma, and 10 rabbits with papillomas, 1 of which also had a skin carcinoma. In the controls given pure benzene, only minor hair loss and chronic dermatitis were observed after 30-40 applications. No gross or microscopic changes were observed in the skin of the controls given sunflower oil. No data were supplied for the untreated control group. All mice and rabbits painted with tar softened with sunflower oil lost weight and died quickly. The average survival time in mice of this group was 44 days, while for the mice treated with benzene the average survival time was 107 days. In the untreated control group, the average survival time was 330 days.

Grigoriev [62] emphasized the development of papillomas after 16 applications in animals painted with tar and sunflower oil. In comparison, the tar softened with benzene induced papillomas and skin cancer only after 60 applications. The author hypothesized that the sunflower oil, acting as a solvent, flowed freely and covered a more extensive area of the skin, increasing the absorption surface. Along with BaP, other toxic components

of the tar, including phenols, pyridine bases, and naphthalene were readily absorbed. According to Grigoriev, the time of tumor development was undoubtedly related to the dose of carcinogenic substance absorbed by the organism. When the tar dissolved in benzene was applied, the presence of a scab decreased the amount of toxic substances that entered the organism in subsequent applications. He further stated that the inflammation that developed after application of the tar dissolved in benzene delayed tumor development somewhat; conversely, the absence of inflammatory changes in the application of the tar dissolved in sunflower oil accelerated the carcinogenic effects. He postulated that carcinogens other than BaP had various coefficients of solubility in benzene and oil, thus explaining the differences in toxicity, number of tumors, and time of tumor development.

Grigoriev [62] concluded that the unrefined coal tar had marked carcinogenic properties and acted as an absorbed toxin, producing exhaustion, weight loss, and early death in the animals. The unrefined coal tar from coke-gas works was judged dangerous for workers, and protective measures were recommended. The study shows different effects, depending on the softening vehicle used. However, it is unfortunate that, for such a marked effect, more specific dosage information was not provided so that a quantitative dose-response relationship could be reported.

Poel and Kammer [63] tested the effects of a light and a heavy coal tar oil applied dermally to mice. The light oil, containing benzene, toluene, xylene, and solvent naphtha, was the residual oil drained from a naphthalene recovery operation. The heavy oil was a mixture of creosote, anthracene oils, and the oil drained from the naphthalene recovery operation. Light oil was diluted with toluene to form a 50% solution, and

heavy oil was diluted with toluene to obtain concentrations of 20 and 80%. The test animals were C57L female mice 10-12 weeks old and male mice 8-11 weeks old. The test solution was applied three times/week on the shaved back of each mouse for its lifespan or until persistent papillomas developed at the application site. Male mice were used to test the effects of light oil; 10 were treated with a drop (0.008 cc) of 0.05% BaP in toluene plus one drop of toluene, 11 with a drop of 50% light oil and a drop of toluene, and 10 with a drop of 50% light oil and a drop of 0.05% BaP. Female mice were used to test the effects of heavy oil, and 10 mice were treated with toluene only.

Nine of the 10 male mice treated with 0.05% BaP developed skin tumors, the 10th died of hepatocellular carcinoma; 8 of the 9 females developed papillomas [63]. All mice treated with solutions of light oil, 0.25% BaP, and solutions of heavy oil developed skin tumors. Toluene produced no papillomas in the female control group. Male mice treated with light oil alone, light oil plus 0.05% BaP, and 0.05% BaP alone developed tumors in 22-41, 6-40, and 25-44 weeks, respectively. Chromatographic and ultraviolet light analysis showed no BaP in the light oil. The authors suggested that light creosote oil produced an additive tumorigenic effect with BaP.

Female mice treated with 0.05% or 0.25% BaP or with 20% or 80% heavy oil, developed tumors in 22-58, 14-25, 22-43, and 19-34 weeks, respectively. All eight mice exposed to 0.25% BaP developed papillomas. All eight subsequently developed epidermoid carcinomas; two showed metastases in the lungs and one showed metastases in the lymph nodes. All eight mice in each group exposed to 80% and 20% heavy oil developed

papillomas, and seven papillomas in each group became malignant. One tumor regressed in the 80% group, and one in the 20% group remained a nonprogressive wart. The authors suggested that, although creosote and BaP produced the same type of carcinomas, the two materials differed in carcinogenic potency, BaP being the more potent carcinogen. While Poel and Kammer [63] referred to creosote, it should be noted that their sample probably contained other carcinogens. Thus, the question of carcinogenicity of creosote, per se, was not resolved. To test the assumption that anthracene oil contains BaP, and because anthracene oil was a constituent of heavy oil, the investigators had a sample of anthracene oil analyzed. They found that it did not contain BaP. The authors therefore suggested that, although the carcinogenic potency of heavy oil approximated that of 0.25% BaP, it was not due to BaP but to other, unidentified, potent carcinogenic substances present in it.

Horton [64] tested five different tars for carcinogenic potency by skin painting on mice. Four typical crude tars from the coking of bituminous coal and one sample produced by the coking of lignite coal were applied to the shaved skin of mice described as having an extremely low incidence of spontaneous skin cancer. The age, sex, and number of animals used and the length of exposure were not reported for any of the groups studied.

The first tar was applied in doses of 10 mg twice weekly, 50 mg twice weekly, or 100 mg three times weekly [64]. Doses of 10 mg of the second tar were applied twice weekly, and doses of 10 mg of the third undiluted tar or 10 mg of a 50% dilution by weight of the third tar in benzene were applied twice weekly. Doses of 50 mg of the fourth tar or 50 mg of the

lignite tar were applied three times a week. Solutions of 15 or 50 mg of BaP in 85% beta-methyl-naphthalene and 15% benzene were also applied.

During the period of tar application, the animals were observed for tumor appearance [64]. For the first tar, a dose-response relationship was seen; 10-, 50-, and 100-mg applications of tar produced tumors in an average of 15.6, 12.6, and 7.0 weeks, respectively. The second tar produced tumors in 24.8 weeks, while the third tar undiluted, and 50% dilutions of the third tar, the fourth tar, and the lignite tar produced tumors in 23.6, 25.1, 21.9, and 17.1 weeks, respectively. BaP in 15- and 50-mg solutions produced tumors in 33.0 and 30.6 weeks, respectively.

Horton [64] developed a numerical index for grading the various materials on the basis of the relative speed of tumor production. This index was referred to as the potency for a minimum concentration of material (PMC). A high PMC value apparently means a greater carcinogenic potency than a low PMC value. The PMC's for the first tar varied directly with the tar dosage. Values of 0.27, 0.37, and 0.63 were calculated for doses of 10, 50, and 100 mg of tar, respectively [64]. The PMC's for the second tar, third tar, and 50% dilution of the fourth tar and the lignite tar were 0.13, 0.14, 0.13, 0.11, and 0.16, respectively. PMC's of 0.08 and 0.10, which did not differ significantly, were calculated for concentrations of 15 and 50 mg, respectively.

Cleaning of the skin with aqueous detergent 5-60 minutes after application of two of these tars 2-3 times/week delayed but did not prevent the appearance of tumors. The delay in the onset was greater in animals washed 5 minutes after dermal application of tar [64].

To determine the relationship between the relative carcinogenic potencies of commercial coal tar distillate fractions and their BaP content, Horton [64] distilled the first tar, determined its BaP content, and calculated PMC values for the crude tar, the nine distillate fractions, a proportionate reblend of the nine cuts, and the pitch residue. A sixth tar, not previously used in experimentation, was also distilled, and the carbolic oil, light creosote oil, and anthracene oil fractions were isolated and tested. Doses of 10 mg of each tar were applied to mice, and the PMC's were calculated.

For the first tar, the highest percentage of BaP was found in the last two fractions distilled and in the pitch residue [64]. For the sixth tar, only the anthracene oil fraction contained any BaP. Analysis of PMC values for the first tar showed the highest values for the crude tar (0.27), followed by the reblend (0.11) and one of the early fractions (0.01). Values of zero were reported for the light creosote and carbolic acid fractions of the sixth tar, suggesting little or no carcinogenic potency for those materials.

To further test the hypothesis that BaP content could be used to estimate the carcinogenic potency of coal tar fractions, the author [64] determined the carcinogenic potency of the other fractions of coal tar. Three fractions were isolated from the second and third tars, viz, acidic compounds, basic compounds, and maleic anhydride-extractable hydrocarbons, which were anthracene, benzanthracene, and dibenzanthracene derivatives. Each fraction was dissolved in benzene at a concentration equivalent to that in the original coal tar, except for the maleic anhydride fractions and the residual tars, for which no concentrations were determined. Doses

of 10 mg of the crude tars were applied twice weekly to mouse skin, and the other fractions and residual tars were applied three times weekly in amounts equivalent to those in 10 mg of crude tar. The time of tumor appearance was noted, and the relative carcinogenic potency was calculated.

Skin tumors appeared most quickly from the residual and crude tars, in 24.8 and 23.6 weeks from crude tars 2 and 3, and 18.4 and 13.4 weeks from their respective residual tars [64]. No tumors were reported from the acidic fractions of either tar. The basic fractions of tars 2 and 3 produced tumors in 48.6 and 40.6 weeks, respectively, and maleic anhydride extracts produced tumors in 34.1 and 32.1 weeks. The PMC values indicated that the residual and crude tars were most carcinogenic, with calculated values of 0.14 and 0.22 for residual tars 2 and 3 and 0.13 and 0.14 for crude tars 2 and 3. Since no tumors were produced by acidic fractions, PMC values were not calculated. Values for the basic fractions of tars 2 and 3 were 0.03 and 0.04, and values for their maleic anhydride extracts were 0.05 and 0.06, respectively.

Horton [64] then analyzed the concentration of BaP in the air at two coke ovens and one tar plant. In the tar plant, high-volume samplers were operated near felt-impregnating vats, pitch-loading operations, the barrelling dock, and the office. At the coke ovens, the collecting equipment was mounted on the larry car. The concentrations of BaP obtained were compared with yearly averages from samples taken at representative sites in the urban atmospheres of London and Cincinnati. The author observed that the concentrations of BaP from benzene extracts of samples of the atmosphere above the two coke ovens, 45.8 and 13.0 μg/cu m, or by the tar plant pitch-loading area, 1.22 μg/cu m, were appreciably higher than

those found in the urban atmospheres of those two cities, 0.01 μg/cu m for Cincinnati and 0.06 μg/cu m for London.

The author [64] then performed an experiment designed to measure the effect of intermittent inhalation of coal tar fumes on mice. The first group of mice had previously developed squamous metaplasia as a result of exposure to air containing unspecified amounts of formaldehyde; the second group had inhaled uncontaminated air for the same unspecified time. The mice were then exposed to air containing coal tar fumes at a concentration of 0.33 mg/liter for 1 hour/day, three times/week, for up to 33 weeks. In both groups, most animals developed proliferative alveolar neoplasia; the two groups did not differ in incidence of neoplasia. One squamous-cell carcinoma was reported, but the authors did not indicate in which group the carcinoma was observed. No alveolar proliferation or carcinoma was seen in the lungs of control mice treated with formaldehyde alone.

Horton [64] compared the carcinogenic potency of various fractions of the first tar with their BaP content in percent by weight and found a correlation between the carcinogenic potencies of the two BaP-containing fractions and their BaP content. The tumor induction rates for the distillate fractions were closely correlated with their BaP content.

Assessing the relative potency of the crude tars, tar acids and bases, maleic anhydride extracts, and tar residues, Horton [64] concluded that no carcinogens were removed in the tar acid fractions and that small amounts of carcinogens were removed in the tar base fraction. However, considerable quantities of carcinogens were removed by the maleic anhydride; the authors presumed that these carcinogens were benz(a)anthracene and dibenz(a,h)anthracene derivatives, and that the

residual tars had high potency values because they contained most of the BaP of the original tars.

This research indicates a dose-response relationship for coal tar, and Horton [64] hypothesized that this correlation might be caused by some factor other than BaP. He speculated on the presence of accelerating factors. The comparison of the relative potencies of crude tars, tar acids and bases, maleic anhydride extracts, and tar residues is also important. However, detailed animal testing information was lacking in the paper. In reporting experimental results, the author did not provide diagnostic criteria or distinguish between tumors and carcinomas. Furthermore, it would have been helpful if the investigator had done at least some preliminary identification work on the "accelerator factor." Definitive work is still needed on the interactions of the major carcinogens known to exist in coal tar.

In 1973, Elgjo and Larsen [65] investigated alterations in epidermal growth kinetics induced by coal tar ointment and methotrexate. Three-month-old male and female hairless mice were used in their experiments. Goeckermann ointment, consisting of 2% coal tar and 2% sulfur in petroleum jelly, was applied at a dose of 180-200 mg to the backs of an unspecified number of mice, 5 days/week, for 4 weeks. In addition, half the mice received methotrexate (5 mg/kg), a folic acid antagonist, by ip injection once weekly. Two control groups received daily applications of 180-200 mg of either petroleum jelly or petroleum jelly containing 2% sulfur, and a third group of untreated mice was also included in the study. At the end of 4 weeks, half the animals in each of the two experimental and three control groups received an ip injection of 0.15 mg of Colcemid, to arrest

all epidermal mitoses, 4 hours before all the animals were killed.

Elgjo and Larsen [65] defined the mitotic rate as the number of arrested mitoses in 50 microscopic fields of skin divided by the time in hours between Colcemid injection and death. The average mitotic rate was 16.6 in the group treated with Goeckermann ointment only and 13.9 in the group that had also received methotrexate. The animals that had been treated with petroleum jelly or petroleum jelly with 2% sulfur and the untreated control group had mitotic rates of 53.3, 121.5, and 48.6, respectively.

Epidermal thickness was also evaluated in 10 mice from each group not treated with Colcemid [65]. The average epidermal thickness in animals treated with Goeckermann ointment alone was 43.2 μm, compared to 41.2 μm in mice that also received methotrexate, an insigficant difference.

Elgjo and Larsen [65] indicated that the hyperplasia induced by the Goeckermann ointment was of the type induced by tar-containing compounds, with a low mitotic rate and a very long mitotic duration. They further suggested that the therapeutic effect of long-term use of Goeckermann ointment, and possibly of other tar ointments, in the treatment of psoriasis could be related to these alterations in epidermal growth indices.

Shabad et al [66] compared the tumorigenic effects of three coal tar-containing ointments in mice. The ointments tested were coal tar ointment (USSR), Ciba coal tar ointment (Switzerland), and Locacorten tar ointment (USA), which had respective BaP contents of 5,190, 5,020, and 225 μg/g, determined spectrofluorometrically. Three groups of 17-24 C57 x CBA hybrid mice of unspecified age were treated with the test ointments 2 or 3 times a

week for 10 or 12 months. The quantity of ointment applied was not reported. All the animals were regularly observed for the development of tumors. At the end of 12-18 months, tumor-bearing mice were counted, and each tumor was examined microscopically. Coal tar ointment, Ciba coal tar ointment, and Locacorten tar ointment killed all the mice within 18 months and produced tumors in 18 of 19, 20 of 21, and 16 of 17 mice, respectively. Locacorten tar ointment induced squamous-cell carcinomas accompanied by keratinization and a few malignant papillomas in mice. Shabad et al [66] concluded that the tar-containing ointments with a high BaP content produced skin cancer in mice.

Woglom and Herly [67] applied full-strength (undiluted) 75, 50, and 25% solutions of gasworks tar in glycerine to the skin of mice. Four groups of 50 mice were treated with the test solution on alternate days for 58 weeks or until tumors spread into the tissue surrounding the site of application. Mice were examined 3 times a week; the tumors were counted, and each tumor was examined microscopically. Mice treated with the test materials lost hair at the application site and developed papillomas with hyperkeratosis and patchy skin. The full-strength tar killed 70% of the mice in 163 days and produced malignant (invasive) tumors in 8 of the 15 surviving mice. Application of 75% tar killed 19 mice in 138 days and produced malignant tumors in 10 of the survivors by the 224th day of treatment; one of these had lymph-node metastasis, one had lung metastasis, and one developed metastases of both the lymph nodes and the lungs. The 50% tar solution killed 23 of 50 mice in 156 days and induced carcinomas in 9 of the surviving mice. The 25% tar killed 20 of 50 mice in 149 days and produced tumors in 15 mice, of which 12 proved to be malignant. Hieger

[68] conducted a similar study and, like Woglom and Herly [67], found that dilution of gasworks tar decreased the mortality of mice but did not decrease the incidence of tumors in surviving mice that received the coal tar.

Gorski [69] investigated the carcinogenic properties of Silesian Pit coal tars and pitches in 80 male and 70 female BN-strain mice. The test substances were 1:1 benzene solutions of hard and soft pitches, of an anthracene fraction from a coke-chemical works, and of two tars from smelting works. The hard pitch contained about 20% (by weight) benzene solubles, while the soft pitch, anthracene fraction, and tars contained about 50% benzene solubles. Each substance was tested on 30 mice. One drop of benzene extract of tar or pitch was applied to the shaved skin of each mouse twice weekly for 5 months. An unspecified number of mice treated with benzene only served as controls. Mice that died in the first 8 weeks were excluded from the study.

Application of hard-pitch solution killed 9 of 30 mice in the first 8 weeks [69]. The remaining 21 mice had an average of 1 papilloma/surviving mouse. With soft-pitch solution, 2 of 30 mice died in the first 8 weeks; there were 14 mice with malignant tumors, and an average of 2.9 papillomas/surviving mouse. Twenty-four mice survived application of the anthracene-fraction solution, with an average of 0.3 papilloma each. For the two smelting-works tar solutions, there were 22 and 26 surviving mice with 6 and 8 malignant tumors, respectively. From these results, the author [69] concluded that soft pitch was more carcinogenic than hard pitch, and that pitches were more carcinogenic than tars.

Wallcave et al [12] tested benzene extracts of two coal tar pitches for their tumorigenic activity. The coal tar pitches were obtained from coke ovens and were of a grade commonly used in roofing. Following several solvent extractions and purification steps, fractions were analyzed by ultraviolet absorption spectrometry. The chemical analysis of the pitch samples showed the presence of fluoranthene, benzo(k)fluoranthene, indeno(1,2,3-ed)pyrene, BaP, and benzo(a)anthracene.

To determine tumorigenic effects, the pitches were tested on 7- to 11-week-old inbred male and female Swiss albino mice [12]. Two groups of mice were randomly selected, each consisting of an equal but unreported number of 25-g males and 20-g females. About 1 square inch of the skin of each mouse was initially shaved and then painted twice a week with 25 μl of a solution of pitch in benzene. Each application contained 1.7 mg of coal tar pitch. A control group of 15 male and 15 female mice was painted with benzene alone. Animals were weighed once a week, and all skin tumors were recorded. Animals were killed when moribund or when they developed highly advanced skin tumors. Necropsies were not performed on some animals because of postmortem decomposition.

The average survival time for coal tar pitch-painted animals was 31 weeks [12]. There were tumors in 53 of 58 coal tar pitch-treated animals autopsied, of which 31 had carcinomas and all 53 had papillomas. In the 26 controls autopsied, there was only one papilloma and no carcinoma. The authors believed the tumorigenic effects of coal tar pitches in mice were caused by the high content of PNA's. However, Wallcave et al did not identify any specific PNA as the tumorigenic agent, because the biologic

testing was conducted with an extract of coal tar pitch rather than with purified fractions.

Similar tumorigenic effects of coal tars or coal tar pitches or their benzene extracts in mice have been reported by other investigators [67-69].

Sall et al [70] tested the basic fraction of creosote in mice for promotion or retardation of the tumorigenic effects of BaP and chemically related PNA's. They conducted several experiments, which are discussed separately. The test solutions, containing BaP or other PNA, the basic fraction of creosote, or both, were applied on the shaved skin of the mice, injected subcutaneously, or implanted under the skin in a cholesterol pellet. The test animals were male and female strain A mice. Only tumors that reached 2 mm diameter and that progressed in size were counted.

In the first experiment, two groups of female mice were painted three times a week for 44 weeks with 0.05% BaP in benzene or with 0.05% BaP in benzene containing 1% of the basic fraction of creosote [70]. Two groups of 20 mice were painted similarly for 44-51 weeks with 0.05% or 0.02% BaP alone. Another control group of 20 mice was painted with a 1% solution of the basic fraction of creosote alone for 51 weeks. BaP at 0.05% plus 1% creosote produced tumors in 19 of 20 mice, while 0.05% BaP alone produced tumors in 18 of 20 mice. The latent period, the time required for appearance of the first tumor, in mice treated with BaP plus creosote was 18 weeks, while the latent period in mice treated with BaP alone was 29 weeks. These results suggested that creosote accelerated the tumorigenic effects of BaP. When mice were painted with 0.02% BaP, either alone or in combination with creosote, there were only two tumor-bearing mice in 44 weeks, but the tumors appeared rapidly during the latter part of the

treatment period. At 60 weeks, 14 of 20 mice treated with 0.02% BaP plus creosote had tumors, as did 10 of 20 mice treated with 0.02% BaP alone. Four of the surviving controls that had not developed tumors at 60 weeks developed tumors by week 82. Application of the basic fraction of creosote alone did not produce tumors in any mice.

In the second experiment [70], groups of 20 female mice received one subcutaneous injection of 1 mg of BaP dissolved in 0.2 ml of lard, and 11 subcutaneous injections (0.3 cc) of a 2% solution of creosote in lard at the same site over a 2-month period. Groups of 20 control female mice were given the same amounts of BaP plus 11 injections of lard containing no creosote. Injection of 1 mg of BaP plus 2% creosote produced tumors in 7, 15, and 17 mice at 4, 5, and 7 months after injection, while 1 mg of BaP alone produced tumors in 11, 14, and 15 mice at the same time intervals. Groups of 20 male mice received a single injection of 0.5 mg of BaP in lard alone, a single injection of BaP plus 11 injections of creosote in lard, or 2 injections of 2% creosote in lard. BaP plus creosote produced tumors in 18 mice 4 months after injection. No data were provided for observations 5 and 7 months after BaP administration in this group. BaP alone also produced tumors in 18 mice at 4 months. Creosote injection did not induce any tumors. Additional groups of 20 male mice received an injection of 0.1 mg BaP, alone or in combination with 2% creosote. There were no controls that received creosote alone. BaP plus creosote produced tumors in 10, 17, and 18 mice 4, 5, and 7 months after injection, respectively, while BaP alone at the 0.1-mg dose produced tumors only in 1, 5, and 6 mice at 4, 5, and 7 months, respectively, suggesting that the basic fraction of creosote promoted the tumorigenic effects of BaP.

Further experiments were conducted with other PNA's [70]. Groups of 20 mice received the test agent, alone or in combination with 2% basic fraction of creosote. In combination with creosote, 0.1 mg of 1,2,5,6-dibenzanthracene produced 0, 6, and 14 tumor-bearing mice at 4, 6, and 9 months, while alone it produced tumors in 0, 4, and 7 mice at the same intervals. In combination with 2% creosote, 20-methylcholanthrene (0.1 mg) produced tumors in 8 and 18 mice at 4 and 6 months. It was not clear from the report how many tumors were produced at 9 months. This test agent alone produced tumors in 12 and 18 mice at 4 and 6 months. While the still lower dose of 20-methylcholanthrene (0.02 mg) plus 5% creosote produced tumors in 1, 7, and 9 mice, the test agent alone at the same concentration produced tumors in 6, 10, and 10 mice at 4, 6, and 9 months, respectively. Similarly, other PNA's tested at doses of 0.05-0.10 mg with creosote produced tumors rapidly, so that the promoting or retarding effects of creosote generally could not be determined. Sall et al [70] therefore calculated the dose of each carcinogen that would produce tumors slowly, with a minimum latent period of 6-7 months in 50% of the mice treated. The doses thus calculated were BaP, 0.1 mg; 1,2,5,6-dibenzanthracene, 0.1 mg; 20-methylcholanthrene, 0.02 mg; 10-methyl-1,2-benzanthracene, 0.05 mg; 9,10-dimethyl-1,2-benzanthracene, 0.05 mg; and 5-amido-10-methyl-1,2-benzanthracene, 0.1 mg.

In the third experiment [70], groups of 20 female mice were implanted with 1% BaP in cholesterol alone, 1% BaP in combination with 5% basic fraction of creosote, or 5% basic fraction of creosote alone. BaP plus creosote produced 2, 4, and 7 tumor-bearing mice at 4, 5, and 7 months respectively. BaP alone produced tumors in 3, 4, and 4 mice. Creosote

alone did not produce tumors in any of the mice tested. These results suggest that creosote did not alter the tumorigenic effects of BaP when implanted in cholesterol under mouse skin.

Although Sall et al [70] concluded that the basic fraction of creosote promoted the tumorigenic effects of BaP when painted on mice, the evidence presented is contradictory and is not supportive of their conclusions.

Cabot et al [71], in 1940, reported the production of skin tumors in mice with BaP in combination with various fractions of creosote. Several fractions of creosote collected between 160 and 300 C during tar distillation were prepared. An unspecified amount of unfractionated creosote was extracted into aqueous hydrochloric acid, referred to as the basic fraction; the remaining creosote was extracted into aqueous sodium hydroxide, referred to as the phenolic fraction. The creosote from which the basic and phenolic constituents had been removed was referred to as a neutral fraction, which was then steam distilled. The distillate was referred to as a neutral distillate, and the residue was referred to as a neutral residue. The solutions of these fractions prepared in benzene were 1% basic fraction, 6.6% phenolic fraction, 25% neutral fraction, 25% neutral distillate, 99.8% neutral distillate, and 99.8% neutral residue (the latter two were essentially neat).

Groups of 20 female mice were painted on the shaved skin of the back 3 times weekly for 20 weeks with test solutions containing one of the above fractions plus either 0.2% or 0.05% BaP. After 20 weeks, application of the test solutions containing 0.2% BaP plus creosote fractions were reduced to two times weekly for 6 weeks and then discontinued. Application of the

0.05% BaP solution plus creosote fractions was carried out 3 times weekly for 38 weeks. Two groups of 20 mice each painted with 0.2 or 0.05% BaP served as controls. The mice were examined weekly, and the number of tumors was counted. Application was discontinued when progressively growing neoplasms about 4 mm in diameter developed and did not regress.

The basic fraction and 25% solution of neutral distillate of creosote, containing 0.2% BaP, produced tumors at 36 weeks in all 20 mice of each group [71]. Other creosote fractions tested with 0.2% BaP produced 7-18 tumors in 20 mice. The control application of 0.2% BaP produced 19 tumors. In contrast, 0.05% BaP alone produced 16 tumors in 20 mice in 52 weeks, and 0.05% BaP in combination with creosote fractions produced 5-19 tumors in 52 weeks. The 6.6% solution of the phenolic fraction and the neutral residue fraction showed retarding effects on tumor production by 0.2% BaP; at 22 weeks, there were 19 tumors with 0.2% BaP alone, 10 tumors with the phenolic fraction plus 0.2% BaP, and only 5 tumors with the neutral residue plus 0.2% BaP. In contrast, the basic fraction promoted the BaP-induced tumorigenesis in mice, producing tumors in eight mice in 15 weeks. There were only three tumor-bearing mice in the control group at this time. The neutral distillate also showed some promoting action.

Lijinsky et al [72] tested creosote, alone and in combination with 7,12-dimethylbenz(a)anthracene (DMBA), on mice to determine whether creosote promoted the carcinogenicity of DMBA. The solutions tested were undiluted creosote No. 1 oil, drypoint 240 C (the temperature at which the last drop of liquid distills), obtained from a still, a 10% solution of this creosote in acetone, and a 2% solution of the basic fraction of creosote in acetone. Four groups of 30 swiss female mice each were used.

One drop of each test solution was dropped onto the shaved back of the mice twice weekly for up to 80 weeks. One group of mice was given undiluted creosote. Three other groups were given a single application of 1% DMBA 1 week before the start of application of the undiluted or 10% creosote or of the 2% solution of the basic fraction of creosote. Fifty mice treated with a single application of 1% DMBA served as controls. At the end of the experiment, the surviving animals were killed and the resulting tumors examined microscopically.

Of the 26 mice surviving the application of undiluted creosote until the appearance of the first tumor, 13 bore skin tumors [72]. These 13 mice had 23 tumors, 16 of which were carcinomas [72]. Application of undiluted creosote and 1% DMBA produced 32 tumors, including 26 carcinomas, in 23 surviving mice, and application of 10% creosote plus 1% DMBA produced 15 tumors, including 8 carcinomas, in 29 surviving mice. Application of 2% solution of the basic fraction of creosote with 1% DMBA did not produce any tumors in 56 weeks. A single application of 1% DMBA alone did not produce tumors in any of the 50 control mice, all of which survived the 80-week observation period.

The authors [72] analyzed the creosote and its basic fraction by a combination of chromatography and ultraviolet spectrometry. The creosote thus analyzed contained carbazole, benz(a)anthracene, chrysene, fluoranthene, pyrene, anthracene, and phenanthrene. A quantitative analysis of the creosote showed that the most abundant chemical constituent was phenanthrene at 47.9 g/liter of creosote, the least abundant was chrysene at 1.27 g/liter, and the concentrations of the other constituents ranged between 2.75 and 7.8 g/liter. The concentration of BaP was 100-120

mg/liter. The authors concluded that undiluted creosote had carcinogenic activity equivalent to that of a 0.01% solution of DMBA, though no chemical agent known to account for this action was found in it by chemical analysis. They [72] speculated that if BaP was present in the creosote oil, the amount was too small to produce cancer in mice. They concluded that only the undiluted creosote was carcinogenic, that the carcinogenicity was not due to BaP, and that creosote promoted the carcinogenic effects of DMBA in mice.

Skin carcinogenic effects of creosote in mice have also been reported by Boutwell and Bosch in 1958 [73]. They applied 25μl of commercial creosote, distilled from high-temperature coke-oven tar between 200 and 400 C, on the shaved skin of mice, twice/week for 28 weeks. A 92% incidence of papillomas and an 82% incidence of carcinomas were observed at 18 weeks, with average induction times of 20 and 26 weeks for papillomas and carcinomas, respectively, [73]. Furthermore, DMBA pretreatment produced more rapid induction of incidence skin tumors than creosote alone.

In 1930, Shor [74] described pathologic changes in the spleen, lymph nodes, kidneys, and thymus of five kittens and two cats that had received subcutaneous injections of a coal tar in olive oil at doses of up to 2 cc/animal. Coal tar administration was carried out for up to 4 weeks. Lack of controls, lack of information on intercurrent disease, and the high doses administered make this study of doubtful significance.

In 1938, Passey [75] tested horizontal-retort tar from a gasworks for carcinogenicity in Airedale dogs. According to the author, Airedales were known to develop spontaneous skin tumors and therefore should be more susceptible to the carcinogenic effects of tar. Twelve 18-month-old

females, raised in the laboratory since weaning, were used. An unspecified amount of coal tar residue was painted on the shaved skin once a week for 7 years. The coal tar residue was phenol-free and soluble in ether. Although the author did not mention specific observation times, the animals were apparently observed periodically for signs of tumor development. When a tumor developed, a biopsy was made for detailed microscopic examination. There were no control animals in the study.

Three of 12 dogs died early in the study, one from wounds inflicted in a fight with her companions, another from subphrenic abscess of uncertain origin, and the third of injuries from getting her head caught under her compartment door [75]. Three of the remaining nine dogs developed skin tumors, one after 6 years and 4 months, and the other two after 6 years and 7 months of tar application. About 6 years after beginning the tarring, a pedunculated fleshy mass was observed in the first dog. This was described as growing to the size of a thrush's egg and then diminishing to the size of a pimple within about 3 months. With continued tarring, it grew into a sessile tumor the size of a walnut. Biopsy results showed a malignant melanoma, with only a few cells containing traces of melanin. Most of the pigment was contained within macrophages. A similar growth pattern was observed in the tumor in the second dog; this tumor was a malignant melanoma with no trace of melanin in its cells. The tumor in the third dog was not examined microscopically at the time of reporting, although the author stated that it was jet black in color. According to Passey [75], no malignant melanoma had been recorded in pigmented animals of other species after treatment with coal tar or other carcinogenic agents. Other clinical effects observed included loss of hair in one dog

and development of tender skin at the application site in all three tumor-bearing and two nontumor-bearing dogs. The dogs otherwise appeared healthy throughout the study.

(2) Lung Effects

In 1967, Tye and Stemmer [76] examined the contribution of phenols to the pulmonary carcinogenic potency of coal tar aerosol. The two coal tars used were from US coke ovens. The first tar had a specific gravity of 1.17 and consisted of 2.7% toluene-insoluble material, 4.5% tar acids, 0.7% BaP, and 6% Diels-Alder "hydrocarbon ring" compounds extracted with maleic anhydride. The second tar had a specific gravity of 1.24 and consisted of 17.8% toluene-insoluble material, 1.4% tar acids, 1.1% BaP, and 2% Diels-Alder compounds.

Five groups of fifty 3- to 5-month-old male C3H/HeJ mice were exposed for 2 hours three times weekly for 55 weeks to aerosols of (1) the unfractionated first tar, (2) the nonphenolic fraction of the first tar, (3) the nonphenolic and phenolic fractions of the first tar, (4) the nonphenolic fraction of the first tar plus the phenolic fraction of the second tar, or (5) the nonphenolic fraction of the second tar plus the phenolic fraction of the first tar [76]. The blends of phenols and tars consisted of 4.5% phenols and 95.5% tar from which the phenols had been extracted. During the first 8 weeks, the mice were exposed to tar at an air concentration of 0.20 mg/liter; excessive mortality compelled a reduction of the concentration to 0.12 mg/liter. A control group was

exposed to air only. Three mice from each group were killed after 4 weeks of exposure, and five mice from each group were killed after 31 weeks. All survivors were killed at the end of 55 weeks, and autopsies were performed; lung tumors were examined microscopically.

Tye and Stemmer [76] observed squamous metaplasia, intrabronchial adenomas, and carcinomas in the exposed animals. The most prominent lesions were intrabronchial adenomas and adenocarcinomas, multiple neoplasms were frequent. The first tumor, an intrabronchial adenoma, was observed at the end of the 46th week in the group receiving the nonphenolic fraction of the first tar. The numbers of mice in groups 1-5 surviving at the end of 45 weeks were 13, 20, 19, 25, and 23, respectively. At 45 weeks, 32 of the control mice were still alive. By the end of the experiment, exposure to the first tar had produced 10 intrabronchial adenomas and 3 adenocarcinomas. The nonphenolic fraction of the first tar produced 11 intrabronchial adenomas and no adenocarcinomas. The nonphenolic plus phenolic fractions of the first tar produced nine intrabronchial adenomas and one adenocarcinoma. The nonphenolic fraction of the first tar plus the phenolic fraction of the second tar produced nine intrabronchial adenomas and one adenocarcinoma. The nonphenolic fraction of the second tar plus the phenolic fraction of the first tar produced 11 intrabronchial adenomas and no adenocarcinomas. No tumors were observed in the controls.

The authors [76] concluded that the occurrence of adenomas was not related to the presence of phenols, but that the higher concentration of Diels-Alder PNA's in the first tar may have been more evocative of this type of lesion. Based on the ultraviolet and mass-spectrometric analysis of the PNA fraction, the authors concluded that 8-methylbenz(a)anthracene may have been the principal carcinogen involved. The authors further pointed out that adenocarcinomas were seen in five mice that received the phenols and in no mice not given phenols, although all these animals received the same PNA's. They hypothesized that phenols were cocarcinogenic because of their irritant properties.

Kinkead [77] studied the effects of aerosolized coal tar on the skin, lungs, liver, and bladder of rats, mice, hamsters, and rabbits. Sprague-Dawley rats, 64 females described only as yearlings and 32 weanlings of each sex, and CAF-1 and ICR mice, 50 males of each strain, were exposed continuously, except for 15 minutes daily, for 90 days to aerosolized coal tar at concentrations of 0.2, 2.0, and 10.0 mg/cu m. Eighty yearling female Sprague-Dawley rats, 9 weanling rats of each sex, 25 male CAF-1 mice, 25 male ICR mice, were exposed for 90 days at 20 mg/cu m. New Zealand white rabbits, 24 females, and Golden Syrian hamsters, 100 males, were exposed at 20 mg/cu m for 90 days. The control animals were 41 female and 41 male Sprague-Dawley weanling rats, 82 female Sprague Dawley yearling rats, 75 male CAF-1 mice, 75 male ICR mice, 24 female New Zealand white rabbits, and 100 male Golden Syrian hamsters.

To produce the aerosol, coal tar from which the light oil fraction had been removed was diluted with an equal volume of benzene to decrease its viscosity, and the insoluble solids were removed by centrifugation [77]. The benzene was then removed from the tar by fractional distillation. Coal tar and air were mildly heated and placed in a pressurized aerosol-generating device; the chamber concentration was regulated by either increasing or decreasing the pressure on the coal tar reservoir. An aerosol particle-size determination showed that 95% of the droplets were 5 μm or less in diameter.

The animals were observed daily for general appearance, behavior, signs of stress, and mortality [77]. Ten percent of the hamsters, weanling rats, and yearling rats from the 20 mg/cu m group and from the control group were killed at the end of the 90-day exposure. Tissues from all animals that died were examined macro- and microscopically. Kidney, liver, and lung sections from some animals in the highest exposure group were analyzed for fluorescent compounds.

Kinkead [77] noted that at the conclusion of the exposure period, the animals exposed at concentrations of 2, 10, and 20 mg/cu m had a considerable accumulation of coal tar on their fur, with the 20 mg/cu m animals being quite brown. At autopsy, a high incidence of chronic murine pneumonia was observed in animals of all species that died during and after exposure. The cumulative animal mortality was said to show a general graded response proportional to exposure concentration. Exposure also had

an effect on the growth of all species tested. All exposed groups gained less weight than the untreated controls during the first 2 months and lost weight during the 3rd month; effects on growth were still apparent at 7 months.

For all four animal species, kidney, liver, and lung analyses after a 30-day exposure at 20 mg/cu m showed an increase in fluorescent material [77]. The fluorescence ratio of exposed tissue to control tissue varied considerably for the organs of each species. The fluorescence ratios for kidney tissue were 3.1, 1.5, 2.1, and 2.1 in mice, rats, hamsters, and rabbits, respectively; for liver, the ratios were 1.5, 1.7, 1.4, and 2.3; and for lung tissue, the fluorescence ratios were 63.2, 6.4, 31.2, and 200.6.

Kinkead [77] also conducted a second experiment, involving aerosol exposure at 10 mg/cu m, in which both the solid particles and the light oil fraction of the coal tar were retained in the aerosolized coal tar sample. The same species and strains of experimental animals were tested, but a smaller number of animals was used in the experimental and control groups. Lung sections were analyzed for fluorescent compounds. An additional 150 CF-1 mice were exposed to the coal tar aerosol and killed serially; groups of 5 mice were killed after the 1st and 7th days of the experiment and monthly thereafter up to 505 days after exposure [78]. Macro and microscopic studies were performed on the CF-1 mice to determine the progressive pulmonary effects of the coal tar aerosol. The results of

these examinations were described in a separate report by McConnell and Specht [78].

Kinkead [77] stated that the presence of the light oil fraction decreased the viscosity of the coal tar and improved the aerosolization process; aerosol particle-size determination showed results similar to those of the previous experiment, with 95% of the total droplets 5 μm or less in diameter. Body-weight changes observed in animals exposed at 10 mg/cu m were similar to those observed at the same concentration in the first experiment. A direct time-dose relationship was seen in the amount of coal tar deposited in the lungs with increased exposure time; after correcting for control values, 1, 7, 30, 60, and 90 days of exposure resulted in retention of 31, 204, 668, 647, and 2,182 μg coal tar/g of lung tissue, respectively, as determined by fluorescence analysis. At 20, 30, and 60 days after exposure, the respective amounts of coal tar retained in the lungs were 380 and 347 μg coal tar/g of tissue, indicating clearance of a considerable amount of coal tar after exposure ended. Comparison of the two experiments shows a similarity in the general effects produced by aerosolization of the benzene-soluble extract and the unprocessed coal tar.

McConnell and Specht [78] described lesions in the liver, kidneys, and lungs of animals exposed to coal tar by the aerosol exposure conducted by Kinkead [77]. It appears that animals used in this study were those exposed to coal tar in the earlier study of Kinkead [77], except for JAX

mice of unspecified sex, which were not described in the earlier study.

In mice, exposure to coal tar aerosols produced several types of epithelial tumors, including squamous-cell papillomas, keratoacanthomas, and squamous-cell carcinomas of the skin [78]. None of these tumors regressed spontaneously, but there was also no evidence of metastasis. In ICR mice, 0.2, 2.0, 10, and 20 mg/cu m of coal tar aerosols produced 0, 2, 3, and 10 tumors, respectively, 505 days after the first exposure. A dose-response relationship for skin-tumor incidence is difficult to establish from these results, since considerably different numbers of animals (from 2 to 36) were used in different groups. During the 2nd and 3rd months of exposure, many control male weanling rats and ICR mice exposed to 0.2 mg/cu m died of an unidentified infection. The incidence rates of skin tumors in ICR mice exposed at 0, 0.2, 2.0, 10, and 20 mg/cu m of aerosolized coal tar were 0, 0, 8, 37.5, and 27.8%, respectively. These percentages were derived from the number of mice alive after 183 days. In JAX mice, there were no skin tumors in animals exposed at concentrations of 0.2, 2.0, or 10.0 mg/cu m, but 10 animals (37%) exposed to coal tar at 20 mg/cu m had tumors at 505 days after exposure. The authors suggested that JAX mice were more resistant to tumorigenic materials. The latent period of skin tumors showed a dose-dependent relationship. ICR mice exposed to aerosolized coal tar at 20 mg/cu m developed the first tumor within 93 days after exposure, and mice exposed at 10 and 2 mg/cu m developed the first tumors at 128 and 142 days after exposure, respectively.

Microscopic examination of the lungs of 50% of the mice killed 99 days after termination of exposure showed moderate pigmentation in the white blood cells in 14 of 15 CF-1 mice exposed to coal tar, but in only 1

of 13 JAX mice. The authors [78] postulated that the two strains differed in the ability to clear coal tar material from the lungs. Three significant types of lesions were also observed in rats and hamsters. There were large numbers of black granules and amber droplets observed in the white blood cells in the lungs of both hamsters and rats. The liver at autopsy was more brown than normal, an effect that was more apparent in the hamster than in the rat. Because mild central lobular necrosis was found in the liver only in exposed animals, it was interpreted as a result of the coal tar exposure. Upon microscopic examination, it was determined that pigment was present in the liver Kupffer cells. Since the pigment tested positive for iron, it was not considered to be coal tar, but it was not explainable on the basis of blood loss from hemolysis.

Sasmore [79] examined tissues from the several animal species studied by Kinkead [77] and McConnell and Specht [78]. The study was based on 8,799 slides from 1,500 animals, including 63 rabbits, 376 hamsters, 498 rats, and 563 mice. Although the methods of data tabulation differed, there was good general agreement between the pathology report and the information presented in the studies of Kinkead [77] and McConnell and Specht [78]. The tumor incidence rates for each species at each exposure concentration except 20 mg/cu m, at which no data were reported, are summarized in Table III-4 [79] for all the organs examined microscopically. No information was given on how long after exposure necropsies were performed.

TABLE III-4

TUMORS FROM EXPOSURE TO AIRBORNE COAL TAR IN FOUR ANIMAL SPECIES

Species	Tumor	Tumor Incidence (%)			
		0.00 mg/cu m	0.20 mg/cu m	2.00 mg/cum	10.00 mg/cu m
Mice	Skin	3	1	1	6
	Lung	30	39	58	77
	Spleen	5	20	5	14
	Kidney	1	3	0	0
	Liver	9	4	11	0
	Urocyst	0	0	3	0
Rats	Skin	10	6	3	0
	Lung	4	3	10	18
	Spleen	8	4	4	8
	Kidney	1	0	0	6
	Liver	1	0	2	3
	Urocyst	-	-	-	-
Hamsters	Skin	0.7	0	0	4
	Lung	0.6	3	0	4
	Spleen	0.7	0	0	4
	Kidney	2	1	0	0
	Liver	0.6	0	0	2
	Adrenals	27	0	57	17
Rabbits	Skin	0	0	0	12
	Lung	0	0	0	0
	Spleen	0	0	0	0
	Kidney	0	0	0	0
	Liver	0	0	0	0
	Urocyst	0	0	0	0

*Adapted from Sasmore [79]

Sasmore [79] concluded that the lung tumors found in mice were dose-related. The lung tissue specimens examined from animals exposed to aerosolized coal tar at 0, 0.2, 2, and 10 mg/cu m showed tumor-incidence percentages of 30, 39, 58, and 77, respectively. The pattern of incidence of lymphosarcomas in the spleen was unusual in that the mid-dose incidence was equivalent to that in controls and the low-dose incidence was the highest of all; nevertheless, Sasmore concluded that this increased incidence of splenic lymphosarcomas in mice was probably related to exposure. He suggested that inhalation exposure to coal tar contributed to an increased incidence of lung tumors in rats. He also indicated that the data were "weakly suggestive" of a relationship of kidney tumor incidence to exposure at 10 mg/cu m. However, it is possible that the rats exposed at 10 mg/cu m may have ingested coal tar by licking their fur, and that in addition to inhalation and skin absorption of aerosolized coal tar, ingestion may have contributed to the observed effects. No important differences in lesion incidence in the kidneys, liver, skin, and spleen were recognized. For rat lung tumors, there were similar percentages of tumors in the control and 0.2 mg/cu m exposure groups, 4% and 3%, respectively, but rats exposed at 2 and 10 mg/cu m showed increases in the occurrence of lung tumors to 10% and 18%, respectively. In hamsters exposed at 10 mg/cu m, the occurrence of lymphosarcomas in the spleen indicated the relationship to exposure at that dose; no effects related to the exposure were observed in any of the rabbit organs.

In a follow-up study, MacEwen et al [80] exposed 75 female ICR-CF1 and 50 female CAF-1-JAX mice, 40 male and 40 female weanling Sprague-Dawley rats, 18 New Zealand albino female rabbits, and 5 male and 9 female Macaca

mullata monkeys to aerosolized coal tar at 10 mg/cu m for 6 hours daily for 18 months. The coal tar was aerosolized by the method previously described by Kinkead [77]. A group of 100 ICR-CF1 female mice was used as controls [80]. After the exposure period the animals were held for an additional 6 months of observation prior to necropsy. At the end of the study, all animals except the monkeys were killed and the tissues examined by light microscopy.

Exposure to coal tar at 10 mg/cu m reduced the body weight of rats and rabbits significantly compared with the controls, whereas monkeys showed no significant change in body weight [80]. Sixteen of 18 test rabbits and 6 control mice died during the test period. During the test period, some (exact number not reported) mice and rats also died and because of cannibalization or post-mortem autolysis, necropsies were not performed. In an earlier 90-day continuous exposure study [78,79], the authors found that exposure to coal tar at 10 mg/cu m produced skin tumors in 44 of 55 (80%) ICR-CF1- mice and in 18 of 43 (42%) CAF-1-JAX mice. Only 3 of 225 ICR-CF1 (1%) control mice and none of 225 CAF-1-JAX control mice developed skin tumors. In this study [80], 18-month intermittent exposure at 10 mg/cu m produced skin tumors in 5 of 75 (7%) ICR-CF1 mice and 2 of 50 (4%) CAF-1-JAX mice. The intermittent exposure produced alveolargenic carcinomas in 26 of 61 (43%) ICR-CF1 mice and 27 of 50 (54%) CAF-1-JAX mice. The numbers of tumors in control mice were 3 of 68 (4%) and 8 of 48 (17%), respectively. The exposed and control groups did not differ in the incidence of other types of tumors, including squamous-cell carcinomas, lymphosarcomas, and subcutaneous sarcomas.

In rats, the incidence of squamous-cell carcinomas in the lungs was 100% in exposed males and 82% in females [80]. Eight percent of the females developed mammary fibroadenomas, and 5% developed other, unspecified tumors. Twenty-one percent of the male rats also developed other tumors. Female control rats had a 13% incidence of tumors, none of which were in the lungs. There were no tumors in control male rats.

During the 18-month exposure, materials that accumulated in the lungs and skin of mice were measured as fluorescence, in terms of μg/g of lung tissue. Data showed that lung fluorescence in the exposed animals increased with the exposure, from 6 μg/g on the 1st day of exposure to 584 μg/g on the 371st day of exposure. There was also an increase in fluorescence of skin from 1.4 μg/sq cm on the 1st day to 6.3 μg/sq cm on the last day, but the data were more variable and less demonstrative of a trend than were the lung data. The 90-day continuous exposure showed larger amounts of fluorescence, with the maximum of 2,200 μg/g on the 90th day of exposure. The dose-related increased incidence of lung cancer in mice and perhaps in rats seems evident, but the authors' other conclusion pertaining to an increased incidence of other tumors are insufficiently supported by the data presented.

In 1958, Roe et al [81] reported studies on the induction of lung tumors in mice by creosote. These investigations were undertaken to substantiate observations that mice obtained from a breeder who housed animals in creosoted cages had a high incidence of lung adenomas. To determine whether creosote would cause lung tumors, mice used in the study were bred in the laboratory in either stainless-steel or creosoted-wood cages. The boiling-point range of the cresote distilled from a high-

temperature coke-oven tar was from 200 to over 400 C. The amount of creosote used to treat the cages was not given, but the authors noted that the cages were "thoroughly impregnated." Mice born and kept in stainless-steel cages were divided into a control group of 24 and an experimental group of 25 mice. The experimental mice had 25 μl of creosote topically applied twice weekly from 3 weeks to 6 months of age and were held for an additional 2 months. The 29 mice born in creosoted cages were kept in these cages and painted with 25 μl of creosote twice weekly for 5 months after weaning; these mice were observed for an additional 3 months. At 8 months of age, all mice were killed, and tumors visible on the surface of the lungs were counted. Gross diagnoses were confirmed microscopically in a number of instances.

In descendants of the animals originally obtained from the breeder, the fifth-generation mice born and housed in steel cages and treated with creosote developed an average of 5.8 lung adenomas/mouse, while mice born and housed in creosoted cages and treated with additional creosote bore an average of 10.8 lung adenomas/mouse [81]. In contrast to baseline observations of approximately 5.8 adenomas/mouse in the original animals obtained from the breeder at 2-3 months of age and examined at 6-8 months of age, the fifth-generation control mice bred in stainless-steel cages had an average of less than 0.5 adenoma/mouse. Based on their earlier reported findings, Roe et al noted that the exposure levels of creosote used had produced skin tumors in mice. They reported that, of the 53 mice receiving skin applications of creosote, 39 had both skin and lung tumors, 5 had only skin tumors, and 9 had only lung tumors [81].

Roe et al [81] conducted a second experiment to test smaller doses of creosote. Thirty 8-week-old mice were treated twice weekly with one drop of creosote, for a total of nine applications in 4 weeks. A control group of 50 mice was treated with 25 μl of either 0.5% croton oil or purified benzene twice weekly for 10 months. After 10 months, both experimental and control mice were killed, and the lung and skin tumors present were observed. Control mice had 15 lung adenomas, an average of 0.3/mouse. There were no skin tumors. Creosote-treated animals had 37 lung adenomas, an average of 1.6/mouse. The number of tumor-bearing mice in each group was not reported.

Roe et al [81] concluded that creosote exposure increased the incidence of adenomas in mice, but they did not always report the total tumor incidence for the treated and control groups. They suggested that exposure to creosote early in life might influence the subsequent induction of lung tumors. They also hypothesized that quantities of creosote that were too small to produce skin tumors were adequate to cause lung tumors.

In summary, the reports in the literature reveal that coal tar produces skin tumors in mice [62,64,67-69,78,79], rats [78,79], rabbits [62,66], and dogs [75] and lung tumors in mice [76,78,79] and in rats [79,80]; coal tar pitch produces skin tumors in mice [12]; and creosote, acting as an irritant, can promote skin tumors in mice [72,73,81] and lung tumors in mice [81].

roofers [30]. Short-term eye effects in pitch workers were successfully treated. The effects were prevented in some cases by using glasses or goggles, wetting down the pitch, or working at night, as in the case of pitch workers loading and unloading coal tar pitch from a railroad car [45,46]. In a health hazard evaluation of roofers [30], 6 of 17 workers showed eye symptoms, and 4 of these 6 had been exposed to airborne coal tar pitch volatiles at concentrations of 0.21-0.49 mg/cu m of air, which were higher than the federal limit of 0.2 mg/cu m. However, the skin and eye effects in the roofers disappeared within 72 hours of exposure. The use of glasses or goggles and other protective devices, such as gloves and respirators, was recommended.

Effects on the respiratory system have also been reported in humans [45,46,49]. Acute effects, such as coughing, sneezing, and swollen nasal mucosa and sinuses, were reported by Leb et al [45] and confirmed by Susorov [46] in workers who loaded and unloaded coal tar pitch from railroad cars. However, these respiratory symptoms disappeared in 8-9 days with medical treatment. Neither group of investigators measured the concentration of coal tar pitch in the air.

Pekker [48], in 1967, found oral disease in 80-90% of 962 coking industry workers examined. Respective occurrences of gingivitis, leukoplakia (white patches on the oral mucosa that may become malignant), and edema of the oral mucosa were 7%, 8%, and 4% in coal tar workers and 4.7%, 6.1%, and 3.7% in pitch coke workers. The prevalence of leukoplakia in one group of workers not exposed to coal tar was only 1.8%. Control values for the other conditions were not given by the author [48].

Correlation of Exposure and Effect

Exposure to coal tar products has been reported to adversely affect the skin, eyes, oral cavity, liver, and lungs.

A single skin application of coal tar preparations in combination with UV light radiation (320-400 nm) caused phototoxic effects (skin erythema) in volunteers [27]. The phototoxicity was dose dependent; a 5% solution of tar in petrolatum caused more phototoxic effects than a 2% or 1% solution. Tanenbaum et al [27] also pointed out that tar plus shorter wavelength UV light (290-320 nm) did not produce phototoxicity. However, the type or source of the tar was not specified [27]. Since coal tars obtained from different sources may show differences in toxicity, it is difficult to correlate the phototoxicity of tars.

Similar photosensitizing effects of coal tar were reported by Crow et al [28], who showed that application of coal tar pitch to the skin of the forearm of a pitch worker and three other volunteers produced skin erythema and wheal formation on exposure to radiation of 330-440 nm. They noted that rays in the sunburn area of 280-320 nm and shorter do not produce photosensitization, an important point in relation to the work of roofers and road workers. They suggested that these skin effects in humans were caused by the anthracene or acridine content of the coal tar pitch, but they gave neither the concentration of pitch applied nor the concentration of anthracene or acridine in the pitch. Short-term exposure (1-8 hours) of roofers to coal tar pitch fumes has also been reported to cause similar photosensitization effects lasting about 72 hours [30].

Exposure to coal tar products also causes burning and watering of the eyes, photophobia, and conjunctivitis in coal tar pitch workers [45,46] and

Oral ingestion of coal tar pitch by ducks [57] and pigs [58] has been reported to cause liver damage. However, Graham et al [58] did not state the concentration of coal tar pitch ingested by the pigs, thereby making it difficult to calculate the hepatotoxic dose of coal tar pitch. Cytotoxic effects such as karyotrophic disturbances, decreased membrane detoxification processes on the rat lung, after an exposure to aerosolized anthracene oil, the heavy fraction of coal tar, have been reported by Perov [60].

Thus, exposure of a few hours to coal tar products produced phototoxic effects of skin burning and itching, erythema, photophobia, conjunctivitis, coughing, sneezing, and swollen nasal mucosa and sinuses in volunteers, roofers, and pitch workers. Gum disease (gingivitis, leukoplakia, and edema of oral mucosa) was reported in coking industry workers. Whether the liver toxicity seen in pigs and rats ingesting clay pigeon fragments is due to materials in clay pigeons other than tar or to the high doses of tar ingested, the observations of hepatotoxicity are judged not relevant to deriving a standard for workers exposed at more realistic concentrations.

Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

Long-term exposure to coal tar products has been found to produce skin cancer in humans. Some fishermen who mended tar-treated nets and held tar-smeared needles between their teeth developed lip cancer [33,34]. Skin cancer in men [35] and one woman [36] in a tar distillation factory has also been reported. Hodgson and Whiteley [37] diagnosed squamous-cell carcinomas in 3% of the workers, acneiform lesions, pitch warts, both

premalignant and malignant, and scrotal cancer in 0.7% of the workers in a patent fuel works. They also found photosensitivity, or smarting and burning of skin in 57% of the workers, and they suggested that there was an increased personal susceptibility to proliferative lesions in these workers [37]. Sladden [38] reported similar carcinogenic effects, including scrotal cancer and malignant lesions on the face, eyelids, orbits, and hands of workers in a patent-fuel works. The incidence of cancer in these workers increased with increasing length of exposure. Long-term exposure to creosote produced squamous-cell carcinomas in a creosote factory worker [43] and in a painter who painted scows with creosote for 3 years [42]. Pierre et al [40] discovered papillomas, keratoacanthomas, and spinocellular epitheliomas in briquette factory workers exposed to unknown concentrations of coal tar pitch dust.

Multiple skin applications of coal tar [74,75], coal tar pitch [12,69], and creosote [63,71-73] produced skin tumors in mice, rats, and dogs, and creosote also caused lung tumors in mice [81]. These observations of skin-tumorigenic effects of coal tar products in animals support those of similar effects in humans.

Long-term exposure to coal tar pitch caused a significantly increased mortality from lung cancer in pitch roofers [49].

Doll et al [54,55] studied several thousand medical histories of employees in gas works and concluded that the mortality from lung cancer in coal carbonization workers, but not in byproducts workers, was significantly higher than the average in the population of England and Wales. Redmond et al [50] reported increased mortality from cancers of the lung and kidney in coke-oven workers in the steel industry. Increased

mortality from lung cancers in workers exposed to tar in aluminum reduction plants or in plants with electrolytic reduction processes has been recently reported [51-53]. However, Redmond et al [50] reported that byproducts workers had no increased risk of dying from cancer. Although Doll et al [54,55] did not measure or report the concentrations of coal tar or coal tar pitch in the air, their conclusions were similar to those of Reid and Buck [56], who, after studying 800 occupational and medical histories, hypothesized that lung cancer mortality in byproducts workers is not related to their occupation. While in some phases of coal carbonization an excess of this lung cancer has not been found, this could be due to the insensitivity of the epidemiologic methods in sorting out the effect of several variables, including smoking. But it is nevertheless evident that exposure to coal tar products in coal carbonization has caused a significant excess of mortality from cancer in several groups [50-52,54,55].

Evidence for the carcinogenic effects of coal tar pitch on the human lung has been supported by a study [77-79] in several animal species (mice, rats, hamsters, and rabbits). Kinkead [77], McConnell and Specht [78], and Sasmore [79] reported a dose-related increase in lung tumor incidence in mice, and MacEwen et al reported lung tumors in mice and rats [80]. No report on mutagenicity, teratogenicity, or effects on reproduction from exposure to coal tar products has been found in the literature.

TABLE III-5

EFFECTS OF EXPOSURE TO COAL TAR PRODUCTS ON HUMANS

Agent	Exposure Concentration and Duration	Subjects			Effects	Reference
		No.	Occupation	Age		
Coal tar	5-60 yr*	8	Fishermen	41-77	Skin cancer	33
Coal tar pitch	10-50 yr*	144	Pitch workers	20-69	Skin and scrotal cancer, warts, photosensitization	37
"	9-40+ yr*	5,788	Roofers	-	Increased lung cancer mortality	49
"	1-43 yr*	10	Briquette factory workers	21-65	Skin cancer	40
Coal tar	25-30 yr*	2	Tar distillers	50,61	Scrotal cancer	35
"	22-30 yr*	2	Laborers	53,64	Groin cancroid, lip cancer	35
Coal tar pitch	<20 yr*	962	Coal tar, coke, benzene naphtha workers	24-45	Decayed teeth, gum disease	48
Coal tar	10 yr*	1	Tar distiller	52	Skin cancer	36
Creosote	1-3 yr*	1	Dock yard painter	64	"	42
Coal tar or coal tar pitch	Unknown	-	Coal miners, fishermen, sailors, painters, carpenters	-	Skin and eye cancer	47
Coal tar pitch volatiles	0.03-0.49 mg/cu m 7-8 hr	34	Roofers	18-60	Skin and eye irritation	30
Coal tar pitch	4-5 hr*	6	Briquette loaders	-	Skin, eye, and upper respiratory irritation, photophobia, enlarged liver	45
"		36	Pitch loaders	19-23	Skin and eye irritation, photophobia	46
Coal tar	1.0-5.0% on skin 90 min	15	Volunteers	-	Skin irritation	27
Creosote	Unknown	2	Gardeners	49,67	Eye irritation	25

*Concentration not given or unknown

TABLE III-6

EFFECTS OF EXPOSURE TO COAL TAR PRODUCTS ON ANIMALS

Species	Route of Exposure	Agent	Concentration and Duration	Effects	Reference
Pigs	Oral	Coal tar pitch	6-15 g/d 5 d	Mortality 100%; liver damage, systemic effects	58
"	"	Liquid coal tar	3 g/d 5 d	Mortality 100%; liver damage	58
"	"	"	3 g/d 2 d	Mortality 50%; no liver damage	58
Ducks	"	Coal tar pitch	0.5-1% diet 4 wk	Mortality 0-30%; liver damage, anemia, systemic effects	57
Mice	Inhalation	Coal tar fumes	330 mg/cu m 40-100 hr over 13-33 wk	Tumor in 1 mouse	64
"	"	Coal tar aerosol	2-30 mg/cu m 90 d	Skin tumors in 8-38%	78
"	Dermal	Coke-oven coal tar	50 mg 3x/wk 5-60 min 27-42 wk	Skin tumors in 85-100% (coal tar washed off with detergent)	64
"	"	"	50% 10 mg 1x/wk 32 wk	Skin tumors in 94%	64
"	"	Coke-oven coal tar basic N compounds	4-20% 10 mg 3x/wk 54-73 wk	Skin tumors in 90-100%	64
"	"	Coke-oven coal tar neutral oil	1% 10 mg 3x/wk 45 wk	Skin tumors in 100%	64
"	"	Coke-oven coal tar phenolic acids	1-13% 10 mg 3x/wk 71-79 wk	No tumors	64

TABLE III-6 (CONTINUED)

EFFECTS OF EXPOSURE TO COAL TAR PRODUCTS ON ANIMALS

Species	Route of Exposure	Agent	Concentration and Duration	Effects	Reference
Mice	Dermal	Gasworks tar	25-100% 3-4x/wk 58 wk	Skin carcinomas in 32-50%	67
"	"	Gasworks tar ether extract	1-100% 2x/wk 60-85 wk	Skin tumors in 40-77%	68
"	"	Smelting-works tar	50% 2x/wk 5 mon	Skin carcinomas in 27-31%	69
"	"	Coal tar ointments	2-3x/wk 10-12 mon	Skin tumors in 94-95%	66
"	"	Soft pitch	50% 2x/wk 5 mon	Skin carcinomas in 50%	69
"	"	Hard pitch	20% 2x/wk 5 mon	Skin carcinomas in 38%	69
"	"	Coal tar pitch anthracene fraction	50% 2x/wk 5 mon	Skin carcinomas in 17%	69
"	"	Creosote	100% 3x/wk 28 wk	Skin carcinomas in 82%, tumors in 92%	73
"	"	"	20-80% 3x/wk 6-44 wk	Skin carcinomas in 88%, tumors in 100%	63
"	"	"	100% 2x/wk 21 wk	Skin and lung tumors in 74%	81
"	"	"	100% 3x/wk 70 wk	Skin tumors in 50%	72
"	"	Creosote + 1% DMBA	10-100% 2x/wk 70 wk	Skin tumors in 38-74%	72
"	"	"	2% 2x/wk 70 wk	No tumors	72