III. BIOLOGIC EFFECTS OF EXPOSURE

Fumes have been defined by Patty [1] as "solid particles generated by condensation from the gaseous state, generally after volatilization from melted substances and often accompanied by a chemical reaction, such as oxidation." The American Society for Testing and Materials [2] defined asphalt as "a dark brown to black cementitious material in which the predominating constituents are bitumens which occur in nature or are obtained in petroleum processing." Asphalt fumes then, for the purposes of this document, are defined as the nimbose effusion of small, solid particles created by condensation from the vapor state after volatilization of asphalt. In addition to particles, a cloud of fume may contain materials still in the vapor state.

The chemical composition of asphalts derived from petroleum varies, depending on the source of the crude oil used to manufacture them [3-7] and the refining process and physical specifications of the finished product [5,8-10]. The major constituent groups of asphalt are asphaltenes, resins, and oils made up of saturated and unsaturated hydrocarbons [7,11]. These major constituents are soluble in carbon tetrachloride and benzene [6], but are not completely soluble in saturated hydrocarbons such as naphtha, hexane, pentane, propane, and n-heptane [4]. The asphaltenes have molecular weights in the range 1,000-2,600, those of the resins fall in the range 370-500, and those of the oils in the range 290-630. Natural asphalts contain considerable amounts of geologic material (rocks, sand, etc) and comparatively smaller amounts of bituminous substances (4-40%); the bitumens of lake asphalts have molecular weights in the range 620-1132.

Small quantities of inorganic materials may also be present, some possibly as organometallic compounds [5,7,9]. Fumes from some representative asphalts have been analyzed, and their chemical compositions are given in Table XIII-1 [5]. The amounts of benzo(a)pyrene found in fumes collected from two different plants that prepared hot mix asphalt ranged from 3 to 22 nanograms/cu m; this is approximately 0.03% of the amount in coke oven emissions and 0.01% of that emitted from coal-burning home furnaces.

Petroleum asphalt is the residue in the fractional distillation of crude oil [9,12,13]. Crude oil is distilled to fractionate the parent mixture into economically valuable distillates, such as naphtha, gasoline, kerosene, and fuel oil. Asphalt is also derived from crude oil by solvent precipitation and by air-blowing. The solvent precipitation process utilizes propane or propane-butane mixtures under controlled conditions to precipitate the asphalt from a residuum stock. The process consists of a countercurrent liquid-liquid extraction using solvent-to-oil ratios of from 4:1 to 10:1. Temperatures in this process are selected to allow suitable viscocity of the propane-oil mixture for handling in the deasphalting tower. The primary objective in this production process is the recovery of either lube or catalytic-cracking feedstock oils, rather than the production of asphalts. Air-blowing is a process for further refining an asphalt stock, termed a flux. Air at temperatures of 400-550 F (204-288 C) is bubbled through the flux, producing dehydrogenation and polymerization reactions. The air-blowing process is generally used to manufacture asphaltic paving binders and saturants for the flooring, roofing, and insulation industries from soft flux stocks. The process allows a consumer to make various saturant grades from the same base flux. Asphalts can also

be further refined, blended with the lighter petroleum fractions, or emulsified with water, depending on the use for which they are designed. Liquid asphalts are produced by blending a diluent with the asphalt. The common diluents are solvents with boiling points close to those of "gas oil," kerosene, or naphtha; asphalts formulated in this manner are termed "cut-back" asphalts. Asphalt in liquid form is also supplied as an emulsion with water. A petroleum asphalt refinery flow chart is shown in Figure XIII-1 [8].

Asphalt has often been confused with tar because the two are similar in appearance and have been used interchangeably as construction materials. Tars, however, are produced by destructive distillation of such organic materials as coal, oil, lignite, peat, or wood [2], whereas petroleum asphalt is produced as the residue from fractional distillation of crude oil. There is obvious confusion in the literature between asphalt and coal tar, and the classification of the two basic substances is often unclear [14-17]. However, even limited chemical analyses show the two substances to be quite different, especially in their proportions of polynuclear aromatic hydrocarbons and known carcinogenic chemicals [3,18]. Asphalt has also been confused with pitch, which is the residue from fractional distillation of tar [2].

The existing confusion in the use of the terms asphalt, tar, and pitch has necessitated a careful review of the literature to determine the nature of the compound that was then under discussion. In many cases, such review has shown that substances listed by the authors as asphalt have really been tars or pitches by the present definition [2], so that these papers are not relevant to this document. In cases where authors have not

provided information about the source of the compound tested, their papers are included in this document on the basis of the authors' terminology and this fact is pointed out in the review. Several papers have presented data from experiments in which animals were exposed to either asphalt or coal tar [3,17,19], or in which the adverse effects in humans from exposure to these two materials were discussed [16,18,20]. The data concerning coal tar exposure in these reports have been included in this chapter, because of the confusion in the terminology and to allow a comparison of the toxicities of coal tar and asphalt.

Extent of Exposure

Occupational exposure to asphalt fumes can occur during the transport, storage, production, handling, or use of asphalt. The composition of the asphalt that is produced is dependent on the refining process applied to the crude oil, the source of the crude oil, and the penetration grade (viscosity) and other physical characteristics of the asphalt required by the consumer [9].

The process for production of asphalt is essentially a closed-system distillation [9]. Refinery workers are therefore potentially exposed to the fumes during loading of the asphalt for transport from the refinery during routine maintenance, such as cleaning of the asphalt storage tanks, or during accidental spills. Most asphalt is used out of doors, in paving and roofing, and the workers' exposure to the fumes is dependent on environmental conditions, work practices, and other factors. These exposures are stated to be generally intermittent and at low concentrations [21]. Workers are potentially exposed also to skin and eye contacts with

hot, cut-back, or emulsified asphalts. Spray application of cut-back or emulsified asphalts may involve respiratory exposure also.

Asphalt sales in the United States have increased yearly from approximately 3 million tons in 1926 [8] to over 27 million tons in 1975 [22]. Of the asphalt produced in 1975, 77.9% was used for paving, 17.4% for roofing, and 4.7% for miscellaneous purposes, such as insulating and waterproofing [22]. Some uses and applications of asphalt are given in Table XIII-2 [8]. Because of the nature of the major uses of asphalt and asphalt products, it is not possible to determine accurately the number of workers potentially exposed to asphalt fumes in the United States. NIOSH has not estimated the number of workers exposed to asphalt fumes, but an estimate of 500,000 can be derived from estimates of the number of workers in various occupations presented in County Business Patterns, 1973 [23].

Historical Reports

Natural asphalt was used prior to 540 BC as a cement for masonry and street construction and as a waterproofing layer for water tanks [8]. Natural asphalt was first used in the United States in sidewalk construction around 1838 and in pavement construction around 1870. The discovery in 1902 that California crude oil yielded an appreciable quantity of semisolid and solid distillation residues increased the use of petroleum asphalt so that, by 1907, the tonnage of petroleum-derived asphalt equaled that from natural sources, such as Trinidad Lake asphalt [9]. By 1963, over 90% of the total asphalt and asphalt products sold in the United States was derived from petroleum. From 1923 to 1936, petroleum tars derived from a thermal cracking process were often used in paving and

industrial products. Since 1936, the use of this process has gradually declined.

Few early reports concerning the biologic effects of asphalt or asphalt fumes have been found in the literature. Henry [24] analyzed 3,753 cases of cutaneous epitheliomas reported between 1920 and 1945 to the Chief Inspector of Factories in Britain under the Workmen's Compensation Act. The definition used for reporting these cases was "epitheliomatous ulceration or cancer of the skin due to pitch, tar, bitumen, paraffin or mineral oil or any compound or residue of any of these substances or any product thereof contracted in a factory or workshop." Henry's analysis consisted of the correlations of occupations, suspected causative agents, and sites of the cancers. In only one instance was the cancer attributed to bitumen (asphalt). This instance involved a facial epithelioma on a worker who had been employed for 22 years at an asphalt factory where only natural bitumen was used. No further details were reported.

In a 1949 communication, Hueper [25] reported that the total number of recorded cancers attributed to oil products from all sources was about 100. He stated that this was an "astonishingly" small number considering the large number of persons exposed to oil products, including heavy lubricating oils, fuel oils, paraffin, tars, coke, and asphalt, throughout Europe and the United States. Sources of these data and the basis for the characterization "astonishingly" small were not given.

Other historical studies of occupational carcinogenesis have placed asphalt workers into broad catagories like "paviors, street masons, concretors, and asphalters" [26], making it impossible to evaluate the number of cancers attributable to asphalt exposure alone.

Effects on Humans

Reports detailing toxic effects of asphalt on humans are scarce, and attribution of asphalt as the causative agent of these reported effects is often uncertain. Workers who came in contact with asphalt often had had previous contact with coal or tar or simultaneous contact with asphalt and tar, and confusion over the definition of asphalt, as in "asphalt is also obtained by coal distillation..." [14], increases the difficulty of analyzing the literature.

Zeglio [15], in 1950, published observations on 22 workers aged 18-61 years who insulated electrical cables and telegraph and telephone lines for a large Italian company. Medical histories emphasizing respiratory disorders were obtained, and clinical and roentgenographic examinations of the respiratory tract and special nose and throat examinations were performed on each worker. Only bitumens (natural asphalt) were reported to have been used in the insulating process, but Zeglio pointed out that "true bitumen" was often adulterated with residual pitch from coal tar distillation. He did not indicate, however, whether the bitumens used by this company had been so adulterated. The workers were exposed to fumes from tanks containing bitumen heated to 120 degrees (presumed to be degrees Celsius, equivalent to 248 F). Although the concentration of the fumes in the working environment was not measured, Zeglio stated that the atmosphere had an acrid odor that was irritating to the nose and throat and that stimulated coughing.

Workers exposed to the atmosphere of the plant complained of coughing with expectoration, a burning sensation in the throat and chest, and frequent hoarseness. Headache and nasal mucous discharge were also

frequently mentioned by the workers as sequelae of exposure. Workers employed in the plant for only a few months were more aware of these annoying sensations than were those employed for several years, and the disturbances usually diminished rapidly after the employees left work (presumably after the end of a work shift). Even though the subjective sensations appeared less intense in the workers with more seniority, they were at the same time more persistent and involved nasal mucous discharge and inflammation, coughing with expectoration, changes in vocal timbre, and frequent loss of voice. Tonsillitis, pharyngitis, acute febrile bronchitis, and nosebleeds were frequent effects and caused employee absence during the cold seasons (not further defined).

During physical examinations, 10 cases of rhinitis, 13 cases of oropharyngitis, 4 cases of laryngitis, and 19 cases of bronchitis were diagnosed in the 22 workers, with some workers having multiple diagnoses [15]. The mucosal involvement, which varied in severity from simple to chronic atrophic inflammation, was sometimes accompanied by scabby exudates and swelling. The pulmonary signs varied from simple, harsh respirations with some rales to severe pulmonary involvement, including basal hypophonesis with increased tympanic zones from emphysema, thoracic hypomobility, extensively harsh respiration with protracted expiration, and rales and sibili. Roentgenographic examination disclosed an increased vascularization in the larger bronchial areas, particularly evident in the mediobasal zones in all the workers with bronchitis. Those workers with the more intense clinical signs also had bronchiectatic formations. No infiltrative or erosive lesions of the pulmonary parenchyma were observed in any of the workers examined.

Zeglio [15] concluded that a simple characterization of bitumen vapors as "irritating" did not recognize the harmful anatomic and functional changes of the respiratory tract that they caused. He pointed out that the size of his population was small and that individual variations in resistance to bitumen vapors may have been more important than the length of exposure to the vapors in determining the severity of the clinical manifestations. He also pointed out that particular factors predisposing the workers to the damaging effects of bitumen, such as fatigue, smoking, and excessive alcohol consumption, were not considered in this study. Zeglio did not report the source of the bitumen used in the workplace, nor did he differentiate between fumes and vapors, terms which he used interchangeably. The characterization of the atmosphere as acrid and irritating, however, suggests the presence of coal tar pitch volatiles in the workplace [21]. Information concerning the bitumen vapor composition and concentration and the length of exposure necessary for eliciting adverse effects, was not included in this report [15]. Thus, it is not possible with these data to determine the relative hazard ascribable to the asphalt fumes.

Guardascione and Cagetti [16] reported on a case of laryngeal cancer in a worker employed in road bituminization. The worker had been employed by the same firm for 31 years, and his primary jobs had been lighting the furnaces for heating the bituminous liquid (containing asphalt, tar, and pitch) and mixing, transporting, and pouring the liquid on the roadbed. When questioned, the worker complained of occasional skin rashes. He also reported noticing the presence of blackish specks in his sputum, chronic bronchial manifestations, and a transitory dysphonia arising from

laryngitis. Approximately 4 years before the laryngeal cancer was diagnosed, the worker had a complete loss of voice lasting 1 year. A diagnosis of squamous cell carcinoma of the left vocal cord was made from biopsy material, and the worker underwent a total laryngectomy.

Guardascione and Cagetti [16] pointed out the problems involved in determining the causative agent for this carcinoma, especially the fact that bitumens were often considered as the same product whether they were natural, were derived from the distillation residue of petroleum, or were derived from tar pitch. They postulated that, since polynuclear aromatic hydrocarbons are generally absent or found only in trace amounts in bitumens obtained from petroleum residues, the only substances used by this worker that had carcinogenic properties were the tar and tar products; however, data to support their assumptions were not presented. This report, though valuable in pointing out a possible occupational hazard, did not provide enough data to correlate exposure and effect. Guardascione and Cagetti's discussion of the carcinogenic propensity of petroleum residue versus tar indicates that the tar mentioned may have been coal tar, but this is not explicitly stated in the report.

Two reports have dealt indirectly with health hazards from asphalt fumes. A NIOSH health hazard evaluation report [18] on a roofing application project presented results from medical interviews, limited physical examinations, and environmental measurements of polycyclic particulate organic matter (PPOM), polynuclear aromatic hydrocarbons (PAH's), benzo(a)pyrene (BaP), and benzo(e)pyrene (BeP).

Thirty-four employees involved in the application of a roof coating composed of coal tar pitch and asphalt were questioned and examined.

Particular emphasis was placed on determining the circumstances surrounding current and previous work-related skin and eye irritation. The skin and eyes of each worker were examined by an occupational physician. Air samples for examination of employee exposure to total particulates, PPOM, PAH's, BaP, and BeP were collected by personal air samplers attached to the workers' collars. Area air sampling was also conducted close to the machines from which fumes were emitted. The samples were analyzed gravimetrically for total particulates. Ultrasonic vibration of the total particulates followed by extraction by cyclohexane yielded the PPOM, which was then further extracted to obtain PAH's and, finally, analyzed for BaP and BeP by flame ionization gas chromatography. Bulk pitch and asphalt samples were also analyzed for PPOM, PAH's, BaP, and BeP.

Twenty-three (69%) of the examined workers complained of apparent skin photosensitivity, which they attributed to exposure to pitch [18]. Fifty percent of the employees also complained of conjunctival symptoms that they thought were related to exposure to pitch as well. During the physical examinations, 6 (18%) of the workers were observed to have conjunctivitis, 6 (18%) showed evidence of localized skin photosensitization reactions, and 5 (15%) had generalized erythemas that might have been caused by exposure to solar radiation alone. A number of chronic skin and eye disorders were noted during the examinations, but these were not discussed in detail in the report. The concentrations of PPOM in the personal air samples obtained for 26 employees exposed to the pitch volatiles varied from less than 0.02 mg/cu m to a maximum of 0.49 mg/cu m. A statistically significant ($P<0.05$) correlation was found between exposure to PPOM from the pitch at concentrations greater than 0.2

mg/cu m on the day of examination and the presence of conjunctivitis observed during examination.

Analyses of the bulk pitch used on this job showed 4.89% by weight of PPOM, which in turn contained 1.9-13% PAH's, and 270 ppm (0.027%) of BaP-BeP, whereas analyses of the asphalt showed that it contained 10.3% by weight of PPOM, that 0.5-3.2% of the PPOM was PAH's, and that BaP and BeP were not detected (less than 6 ppm) [18]. The authors concluded that these results indicated a significant difference between the composition of pitch and that of asphalt, with the pitch containing more higher-molecular-weight PAH's than the asphalt.

No attempt was made in this study to differentiate medically between health effects caused by asphalt fumes and those caused by coal tar pitch volatiles; however, employees were asked to list subjective symptoms caused by working with the asphalt [18]. None of the employees questioned described any symptoms that they believed to be related to exposure to asphalt except for occasional burns from contact with the hot asphalt. The authors concluded that there was no evidence that asphalt fumes made an important contribution to the acute eye and skin problems suffered by these roofers.

A similar study, reported by NIOSH [20] in 1976, obtained roofing workers' responses to a questionnaire pertaining to causes of skin and eye irritation. As in the previous study, virtually no irritation was attributed to asphalt by the workers. These studies [18,20] indicate that asphalt fumes are not considered a hazard by employees who work with asphalt. However, no data were reported for possible respiratory effects,

nor was it clear if the questionnaire or physical examination addressed these possible problems.

Epidemiologic Studies

No workplace concentrations of asphalt fumes or exposure conditions of workers were given in the one epidemiologic study found. Subjective data gathered in response to a questionnaire have been reported and are included in this section.

Results of a health survey by Baylor and Weaver [27] of asphalt workers from 7 asphalt companies and a control group from 25 oil refineries were published in 1968. A medical assessment including a physical examination and detailed medical and occupational histories was conducted as completely as possible on each of 462 asphalt workers and 379 refinery workers in a control group. Employees with 5 or more years of work in the asphalt industry were included in the asphalt exposed cohort. The physical examination emphasized the skin and the respiratory tract and included chest roentgenograms. The questionnaire covered number of years in asphalt work, type and geographic source of asphalt used, and smoking and weight histories. Lung cancer had previously been diagnosed in one of the workers in the control group. Skin cancers were reported in the medical histories of two asphalt workers and four workers in the control group. At the time of the survey, skin cancer was present in four asphalt workers, but two of these workers had had skin cancer prior to beginning work in the asphalt operations. The medical histories also reported one carcinoma of the stomach in an asphalt worker and one carcinoma of the colon in a worker in the control group.

Instances of respiratory disease other than cancer were recorded in the medical histories of 31 of 360 asphalt workers (8.6%) and in 12 of 277 control workers (4.3%) [27]. It was not stated whether these past medical histories referred only to time before asphalt exposure. The majority of these cases had been diagnosed as chronic bronchitis, with a few cases of asthma or emphysema. At the time of the physical examination, instances of lung disease were diagnosed in 40 of 462 asphalt workers (8.6%) and in 24 of the 379 control workers (6.3%). None of these illnesses was described as advanced, severe, or incapacitating, and several were diagnosed solely on the basis of increased bronchial markings on the chest roentgenograms. A publication of the National Center for Health Statistics [28] reported a combined incidence of chronic bronchitis, emphysema, and asthma of 11.8% for males, 16 to 65 years old, in the "usually working" category. A comparison of this value with those for the exposed workers yields relative risks which are not significantly different by the normal-deviate test.

The medical histories reported instances of noncarcinogenic skin disease in 37 asphalt workers (10.3) and in 47 of the workers in the control group (17%). During the physical examination, 26 asphalt workers (5.6%) and 20 workers in the control group (5.3%) were found to have skin diseases, mainly localized and transitory dermatitis; none of the cases was considered extensive or severe. Other health problems discovered during the physical examination included hypertension in 27 asphalt workers (5.8%) and 27 control workers (7.1%), peptic ulcer in 12 asphalt workers (2.6%) and 8 control workers (2.1%), heart disease in 17 asphalt workers (3.7%) and 14 control workers (3.7%), and other miscellaneous disorders paralleling what would be expected in the general population. Incidental

findings indicated that the most serious threats to the health of both the asphalt workers and the control workers were obesity and heavy cigarette smoking. The findings indicated that the asphalt workers were not under a significantly greater health hazard than were the control refinery workers.

Additional information was requested from companies involved in highway construction, roofing, trucking, and insurance, and from State Highway Commissions and Boards of Health, to ascertain health problems attributable to occupational exposure to asphalt [27]. Information secured in this way may not be highly reliable. Thirty-one construction or paving companies reported only one case of ill health that could have been attributed to exposure to asphalt in their 11,478 man-years of work experience with it. Of the 15 states that replied to the questionnaire, 13 cited no cases of illness caused by occupational exposure to asphalt (although over 100 million gallons of asphalt per year were used by 1 of the states), 1 state reported 1 case of transitory nasal irritation caused by asphalt fumes, and 1 state reported 14 cases of dermatitis resulting from contact with asphalt; no further details were supplied.

Three large roofing companies employing over 1,100 asphalt workers reported no evidence of ill health attributable to asphalt [27]. The 112 asphalt roofing employees of 1 company averaged over 12 years of experience with asphalt, with 23 workers having over 20 years of experience. Four trucking companies with a total of more than 5,000 drivers exposed to asphalt fumes and dust reported no known cases of lung or skin disease attributable to asphalt. Five large insurance companies responding to the questionnaire, 1 of which serviced over 43 companies whose primary business was asphalt production or use, reported no known cases of compensation

involving occupational exposure to asphalt. Another insurance company reported four claims involving asphalt: one case of headache, one case of silicosis secondary to asphalt, one case of leukoplakia, and one case of dermatitis. Followup details were not available for these claims.

Baylor and Weaver [27] concluded that "...petroleum asphalt cannot rationally be considered a hazardous substance." They did, however, point out that individual predisposition might cause some workers to be subject to health problems promoted by contact with asphalt or its components, and that their study related to the present commercial use of asphalt only. They also stated that their conclusion did not imply that all asphalt is completely nonhazardous under all circumstances.

Because of the lack of detailed results and exposure data in this report, quantitative evaluation of the results is not possible. Information from past medical histories of the current workforce concerning lung disease other than cancer indicates that the relative risk was 1.96 for the asphalt workers compared with that for the controls, which is significant at the $P<0.05$ level. The relative risk for current lung disease, however, was not significantly different for the two groups, and the lung disease frequency for the asphalt workers was not significantly different from the lung disease frequency for the US working population [28]. Without further information, an accurate assesment of the potential occupational hazard from asphalt fumes is not possible; however, the authors' conclusion that the workers studied were not under an appreciably greater hazard than the controls is reasonable on the basis of the statistics reported.

The human studies reviewed tend to suggest that the occupational health hazard from exposure to asphalt fumes is minimal, although the work of Zeglio [15] indicates that such exposure may be a contributing factor to respiratory irritation and noncarcinogenic diseases in mixed exposure situations.

Animal Toxicity

This section is divided into three parts to facilitate comparison of the animal data with potential workplace exposure to both asphalt fumes and asphalt and to briefly review the literature related to some of the toxic constituents found in some asphalts. Discussion of some of the problems involved in comparing studies of these constituents is also included.

(a) Exposure to Airborne Asphalt Fumes and Aerosols

NIOSH has not been able to find reports of experiments to determine dose-response relationships for asphalt fumes or reports demonstrating a carcinogenic potential for asphalt fumes. Irritations of the eyes and respiratory tract of animals subjected to extreme exposure conditions have been reported, but environmental concentrations of the fumes for these exposures have not been presented.

Observations of the effects of asphalt vapor on the eyes of rabbits were presented by Truc and Fleig [29] in 1913. The asphalts used for these experiments came from the United States and England but were not further identified. The vapors were generated by heating the asphalt in a retort until dense oily vapor was given off. The vapor was then directed onto the eyes of immobilized rabbits. Concentrations of the vapor in the air contacting the eyes and durations and frequencies of the exposures were not

reported. Only minor transient conjunctivitis was noted in the rabbits exposed to asphalt vapors. A slight infiltration of the cornea was sometimes noted after frequent exposures, but this disappeared within several days after the exposures ended. No other signs of toxicity were observed in the rabbits.

Changes in the respiratory tracts of guinea pigs and rats after inhalation of fumes from petroleum asphalt and coal tar pitch were reported in 1960 by Hueper and Payne [19]. Fumes were generated by placing asphalt or coal tar in an evaporating dish in the exposure chamber and heating the dish to 250-275 F (121-135 C) with an electric heater. Cooled air was delivered to the exposure chambers from air-conditioning units adjusted to maintain a chamber temperature of 75 F (24 C). Fumes were generated for 5 hours a day, during which time 10-30 g of the coal tar or 2-10 g of the asphalt were volatilized. The volatilized amounts were replaced daily with equal weights of the parent material, and fresh material was placed in the heating dish once a week. The exposures were carried out on 4 days each week for 2 years. Thirty 2-month-old S13 guinea pigs and 65 2-month-old female Bethesda black rats were exposed in each of the two chambers.

Some guinea pigs and rats exposed to the asphalt fumes developed "extensive chronic fibrosing pneumonitis with peribronchial adenomatosis, associated in the rats with squamous cell metaplasia of the bronchial mucosa or of frequently noted bronchiectatic lumens [19]." None of the adverse changes assumed a cancerous character, and they were stated to have been often observed to result from nonspecific chronic pneumonitis or the respiratory or intravenous administration of various other substances (not further defined).

Hueper and Payne [19] stated that these data, in addition to the results of other studies involving the inhalation of various "carcinogenic" dusts, fumes, or vapors, indicated that the respiratory tract of experimental animals appeared to be much more resistant than the human bronchial tree to "inhaled carcinogens," even when the inhaled carcinogens were administered in much higher doses than those encountered by workers under the worst occupational conditions. They also speculated that the degree of exposure of the lung tissue to inhaled carcinogens was usually inadequate for eliciting a carcinogenic response in experimental animals. No experimental data leading to the authors' characterization of asphalt fumes as carcinogenic were presented in this report. This study did, however, demonstrate a significant respiratory hazard from long-term exposure to high concentrations of asphalt fumes.

Estimate of exposure concentrations can be made for this experiment by making assumptions concerning the rates of airflow through the exposure chambers. Indirect calorimetric experiments suggest that this flow through the chamber would probably be in the range of 1-10 cu m/hour. If airflows of either 1 or 10 cu m/hour are assumed and the approximate amount of asphalt volatilized/hour is calculated from the authors' data [19], the possible range of the exposure concentrations becomes 40-2,000 mg/cu m. These calculations indicate that the exposures in this experiment were greater than are likely to be encountered by workers during representative occupational exposures to asphalt fumes. See Chapter IV for futher discussion of concentrations of asphalt fumes found in occupational situations.

Studies of exposures of experimental animals to petroleum asphalt aerosol and smoke (containing fumes) were reported by Simmers [30] in 1964. In the first experiment, 10 male and 10 female C57BL mice were exposed to an aerosol of unstated concentration generated from asphalt derived from a California crude oil. The aerosol was generated by discharging an emulsion of asphalt in hot water through a nebulizer into a large chamber. The aerosol was admitted in 2-second pulses for 16 seconds in each minute; this periodic pulsation was adequate to maintain a fog of asphalt in water for the full 30-minute daily exposure. Exposures were carried out 5 days a week for up to 82 weeks. The animals were restrained with their muzzles projecting into the aerosol chamber.

Autopsies were performed on 17 mice after they died or were killed [30]. Three of these had survived 410 exposures and 10 had survived 280 or more exposures. The number of animals surviving fewer than 280 exposures was not reported and could not be determined from the reported data. The last animal was reported to have been killed 16 months and 18 days (approximately 72 weeks) after the experiment began, although this is inconsistent with the author's statement that exposures were made for up to 82 weeks. The alveolar spaces sometimes contained fluid, and patchy regions of emphysema and bronchiolar dilatation were occasionally observed. A few cases of pneumonitis, localized bronchitis along with minimal peribronchiolar round-cell infiltration, and a papillary adenoma were also observed. To show that the asphalt was actually being deposited in the respiratory tract, four mice were exposed to an aerosol of asphalt radiolabeled with I-131 for either 15, 30, 45, or 60 minutes. The trachea and lungs of these animals were then removed, separated, weighed, and

examined for the radioactive iodine. This experiment showed that the asphalt was being deposited in these organs and that its concentration in the trachea was approximately twice as great as that in the lungs.

Another experiment was conducted to determine the effects of asphalt "smoke" (containing fumes) on mice [30]. Six cages, each containing five C57BL mice, were held in an exposure chamber. "Smoke," generated by heating the asphalt to 250 F (121 C) with an electric heater, was forced through the chamber by a fan. The placement of the cages in the exposure chamber was rotated daily to equalize the effects of any concentration gradient of the "smoke" from the inlet and outlet. Animals were exposed from 6 to 7.5 hours daily, 5 days/week, for a maximum of 21 months. During the course of the experiment, 2,236.6 g of asphalt were volatilized to produce the "smoke" that was blown through the chamber. Food was continuously available in three of the cages, but it was removed during the exposures from the other cages. Controls consisted of six nonexposed male mice that were killed at 20 months of age.

In this experiment, 21 of the 30 exposed mice were subjected to necropsy [30]. Nine of these mice survived 401 days of exposure to the asphalt "smoke," and 15 were exposed to the "smoke" for over 300 days. The last animal was killed after 21.2 months. Again, the length of exposure and the time of killing of the last animal are discrepant, but in a possible way in this instance. During the experiment, the inside of the exposure chamber became covered with a yellowish-brown, oily material that had a strong petroleum odor and showed a yellowish-green fluorescence when illuminated with ultraviolet light. The animals whose food was contaminated with this material ate as much and maintained their body

weights as well as the animals eating the uncontaminated food. No gross evidence of gastrointestinal tract tumors was found in the animals eating the contaminated food, although a few gross lesions were observed. When examined microscopically these lesions were judged not to be neoplastic.

Bronchitis with abscess formation, loss of bronchial cilia, epithelial atrophy and fragmentation, necrosis, and flattening of the epithelium, along with pneumonitis, were frequent findings in lungs of the animals that had inhaled asphalt "smoke" [30]. One bronchial adenoma was also reported. Epithelial hyperplasia occurred occasionally, as did emphysema, often associated with focal lung collapse. Large areas of peribronchial round-cell infiltration were common and extreme bronchial dilatation was sometimes observed, but no tumors were reported. In both experiments, the adverse changes noted in the tracheobronchial tree and lungs of the exposed animals were scattered, with normal areas being found in all animals. Some animals were relatively refractory to the "smoke" and aerosol, while others showed advanced adverse changes after relatively few exposures.

Simmers [30] stated that the tracheobronchial and pulmonary changes observed in these experiments closely paralleled those described in other experiments on the respiratory effects of various air pollutants. He suggested that the changes in the tracheobronchial trees and lungs of mice breathing air polluted with polycyclic aromatic hydrocarbons (PAH's) might have been nonspecific phenomena and that the degree of change was dose-dependent. He also indicated that these findings paralleled the observed fact that not every human exposed to air pollutants shows the same adverse reactions. From the data presented, no statement proposing a dose-response

relationship between polycyclic aromatic hydrocarbon content and degree of adverse change can be supported. The adverse effects observed in these animals closely parallel those observed by Hueper and Payne [19] and indicate again that nonspecific respiratory irritant effects are caused by chronic exposure to high concentrations of asphalt fumes.

Exposure concentrations in this experiment can also be estimated by assuming a chamber airflow of 1-10 cu m/hour and calculating the amount of asphalt volatilized/hour. These calculations indicate a range of possible concentrations of 74-929 mg/cu m. As in the previous experiment, these estimates of the exposure concentrations would mean that the animals used in this experiment were subjected to considerably higher total exposures than would be expected to impinge upon humans during a lifetime of work in the asphalt industry.

The adverse respiratory effects noted in response to long-term exposure to high concentrations of asphalt fumes were similar to those elicited by nonspecific respiratory irritants. The character of these adverse effects indicates that these exposure situations produce lesions that may not be totally reversible. Although these reports raise concern about the possible induction of pulmonary cancers in the animals exposed by inhalation to the airborne volatile components of asphalt, the evidence is insufficient to justify the conclusion that fumes or aerosols of asphalt are carcinogenic. No lesions or tumors of the skin were reported for any of the animals exposed to asphalt fumes in these experiments.

(b) Exposure to Asphalt and Asphalt Mixtures

The biologic responses of animals to exposure to asphalt are dependent on the route of exposure, the crude from which the asphalt was derived, and the method of asphalt extraction from that crude source. The adverse effects reported in animals after exposure to asphalt have often been in response to exposure situations that would seem unlikely to occur in the workplace environment.

In 1959, Simmers et al [31] assessed the carcinogenic potential of a mixture of steam-refined and air-blown asphalts from six different samples supplied by southern California refineries. The asphalts were pooled for this experiment, and a portion of this pooled sample was mixed with sufficient benzene to make it fluid enough to be painted on the skins of animals. A second portion of the pooled asphalts was suspended in olive oil to give a 1% emulsion for subcutaneous injection.

Four groups of C57BL mice were used in this study [31]. In Group 1, which consisted of 32 male and 36 female mice, the asphalt-benzene mixture was applied to the skin of the interscapular region twice weekly with a glass stirring rod. Group 2 consisted of 31 male and 32 female mice that were treated similarly to those in Group 1, but with benzene alone. Group 3, consisting of 33 male and 29 female mice, was injected subcutaneously in the interscapular region with 0.2 ml of the asphalt-olive oil suspension twice weekly; after 41 weeks, the frequency of injection was reduced to once a week because the volume of material in the injection region became excessive. Group 4 consisted of 32 male and 28 female mice that were injected with olive oil alone in the same way as those in Group 3.

Development of cancers in Group 1 was preceded by loss of hair at the painting site, dryness and scaling of the skin, and formation of papillomas [31]. Fifty-four weeks elapsed between the initiation of treatment and the appearance of the first of 12 epidermoid carcinomas at the site of painting. Four mice of this group were alive with well-developed papillomas at the time the paper was presented for publication, and one mouse with an especially large papilloma had died. Hair loss and dry and scaling skin were the only signs reported in Group 2. Group 3 developed injection site tumors consisting of one rhabdomyosarcoma and seven fibrosarcomas. The first sarcoma was observed 36 weeks after injection. No evidence of tumor formation was reported for Group 4. No evidence of metastasis was reported in any of the tumor-bearing animals. The authors concluded that pooled asphalt from western US crude oil sources contained a substance or substances that induced formation of tumors at the contact sites when applied to the skin or injected subcutaneously into C57BL mice.

Because exposure concentrations were not given and because results were reported as the total number of malignant growths rather than as the number of animals with malignant growths, it is not possible to determine a dose-response relationship from this report. The report does, however, clearly demonstrate that asphalt mixed with benzene or olive oil can induce neoplasms in mice. Although these were judged to be malignant on the basis of their morphologies, no metastatic lesions were reported. The authors did not address the possible cocarcinogenicity and irritating or promoting effects of the mechanical action and lipolysis of the dilution media, which might affect the tumorigenic potential of the mixture.

Another study published by Simmers [32] in 1965 was designed to test the carcinogenicity of asphalt that had not been mixed with diluent. In this study, a mixture of three samples of air-blown asphalt was used in one series of experiments, and a mixture of three samples of steam-refined asphalt was used in another series of experiments. The two pooled samples differed quantitatively as to the content of each major chemical fraction: the steam-refined asphalts contained 24% asphaltenes, 31% aromatics, 12% saturated compounds, and 33% resins, while the air-blown asphalts contained 41% asphaltenes, 26% aromatics, 11% saturated compounds, and 22% resins. To make asphalt fluid enough for painting and injection, it was heated by a hot water heat-exchange system to temperatures between 70 and 100 C (158-212 F). The temperatures of the asphalts when they were applied to the mice were not reported.

Twenty-five male and 25 female C57BL mice, approximately 6 weeks old, were painted with air-blown asphalt from 1 to 3 times each week, depending on skin condition [32]. The hair over the scapular region was closely clipped before the paintings began, and 75-100 mg of asphalt was applied at each painting. The method of determining the amount of asphalt applied during each painting was not reported. After 7 weeks, 14 males and 18 females from this group survived an epizootic of pneumonitis. The number of paintings for those animals surviving the epizootic ranged from 22 for an animal found dead after 63 days to 270 for a mouse killed after 21 months and 23 days. A similar group of 25 male and 25 female mice of the same age was painted three times a week with steam-refined asphalt. Fifteen males and 12 females from this group survived the epizootic. After 1 year of treatment, one male and five females survived. Causes of

mortality for the other animals were not reported, although all showed unspecified skin reactions to asphalt. Eight male and five female mice were therefore added to this group to complete the study. The number of paintings for the animals from this group on which autopsies were performed ranged from 16 to 240. No controls were reported for either of these groups.

Simmers [32] stated that the abilities of the undiluted asphalts to coat the skin were poor. Because the asphalt hardened into a plaque, which the animals often pulled off along with attached skin, Simmers conducted another set of experiments, using air-blown asphalt diluted with toluene (10:1). Ten male and 10 female mice were painted with this mixture 3 times weekly for 2 years, or for a total of 284 paintings. The asphalt-toluene applications averaged 20-30 mg/painting. To maintain the paintable consistency of the mixture, toluene had to be added periodically because of its rapid evaporation. An exact determination of the asphalt concentration was not possible because of this evaporation and the repeated addition of solvent. Five male and 10 female mice received applications of toluene alone, 3 times a week for 19 months, for a total of 230 applications, and served as controls. The author stated that he did not estimate the amount of toluene applied because of its rapid evaporation.

Dermatitis described by the author as chronic was usually observed at the site of air-blown asphalt painting [32]. One adenoma of the lung, one papilloma at the site of painting, and one tumor of skin accessory-structure origin were found in this group; no carcinomas were reported.

In the group painted with steam-refined asphalt, three animals developed epidermoid carcinomas at the site of application [32]. One of

these was of skin accessory-structure origin. Two papillomas were also found in this group.

In the group painted with air-blown asphalt mixed with toluene, 9 epidermoid cancers, including 1 of skin accessory-structure origin in an animal painted 147 times, were identified [32]. One cancer in an animal painted 240 times involved a regional lymph node, and another animal painted 252 times had a cancer that had invaded the scapula. Two lung adenomas were observed in other animals. In two animals, the only abnormal condition observed was chronic dermatitis.

Tissue samples from six of the toluene controls were examined microscopically, and one of these mice had a small papilloma [32]. All showed loss of hair, scaling, and thickening of the dermis and epidermis. These findings indicated that the general irritant effects observed were probably caused by the solvent used and not by the asphalt. Examination of the toluene showed a faint apple-green fluorescence under ultraviolet light, indicating the presence of contaminants.

In yet another experiment, 25 male and 25 female C57BL mice each were given 1 subcutaneous injection in the interscapular region of 200 mg of steam-refined asphalt [32]. After 111 days, nine males and four females, having no palpable asphalt deposits, were reinjected with another 200 mg/animal of steam-refined asphalt. Another group with the same number of mice was injected with the same dose of air-blown asphalt. After 4 months (120 days), 11 males and 7 females in the second group were reinjected as above.

In the mice injected subcutaneously with steam-refined asphalt, one adenoma of the lung was discovered, but no carcinomas [32]. On autopsy,

the asphalt was found in the abdominal and thoracic cavities, remote from the intended injection site, in 5 of 15 animals. Wherever the asphalt was found, it was covered by a thin, relatively acellular sheath. Twenty-one animals died during the 23 months of the experiment, the most frequent cause of death being pneumonitis.

In the group of mice injected with air-blown asphalt, one female developed a rhabdomyosarcoma primary to the site of asphalt injection and metastatic to the lungs and liver [32]. A second animal also had a rhabdosarcoma at the site of injection, and a third animal developed a carcinoma, apparently arising from skin accessory-structures, that had metastasized to the left lung.

Simmers [32] concluded that the "low yield" of cancers in the groups painted with undiluted asphalts may have been a result of the inability of the asphalt to maintain an intimate skin contact, since cancers were found when the asphalt was mixed with toluene, thereby making it more fluid. He stated that the small number of cancers found in the injected groups was probably because the chemicals present in the asphalts were not extremely carcinogenic. He also speculated that the carcinogenic hazard to workers using molten asphalt would probably be "inconsequential," since prolonged intimate contact with the skin or subcutaneous injection of the substance would be highly unlikely.

Simmers' [32] method of reporting results leaves some confusion as to how many animals actually developed carcinomas, since he reports the total number of carcinomas and not the number of animals with carcinomas; however, a comparison of his summary statements with the data presented in his tables indicates that he was reporting one carcinoma/mouse in this

study. The large increase in carcinomas in the animals receiving asphalt mixed with toluene is an interesting finding. Since the toluene fluoresced, indicating the possible presence of PAH's, the toluene may have contained carcinogenic or cocarcinogenic contaminants, which renders uncertain the interpretation of the data from this part of the study.

Hueper and Payne [19] subjected various experimental animals to skin painting or to intramuscular (im) injection with one of four road asphalts, a roofing asphalt, or coal tar. The animals used for these studies were C57BL mice, Bethesda black rats, and New Zealand rabbits. The four road asphalts were diluted with acetone so that they could be applied more easily. Applications to the nape of the neck were made two times weekly for up to 2 years. Controls for the painting experiments consisted of 200 mice and 60 rats that were colony animals. One road asphalt was applied to 50 male and 50 female mice, and the other 3 road asphalts were each applied to 25 male and 25 female mice. The extent of dilution of the asphalts and the amounts applied were not specified by the authors.

Two skin carcinomas and 2 papillomas were observed in the 250 mice exposed to the 4 road asphalts by skin painting [19]. Four instances of leukemia and one Kupffer-cell sarcoma were also attributed to the action of these asphalts.

The petroleum roofing asphalt was tested for its carcinogenic potential by painting the heated, undiluted asphalt on the napes of the necks of 25 male and 25 female mice twice weekly for a maximum period of 2 years [19]. Following the same schedule, this asphalt was also painted on the insides of the ears and on 2-cm-square shaved areas of the backs of six rabbits. No neoplastic reactions were observed in these animals.

For im injection, each of the asphalts was diluted 1:1 with tricaprylin [19]. Each tricaprylin-asphalt mixture was then injected into the right thigh muscle of a separate group of 50 mice and 30 rats in doses of 0.1 ml for the mice and 0.2 ml for the rats. Injections were given at 2-week intervals, 6 times for the mice and 12 times for the rats. Subcutaneous injections of tricaprylin, amount and schedule unspecified, were given to 144 mice that were used as controls.

In the injected animals, 3 sarcomas were seen at the site of injection in 200 mice and 13 sarcomas at the site of injection in 120 rats [19]. Other sarcomas of the liver and ileocecal lymph nodes and carcinomas of the uterus seen in the experimental groups were the same (not further defined) as those in diluent controls.

A coal tar pitch distillate was obtained by heating coal tar to 250-275 F (121-135 C), collecting the fumes on glass fiber filters, and extracting them with dichloromethane, benzene, and acetone [19]. After evaporation of the solvents, the extract was diluted with olive oil in a ratio of 1:3. Fifty male and 50 female mice, about 8 weeks old, each received 6 injections of 0.15 ml of this mixture at 2-week intervals into the right thigh muscle. Twenty-five male and 25 female mice had the original coal tar, heated sufficiently to make it fluid, applied to the nape of the neck twice weekly for a maximum of 2 years. The tumor incidence for the group of animals receiving applications of asphalt was 4.0%, while incidence for the group of animals receiving applications of coal tar pitch or coal tar pitch distillate was 50.7%.

The painting of coal tar on the skins of 50 mice resulted in 22 carcinomas and 4 papillomas, and the im injection of the coal tar

distillate extract resulted in 50 injection site sarcomas in 100 mice [19].

Hueper and Payne [19] concluded that the road asphalts tested were mildly to moderately carcinogenic for the skin and soft tissues of mice and rats and that occupational and environmental exposure to petroleum road asphalt "may be associated with cancer hazards to the tissues of contact." The asphalts tested, however, were mixed with solvents not used in the asphalt industry. Under these exposure conditions, 2.8% of the 250 mice painted with road asphalt and 1.5% of the 200 mice injected with road asphalt exhibited malignant growths attributed to the asphalt, and the roofing asphalt tested did not induce any malignant growths. While there is adequate demonstration of a carcinogenic hazard to the animals in this study, it is not clear that an occupational carcinogenic hazard from asphalt should be inferred from the experiment.

The carcinogenic properties of six grades of petroleum residues derived from Russian crude oil sources and of coal tar pitch were studied by Kireeva [17]. A 40% solution of petroleum tar, asphalt, or coal tar pitch in benzene was painted on white, strain SS-57 mice once a week for periods up to 19 months. Applications were discontinued at the appearance of toxic effects or marked weakening of the animals. The dose delivered at each application was not reported. Animals that survived the application period received approximately 70 applications. Microscopic examinations were performed on the tissues of most of the animals.

Four asphalts were tested [17]. For one asphalt, 2 of 50 animals developed skin tumors, the first tumor appearing in the 16th month; one animal had a squamous cell carcinoma and one had a sebaceous adenoma. Pulmonary adenomas and adenocarcinomas were present in five mice of this

series. Another asphalt painted on a group of 50 mice resulted in 1 subcutaneous fibrosarcoma, 1 papilloma, 1 pulmonary adenoma, 2 lymphoreticular sarcomas, and 1 hepatic hemangioma. The first skin tumor appeared during the 12th month, but regressed during the 13th month. The first persistent skin tumor appeared in the 16th month, and 4.6% of the animals eventually developed skin tumors. In a group of 40 mice exposed to a third asphalt, no skin tumors developed, but a pulmonary adenoma appeared in 1 animal. One pulmonary adenoma and 1 skin tumor that regressed were found in 37 mice exposed to a 4th asphalt. The 23 animals in the control group, painted with benzene alone, developed no skin tumors, although 1 animal developed pulmonary adenomas.

Fifty-two mice were tested with a petroleum tar [17]. The first skin tumor appeared at 9 months, and 18.4% of the animals alive at this time eventually developed tumors. Of the nine mice with tumors, five had squamous cell carcinomas, one had a fibrosarcoma, and three had papillomas of the skin. Pulmonary adenomas and adenocarcinomas also occurred in seven of these mice, and two cases of unspecified systemic lesions were reported.

Forty-seven mice were tested with another petroleum tar [17]. Tumors developed in 9.5% of the 42 mice from this group that were alive at the time of the first tumor appearance at 10 months. Of the four mice with tumors, two had papillomas and two had squamous cell carcinomas. In addition, all four animals had primary pulmonary adenomas.

Coal tar pitch was applied to the skins of 49 mice [17]. The hair was lost from the site of painting after the first application, and the first tumor appeared after 3 months. The majority of the animals developed multiple tumors, both small papillomas and large cornified disintegrating

tumors. Skin tumors, mainly squamous cell carcinomas with marked keratinization, were found in 86% of these mice. A few animals had infiltrative nonkeratinized foci with markedly atypical cells. Pulmonary adenomas were identified in eight mice, and one mouse had a squamous cell carcinoma of the stomach. The malignant tumors had a marked tendency to metastasize.

The mice receiving applications of petroleum tar or asphalt lost the hair at the site of painting more gradually than those mice painted with coal tar pitch, and their hair gradually grew back during the course of the experiment [17]. During the first 4-5 months, these animals lost weight, were sluggish, and had a marked thinning of the coat.

Nontumorigenic skin effects were observed in both the control and the experimental groups [17]. These effects included epidermal atrophy, focal hyperplasia, and atrophy of the hair follicles. Atrophy of the sebaceous glands in the controls and partial or complete atrophy of the skin papillae and hyperkeratosis with acute and chronic inflammation in the experimental animals were also reported.

Kireeva [17] concluded that the blastomogenic properties of asphalts were considerably weaker than those of coal tar pitch. Kireeva also stated that there was a definite correlation between the benzo(a)pyrene content of the substances tested and their carcinogenic activity, but no analytical data were included in the report to support this statement. The work of Kireeva clearly demonstrated different carcinogenic activities for the benzene solutions of coal tar pitch, petroleum tar, and asphalt used in this study. Two of 177 animals (1.1%) painted with the asphalt-benzene mixture developed malignant skin tumors, whereas 7.1% of the animals

painted with petroleum tar and 86% of those painted with coal tar pitch responded in this way.

Wallcave et al [3] attempted to correlate the PAH contents of eight asphalts and two coal tar pitches with the extent of tumor induction in mice whose backs were painted with these substances. Chemical analyses and separations of the PAH fractions of the asphalts and coal tar pitches were carried out by extraction of the parent materials and subsequent chromatography to produce an "interference-free" PAH fraction. A concurrent test column with known amounts of four PAH's was used as a control.

An estimate of recovery efficiency was made by adding benzo(a)pyrene (BaP) to the asphalt and then analyzing by the above procedure [3]. It was determined that recovery was approximately 65%. BaP concentrations in the asphalts ranged from "not detected" to 27 ppm for the unsubstituted compound and from "not detected" to 69 ppm for the alkyl derivatives. Benz(a)anthracene ranged from "not detected" to 35 ppm for the unsubstituted compound and from 0.05 to 109 ppm for the alkyl derivatives. Other PAH's were present in the same range of concentrations. The BaP concentrations in the two coal tar pitches were 0.84 and 1.25%, and the benz(a)anthracene concentrations were 0.89 and 1.25%. A larger number of PAH's were identified in the coal tar pitches, and each PAH was present in much higher concentrations in the pitches than in the asphalts. For skin application, the asphalts were dissolved in benzene to form 10% solutions and the coal tar pitches to form 9% solutions with respect to the PAH content of the parent material.

Random-bred Swiss albino mice, 7-11 weeks old, with average weights of 20 g for female and 25 g for males, were used in the study [3]. A patch of hair approximately 1-inch (2.5 cm) square was shaved from the back of each animal at the beginning of each experiment and was kept nearly free of hair during the experiment by periodic clipping with scissors. Twenty-five microliters of each material, containing PAH's equivalent to approximately 2.5 mg of asphalt or 2.2 mg of pitch, was applied to the shaved area twice a week for an average of 81 weeks for the asphalt-exposed animals and 31 weeks for the pitch-exposed animals. Each asphalt or pitch was applied to a separate group of animals that ranged in size from 24 to 32 animals at the time of autopsy. A control group of animals was painted with benzene alone twice a week. Autopsies were made on a total of 218 animals exposed to asphalt, 58 exposed to coal tar, and 26 painted with benzene. Skin sections and all grossly abnormal organs were studied microscopically in order to characterize the tumors.

Abnormal features observed in the mice to which either asphalt or coal tar pitch was applied were epidermal hyperplasia, inflammatory infiltration of the dermis, and occasional ulceration and abscess formations [3]. Amyloid accumulations in the spleen and kidneys were frequent in animals painted with asphalt. The authors did not expand on this observation. Carcinomas of the breast, adenomas of the lungs, malignant lymphomas, osteomas, stomach papillomas, endometrial carcinomas, mesotheliomas, fibrosarcomas, and malignant schwannomas were consistently found in both exposed and control groups and their character and frequency were not significantly different. Skin tumors were found in 6 of 218 asphalt-painted animals, and 1 of these was classified as a carcinoma.

Fifty-three of 58 animals (91.4%) that received applications of coal tar pitch developed 84 skin tumors, 31 of which were classified as carcinomas. One of 26 control animals developed a papilloma.

Wallcave et al [3] concluded that the strong tumorigenic activity of coal tar pitch was "in accordance" with the high PAH content of this material, but that the number of tumors in the asphalt-painted group was too small to permit conclusions about the relationship of the tumorigenicity of asphalt to its PAH content. They suggested that the differences in carcinogenicity between the asphalts and coal tar pitches could result from the different methods of production for the two classes of materials, especially the temperatures involved in their manufacture. The maximum temperatures involved in asphalt production were reported as 350-400 C (662-752 F) and the temperatures generating coal tar pitch were reported as having been in excess of 1,000 C (1,832 F).

The different carcinogenic potentials of asphalts and coal tar pitches is well supported by the experimental data, but the hypothesis presented for this differential carcinogenicity (difference in manufacture) is not based on the data obtained from this experiment and is probably only a partial explanation. The differing sources for asphalt and tar (petroleum and coal, respectively) certainly contribute also to different compositions of these products.

In each of these papers, the adverse effects reported have been in response to exposures that are unlikely to be faced by US workers. Some of the studies with asphalts have involved solvents not used in the asphalt industry, and the exposure schedules have not included washing between subsequent applications. Even under these exposure conditions,

carcinogenic effects were observed in relatively few of the experimental animals, and the authors' estimations of the hazards of contact with asphalt have been contradictory [3,17,19,31,32].

(c) Exposure to Asphalt Constituents

Studies [11,33] have implicated some asphalt constituents as presenting carcinogenic hazards. Although these studies cannot realistically be used to develop an environmental concentration limit for asphalt fumes, they are included in this document in order to represent fully the types of experiments that have been conducted to determine asphalt toxicity.

In 1965, Simmers [11] described the carcinogenic responses elicited in mice by the combined saturated and aromatic fractions of a steam-refined asphalt. The parent asphalt was divided into four fractions (asphaltenes, aromatics, resins, and saturated compounds). The procedures for separation of the asphalt fractions involved dissolving the asphalt in benzene followed by precipitation of the asphaltenes with n-pentane, filtration, absorption of resins and polar compounds on clay in a recycling column, absorption of the aromatic and saturated constituents on an alumina-silica gel column, and elution of the saturated components with pentane and of the aromatic ones with benzene. Examination by ultraviolet fluorescence of the four fractions showed that most of the fluorescent activity was in the saturated and aromatic fractions. A mixture of the saturated and aromatic components (freed of solvent) was used in this study.

Twenty-five male and 25 female C57BL mice 20-22 weeks old were used in this study [11]. The mixture of the two fractions was rubbed into the fur of the interscapular area with a glass stirring rod three times a week.

The weight of each application was determined to be approximately 33.4 mg by making 10 separate applications on a dried, weighed mouse pelt and then reweighing the pelt.

Autopsies were performed on 40 of the original 50 animals but 10 of these were not examined microscopically because they showed no gross evidence of neoplastic formations [11]. The minimum number of paintings was 72 and the maximum number was 242. Eleven animals survived the maximum number of paintings. Hair loss, along with dry and scaly skin, was a consistent finding in all animals.

Thirteen of the 30 mice that were studied microscopically had cancers, including 7 epidermoid carcinomas, 5 basal cell or basosquamous carcinomas, and 1 leiomyosarcoma underlying a papilloma [11]. In addition, one animal had an epidermoid carcinoma of the anus and a leiomyosarcoma of the small intestine, and another one had a carcinoma probably of sebaceous gland origin. In one of the animals, an epidermoid carcinoma had metastasized to the lung.

Simmers [11] concluded that, since the aromatic-saturated asphalt fractions tested had a much greater carcinogenic potential than the parent asphalt that he had previously tested [32], the carcinogenic activity of asphalt probably resided in these fractions and was possibly due to the PAH's in them. Simmers' conclusions are reasonable, based on these data and his previous work, but testing for carcinogenic activity of the other fractions and the determination of dose-response relationships are necessary to confirm them.

In a further study, Simmers [33] reported on the effects of subcutaneous injection of the saturated and aromatic fractions of asphalt

into mice. The mixture was obtained in the same manner described previously [11]. In the first experiment, 20 male and 27 female C57BL mice, 9 weeks old, were injected once interscapularly with 0.5 ml of the asphaltic material. In the second experiment, 26 male and 23 female mice were injected with 0.25 ml of the material every other week for 16 weeks, making a total injected volume of 2 ml/animal. A third experiment began with 12 male and 16 female mice 2.5-3 months old. One-milliliter injections were given to these mice for an average total dose of 9.7 ml/animal. The maximal number of injections, 11 during 13.5 months, was given to 8 mice. Three females escaped and 9 males died by the 15th day of this experiment because of an experimental error, and these mice were replaced by 11 male mice, 5.5 months old.

In the first experiment, autopsies were made on 36 mice and tumors were observed in 8 of them [33]. Four adenomas were found, along with four adenocarcinomas of skin accessory-structure origin. One instance of lymphatic leukemia was also reported. In the second experiment, autopsies were made on 39 mice and 7 tumors were reported; these included 1 adenoma of the lung, 2 leiomyosarcomas, 1 adenocarcinoma of the skin accessory structures metastatic to the liver, 1 adenocarcinoma of the lung, 1 fibrosarcoma, and 1 infiltrating lymphoma or small-cell carcinoma of the lung. In the third group of mice, autopsies of 19 animals revealed 7 tumors, including 4 adenocarcinomas and 2 adenomas. One animal in this group had lymphocytic leukemia. A total of 22 tumors were found in these experiments and 15 were classed as malignant. The average survival times of the mice that were studied microscopically were 17 months for the first group, 16.5 for the second, and 13.4 for the third.

Simmers [33] noted that there was relatively little difference between the first and second groups, which received total asphalt fraction doses of 0.5 and 2 ml/animal, respectively, but that there was a large difference between these two groups and the third group, which received an average of 9.7 ml/animal, both in length of survival and in percentage of tumors found during autopsies of the animals. He stated that these observations supported the hypotheses that the tumorigenic effects were dose-related and that the tumorigenic properties of hydrocarbons were more dependent on the dose administered than on the length of exposure. Although NIOSH does not agree entirely with the author's choice of adjective, it does agree that there is a difference between the third group and the other two in tumorigenesis (7 found versus 4 expected on the basis of the combined incidence in the other two groups) and length of survival (13.4 months versus the minimum of 15.7 months expected on the basis of the combined durations of life in the other two groups).

The carcinogenic potential demonstrated in the two previous studies indicates that there is a hazard from the saturated-aromatic fraction of asphalt, although animal studies with undiluted asphalt, as well as reports of human exposure studies [18,20,27] previously discussed, indicate that this hazard is minimal under workplace conditions. The literature [19,32] indicates that the asphalt constituents responsible for inducing neoplastic growths are present only in amounts that are not likely to induce neoplasias, and that only by fractionating or solubilizing the asphalt with specific solvents can a concentration of these potential carcinogenic constituents be obtained that is high enough to increase significantly the probability of malignant growths.

Comprehensive reviews of the complexities of the carcinogenic response are available from several sources [34-36]. Carcinogenic chemicals can be categorized as either direct carcinogens or procarcinogens [36]. The procarcinogen group contains the PAH's. The PAH's are metabolized by specific enzyme systems to ultimately yield epoxides, which are thought to be the active carcinogens. Conversely, enzymes such as epoxy hydrase and glutathione transferase detoxify these epoxides, so that the probability of cancer induction in an animal after exposure to the procarcinogen is a resultant of the relative rates at which the activating and detoxifying systems are able to operate.

The PAH epoxides may exert their carcinogenic potential as strong alkylating agents, which can alkylate the DNA or RNA bases or a variety of nucleophilic groups, such as sulfhydryl, carboxyl imino, or phosphoro. A covalent binding to DNA bases has also been observed with the benzpyrenes and other polycyclic hydrocarbons; this system requires activation by radiant energy or through free radical formation.

The total amount of alkylation or covalent binding is dependent on the initial concentrations of a carcinogenic substance. Since other factors also influence the expression of the carcinogenic potential, eg, detoxification reactions and DNA repair, "trace" quantities of these carcinogens have a very low probability of eliciting a tumor. Not enough information is currently available to determine the rates and probabilities of the various competing reactions in vivo. Further, there is no information that indicates the extent of somatic mutation that would justify prediction of a greater carcinogenic influence than that which occurs naturally.

The carcinogenicity of various PAH's is generally accepted on the basis of animal experiments [37-39]. Several of these PAH's have been found in petroleum asphalt and have been implicated as the causative agents for the neoplastic reactions caused by asphalt in animal experiments [3,17]. Especially well documented is the case for the carcinogenicity of benzo(a)pyrene (BaP) [37-40]. The maximum reported BaP content of asphalts from different crude sources were: 0.6 ppm in an asphalt from a Russian crude oil [41]; nondetectable (less than 6 ppm) from a US roofing asphalt [18]; 0-27 ppm in eight US paving asphalts [3]; and 11, 14, and 22 μg/1,000 cu m (1.1, 1.4, and 2.1 x 10*6 ppm; * means "to the negative power of") in the asphalt fumes from two US paving plants [5]. Two emission studies reported no detectable BaP in emissions from asphalt kettles [42], and BaP as approximately 0.00003% of the total particulate emissions from saturant plants and 0.00008-0.00019% of the total particulate emissions from air-blowing facilities [43]. In comparison, the concentrations of airborne BaP for January through March 1959 from 74 American cities in 49 states, the District of Columbia, and Puerto Rico ranged from 0.11 to 61 μg/1,000 cu m (0.01 to 6.1 x 10*6 ppm) with an average of approximately 11 μg/1,000 cu m (1.1 x 10*6 ppm) [44]. These values indicate that the BaP concentrations reported in asphalt fumes [5] are no higher than background concentrations found in many American cities. Other PAH's in various asphalts have been reported as being in the same range as the BaP [3]. Although data of this type suggest a possible carcinogenic potential for asphalt and asphalt fumes because of the presence of a known carcinogen, they also indicate that the hazard faced by asphalt workers is of the same order of magnitude as that faced by the general population exposed to urban air.

The presence of known carcinogenic chemicals in some asphalts is a cause for concern. The occupational health hazard faced by asphalt workers is difficult to assess, however, on the basis of the presence of these chemicals alone, because of the interactions of various PAH's and the dependence of tumor yield on experimental procedure.

Hieger [45] reported the results of experiments performed to demonstrate the dependence of tumor yield on factors that are generally ignored when comparing the results from different experiments dealing with carcinogenic substances. These factors, such as the number of applications, volume of injected material, and potentiation and inhibition of carcinogenesis within the same class of chemicals, are of extreme importance in trying to correlate the results of several separate experiments to determine concentrations for persons working in a complex environment that will have minimal, if any, impact on the worker's health. Hieger's experiments were designed to investigate the effects of (1) the frequency of application of a carcinogenic substance, (2) the vehicle used for injection of a carcinogen, and (3) the volume of injected material on tumor formation, and to determine minimal doses for tumor formation for single subcutaneous injections of dimethylbenzanthracene and BaP.

The interscapular skins of 75 C57BL mice were painted with a 0.75% solution of BaP in benzene/liquid paraffin (9:1) at the following intervals: once at the beginning of the experiment, once after 8 weeks, and once after 20 weeks [45]. Of the 75 mice, only 2 developed papillomas. Another 75 mice were painted with a similar solution containing 0.25% BaP once every 2 weeks for 30 weeks, increasing the number of applications over the first group but maintaining the same total dose delivered. This group

developed 25 papillomas, 20 of which developed into epitheliomas.

Single subcutaneous injections of 20 μg of BaP in 0.2 ml of olive oil yielded 22 injection-site sarcomas in 65 mice (33.8%) of the Swiss, F2, and C57BL strains [45]. Seventy-five mice similarly injected with the same solution containing an addition of 10% cholesterol developed 27 sarcomas (36.0%). Addition of 66% of stearic acid to the original solution of BaP in olive oil resulted in single injections producing only 10 sarcomas among 59 mice (16.9%). The difference between the results in the first two groups is not statistically significant, but the incidence of sarcomas in the third group is clearly lower than that in the other two.

Seventy-five mice of the C57BL, Swiss, F2, and stock strains were given single subcutaneous injections of 20 μg of BaP in olive oil as in the previous experiment, but in a volume of 0.01 ml instead of 0.2 ml [45]. In this case 4 animals (5.3%) developed tumors as compared with 22 (33.8%) in the previous experiment. Forty-five C57Bl, BALB, and stock mice were then given injections of 0.02 ml of BaP solution at 10 different sites, for a total injected volume of 0.2 ml (20 μg of BaP). Two animals (4.4%) developed tumors.

Single subcutaneous injections of dimethylbenzanthracene and BaP into mice of the C57BL, BRO, BALB, Buffalo, and stock strains showed the threshold dose for injection site sarcoma formation to be 1.25-5 μg/0.2 ml for dimethylbenzathracene and 1-8 μg/0.2 ml for BaP [45].

Hieger [45] demonstrated that 15 applications of a carcinogen resulted in more tumors than did 3 applications of the same carcinogen even though the total dose applied was the same. He also showed that the vehicle for injection of a carcinogen could affect the tumor incidence and

that small volumes of injected material (0.01 ml) would result in fewer tumors than larger volumes would (0.2 ml) even though the total doses of carcinogen delivered were the same. Finally, he demonstrated that both dimethylbenzanthracene and BaP have finite no-observable-effect doses for production of neoplasias.

Several other reports have indicated a no-observable-effect concentration for BaP using different animals and routes of administration. In a study using 180 young adult male Syrian golden hamsters, Feron et al [46] reported the results of weekly intratracheal instillations of BaP. Each instillation consisted of 0.2 ml of 9% saline solution in which 0, 0.0625, 0.125, 0.25, 0.5, or 1.0 mg of BaP had been suspended. Doses at each of these concentrations were instilled into 30 animals weekly for a period of 52 weeks. The experiment was terminated after 78 weeks, and autopsies were performed on the animals. Carcinomas were observed only in the animals that received the two highest total doses. A dose-response relationship was demonstrated for nonmalignant tumor formation, and 3 of 30 animals had such tumors at the lowest total dose of BaP, 3.25 mg/animal. Papillomas of the trachea and adenomas of the bronchioles and alveoli were the only tumors reported in the four lowest dose groups. The extent and complexity of the tumors were much greater in the two highest dose groups, and the carcinomas were limited to these two groups. Nonneoplastic reactions included hyperplasia and squamous metaplasia of the tracheobroncial epithelium, alveolar metaplasia, and adenomatoid peribronchiolar lesions.

A report by Payne and Hueper [47] indicated that 12 monthly subcutaneous injections of BaP into C57BL mice were more effective in

eliciting tumor formation than was a single injection of the same total dose. However, this fact became apparent only at total doses above 0.1 mg. At total doses of 0.05 mg, both groups had the same incidence of tumor formation, 10%, after 2 years. At total doses of 0.025 mg, 10% of the single-injection group showed tumor formation. At either a single injection of 0.008 mg, or 12 monthly injections for a total dose of 0.013 mg, none of the animals developed tumors within 2 years. The authors concluded that low-level recurring exposures to a carcinogen were more hazardous than was a single exposure to the same total amount. From the data reported, this conclusion would only be valid for doses above a certain value, approximately 0.1 mg in these experiments.

Poel and Kammer [48] reported tumor formation in C57BL mice after 75 applications of BaP at 1 μg/animal were applied to the shaved interscapular area 3 times weekly. Neither incidence of tumors nor the differential classification of the tumors as either carcinogenic or noncarcinogenic was reported in the paper. The authors concluded that, at doses as low as 1 μg/animal, BaP was a tumorigen and that the threshold concentration for tumor induction must be some value lower than this dose.

In a later paper, Poel [49] reported that single applications of less than 376 μg BaP to the skin of C57BL mice produced only transient papillomas, and only at doses of 752 μg/animal and greater were epidermoid carcinomas observed. In another series of experiments involving repeated applications of 19 μg of BaP to the shaved interscapular skin of mice, 1 exposure elicited no tumors in 8 mice, 10 exposures elicited 5 papillomas in 8 mice, 20 exposures elicited 7 papillomas in 8 mice, and 72-117 exposures were necessary before any epidermoid carcinomas were observed.

At the lowest dose tested, 0.15 μg of BaP/animal, 5 of 55 animals showed induced nonmalignant tumors between 42 and 62 weeks after the initiation of exposure. None of these had developed into a malignant tumor by the 75th week, which was the end of the experiment. Poel suggested that BaP at a dose of 0.15 μg/animal administered 3 times weekly could be considered a "threshold level" for carcinogenesis, producing only transient or noninvasive tumors in a minority of the animals and not significantly affecting their lifespans.

Solutions of BaP in acetone with concentrations varying from 0.0001 to 0.5% were painted over the entire backs of Swiss, CAF1, and C57BL mice three times a week for 7-24 months [50]. Concentrations that did not elicit papillomas or carcinomas were 0.001% in Swiss mice, 0.0005% in CAF1 mice, and 0.001% in C57BL mice. The authors stated that "there is obviously a level below which even lifelong exposure to a given amount of carcinogen will not produce tumors in the experimental animal." The lack of determination of the amount of solution or BaP applied during each skin painting makes calculation of the no-observable-effect dose impossible.

In addition to studies showing the carcinogenicity of single PAH's and complex mixtures of these hydrocarbons, several studies have indicated the complexity of the carcinogenic response in experimental animals. Scribner [51] reported the tumorigenic effects of the PAH's phenanthrene, pyrene, picene, benzo(b)chrysene, and anthanthrene, after tumor promotion with 12-O-tetradecanoylphorbol-13-acetate. These PAH's had formerly been thought to be nontumorigenic. He found also that benzo(e)pyrene and anthracene, whose tumorigenicity had been disputed, both induced papillomas, benzo(e)pyrene being more tumorigenic than anthracene under the

conditions of this experiment. Slaga et al [52] also showed the tumor-initiating capacity of benz(a)anthracene following promotion with 12-O-tetradecanoylphorbol-13-acetate.

Steiner and Falk [53] showed that 1,2-benzanthracene and chrysene were carcinogenic, and that their tumorigenic capacities were potentiated when they were injected together. When 1:2,5:6-dibenzanthracene was injected with 1,2-benzanthracene, however, there was apparent inhibition of carcinogenicity, indicating a possible antagonizing effect.

Benzo(a)pyrene has also been shown to be mutagenic, inducing lethal mutations on the X-chromosome in Drosophila males [54,55] and causing frameshift histadine-revertant induction in Salmonella typhimurium [56]. It has transformed normal hamster embryo cells in culture, causing a hereditary random pattern of growth, the ability to grow continuously in culture and to develop progressively as tumors after subcutaneous innoculation into adult hamsters [57]. Benzo(a)pyrene has also been shown to be mutagenic by the mouse dominant-lethal test [58].

An experiment in which mice were given access to 1 mg of BaP/g of food for their entire life spans, however, showed no effects on fertility or on the gross morphologies of their offspring [59]. This study indicates that ingestion of BaP caused no teratologic effects and no visibly detectable mutagenic alteration and thus draws attention to the importance of route of exposure and animal system used in eliciting a response.

These reports on the carcinogenic and mutagenic potentials of selected polynuclear aromatic hydrocarbons are cause for concern as to the adequacy of any recommendation of finite environmental limits for worker exposure to mixtures containing them. Because of the multiple factors

affecting carcinogenic potency demonstrated by these and many other reports, it is not feasible to attempt to predict from the results the magnitude of the potential occupational health hazard faced by workers exposed to mixtures, such as asphalt, which contain small percentages of these compounds. While the absence of human data and the paucity of reliable animal data demonstrating adverse effects should not be taken to justify the assumption that any mixture containing known hazardous chemicals is completely safe, this situation in the case of a mixture as widely used as asphalt does suggest that the hazard to health from occupational exposure to asphalt or asphalt fumes is minimal. No reports suggesting mutagenic or teratogenic effects of asphalt or asphalt fumes have been found in the literature.

Correlation of Exposure and Effect

Studies correlating biologic effects of asphalt fumes with exposure in workplace environments have not been found by NIOSH, and reports detailing exposure and effects in animals are not abundant.

Irritation of the mucous membranes of the respiratory tract was reported in 22 workers in an insulating company in Italy [15]. Symptoms and signs in these workers, who were exposed to fumes from bitumens heated to 120 (presumed to be degrees Celsius, equivalent to 248 F), included burning sensations in the nose, throat, and chest, nasal mucous discharge, coughing, expectoration, and loss of voice. These exposures were at a concentration described to have been associated with an acrid odor and to have been irritating to the roof of the mouth. The determination of asphalt fumes as the causative agent in this report was suspect since the

authors stated that true bitumen was often adulterated with residual pitch. In another questionnaire study, 34 roofing workers complained of occasional thermal burns from contact with hot asphalt; they stated their belief that they experienced no respiratory effects or skin effects other than the burns when they worked with asphalt, and the authors concluded that asphalt fumes could not be seriously implicated as causes of certain acute eye and skin problems among these men. Seventeen other roofing workers attributed no adverse skin and eye effects to work with asphalt [20]. Two state boards of health, replying to a questionnaire [27], reported 1 case of transitory nasal irritation and 14 cases of dermatitis resulting from exposure to asphalt, but no exposure details were given. Thirteen other state boards of health reported no adverse effects attributed to exposure to asphalt. Thirty-one construction and paving companies with a total of 11,478 man-years of worker experience mentioned only one case of ill health (details not given) said to be attributable to asphalt [27]. Three roofing companies employing over 1,100 workers claimed that there was no evidence of ill health attributed to asphalt. A health survey [27] of 462 oil refinery asphalt workers indicated no significant health problems when compared with a cohort control group of 379 other refinery workers. Comparison of lung disease data from the asphalt workers with statistics on lung disease in the US working population also indicates no significant difference [28]. These reports indicate that asphalt and asphalt fumes constitute a minimal occupational health hazard under present commercial usage conditions in the United States, considering the large number of workers exposed.

Animals exposed to asphalt fumes at high concentrations showed effects similar to those experienced by the Italian workers [15]. Thirty guinea pigs and 65 rats exposed 5 hours/day, 4 days/week, for 2 years, to the fumes generated by volatilizing 0.4-2 g asphalt/hour developed pneumonitis with dilatation of the bronchi, peribronchial adenomatosis, and squamous cell metaplasia of the bronchial mucosa [19]. Thirty mice similarly exposed for 6-7.5 hours/day, 5 days/week, for 21 months, to the fumes generated by volatilizing 0.74-0.93 g asphalt/hour and 20 mice exposed to an asphalt aerosol showed similar effects, including epithelial atrophy, abscess formation, and emphysema with focal lung collapse [30]. Assuming an airflow through the exposure chamber in each of these experiments on the order of 1-10 cu m/hour, the air concentrations of the asphalt volatiles can be estimated to be in the range of 40-2,000 mg/cu m. In both of these experiments, the effects observed were patchy and were clinically similar to those produced by the inhalation of any chemical irritant, with some animals being refractory to the irritant actions of asphalt fumes. Blowing asphalt fumes directly onto the eyes of rabbits caused conjunctivitis and a slight infiltration of the cornea [29]. These conditions were transient and disappeared after the exposure was discontinued.

A dose-effect relationship between exposure to asphalt fumes and the respiratory and eye irritation observed in the animals cannot be determined because exposure information was not reported. These reports do indicate that asphalt fumes have a potential respiratory irritant effect at concentrations estimated to be between 40 and 2,000 mg/cu m.

Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

Two studies [16,24] examined asphalt as a possible human carcinogen. One study [24] reported one case of cutaneous epithelioma caused by asphalt out of 3,753 cases reported to have been caused by other substances. The other study [16] suggested that previous or concomitant exposures to other carcinogenic substances, such as coal tar pitch, may have been the confounding factors.

After dermal application of asphalt alone, not mixed with a solvent, 3 malignant and 4 nonmalignant tumors were observed in 122 mice and no tumors were seen in 6 rabbits [19,32]. The incidence of neoplasms, both malignant and nonmalignant, ranged from zero to 9.5% in four separate experimental populations.

Dermal application of asphalt in a diluent on animals caused the same types of nonneoplastic reactions as did application of the solvent alone, including hair loss, chronic dermatitis, and dryness and scaling of the skin at the application sites [3,11,17,31,32]. Neoplasms, both malignant and nonmalignant, were reported for animals painted with a solution of asphalt with from 2.75 to 25% of the animals in the experimental populations developing neoplasms. A control group of animals in one experiment had a 3.8% incidence of spontaneous tumor formation [3]. When a mixture of only the aromatic and saturate fractions of asphalt was painted on another group of animals, 32.5% of the animals developed neoplasms [11]. These results indicated that under these experimental conditions, asphalt had the potential to induce tumors in the tissues of contact and that this potential pertained largely and perhaps exclusively to the aromatic and saturate fractions. Coal tar, which had been shown to contain a greater

percentage of PAH's than asphalt [3], had a greater tumor-inducing potential, with 52-93% of the animals showing neoplastic formations under similar skin painting conditions [3,17,19]. The results from these skin-painting experiments support the hypothesis that the carcinogenic potencies of these mixtures increase with their polynuclear aromatic hydrocarbon contents.

Dose-response data for skin application of asphalt or asphalt in a solvent are not available in any individual report. However, it may be possible to obtain some rough information of this sort by comparing data from different experiments. In one experiment [3], an average total dose calculated to be 405 mg/animal and applied over 81 weeks caused neoplastic reactions in 6 (2.75%) of 218 mice. In another experiment [32], an average total dose calculated as 20-27 g/animal applied over 90 weeks caused neoplastic reactions in 2 (6.2%) of 32 mice. Because of the differences in asphalts used for each experiment, and because the neoplastic response has been shown to be dependent on details of the experimental procedure [45], comparison of dose-response relationships from different experiments is not feasible.

Injection of hot asphalt into experimental animals has also elicited neoplastic reactions. Subcutaneous injections of asphalt or asphalt mixed with olive oil resulted in a 2% incidence of neoplasms in 50 mice [32] and a 12.9% incidence of neoplasms in 62 mice [31]. Injection of the combined aromatic and saturate fractions of asphalt gave results that indicate a possible dose-response relationship [33]. Doses of 0.5 ml/animal produced neoplastic growths in 22.2% of 36 mice, while doses of 0.25 ml/animal, given 8 times for a total dose of 2 ml, produced neoplasms in 17.9% of 39

mice, and repeated doses of 1 ml/animal given for an approximate total dose of 9.7 ml produced neoplasms in 36.8% of 19 mice [33]. One problem with injecting different volumes of carcinogenic material is the possibility that the volumes administered play an important role in cancer induction [45]. The incidence of neoplastic growths following the injection of asphalt or asphalt in a carrier was definitely lower (1.5-12.9%) than the incidence (17.9-36.8%) of neoplasms after injection of the combined aromatic and saturate fractions of asphalt [19,31-33]. The differences in tumor incidence might be accounted for by the difference in the quantity of the PAH's applied to each group because of the concentration procedure for the saturate-aromatic fractions, and because of the higher doses administered. This indication is supported by an experiment in which the extracted volatiles from coal tar pitch, which are known to contain more PAH's than asphalt, were injected, with the subsequent development of neoplasms in 50 of 100 mice [19].

There have been few studies of the effects on animals of exposure to asphalt, and the authors' estimations of the potential hazards of exposure to asphalt are contradictory. Factors contributing to tumor induction, such as temperature of material applied, mechanical irritation of the skin from burns, tearing, and the application procedure, tumor-promoting effects, lipolysis, possible cocarcinogenicity of solvents and carriers used, and the influences of the total amount of material applied on the results from application of a constant dose of carcinogen, have been ignored for the most part. In light of the absence of reports suggesting an occupational carcinogenic hazard from asphalt or asphalt fumes, it appears that one or more of the aforementioned factors may be more

important in eliciting the neoplastic response than the asphalt itself applied.

Usual sanitation, work practices, and protective clothing may decrease the probability of expression of the carcinogenic potential that may be associated with asphalt fumes sufficiently for the probability of expression of this potential in workers with asphalt not to be statistically different from that of the carcinogenic potential from radiant energy of various characteristics and from incidental contaminants of the environment in the general population. No reports suggesting mutagenic or teratogenic effects of asphalt or asphalt fumes have been found in the literature. Properly designed epidemiologic studies to evaluate the potential risk of developing cancer from exposure to asphalt fumes have not been found.

Summary Tables of Exposure and Effect

The effects of exposures to asphalt fumes and asphalt presented in Chapter III are summarized in Tables XIII-3, XIII-4, and XIII-5. Data concerning exposure to asphalt fractions or to asphalt constituents are not included in these tables.