III. BIOLOGIC EFFECTS OF EXPOSURE

Carbon black has been defined by the American Society for Testing and Materials [1] as a "material consisting of elemental carbon in the form of near-spherical colloidal particles and coalesced particle aggregates of colloidal size, obtained by partial combustion or thermal decomposition of hydrocarbons." It can be distinguished from other commercial carbons, such as coke and charcoal, by its finely particulate nature and by characteristics of the particles observable by electron microscopy, eg, shape, structure, and degree of fusion [2].

Carbon black is made either by partial combustion or thermal decomposition of liquid or gaseous hydrocarbons in a limited air supply [2]. Carbon black is classified as furnace, thermal, or channel depending on the manufacturing process. Furnace black is produced in a continuous process by burning oil, natural gas, or a mixture of the two in a refractory-lined furnace with a deficiency of air. Thermal black is produced in a cyclic process by the thermal decomposition of natural gas in two checkerbrick type furnaces. Channel black is made by impingement of underventilated natural gas flames on a cool surface such as channel iron; the black is deposited on the cool surface. Because the price of natural gas rose and pollution control was difficult, channel black production in the United States decreased during the last few years and ended in September 1976. Several foreign reports (see Effects on Humans) indicated that carbon black has also been produced from anthracene oils, coal tar or cycloparaffins. The extent of use of such materials in the United States for producing carbon black is unknown.

Carbon black is essentially 88-99.5% elemental carbon, 0.4-11% oxygen, and 0.05-0.8% hydrogen (residual hydrogen from the hydrocarbon raw material) (see Table XII-1) [2]. The hydrogen is more or less evenly distributed by true valence bonds on the carbon atoms, which leads to an unsaturated state. Carbon black contains 0.06-18% volatile matter or chemisorbed oxygen on the carbon surface in the form of carbon-oxygen complexes, which are removable only by heating to above 900 C. The amount of chemisorbed oxygen influences certain properties of the carbon black. For example, as the chemisorbed oxygen increases, the carbon black becomes more hydrophilic and its water sludge more acidic [3]. This is very important in the production of different grades of rubber.

Carbon black may also contain 0.01-0.2% sulfur, 0.01-1% ash (mainly soluble salts of calcium, magnesium, and sodium), and 0.1-1.5% material extractable by refluxing with organic solvents and containing a number of complex organic compounds (Table XII-1) [2]. Particulate polycyclic organic material (PPOM), polynuclear aromatic hydrocarbons (PNA's), and polycyclic aromatic hydrocarbons (PAH's) are terms frequently encountered in the literature reviewing carbon black and various petroleum products. PPOM refers to condensed aromatic hydrocarbons normally arising from pyrolysis of organic matter [4]. PAH's (also referred to in the literature as PNA's) in the occupational environment can result from heavy petroleum fractions and other materials. In most of the furnace blacks, PAH compounds such as pyrene, fluoranthene, 3,4-benzpyrene, anthanthrene, 1,2-benzpyrene, 1,12-benzperylene, and coronene have been found [5]. Analysis of N-339 type oil furnace black revealed 23 ppm of 3,4-benzpyrene and 92 ppm of coronene; analysis of N-990 type medium thermal black showed 192 ppm of 3,4-benzpyrene and 472 ppm of coronene [3]. In one type of SRF-carbon black made in 1964, which, according to the authors, was "not typical" of furnace blacks, anthracene (1.23 ppm),

phenanthrene (4.5 ppm), fluoranthrene (6.5 ppm), pyrene (45.8 ppm), 1,2-benzanthracene (0.82 ppm), chrysene (3.19 ppm), 1,12-benzperylene (38.9 ppm), phenylene (0.86 ppm) anthanthrene (149.42 ppm), coronene (94.6 ppm), 9,10-dimethyl-1,2-benzanthracene (1.5 ppm), 1,2-benzpyrene (10.5 ppm), 3,4-benzpyrene (6.5 ppm), and o-phenylene pyrene (7.8 ppm) were detected [6]. Of these PAH's, the last four were pointed out by Quazi and Nau [6] to be known carcinogens, with a summed concentration of 26.3 ppm. If one adds to these the other six compounds listed in NIOSH's list of suspected carcinogens [7], one obtains a total concentration of 88.4 ppm of possibly carcinogenic materials in this sample of carbon black.

Thus, it is apparent that the PAH's in carbon blacks vary both qualitatively and quantitatively depending on the type and grade of the carbon blacks and possibly the type of raw materials used for their production. Analysis of a typical rubber grade, N-774 type, oil-furnace black also found trace amounts of phenol (0.6 ppm); lead (2.7 ppm); cyanides, mercury, cadmium, beryllium, and cobalt (<0.05 ppm); and antimony, arsenic, barium, bismuth, chromium, selenium, thallium, vanadium, and molybdenum (<0.5 ppm) [3].

Lampblack, acetylene black, charcoal, bone black, and graphite have been confused previously with carbon black by a number of investigators. Some of the characteristics used to distinguish these carbonaceous materials from carbon black include particle size, physical structure, surface area, and percentage of carbon [8]. The particle size of these materials varies considerably. Charcoal, boneblack, and graphite are ground to a predetermined mesh size, such as 325 (44 μm). The other materials have particle size ranges (μm) as follows: channel black, 8-30; furnace black, 18-80; acetylene black, 40-50; fine thermal black, 160-190; medium thermal black, 450-500; and lampblack, 65-100. The reinforcing properties and color intensity of carbon black depend primarily on particle size. The thermal carbon blacks have a larger particle diameter than the furnace carbon blacks [2]. Generally, the smaller diameter carbon black particles impart a greater degree of reinforcement and abrasive resistance to rubber. Hence, the furnace carbon blacks possess a high degree of rubber reinforcement and abrasive resistance and may be used in various parts of a tire, while the larger particle diameter thermal carbon blacks provide a low degree of rubber resistance and are used in such rubber products as gaskets, mats, and mechanical goods. Also, the larger diameter carbon black particles have a larger surface area providing a better opportunity for adsorption of various materials [2].

Carbon black and other carbonaceous materials have different surface areas/unit volume [8]. Generally, the surface area/unit volume of substances increases as the particle size decreases. However, because they are porous, charcoals have a very large surface area relative to carbon black. Another characteristic distinguishing these materials is structure. Microscopic hexagonal crystallites oriented randomly are characteristic of carbon black, while the carbon atoms of graphite are arranged in sheets of regular hexagons.

The only chemical difference that has been thoroughly investigated in these materials is their percentage of carbon [8]. A partial explanation for this is that their use in industry depends on their physical rather than their chemical properties. The percentages of carbon are: channel black, 85-95; furnace black, above 99; thermal black, 95-99.5; lampblack, 90-99; charcoal, 50-95; bone black, 10-20; and graphite, 78-99.

Extent of Exposure

In 1976, eight companies operated 32 carbon black plants in the United States [9]. They produced 3,004 million pounds of furnace and thermal black and sold 3,035 million pounds, 111 million of them to foreign countries. Of the 2,924 million pounds sold domestically, 2,720 million (93%) were used in pigmenting and reinforcing rubber, 80 million in inks, 19 million in paints, and 3 million in paper. The remaining 102 million pounds were used in plastics, ceramics, foods, chemicals, and other miscellaneous products and in metallurgic processes like carburization. It is estimated that about 67% of the carbon black sold to the rubber industry was used by tire manufacturers.

Worker exposure to carbon black may occur during production, collection, and handling of the substance, particularly during pelletization, screening, packaging, stacking, loading, and unloading [10]. Exposure may also occur when cleaning equipment, when leaks develop in the conveyor system, and from spills. Table XII-2 is a list of primary occupations in which carbon black exposure occurs. NIOSH has estimated that 35,000 employees were engaged in operations that involve direct or indirect exposure to carbon black.

Historical Reports

In 1929, Borchardt [11] reported on lung effects in five rabbits exposed to carbon black, 1 hour/day, for 14 months. Exposure concentrations of carbon black were not included in the report. Examination of lung sections by microscope at 4 and 9 months after exposure began showed several inflammatory pus-filled foci and macrophages containing the carbon black in the alveoli and secondary lymph nodes. Pronounced accumulation of the carbon black dust in the hilar lymph nodes was found after 14 months of exposure. No evidence of lung fibrosis was observed, and Borchardt stated that the self-cleansing of the lungs by lymph washing was high.

Effects on Humans

Most reports describing the effects of carbon black on humans have dealt with pulmonary effects, while a few dealt with the effect on oral mucosa, skin, and heart. Whether carbon black is the causative agent of the observed health effects is sometimes uncertain because of the prevalence of both mixed exposures and confusion in the definition of the term "carbon black." Also, the environmental concentrations at which people are exposed have seldom been given, and those concentrations that are available are for total dust rather than for carbon black alone.

Kareva and Kollo [12], in 1961, described roentgenographic changes in chests of 89 USSR carbon workers who had been exposed to carbon black containing particles measuring 10-400 nm, high temperatures, and carbon monoxide in their work environment. Of these 89 workers, 34 had worked for up to 5 years, 26 for 5-10 years, and 29 for 10-17 years.

Of the 34 with less than 5 years of experience working with carbon black, the films of 5 aged 29-38 years, who had worked in a dusty operation for 4 years, showed some deformation of the pulmonary outline and the presence of limited microalveolar formations [12]. A fresh tubercular process was found in 1 of these 34 workers, while 7 others had old fibrofocal pulmonary tuberculosis.

Of the 26 workers with 5-10 years of exposure, fine loop-like fibrotic changes with isolated nodular formations were found in the roentgenogram of 1 who had been exposed to carbon black for 9 years [12]. Fine loop-like deformations of the pulmonary outline were noted in the middle region of chest X-ray films of six workers, five who were 33-37 years old and one who was 48 years old. All six of these persons, who had worked for 7-9 years, were suspected of having pneumoconiosis. In five workers, old fibrofocal pulmonary tuberculosis was detected. In the remaining 14 workers of this group, who were 28-56 years old, the only change found in the pulmonary outline was a linear shadow of thickened interlobar pleura in 4.

Of 29 who had been engaged in carbon black production for 10-17 years, stage I pneumoconiosis was found in 3 who had worked for 11-13 years [12]. Their chest X-ray films revealed an increased transparency of the lung tissue with reinforcement and deformation of the pulmonary outline. Fibrotic microreticular changes with consolidated foci 2-3 mm in diameter were found in the middle of both lungs and to a lesser degree in the lower region. The fibrotic changes were more pronounced on the right side. Nine workers in this group were suspected of having pneumoconiosis because they had deformation and reinforcement of the pulmonary outline and microreticular fibrosis in the middle of the lungs; four of them also showed thickened interlobular pleura, and two of them had egg shell type changes in lymph nodes and thickening of the bronchial walls. Three of the nine subjects suspected of having pneumoconiosis also had old fibrofocal pulmonary tuberculosis. All the workers suspected of having pneumoconiosis were 28-37 years of age. Of the 17 members of this group not showing or suspected of having pneumoconiosis, 1 had pronounced emphysema, 4 had old fibrofocal tuberculosis, and 1 had a fresh tubercular process.

The authors [12] noted that, although none of the changes in chest X-ray films were characteristic of carbon black exposure alone, the degree of change was a function of the duration of exposure in a dusty environment. Since the pneumoconiosis observed in these workers was not very severe, Kareva and Kollo assumed that it evolved benignly. The authors also stated that carbon black had effects on the body and that it was not possible to correlate dust levels, exposure to carbon black, and tubercular infections.

Komarova [13], in 1965, reported on adverse effects on the health of carbon black workers who packaged active and semiactive furnace and lamp blacks in the USSR. Coal tar pitch distillate was used in the production of active and semiactive carbon blacks. More than 80 workers, mostly 30-40 years old, were studied. Fifty-six percent of these workers had 1 year or less of work experience, 24% had 2-4 years, 8.5% had 5-10 years, and 8.5% had over 10 years. The work experience of the remaining 3% was not presented. These workers were exposed at dust concentrations of 10-1,000 mg/cu m and at carbon monoxide concentrations of 5-120 mg/cu m. Although the overall morbidity of all the carbon black plant workers decreased by 23% in 2 years, packaging workers experienced a morbidity increase of two or more times, so that 95% of the workers had been ill at the end of the 2-year observation period. The workers involved in packaging carbon black had increased morbidity from heart disease, influenza, mucous membrane inflammation, and oral and skin diseases; women also had an increased incidence of unidentified diseases of the reproductive organs. Workers who packaged lamp and furnace blacks had higher morbidity than those packaging active or semiactive carbon blacks; they also suffered from acute gastrointestinal diseases and bronchitis.

Periodic physical examinations found no abnormalities in 8% of the workers in the packaging department [13]. The remaining 92% complained of dryness and tickling in the throat, reduced senses of smell and hearing, skin irritation after showering, or discolored sputum and stools. Komarova attributed the dermal effects on these workers to the irritative properties of carbon black. The greatest percentage of workers had changes in the upper respiratory tract and ears, and almost half showed evidence of bronchitis, pneumosclerosis, or myocardial dystrophy. Decreased functional capabilities of the cardiovascular and respiratory systems were found more frequently in workers with over 5 years of exposure, but according to Komarova, the workers with 2-4 years of work experience had the greatest number of abnormalities. Komarova reported that the blood carboxyhemoglobin concentration was 13% in the packaging department workers and 9% in an unspecified control group. She believed that a carboxyhemoglobin concentration over 10% was associated with carbon monoxide intoxication and hence indicated potential harm to the workers. Disturbing features of this report include high but unexplained carboxyhemoglobin levels in controls, and the lack of information on procedures for the diagnosis of such effects as pneumosclerosis and myocardial dystrophy. With the high concentrations of airborne carbon black and/or carbon monoxide alluded to, pulmonary and cardiovascular effects might be expected. However, the specific effects noted need more description and confirmation before being attributed to carbon black.

Komarova and Rapis [14], in 1968, reported the condition of the respiratory systems of USSR carbon black workers. The authors stated that a significant number of workers in the plant complained of cough with expectoration, shooting pains in the chest, breathing difficulties, and headaches; they did not explain their basis for attributing significance to these effects, whether comparison with a control group or some other basis. Physical examination revealed indications of bronchitis, emphysema, signs of pneumoconiosis, and enlarged lymph nodes. The authors stated that no significant lung changes were noticeable on fluorography. A total of 66 workers (64% women and 36% men) mainly 35-40 years old were examined; 20 had worked with carbon black for 3-6 years, 15 for years, and 31 for more than 9 years. Fifty-two of these, 14 who had worked for 3-6 years, 13 who had worked for 6-9 years, and 25 who had worked for 10-16 years, were examined by spirography and teleroentgenography. None of the examined workers had any history of pulmonary, cardiovascular, nervous, or gastrointestinal diseases or of hyperthyroidism. The cardiothoracic ratios (ratio of the sum of the diameters of the right and left ventricles to the sum of the width of the right and left pulmonary fields above the diaphragm) were determined during the Valsalva maneuver and under normal conditions. In healthy subjects, this ratio is always higher under normal conditions than during the Valsalva maneuver. In subjects with pneumoconiosis, these indices are nearly identical or even reversed because of loss of pulmonary elasticity.

In 17.9% of those tested, the breathing rate was increased, and in 31.3%, the respiratory volume was decreased [14]. Fifty-five percent had a 12-80% reduction in minute volume associated with a 5-27% increase in oxygen consumption/minute. Vital capacity was reduced in 27%, and maximum pulmonary ventilation was reduced in 35.2%. Hyperventilation was seen in 27% of the workers. When the individual indices of pulmonary function were compared, evidence of oxygen deficit was found in 53% of the workers, primarily in those with 10-16 years of work experience with carbon black. Although hyperthyroidism was not found in any of the workers, 70.5% of those examined had a 21-25% increase in basal metabolism.

Of the 14 workers with 3-6 years of exposure, the chest roentgenograms of 5 showed pneumosclerotic changes in the middle and lower regions of the lungs [14]. Their cardiothoracic

ratios also indicated a decrease in pulmonary ventilation indices. Of the 13 workers with 6-9 years of work experience, 1 showed evidence of stage I pneumoconiosis, which was characterized by interstitial sclerosis in the middle and lower lung regions and radial opacities extending to the lung root. The nodular changes were primarily confined to the middle region. The cardiothoracic ratios of this worker under normal conditions and during the Valsalva maneuver were identical, indicating a loss of lung elasticity. Five additional workers of this group had incipient pneumoconiosis, which was characterized by reticular looped interstitial sclerosis, primarily in the lower region of the lungs. Based on cardiothoracic ratio analysis, the ventilation indices of the group were decreased. Of the 25 subjects with 10-16 years of exposure to carbon black, 6 had signs of stage I pneumoconiosis. The cardiothoracic ratios of two were lower under normal conditions than during the Valsalva test, indicating decreased lung elasticity. Eight others of this group had incipient pneumoconiosis. The ventilation indices of these eight subjects were reduced. There were no differences among the three exposure groups in either vital capacity or maximum pulmonary ventilation. The authors concluded from their investigation that diffuse, sclerotic-type pneumoconiosis could be found in workers engaged in carbon black production for 10-16 years. One of 10 workers with 6-9 years of experience also had signs of pneumoconiosis, which suggests that increasing duration of exposure may be associated with increasing risk.

The authors [14] did not adequately describe the basis for many of the comparisons of the data presented in this report. They did not state if the spirometric indices were age-adjusted or whether allowance was made for other possible determinants of toxic effects such as smoking.

Komarova [15], in 1973, presented the results of a study of the health effects experienced by workers in three carbon black plants producing active and semiactive lamp and spray furnace blacks from liquid raw materials in the USSR. The numbers of workers exposed to the four different carbon blacks were not given. The furnace black contained adsorbed carbon monoxide and 3,4-benzpyrene in concentrations ranging from traces to 0.003%. The furnace black workers in this study were also exposed to carbon monoxide, which was at or above the maximum permissible concentration (MPC) of 20 mg/cu m in 74% of the samples, to hydrocarbons, which exceeded the MPC of 300 ppm in 13.5% of the samples, and to dust (presumably predominantly carbon black), which exceeded the MPC of 10 mg/cu m in 75% of the cases. In general, furnace black workers spent up to 80% of their time at these concentrations of dust and carbon monoxide, and packers of lamp and spray blacks spent 93.8% of their time.

Although no specific data were given, Komarova [15] stated that a study of the lost time morbidity of various carbon black workers revealed that the highest time-loss morbidity occurred in packers, loaders, granulator operators, and transportation device operators. These workers were exposed primarily to carbon black dust and carbon monoxide.

Physical examination of 643 workers revealed health problems in more than half [15]. In addition to the clinical pictures previously reported [13,14], these workers complained of general weakness and malaise. According to the author, complaints were most common in persons who had worked in dusty operations for 6 years or more. Bronchitis was diagnosed in 30.2% of the workers. Undescribed functional changes in the ear, nose, throat, and lungs occurred in 75%. Blood analysis revealed leukopenia, leukocytosis, an elevated erythrocyte count, and an increased erythrocyte sedimentation rate.

Pulmonary function was further studied with a spirograph in 51 workers with 3-22 years of exposure to carbon black [15]. Thirty-four had changes in pulmonary function, including a 22% reduction in vital capacity. When workers engaged in dusty operations breathed oxygen, respiratory frequency, depth, and minute volume decreased and oxygen consumption increased. Chest roentgenograms revealed early signs of pneumosclerosis in 18 workers. Chest roentgenograms of seven workers showed the intense imaging of pulmonary stroma and the characteristic reticular loop-shaped structures, mainly in the middle and lower areas of the lungs, of stage I pneumoconiosis. The author compared the carboxyhemoglobin concentrations of 136 experimental subjects who were presumably exposed to carbon black with those of 37 control subjects, who were presumably not exposed. The mean concentration of carboxyhemoglobin of plant workers was 8.4 ±0.6%, that of controls 5.7 ±0.7%. The carboxyhemoglobin concentration increased by about 26% by the end of the workweek. With prolonged exposure (unspecified) it decreased by about 2% although the actual concentration (7.70 ±7%) remained above that of the controls.

Komarova [15] concluded that the major health hazard in the production of carbon black was exposure to carbon black dust and carbon monoxide, and that prolonged exposure can lead to the development of a diffuse sclerotic type of pneumoconiosis. Therefore, she recommended that the production of carbon black be completely automated to minimize worker exposure and consequent health effects. This report is a summary of dissertations from several of her students; important details missing from this report may have been described in the theses themselves which are unavailable.

Gabor et al [16], in 1969, described the condition of the respiratory system of workers who produced furnace, thermal, or channel blacks in Rumania. The number of employees working with each carbon black and the age, sex, and length of employment in carbon black production of the workers were not presented. The concentrations of airborne anthracene were between 1.25 and 2.11 mg/cu m in the early stages of production. The 6-hour concentrations of 3,4-benzpyrene, 1,2,5,6-dibenzanthracene, chrysene, and 10,11-benzofluoranthene were 260-510, 64-705, 150-200, and 1,330-3,000 μg/cu m, respectively, during thermal black production. During furnace black production, the 6-hour concentrations of 3,4-benzpyrene, chrysene, and 10,11-benzofluoranthene were 52, 70, and 300 μg/cu m, respectively. In the channel black production area, the 6-hour concentration of chrysene was 45 μg/cu m and that of 10,11-benzofluoroanthene was 480 μg/cu m. Analysis of the thermal black for 3,4-benzpyrene, 1,2,5,6-dibenzanthracene, chrysene, and 10,11-benzofluoranthene content revealed 345, 331, 510, and 1,200 μg/g, respectively. Furnace black contained 68 and 28 μg of 3,4-benzpyrene and chrysene, respectively, in each g of black, while the concentrations of 1,2,5,6-dibenzanthracene and 10,11-benzofluoranthene were not detectable. Channel black contained no detectable amounts of the four PAH's.

Of the workers who producd carbon black, 72 were examined by roentgenograms, and 82 were given pulmonary function tests, eg, vital capacity (VC), a function described only as MEVS (possibly FEV 1), bronchial caliber, alveolar motor force, and partial pressure of carbon dioxide in alveolar air [16]. Chest roentgenograms revealed pneumoconiosis in 10 workers (13.9%), and nonspecific lung lesions indicated early pneumoconiosis in 5 (7%). The chest X-rays of these workers were described as showing small soft nodules in the hilar regions of both lungs and clusters of nodules throughout the lung fields. According to the authors, the frequency of such lung lesions was highest in channel black workers, followed by furnace and thermal black workers. Although none of the carbon black workers experienced labored breathing on exertion, VC and

MEVS were less than 75% of the theoretical values in 16.7-17.4% of the workers. The decrease in MEVS was reportedly greatest in thermal black workers. The alveolar motor force in all carbon black workers was 20-57% below the control values. This statement is the only mention of controls in the study. Alveolar hypoventilation was indicated by a partial pressure of carbon dioxide greater than 45 mmHg following moderate physical exercise in 16-24% of all the carbon black workers examined, whereas 50% of the thermal black workers had such signs.

Gabor et al [16] believed that the carcinogenic hazard in carbon black production arises from handling anthracene oils and carburation residues that contain free PAH's or from the polycyclic hydrocarbons desorbed from carbon black with temperatures above 200 C or treating with solvents. While these investigations focused on the carcinogenic hazard associated with carbon black production, the authors did not specifically investigate the incidence of cancer among these workers. The incidence of pneumoconiosis in the carbon black workers does not appear to be related to either the concentration of airborne polycyclic hydrocarbon or the concentrations of adsorbed polycyclic material in carbon blacks. Workers engaged in thermal black production, which resulted in the highest concentrations of airborne PAH's, had the greatest decrease in MEVS and the highest incidence of alveolar hypoventilation.

In 1970, Slepicka et al [17] described carbon black induced changes in persons who had worked in the production of channel and furnace blacks from anthracene oils for more than 10 years in Czechoslovakia. Samples of air analyzed during this period contained 8.4-29 mg of dust/cu m of air and unspecified aromatics of 100 and 150 mg/cu m. Analysis of the ash content of carbon black found no detectable amounts of silica.

Of 52 workers, 9 who had been exposed for 10-38 years (average 21.5) and were 45-60 years old (average 57.2) had changes in their chest X-ray films [17]. Of the nine, one had generalized nodulation, two had reticulation with developing nodulation, five had numerous and dense opacities dispersed over a larger portion of the pulmonary field, and one had opacities up to 1.5 mm diameter occupying at least two of the upper intercostal areas but not extending beyond a third of the pulmonary field.

Slepicka and coworkers [17] presented the results of a detailed medical examination of a 51-year-old man, a smoker, who had been exposed to carbon black for 20 years. Results of his pulmonary function tests (FEV 1 and FVC) indicated a slight, obstructive, restrictive disorder of the lungs. Microscopic examination of a transthoracic pulmonary biopsy revealed accumulation of large quantities of black pigment that obliterated some of the alveoli with no evidence of fibrosis. His chest X-ray films showed a generalized nodulation. The authors suggested that the lack of fibrosis in the transthoracic pulmonary biopsy does not prove that carbon black has no fibrogenic potential, because their examination could only give an approximate estimate of the changes in the whole lung. Basing their evaluations on the results of their own investigations and those of others, the authors concluded that the observed lung changes were caused by dust from carbon black containing negligible amounts of silica. Although aromatics were present in the work environment, their contribution to the development of the lung changes in carbon black workers was not considered important by the investigators because there was no evidence of more serious disruption of pulmonary function and no progression of radiologic changes following long-term exposure. In 1975, Troitskaya et al [18] reported effects on the health of 357 workers in four plants in the USSR. The workers all had over 6 years of experience making furnace, channel, and thermal blacks, and workers were exposed to dusts liberated when producing, extracting, processing

(screening, compacting, and granulating), and packaging carbon black. Dust concentrations were also high during equipment repair and emergency breakdown. The carbon monoxide content in the work areas was reported to exceed the MPC of 20 mg/cu m by an average factor of 1.5-5. The workers spent 60-90% of their time in dusty and gaseous areas and 40% in operations involving physical stress. The atmospheric concentrations of the various types of carbon blacks were not given.

Physical and roentgenographic examination of the 357 workers revealed pneumoconiosis in 17 (4.8%) who had worked in dusty areas an average of 16 years [18]. Coniotuberculosis was found in three (0.8%), with a mean of 8 years of work in dusty areas. Seven (2%) had tuberculosis and 13 (3.5%) had chronic bronchitis. One of the 17 workers with pneumoconiosis had worked in another dusty occupation. Workers engaged in channel black production had the highest incidence of pneumoconiosis. The furnace black workers at one plant also had a high incidence of pneumoconiosis even after only brief employment in the plant; the authors attributed this to the high dust concentrations in their workplace. These results agree with the findings of Gabor et al [16], who also found that pneumoconiosis occurred in more channel black workers than in furnace and thermal black workers. Chest roentgenograms of workers with pneumoconiosis showed a spotty, fine reticular structure throughout the lungs and thickening of the bronchi, vessels, and periacinous tissue in the middle and lower regions [18]. These structural changes were reportedly accompanied by functional changes, eg, decreased VC, respiratory minute volume, and maximum respiratory capacity. In 118 (33%) of the workers, who had an average increase of 6-9 vol% in the carboxyhemoglobin concentration in their blood, weakness in the autonomic nervous system, ie, the so-called asthenic vegetative syndrome, was diagnosed. Troitskaya et al therefore speculated that the observed functional changes in the nervous system of these workers may have been related to the effects of exposure to carbon monoxide.

Because the authors [18] found a high incidence of pneumoconiosis in workers with short-term exposures to carbon black and no differences between the seven types of industrial carbon black in experimental pulmonary fibrogenesis, they suggested that a single limit, ie, 6 mg/cu m as the MPC, would be adequate protection against the fibrogenic properties. However, after considering reports on the carcinogenic potential of carbon black extracts and of the presence of benzpyrene in carbon black at concentrations as high as 54 μg/kg of carbon black, they recommended that the MPC of carbon black be limited to 4 mg/cu m, with a maximum benzpyrene concentration of 35 mg/kg of carbon black. The 4 mg/cu m concentration was chosen so that the MPC of 0.15 μg/cu m for benzpyrene would not be exceeded.

Capusan and Mauksch [19], in 1969, reported the 5-year incidence of skin diseases in workers producing lamp black (carbon black) by large-scale "sooting of a wick" in a petroleum lamp. Lamp black manufacture by this method involved combustion of hydrocarbon (brown coal tar) and naphthene (cycloparaffin) wastes. Benzene extracts of the lamp black had maximum ultraviolet absorption between 270 and 340 nm. Although the authors did not specify what the absorption maximum indicated, it probably indicated the presence of polycyclic aromatic compounds. An unspecified number of the workers (96%) were regularly given dermatologic examinations. Workers were examined after they had showered at the end of a working day. The incidence of skin diseases in the lamp black workers was expressed by the maximum and minimum percentages that were seen during the 5 years, because 80% of the workers had been transferred to other departments by the end of the 5-year observation period.

The authors [19] stated that soiling of the skin was very heavy on exposed areas and less under the protective clothing. Because of such heavy soiling, the workers washed themselves with soap and warm water repeatedly and vigorously. Despite these washup procedures, embedded carbon particles led to a marked follicular coniosis, which appeared as black spots on the skin.

Washing also produced an alkalinized and degreased skin surface, resulting in fissures and a predisposition toward irritation dermatitis [19]. The skin conditions of these workers were classified as specific dermatosis, which occurred in 53-80% of the workers, and unspecific dermatosis, which occurred in 10-16%. Among the workers with specific dermatoses, stigmata with fissured hyperkeratoses of the palms were found in 23-32%, and linear tattooing of the backs of the hands and forearms was found in 1.6-3%. The incidence of specific progressive dermatoses, eg, follicular conioses, was 22-31%, while that of acneiform conioses was 7-20%. Nonspecific dermatoses, such as pyrodermias (1-4%), inguinal and plantar epidermophytias (4-5%), eczemas and eczematides (1.8-4%), diffuse pruritis after a warm bath (0-1.6%), and utricarial eczema after a warm bath (0-1.6%), were much rarer. Although the progression of the skin diseases in some workers was severe, only 1.6-2% of the workers required treatment. Some workers suffered from more than one skin disease. A group of 22-36% of the workers did not show any dermal effects over the 5 years. There was no phototoxic dermatitis nor were there any carcinomas observed in any of the workers even though they were specifically examined for carcinomas in unspecified organs.

Because of the problems associated with increased soiling of the skin in the production of lamp black, protective measures were taken [19]. The dusty processes were automated, and a bentonite-based skin cream was used by the workers with favorable results. Although Komarova [13,15] had also noted some skin effects in carbon black workers, the present study reported these effects in greater detail.

Maisel et al [20], in 1959, reported carcinoma of the parotid duct in a 53-year-old chemist who had had a private, and not particularly well ventilated, laboratory for the experimental production of carbon blacks. At the time the malignancy was diagnosed (1956), only six similar cases were known, but exposure to carbon black had not been involved in any of them. The patient had produced experimentally more than 170 furnace carbon blacks with particles of 50-100 μm in diameter and had handled most of the commercial types with mean particle diameters of 35-270 μm for 11 years [20]. His experimental carbon blacks usually had been produced from mixtures of city gas and natural combustible gases and contained 0.5-5% acetone extractables. For 3 years during this employment, exposure to carbon black had been high. The air in his laboratory was reported to have been sooty with carbon black, and the chemist at times literally ate and breathed it; he reported having noted a gritty black material in his mouth and having seen black material on his handkerchief when he sneezed. Four years prior to hospitalization, because he constantly felt tired and in poor health, he discontinued work and took no alternative employment. For a number of years prior to hospitalization, he had had intermittent puffiness of both cheeks alternating between the sides with some swelling of the eyelids. Two weeks prior to hospitalization, he developed a swelling of the right cheek. This disappeared gradually, and he became aware of a hard nodule in his right cheek. These conditions were believed to be related to penetration of carbon black from the man's mouth into the duct of the parotid gland and retrogradely up the duct into the gland.

Maisel et al [20] concluded that, because of the known carcinogenic potentials of the polycyclic hydrocarbons in carbon black, the parotid duct cancer in this patient could have been produced by carbon black. They hypothesized that the carbon black particles could travel through the parotid duct to the parotid gland in a manner similar to that used by the bacteria that cause "surgical parotitis," ie, reverse peristaltic saliva flow. The authors believed that the presence of squamous-cell metaplasia in the left parotid gland, probably a precancerous lesion, and the presence of black material, presumably carbon black, reinforced their conclusion that carbon black could have produced the parotid duct cancer, but they conceded that the black material found was not analyzed for either polycyclic hydrocarbons or carbon.

In the absence of such information, and since the chemist during his research career probably had exposures to a number of other chemicals that might have acted as initiators, promoters, or synergists in the overall carcinogenic response, no definitive conclusion on the causative role of carbon black in the production of parotid duct carcinoma can be derived from this single case.

Epidemiologic Studies

(a) Cancer

Ingalls, with two collaborators, published a series of epidemiologic studies of cancer among employees of the Cabot Corporation [21-23]. The corporation employed in 1949 a comparatively small number of women, who were omitted from the study because of the different mortality experiences of men and women. Causes of death were obtained from death certificates from the insurance carrier for the corporation. There were 1,085 workers employed on July 1, 1949 [21] and 1,411 workers employed on January 1, 1957 [22] at the carbon black plants.

In the first two studies [21,22], the incidence of cancer in men who produced carbon blacks was compared with that in men working in the same factories but who were involved in clerical, maintenance, or shop related jobs thought not to have involved contact with carbon black. In the third study [23], men who produced carbon blacks in factories in Louisiana and Texas were compared with those working in other facilities in the same two states.

The first study [21] considered the working force at plants in Texas, Louisiana, and Oklahoma from July 1939 through June 1949. The second paper [22] extended the study to January 1957. The third paper [23] continued the study for another 18 years, to the end of 1974. The carbon black workers suffered 14 deaths due to cancer in a total of 19,183 work years, whereas the control workers had 8 deaths in a total of 16,323 work years. These figures yield mean yearly incidences of death due to cancer of 0.73 per 1,000 among the carbon black workers and of 0.49 per 1,000 among the noncarbon black workers. In both groups, the malignant tumors occurred mostly in the respiratory system. The next most common site of malignancy among the carbon black workers was the lymphatic-bone marrow complex, followed by the digestive system and unspecified organs or tissues. One malignant tumor of the genital organs was recorded. Among the controls, the digestive system, the lymphatic-bone marrow complex, the skin, and an unspecified organ or tissue each was the site of one malignant tumor. The only site of malignancy likely to be found significantly more often among carbon black workers than among the noncarbon black workers was the lymphatic-bone marrow complex. There were 4 deaths due to leukemia among the 19,183 work years of the carbon-black workers whereas only 1 occurred among the

16,323 work years of the control groups. In other words, leukemia was 3.43 times as frequent a cause of death due to malignancy in the carbon black workers as in the noncarbon black workers.

The first two papers [21,22] give figures also for workers who had developed cancers but were still alive. These show that there was a total incidence of cancer among the carbon black workers of 10 in 12,636 work years, or a mean yearly incidence of 0.79 per 1,000 whereas the noncarbon black workers developed 7 cancers during 8,964 work years, for a mean yearly incidence of 0.78 per 1,000.

When the values for the incidence of malignant tumors among the workers for the Cabot Corporation were compared [21] with those for workers in oil refineries, both being rated expectantly on the basis of age-specific death rates for cancer among men in the United States during 1940, the standardized mortalities were 0.60 for carbon black workers, 0.66 for the non-carbon black workers, and 0.89 for the oil refinery workers. Comparison [22] of the total incidences of cancer between the two groups of workers for the Cabot Corporation with those expected on the basis of figures for New York State during 1950 yielded standardized morbidities of 0.82 for the carbon black workers and of 0.45 for the controls. The standardized mortality from cancer for carbon black workers was 1.8 times that for the controls. When compared with the annual incidence in the white male population of the Dallas-Fort Worth area, as reported in an NCI monograph [24], melanomas of the skin were found 2.5 times as often in carbon black workers and 3.3 times as often in other employees.

These three epidemiologic studies neither prove nor disprove that carbon black is a carcinogen. The standardized morbidity for carbon black workers, in comparison with that for the other workers, suggests that carbon black may be a carcinogen. This possibility is rendered more likely, although no quantitative value for the increase can be assigned, by the apparent finding that carbon black may cause leukemia. These two suggestions of malignant neoplastic activity at least raise suspicions of an excess cancer risk associated with exposure to carbon black. Later sections of this document review other evidence pertaining to this question.

(b) Other Effects

In 1975, Valic et al [25] reported the results of a study conducted in 1971 of functional and radiologic lung changes in workers exposed to carbon black. The subjects were 35 male workers, 22 smokers and 13 nonsmokers, who had been part of a study conducted in 1964. Their average age was 38.8 years, and they had been exposed an average of 12.9 years. Analysis of air samples from their work environment in 1964 showed geometric mean (±S.D.) total and respirable carbon dust concentrations of 8.5 ±1.6 mg/cu m and 7.2 ±1.8 mg/cu m, respectively, with a geometric mean particle diameter of 0.65 μm. In 1971, the geometric mean concentrations were 8.2 ±1.6 mg/cu m of total and 7.9 ±1.7 mg/cu m of respirable carbon dust, with a geometric mean particle diameter of 0.78 μm. A group of 35 males, matched with the exposed group in age, height, smoking habits, and socioeconomic status, but not exposed to significant concentrations of dust in their work environment, were selected as the controls.

The FVC and FEV 1 of each group was measured by recording five trials by each subject and taking the mean of the two highest values for statistical analysis [25]. Chest roentgenograms of each subject were also made to evaluate the changes in lung tissue. In 1964, the FEV 1 and

FVC of carbon black workers were not significantly different from those of the controls. However, in 1971 both the mean FVC and the mean FEV 1 of all carbon black workers were 12% below those of the controls ($P<0.05$). The FVC and FEV 1 in nonsmoking workers were not significantly different from those of the controls but those of workers who smoked or had chronic bronchitis were about 1% below those of the controls.

The authors [25] believed that the decreased ventilatory capacities of the control workers from 1964 to 1971 could be attributed to improper selection of the group, since some of the control subjects lived near carbon black plants and may therefore have been exposed at high atmospheric concentrations of dust particles. The authors noted that measurement of atmospheric particle concentrations near the plant confirmed their belief, but they did not present these results. The authors also stated that a large decrease in control FVC and FEV 1 values occurred between 1964 and 1971, but those in 1971 were lower than those in 1964 by only 2-3%. Because of the problems with the control population, the authors analyzed their data using normalized lung function decreases. The calculated average annual decreases of FVC and FEV 1 in all carbon black workers were four and three times higher, respectively, than those predicted for a normal population. The authors thought that the control population may not have been properly chosen which may cast some doubt upon the reliability of the observations. The chest roentgenograms of 6 of 35 workers (17.1%) showed minute reticular and nodular markings (interstitial fibrosis), mainly in the middle and basal parts of the lungs. These six workers had been exposed an average of 15.6 years; of three who had signs of pneumoconiosis, one had had no chest radiographic changes during the first survey in 1964.

In 1971, Smolyar and Granin [26] studied the oral mucosa of workers exposed to carbon black. Oral examinations were conducted on 600 workers; 300 of these worked in production areas with high concentrations of active furnace black. The concentration of carbon black and duration of exposure to carbon black was unknown, but was characterized in a preceding thesis by Smolyar [27] as 2-3 times the maximum allowable concentration (MAC) for carbon black in the furnace area of the plant, and 4-11 times the MAC in the trapping and collecting departments. The author also stated that these workers were exposed to other toxic substances including anthracene oils. The remaining 300 subjects, who worked in factories without occupational hazards (probably not exposed to carbon black), served as controls [26].

Significant amounts of carbon black were found on the teeth, oral mucosa, and posterior wall of the throat and in the saliva of the carbon black production workers [26]. Twenty-four of these workers had keratosis and 36 had leukoplakia, while only 7 control subjects had keratosis and 16 had leukoplakia. The basis for this diagnosis was not reported. This increased incidence of keratosis and leukoplakia in the exposed workers was reported to be statistically significant ($P<0.003$). Keratosis and hyperkeratosis were observed primarily where carbon black accumulated, at such sites as the oral mucosa, the transient folds, cheeks, gums, and tongue. Leukoplakia was frequently found in the mucosa lining the corners of the mouth and cheeks, but it occurred occasionally on the tongue and lower lip.

Oral mucosal lesions, such as keratosis, hyperkeratosis, and leukoplakia, which the authors [26] considered to be pretumorous, occurred more frequently in workers who produced carbon black than in other workers. Smolyar and Granin concluded, therefore, that such lesions resulted from long-term exposure to carbon black dust and anthracene oil, the latter material presumably being the raw material from which the carbon black was produced.

Animal Toxicity

Studies performed with experimental animals have reached contrasting conclusions regarding the hazards of carbon black exposure. It was not always clear in these experiments exactly what material was administered to the animals because of the interchangeable use of the term carbon black with other carbonaceous materials, such as soot.

(a) Inhalation and Intratracheal Studies

In 1962, Nau et al [28] reported the effects of inhalation exposure to channel and furnace carbon blacks on mice and monkeys. Channel black consisted of particles with an average diameter of 25 nm, and furnace black contained particles with an average diameter of 35 nm. Rhesus monkeys were exposed to channel black at 2.4 mg/cu m or to furnace black at 1.6 mg/cu m for 7 hours/day, 5 days/week, some for more than 13,000 hours (more than 7 years). The senior author has subsequently stated that the exposure concentrations reported in his article are incorrect and should be 1.6 mg/cu ft and 2.4 mg/cu ft for furnace black and channel black, respectively, [29]; thus the corrected exposure concentrations are 56 mg/cu m for furnace black and 85 mg/cu m for channel black. Throughout the exposures the appearance of the monkeys was continuously monitored as an indication of health. Chest roentgenograms and electrocardiograms of exposed and control monkeys were examined periodically. Lung tissue samples from monkeys exposed to channel black for 4,063 and 4,259 hours (about 2.3 years) were examined for microscopic changes. It was unclear whether the samples were removed at necropsy or during surgery.

No adverse health effects were observed on either group of exposed monkeys [28]. Monkeys exposed to either carbon black had slight, blotchy, irregular areas of infiltration into their lungs, mainly throughout the lower portions, after 250 hours of exposure. These changes increased after 700 to 1,500 hours of exposure. Well-marked, extensive changes in the chest roentgenograms, characterized by definite areas of opacity, appeared in all monkeys exposed for 1,500 hours or more. There was no striking change in the appearance of chest roentgenograms of monkeys exposed for 2,000 hours and that of animals exposed for 1,500 hours. Deposits of carbon black were found in the mucosa, submucosa, or adjoining structures of the nasal, oral, pharyngeal, laryngeal, or tracheal air passages of the exposed monkeys. Intraalveolar carbon black was found only in rare instances and then in pigmented macrophages; however, carbon black was deposited within the walls of the alveoli, and channel black penetrated into the interstices more readily than did furnace black. The monkeys' lungs showed a pattern of diffusely distributed focal nodular pigmentation interspersed with large areas of unpigmented alveoli. Although the physical presence of carbon black alone usually accounted for the thickened alveolar walls, cellular proliferation, also seen occasionally, occurred more frequently with channel black exposure. A proliferation of interstitial cells was seen in the lungs of a few exposed animals, but this rarely led to minimal or variable fibrosis. Prominent aggregates or nodules of carbon black were noted in the peribronchial and perivascular soft tissue, and the subpleural lymphatics were also distended with carbon black. Exposed monkeys did not suffer from pneumonia, but centrilobular emphysema in varying degrees was observed occasionally. The authors noted that this may have been from the physical presence of carbon black or may have been a sequel to an old inflammatory reaction.

Electrocardiographic studies of exposed monkeys revealed minimal right atrial and right ventricular strain after 1,000-1,500 hours (0.55-0.82 year) of exposure to channel black or after

2,500 hours (1.37 years) of exposure to furnace black [28]. These changes increased in severity in both groups of monkeys, becoming most severe after 10,000 hours of exposure.

Nau et al [28] also exposed two groups of 132 and 148 10-week-old male C3H mice, under the same regimen, to channel black at 85 mg/cu m and to furnace black at 56 mg/cu m, respectively. The channel black group was subdivided into 14 groups of 2-22 that were exposed for 200-3,000 hours (up to 20 months). The furnace black group was subdivided into 13 groups of 5-33 mice, which were exposed at 56 mg/cu m for 444-3,000 hours. A group of 29 female (aged 9-12 months) and 63 male (aged 3-24 months) C3H mice and 19 C3H mice (aged 24 months) of unspecified sex breathing ambient air served as controls. All mice were monitored throughout the exposure period for signs of toxic activity. At the end of exposure, both control and exposed mice were weighed, and chest roentgenograms of 30 mice exposed to channel or furnace black for up to 3 weeks and of an unspecified number of control mice were examined. The carbon monoxide diffusing capacity of the lungs was studied in one control mouse and one mouse exposed to carbon black; carbon monoxide and hemoglobin concentrations and ratios were determined 5, 10, and 20 minutes after exposure at a known concentration of carbon monoxide. Exposed mice were killed either at the end of exposure or after 4.25-6.5 months in the channel black groups and after 4.75-6.25 months in the furnace black groups. Control mice of similar age groups were also killed. The lung and heart weights of both the exposed and control animals were recorded. The carbon contents of lungs from exposed and control mice were determined, and tissues from various organs were examined microscopically.

Neither group of exposed mice exhibited any signs of toxicity during the experimental period [28]. Mice exposed for up to 3 weeks to channel or furnace black dust had no abnormalities in their chest roentgenograms. The authors believed that this apparent lack of difference between the roentgenograms of the chests of exposed and control mice was caused by the motion of the animals. Roentgenographic examination of freshly removed lungs revealed that the lungs of exposed animals were more uniformly radiopaque. The authors believed that these changes correlated well with the visibly decreased elasticity and the increased weight of the lungs. The lung-to-body weight ratios of control, channel black, and furnace black groups were 0.7-1.0 (average 0.83), 1.1-3.3 (average 2.1), and 1.2-2.4 (average 1.7), respectively. There were no differences between the carbon monoxide diffusing capacities of lungs of exposed and control animals. Deposits of carbon were found in the mucosa, submucosa, or adjoining structures of the nasal, oral, pharyngeal, laryngeal, and tracheal air passages of mice exposed to either type of carbon black. In the alveoli of the exposed mice, carbon black was found both in a free state and, at times, as an aggregate within the macrophages, especially in mice exposed to furnace black. Diffuse pigmentation was present throughout the pulmonary parenchyma within the first 1,000 hours of exposure and reached maximum intensity by 2,000 hours. Carbon black was also found within the walls of the alveoli. Channel black penetrated into the interstitial tissue more readily than did furnace black. Carbon black appeared in the interstitial spaces after 1,000-2,000 hours of exposure. It remained either free or within macrophages and was more dense and compact than the carbon black found in the intraalveolar space. Exposed mice, particularly those less than 6 months old, had bronchopneumonia within 1,000 hours of exposure, but the incidence decreased with further exposure and was rare in those exposed for more than 2,000 hours. Of the two types of carbon black, furnace black produced pneumonia more frequently. Mice had only occasional centrilobular emphysema following carbon black exposure. As with monkeys, when emphysema did occur, it varied in degree.

After 1,000 hours of exposure, the average ratio of heart weight-to-body weight of exposed mice was slightly higher (0.56 channel black, 0.61 furnace black) than that of the controls (0.51) [28]. Examination of the skin of the mice exposed to channel or furnace black sometimes showed atrophy or hyperplasia of the epidermis, fibrosis of the dermis, or both. Also, subcutaneous edema was found more consistently in mice exposed to channel black. Livers of a few exposed mice contained carbon black within the Kupffer cells and showed a higher frequency of amyloidosis than did those of the control animals. The spleens of the exposed animals also had a higher incidence of amyloidosis; there rarely was carbon black within the phagocytic cells. Amyloidosis, cortical scarring, and fibrosis of the kidneys were more prevalent in the exposed mice. Phagocytic cells around the proximal convoluted tubules and the glomeruli of the kidneys of some of the exposed animals showed carbon black particles.

The carbon black contents of the pooled lungs of five animals each from the channel black, furnace black, and control groups were 39.5 mg for those exposed 443 hours to 83.3 mg for those exposed 3,089 hours, 26.3 mg for those exposed 444 hours to 66.7 mg for those exposed 1,109 hours, and 1.8 mg respectively [28]. The lungs of mice exposed to channel black thus appeared to retain more carbon black than did those exposed to furnace black. Lungs of mice given a recovery period of 4.75 months after exposure contained 51.6-111.2 and 47.4-51.1 mg of carbon in the channel and furnace black groups, respectively. Therefore, the recovery period did not clear the lungs of carbon black.

Nau et al [28] concluded that prolonged exposure to carbon black (channel or furnace) did not significantly affect the health of hamsters, mice, guinea pigs, rabbits, and monkeys, although the dust accumulated in the pulmonary system. This report, however, dealt only with effects of carbon black on mice and monkeys. Because the study revealed a number of effects on organs other than the pulmonary system, the authors' conclusion is open to question. Also, as noted earlier in this section, there has been some confusion as to whether the concentrations were in mg/cu m or mg/cu ft.

Nau et al [30], in a 1976 report, evaluated the effects of inhalation exposure to carbon black containing 0.04-1.32% benzene extractables on monkeys, mice, hamsters, and guinea pigs. Six male and six female rhesus monkeys of unspecified age were exposed to thermal carbon black at a concentration of 53 mg/cu m, 6 hours/day, 6 days/week, for a total of 5,784 hours (approximately 3 years). Eight monkeys were used as controls. Monkeys were weighed and given chest roentgenograms before exposure and at regular but undescribed intervals thereafter. At the end of the exposure, the monkeys were killed, pulmonary function studies were performed before and after death, and lungs of monkeys of both groups were examined microscopically. The mean myocardial fiber diameter of the wall of each heart chamber was measured in 14 hearts, 4 of which were from monkeys exposed to thermal black. Hearts of some unexposed monkeys were also included in this analysis.

Throughout the exposure period, exposed monkeys did not show any physical signs of illness [30]. Pulmonary function tests both before and after death showed no impaired lung function from thermal black exposure. However, microscopic examination of sections of lungs showed marked differences between the lungs of exposed monkeys and those of controls. A great accumulation of carbon black particles was found in the lymphatics surrounding the bronchioles, with the surrounding alveolar wall structures frequently absent. The authors considered this lesion to be anatomically similar to centrilobular emphysema, although this condition does not occur

in monkeys because they lack the typical interlobular septal pattern. Emphysematous changes in the exposed monkeys were classified as moderate to severe. The changes in pulmonary vasculature suggested pulmonary hypertensive vascular disease. Morphometric analysis of hearts of exposed animals showed a right ventricular, septal, and, to a lesser degree, left ventricular hypertrophy. The authors, however, noted that the small number of hearts of exposed monkeys examined precluded any conclusion from these observations.

Nau et al [30] also exposed a group of 60 hamsters to thermal carbon black at either 53 mg/cu m for 236 days or at 107 mg/cu m for 172 days. No control group was described. The age, sex, and number of hamsters in each exposure regimen were not reported. At the end of exposure, all the hamsters were killed and sections from the larynx, trachea, hypopharynx, and cervical esophagus were examined microscopically. Hamsters exposed at 107 mg/cu m of thermal black for 172 days showed no abnormal changes in any of the four areas examined. However, 5 of 17 of those exposed at 53 mg/cu m for 236 days had subepithelial changes in the thyroarytenoid fold consistent with edema, 13 of 17 showed retention of amorphous eosinophilic material in the subglottic glands, and 7 of 17 showed similar retention in the tracheal gland.

Nau et al [30] exposed 60 guinea pigs of unspecified age to thermal carbon black by inhalation at 53 mg/cu m, 6 hours/day, 6 days/week, for an unspecified length of time. The lungs of exposed guinea pigs showed no significant gross changes; however, microscopic examination revealed exogenous brown pigment in the interstitial histiocytes. Some of the phagocytes containing the ingested pigment lay free in the alveoli, and there was no significant proliferation of fibrous tissue. All other organs examined were normal.

Nau et al [30] concluded that inhalation of carbon black did not result in pulmonary function changes in monkeys, but it may have resulted in perifocal emphysema and right ventricular, septal, and left ventricular hypertrophy.

Snow [31], in 1970, investigated the effects of inhalation of furnace-thermal carbon black on the larynx and trachea of golden hamsters. The furnace-thermal black used in these studies had an average particle diameter of 150-200 nm and contained 1-2% by weight benzene-extractable materials. A total of 51 male and 6 female golden hamsters, 1.5 months of age, were divided into 3 control and 3 experimental groups. All hamsters in the experimental groups were exposed 6 hours/day, 5 days/week. One experimental group, containing six male hamsters, was exposed to carbon black at 105-113 mg/cu m for 53 days (318 hours). The second group, containing 8 male hamsters, was exposed at 105-113 mg/cu m for 172 days (1,032 hours), while the third group of 17 males was exposed at 55-58 mg/cu m for 236 days (1,416 hours). There were three unexposed control groups, one containing 6 male and 6 female hamsters, a second with 3 male hamsters, and a third with 11 male hamsters. Within 1-10 days after exposure, all hamsters were killed, and longitudinal laryngeal and tracheal sections were examined microscopically. One male hamster from the first group, three males from the second group, and two males and one female from the first control group died during the experiment from causes unrelated to carbon black.

Except for mild, chronic inflammation of the larynx and trachea, no microscopic variation was found in the three control groups at varying ages or between males and females of the first control group [31]. This state of chronic inflammation, characterized by widely scattered polymorphonuclear leukocytes, lymphocytes, monocytes, and mast cells, was accepted as normal.

Because of this, there was no difference between the microscopic appearance of the larynx and trachea of exposed hamsters from the first and second groups and that of their respective controls. However, 5 of 17 exposed hamsters of the third group showed edema of the thyroarytenoid fold in the lamina propria and retention of amorphous eosinophilic material often containing carbon particles in the subglottic and tracheal glands. Retention of glandular secretion was seen in the subglottic area in 13 and in the trachea of 7. In several instances the glandular secretions resulted in deformity of the subglottic and tracheal lumina; the resulting appearance suggested cyst formation. Cells surrounding the amorphous eosinophilic material were flattened, but no conclusions were drawn on the significance of this finding. Carbon black particles were also observed on the epithelium and in macrophages in the mucous blanket; however, no carbon black was found in the epithelium. There was no evidence of lymphatic transportation or accumulation of carbon black.

Snow [31] concluded that carbon black had pathogenic potential in both the upper and lower respiratory tract and that inhalation of carbon black was not innocuous. The adverse respiratory effects observed appeared to be related to the duration of exposure rather than to the concentration of the carbon black, and no carcinomas or other effects related to the PAH's were reported.

In 1975, Troitskaya et al [18] studied the effects of inhalation and intratracheal administration of carbon black on rats. Seven types of industrial carbon black, three low-dispersion types with particle diameters of >45-50 nm and four high-dispersion types with particle diameters of 32-35 nm [32]) were used. Some rats were given carbon black intratracheally at doses of 50 mg in 1 ml of rat serum; others were exposed to a low-dispersion carbon black (PM-50) at 240 mg/cu m in an inhalation chamber. No other details of the experimental protocol were given. Some rats exposed to carbon black and some controls were killed after 3 or 6.9 months.

The effects of carbon black on the lungs were reported to be similar in rats exposed by inhalation and in those given carbon black intratracheally [18]. Three months after the intratracheal administration, microscopic examination of sections of the lungs revealed a proliferative cellular reaction involving thickened interalveolar septa, enlarged emphysematous alveoli, and a large number of alveolar phagocytes, histiocytes, fibroblasts, and collagen fibers in the areas of dust accumulation. The emphysematous changes continued with time, and by 6.9 months the fibrotic changes also were more apparent; the collagen grew thicker. These changes were more pronounced with channel black than with furnace black of the same particle size.

Troitskaya et al [18] reported that, after 3 months of exposure, the lungs of control rats showed physical and chemical differences when compared with those of rats exposed to carbon black. Differences were found in the weight of the lungs and lymph nodes and in the hydroxyproline and lipid concentrations. Although the differences between the controls and those rats exposed to the low-dispersion carbon blacks were reported to be statistically significant, the values for the high-dispersion type approached those of the controls by the end of the experiment. This was interpreted as indicating fairly rapid elimination of these carbon blacks from the lungs and lymph nodes. Administration of low-dispersion carbon black resulted in increased lung and lymph node weights with increased exposure. In comparison, exposure to high-dispersion carbon blacks resulted in a fibrous reaction much earlier. Since high-dispersion blacks were apparently eliminated from the lungs more rapidly than the low-dispersion ones, the effects of low-dispersion blacks were more clearly evident at the end of the experiment. Troitskaya et al concluded that

long-term inhalation of carbon black may lead to the development of diffuse sclerotic pneumoconiosis and that carbon black must be considered fibrogenic. Because of the results presented here and the clinical observations of pneumoconiosis in workers in carbon black plants, the authors suggested that a single limit of 6 mg/cu m could be recommended as the MPC inasmuch as the fibrogenic potentials of the various carbon blacks investigated did not differ significantly. However, because they had found reports of the carcinogenic potential of extracts of carbon black, they recommended that the MPC be set at 4 mg/cu m with a maximum benzpyrene content of 35 mg/kg so that the MPC for benzpyrene (0.15 μg/cu m) would not be exceeded.

In 1971, Smolyar and Granin [26] reported the effects of carbon black exposure on the oral mucosa of mice and rats. A total of 137 white mice and 75 white rats of unspecified age and sex were divided into 2 groups. The experimental group of 110 mice and 60 rats was exposed to carbon black concentrations similar to those encountered in the production area. The production areas were not identified, and the concentrations of carbon black were not given. Of 170 exposed animals, 70 were killed after 2 weeks, 45 after 1 month, and the rest after 2 or 3 months. Controls were also killed, presumably at the same intervals. The oral cavities of all animals were evaluated by gross and microscopic examinations.

After 2 weeks of exposure, microscopic examination showed that 26 of 70 animals had abundant carbon black on the mucosal surface and in the submucosal and epithelial layers [26] . This carbon black accumulation was associated with atrophy, hyperkeratosis, and desquamation of the keratinous masses. The endothelium and the lumen of the small and large dilated blood vessels of the oral mucosa contained abundant carbon black particles and many erythrocytes, resulting in hyperemia, plasmorrhagia, and hemorrhages. In 45 animals examined after 1 month of exposure, 34 developed hyperkeratosis, dyskeratosis with desquamation, and acanthosis. The keratinous masses contained large amounts of carbon black, and the hyperkeratoses were focal and well-defined. Polyemia of the veins and diapedetic hemorrhages were evident in the subepithelial tissue, and tiny cyst-like cavities filled with keratinous masses and carbon black were seen in the epithelial sulci. All 55 animals exposed to carbon black for 2 or 3 months had atrophic, necrotic, and erosive-ulcerous lesions. Also, focal inflammation with infiltration of histiocytes and free leukocytes was found in the areas of epithelial hyperkeratosis. These observations led Smolyar and Granin to conclude that the frequency and degree of manifestation of oral mucosal lesions depend on the length of exposure to carbon black.

Shabad et al [32], in a 1972 report, investigated the effects of intratracheal administration of carbon black with adsorbed benzpyrene on rats of unspecified age and sex. More than 50 rats received six 10-mg doses of a preparation called thermatomic black (particle size 300 nm) with 0.1 mg of adsorbed benzpyrene per dose. Another group of more than 52 rats received similar doses of 10 mg of channel black (particle size 13 nm) with 0.1 mg of adsorbed benzpyrene. An undescribed number of rats, the control groups, were given benzpyrene in six doses of 0.1 mg each.

In both groups given carbon black, the lung tissue was reported to contain unspecified precancerous lesions in the areas of carbon black accumulation after the 2nd month of administration [32]. In animals that died later, there were quantitative and qualitative differences in the characteristics of the tumors found. The number of deaths in each group was not presented. At 10 months, 12 of 50 rats surviving exposure to thermatomic black with adsorbed benzpyrene had lung tumors. Although no lung cancers were found in this group, reticulosarcoma of the

peribronchial and perivascular lymphoid tissue was detected in 11 (22%). At 16 months, of the 52 rats that had survived exposure to channel black containing adsorbed benzpyrene, 21 (40.4%) had lung neoplasms, 5 (9.6%) of which were squamous-cell carcinomas. The control rats had neither tumors nor precancerous lesions.

Shabad et al [32] concluded that carbon black distributed throughout the lung tissue provided a greater contact surface area for the adsorbed carcinogen benzpyrene and facilitated the increased desorption and resorption of the carcinogen. Justification for this conclusion was based on the observation that tumor production occurred only in the groups of rats that received benzpyrene adsorbed on carbon blacks. Although this may be a valid conclusion, carbon black also might have acted as an irritant promotor in the groups that received benzpyrene adsorbed on carbon black.

In a similar experiment, Pylev [33], in 1969, reported the effects of intratracheally administered 3,4-benzpyrene adsorbed on channel black on the lungs of rats. Rats of unspecified age and sex were divided into two groups; of these, one group of 68 received 6 intratracheal insufflations of 0.1 mg of 3,4-benzpyrene adsorbed on 10 mg of channel black at 10-day intervals, while the other group of 15 rats similarly given 6 intratracheal insufflations of 0.1 mg of 3,4-benzpyrene alone served as controls. The lungs of rats of both groups were examined by microscope for changes in structure during the experimental period of 6 months. The changes in control animals that died 4.5 months after the beginning of the experiment were compared with those of experimental rats that died between the 1st day and 6th month of the experiment. While the control rats showed no changes in their lungs, rats given 3,4-benzpyrene adsorbed on carbon black had inflammatory changes, such as exudative hemorrhagic pneumonia, focal abscess-forming and necrotic pneumonia, and chronic interstitial pneumonia. In later stages (3-4 months), there were also areas of atelectasis with signs of pneumosclerosis. In addition to these inflammatory responses, a number of pretumorous changes were also noted. Of the 68 experimental animals, diffuse hyperplasia and proliferation of the epithelium in the small and medium bronchi were found in 11, diffuse hyperplasia and proliferation of the peribronchial mucous glands in 10, focal growth of the bronchiolar epithelium without cellular metaplasia in 12, focal growth of the bronchiolar epithelium with signs of planocellular metaplasia in 6, and 5 cases of adenomatous growths.

The author [33] concluded that 3,4-benzpyrene adsorbed on carbon black was released in the lung to cause pretumorous changes. He also concluded that 3,4-benzpyrene adsorbed on carbon black was retained in the lungs longer than when the carcinogen was given unadsorbed. Although such prolonged retention of the adsorbed 3,4-benzpyrene had been reported by other investigators [34,35], Pylev [33] presented no data to arrive at a similar conclusion.

In 1974, Farrell and Davis [36] investigated the effect of particulate carriers including carbon (nut shell charcoal), on the development of respiratory tract cancers by intratrachelly administering them with 3,4-benzpyrene to hamsters. They found that while the control groups that received 25 weekly doses of 0.2 ml of 2% carbon particles in 0.5% gelatin in saline developed no tumors, 92 of those given similar doses of carbon particles but with 2% 3,4-benzpyrene developed 134 carcinomas (81 of these had one or more carcinomas) within 10-14 weeks of the experiment.

(b) Dermal Studies

Only a few studies of dermal effects by carbon black, using various solvents, are available. These studies have not indicated any major dermal effects but have associated some systemic problems with carbon black exposure.

In 1952, Von Haam and Mallette [37] presented the results of an investigation on the carcinogenicity of carbon black and its extracts by application to the skin of Swiss mice. The age, weight, and sex of the mice were not reported. The preparations of carbon black extracts and their fractions also were not described. A total of 212 mice were divided into 17 groups of 5-12 each. Of these 17 groups, 3 received a 1% acetone solution of one of the 3 unfractionated carbon black extracts on a small area of their backs, which were clipped free of hair. The remaining 14 groups were similarly tested with 1% concentrated fractions of carbon black extracts in acetone containing 0.5% croton oil. The method of extraction and fractionation were not reported. A group of 20 mice painted with 0.5% solution of croton oil in acetone served as the negative control, while another group of 20 mice receiving 1% 3,4-benzpyrene in acetone containing 0.5% croton oil was used as a positive control.

The various preparations were topically applied to the designated groups of mice at weekly intervals for up to 315 days [37]. The amounts of material in each application were not reported. The areas of skin to which the material was applied were fixed, sectioned, stained, and examined microscopically for all mice that died during the experiment. The time or cause of death of mice was not described. The production of tumors at the site of application was monitored throughout the experiment, and the tumors were photographed as they developed and sections of the tumors were examined microscopically at the end of the experiment. None of the mice in either the negative control group or the three groups receiving unfractionated carbon black extracts developed cancers. Of the 20 positive control mice, 11 of 15 survivors developed cancers. Of 212 mice, 126 survived the entire experiment. Four of the 14 fractionated extracts were carcinogenic in mice. Six of 27 surviving animals of the groups given 1 of these 4 fractionated extracts developed advanced squamous-cell carcinomas and had ulcerations covered by crusts. While the cancers in these experimental animals developed between 127 and 196 days, those in positive control mice developed within 28 to 162 days of the beginning of the experiment. Two of the mice that received 1 of the 3 types of unfractionated extracts and 11 mice of the groups which were given 6 of the 14 fractionated extracts not found to be carcinogenic developed papillomas, which were characterized by hyperkeratinization, proliferation and thickening of hair follicles, and epithelial proliferation. Some of these papillomas reportedly had a tendency to disappear spontaneously. According to the authors, epithelial proliferation, which might or might not have developed into cancer had the animals lived longer, was found in 29 of the animals on microscopic examination of the skin at the area of application.

Von Haam and Mallette [37] concluded that commercial carbon blacks contained extractable carcinogenic materials. Contrasting their findings with the epidemiologic results of Ingalls [21], the authors offered some explanations for the discrepancy. They believed that prolonged skin exposures to carbon black might not occur in the industrial environment because of well-controlled industrial hygiene measures, and that, hence, effects on human skin were unlikely to develop. However, they thought that a more reasonable explanation could be based on their experimental finding that unfractionated extracts of carbon black did not produce any cancers in mice. They believed that this finding may have resulted from the low concentrations of carcinogenic material in the commercial blacks or from firm adsorption of these materials by the carbon black and consequent negation of their carcinogenic properties. There are major

discrepancies between the values presented in the text and those in the tables of the report, which leave the authors' conclusions questionable.

Von Haam et al [38], in 1958, reported the effects of five carbon blacks of differing physical and chemical properties on the carcinogenicity of 3,4-benzpyrene in mice. Two of the carbon blacks tested had large surface areas and low pH, one had a small surface area and low pH, and two had small surface areas and high pH. Adsorbed or unadsorbed benzpyrene was applied twice weekly to the skin of mice as a 0.5% acetone solution. Control mice were treated with 6-60% carbon black in acetone.

The results [38] showed that unadsorbed 3,4-benzpyrene produced a 96% fatal tumor incidence within 2-9 months, while none of the carbon blacks alone caused any tumors in the same time. Of a total of 240 mice treated with 3,4-benzpyrene adsorbed onto a carbon black, 54-69% developed tumors within 3-6 months. The survival rates were somewhat higher among mice painted with adsorbed carcinogen, compared with that for mice painted with unadsorbed carcinogen: 33-57% were alive after 9 months. The latency period for tumor induction was 1 month longer in mice painted with adsorbed carcinogen than in those to which the unadsorbed carcinogen was applied.

The authors [38] noted that some of the 3,4-benzpyrene in the acetone solution acted as a free carcinogen because this solvent eluted 10-23% of the adsorbed compound from carbon black. They also tested dry powders of adsorbed and unadsorbed carcinogen and found that, after 24 months, none of the mice rubbed with either dry adsorbed carcinogen or dry carbon black developed any tumors. Twelve percent of the mice treated with dry unadsorbed carcinogen developed tumors. The authors concluded that the carbon blacks tested did effectively block the carcinogenicity of 3,4-benzpyrene, although in differing degrees. They suggested that surface area and pH are significant variables in adsorption, with large surface area causing increased adsorption. While it is generally accepted that an increase in surface area allows for an increase in adsorption and while changes in pH will effect disassociation of different materials and their adsorption capabilities, the author did not provide data to specifically identify differences in BaP adsorption onto carbon black with varying surface areas and pH's. They attributed the tumors in the experiments using acetone to the action of free carcinogen eluted by the solvent.

In 1958, Nau and associates [39] studied the effects of skin contact with carbon black on several animal species. Whole carbon black, extracted carbon black, the "free" benzene extract of carbon black, a known carcinogen, and a known carcinogen adsorbed to carbon black were tested on 6- to 10-week-old CFW white and C3H brown mice, white rabbits, and rhesus monkeys weighing 5-7 pounds. All experimental mice were painted with the experimental agent up the middle of the unshaved back from the base of the tail to the neck 3 times/week.

Groups of 10-40 C3H or CFW mice received 140-226 applications of whole or extracted carbon black in cooking oil, mineral oil, carboxymethylcellulose (CMC) and water, or water [39]. The total amount of carbon black ranged from 3.63 to 23.4 g. Control groups received similar applications of the various vehicles for carbon black, and a group of 943 mice served as untreated controls. All mice were examined twice daily. Mice with abnormal signs were killed, and all organs and tissues were completely examined for gross and microscopic changes. Dead mice were similarly examined.

Carbon black was also painted on the shaved abdomens of rabbits 3 times/week [39]. Four rabbits received 66-160 applications of carbon black in cooking oil or in CMC and water to their shaved abdomens; the total amounts of carbon black applied were 116-324 g. In addition, 3 monkeys received 167-404 applications of 20% extracted or whole carbon black in cooking oil or CMC and water to both axillas and groin. The amounts of carbon black applied were 327-948 g. Rabbits and monkeys were observed regularly. Those with abnormal signs were killed, and complete gross and microscopic examinations of all organs and tissues were performed on these animals and those dying from the experiment or other causes.

No tumors were produced at the application sites on the skins of mice, rabbits, or monkeys by whole carbon black in various solvents, even when applied in large amounts for more than 12 months [39]. Adenomas of the stomach were found in two mice, and lymphosarcomas of the spleen, colon, and lymph nodes were found in five. A small-cell sarcoma of the chest wall was observed in one monkey. No tumors were found in mice painted with water and 1% CMC, cooking oil, or mineral oil.

In 1976, Nau et al [30] also described the effects of skin application of three grades of thermal black to the skins of mice. A total of 240 mice C3H mice of unspecified age was divided into 4 groups of 60 each. Each group was further divided into 3 subgroups of 20 each. Mice in the subgroups had a 20% emulsion of medium, fine, or "nonstaining" thermal black mixed with mineral oil for one group, corn oil for another, or with water for a third painted on their shaved backs 3 times a week. A total of 123 applications were given in 41 weeks. The three subgroups of control mice each received one of three vehicles. Examination of the skins of the various groups and subgroups given three types of thermal black revealed no detectable changes with any of the suspensions of carbon black.

Pikovskaya et al [40] tested the skin carcinogenicity of two types of petroleum-based carbon blacks, TM-15 and TM-30. Preliminary extraction studies with various solvents (acetone, hot benzene, and a chloroform-methanol mixture) showed varying amounts of PAH's with benzo(a)pyrene, anthracene, benzo(ghi)pyrene, phenanthrene, pyrene, perylene, dibenzathracene, benzfluorene, phenanthrene, and carbazole specifically identified. They stated that the benzo(a)pyrene content of the petroleum-based blacks (TM-15, 0.69-2.4 ppm; TM-30, 0.81-2.1 ppm) was much less than the amounts found in carbon blacks from other sources, ie, coal tar oils (30-50 ppm), shale oils (14 ppm), and gas, electrically cracked (ppm unstated).

CC-57 brown and white mice were divided into groups of 65-70 animals and painted with the test materials 3 times per week for their entire lives. The longest exposure was 184 applications in 18 months. The mice painted with benzene extracts from TM-15 black developed skin tumors 5 months after the initiation of the test; 8.77% of the animals who survived after the appearance of the first tumor developed skin tumors and 3% of these skin tumors were malignant. This number of skin tumors was stated to be markedly different ($P<0.05$) from the spontaneous rate (0.4-0.6%). In those painted with benzene extracts of TM-30 blacks, 3% of the two groups of animals were painted with oily suspensions of either TM-15 or TM-30 blacks; no animals developed tumors. The authors concluded that carbon black has weak carcinogenicity and recommended that where direct contact with carbon black was necessary, TM-30 black be used instead of TM-15 because of the lower tumor incidence it produced. They further stated that the benzene extracts produced a higher incidence of skin tumors than pure benzo(e)pyrene even though the benzo(a)pyrene content of the extracts was the same as that used in pure benzo(a)pyrene studies. They attributed this increase to the presence of other PAH's.

(c) Oral and Parenteral Studies

Nau et al [30] studied the effects of feeding thermal black to mice. A group of 8-week-old male and female C3H mice had 10% thermal carbon black added to their diet. A group of 20 control male and female mice of similar age received the same diet without carbon black. The animals were killed after 72 weeks and unspecified organs were examined for gross or microscopic changes. Both gross and microscopic examinations revealed no significant changes in mice fed thermal black.

In 1958, Nau et al [41] described a series of feeding experiments in which CFW and C3H mice were administered diets of dry dog food mixed with cottonseed oil or water (both containing CMC). Various commercially obtained whole carbon blacks, benzene-extracted carbon blacks, benzene extracts of carbon blacks, known carcinogens, or extracted carbon blacks adulterated with known carcinogens were added to these diets. Each substance or mixture tested was administered in diets mixed with both oil and water individually. Mice were 6-10 weeks old at the outset of feeding, and feeding continued for 12-18 months. All mice were then killed, and tissues and organs were examined for gross and microscopic changes. Animals that died in the course of feeding were similarly examined. Appropriate controls were included in each experiment.

The authors [41] reported no deviations from normal or from controls in mice fed 10% whole carbon black in diets mixed with either oil or water. The number of mice tested and the total dose of carbon black ingested were not given. Similarly, 30 mice fed a mean of 207 g each of a diet containing 10% of benzene-extracted carbon black and mixed with oil showed no ill effects. Among 100 mice each fed 182-243 g of a diet containing 10% of benzene-extracted carbon black but mixed with water, 4 had malignant skin tumors, 3 developed benign papillomas, and 1 developed an intracutaneous fibrosarcoma. Nau et al attributed the observed effects to such factors as transference of free extractive to the skin through biting and grooming. They concluded that the diets containing benzene-extracted carbon black produced no deleterious effects.

Nau and coworkers [41] next evaluated the effects of 0.02% and 0.08% dietary benzene extract of carbon black and 0.02% dietary methylcholanthrene, a known carcinogen. Both agents were dissolved in benzene, and the resulting solutions were mixed with flour. The mixtures were dried and pelletized. Mice were fed a diet of 15% flour mixture combined with 85% dog food and mixed with either water or oil. Amounts ingested were recorded for each animal, and doses were calculated.

The results [41] were that 10 of 80 mice fed a total of 0.261-0.509 g of 0.02% benzene extract during 12-18 months in a moistened diet developed gastrointestinal cancers consisting of "questionable" squamous metaplasias, 1 submucosal lymphosarcoma, 1 squamous cell carcinoma, and 1 early adenocarcinoma and 2 developed soft tissue tumors of questionable origin. In contrast, 30 mice fed a total of 0.366 g in a diet mixed with oil during 18 months developed no lesions. Of 80 mice fed 0.02% methylcholanthrene in a moistened diet for 12-15 months (total dose, 0.261-0.344 g), 31 developed stomach and gastrointestinal cancers, while 44 of 110 mice fed the same diet mixed with oil base for 12-13 months (total dose, 0.195-0.245 g) developed stomach and pancreatic carcinomas. A diet of 0.08% benzene extract in a diet mixed with water produced 2 gastrointestinal cancers and 2 leukemias in 21 mice, and the same diet with an admixture of oil

produced 4 stomach cancers in 22 mice. Most of the observed malignancies were of the squamous-cell type. They concluded that ingestion of the benzene extract of carbon black leads to production of the same types of gastrointestinal cancers induced by methylcholanthrene.

To determine the effects of feeding an adsorbed carcinogen, the authors dissolved methylcholanthrene in benzene and added to extracted carbon black in a chromatographic column with or without subsequent heating of the mixture [41]. The mixture of carbon black and adsorbed methylcholanthrene was dried, sieved, and added to water- and oil-based food mixtures. Nau et al reported that ingestion by mice of 0.253-0.425 g of methylcholanthrene adsorbed onto 123-237 g of extracted carbon black with and without heating in diets mixed with either oil or water resulted in no change in 2-17 months.

The authors [41] concluded that carbon black can adsorb methylcholanthrene sufficiently strongly to prevent its carcinogenic effect after ingestion, and that carbon black itself does not cause cancer. They did not consider the question of possible species differences in spontaneous tumor production rates, nor did they give percentage yields of tumors in most instances.

Steiner [42], in 1954, reported a series of experiments undertaken to determine the carcinogenicity of carbon black in a variety of circumstances. Two carbon blacks were used: a furnace black with a surface area of 15 sq m/g and an average particle diameter of 80 nm and a channel black with a surface area of 380 sq m/g and an average particle diamater of 17 nm. A total of 600 C57BL mice 5-5.5 months old, in groups of 50 each, of both sexes were used. Experiments lasted 20 months; all survivors were killed and necropsied and all lesions were sectioned and microscopically examined. In addition, many injection sites were examined microscopically throughout the studies. Percentage tumor yields were calculated from the "effective total," defined as the number of mice alive 5 months after the experiment began, when the first tumor deaths occurred with the most potent agent.

In the first series of experiments, Steiner [42] compared the carcinogenicity of the furnace black, which contained benzene-extractable 3,4-benzpyrene and other aromatic hydrocarbons, with that of the channel black, which contained no benzene-extractable hydrocarbons. Four experimental groups received, respectively, single subcutaneous (sc), interscapular injections of 30 mg of either furnace black (containing approximately 0.09 mg of benzene-extractable 3,4-benzpyrene) suspended in tricaprylin, channel black made up in tricaprylin, or 3.5-mm by 30-mm pellets of furnace or channel black. A control group was injected with tricaprylin only. The furnace black solution produced rapid encapsulation and fibrous tissue response. Tumors began to appear in the 7 months after the administration. Of an effective total of 46 survivors after 5 months, 18 (39%) subsequently developed sarcomas and died within 20 months. The channel black solution produced a similar fibrous tissue response but no tumors. Injection of furnace black pellets produced only a 4.3% tumor yield, with sarcomas found in two mice. Channel black pellets produced a sarcoma in one mouse. Controls developed no tumors.

The author [42] concluded that carbon black containing benzene extractable materials was carcinogenic only when an eluent, in this case tricaprylin, was provided and that channel black with no benzene-extractable content was biologically inactive. He noted the importance of the solvent in the carcinogenic response to furnace black, emphasized the conditional nature of this observed biologic activity, and related it to particle size, ie, carbon blacks with small particle diameters adsorb aromatic hydrocarbons.

To test whether 3,4-benzpyrene would retain its carcinogenicity when added to a carbon black of small particle size, Steiner [42] prepared 300-mg pellets and tricaprylin suspensions of the channel black previously described and added 0.09 mg of 3,4-benzpyrene to each. Two groups of 50 mice each were injected as before, and a control group of 50 mice was given 0.09-mg doses of 3,4-benzpyrene administered in tricaprylin. Although 3,4-benzpyrene in tricaprylin produced a 95.1% sarcoma yield within 15 months, with an average time to death of 233 days, no tumors were produced in either group treated with 3,4-benzpyrene added to channel black, and survival rates were high [42]. Steiner noted that the presence of tricaprylin as an eluent had no effect on the carcinogenicity of the channel black and 3,4-benzpyrene mixture and concluded that the reduction of the carinogenicity of the 3,4-benzpyrene in these mixtures was caused by its adsorption, which overcame the solvent action of the tricaprylin.

A final series of investigations [42] was undertaken to determine whether the activity of the carcinogens in the benzene-extractable furnace black could be eliminated by benzene extraction, chromic acid treatment, or mixing of benzene-extracted furnace black with noncarcinogenic, nonbenzene-extracted channel black. Fifty mice each received a single 1-cc injection of benzene extract from 300 mg of furnace black dissolved in tricaprylin. Two other groups received similar injections of the carbon black residue remaining after benzene distillation and of furnace black steam bathed in chromic acid for 3 hours. A final group received 600-mg injections of equal parts, by weight, of furnace and channel blacks made up in tricaprylin.

Results of these studies [42] showed that the benzene extract of furnace black produced a 49% incidence of sarcoma at the injection site and had virtually the same carcinogenic potency as the whole furnace black. The furnace black residue induced only one sarcoma, giving a 2.7% tumor yield. Mice injected with the chromic acid-treated furnace black and the combination of furnace and channel black developed no tumors. Steiner concluded that adsorption and destruction of the carcinogens was a more effective way of neutralizing them than solvent extraction, although solvent extraction almost eliminated carcinogenic activity. He again emphasized the conditional nature of the biologic activity of carbon black.

In 1958, Von Haam et al [38] performed a series of animal experiments using different routes of administration to investigate the effects of seven commercially prepared carbon blacks on the biologic activity of two known carcinogens, 20-methylcholanthrene and p-dimethylaminoazobenzene. The physical and chemical properties of the carbon blacks tested varied widely, ranging from 10 to 40 acres/pound total surface area, 13-29 nm average particle diameter, and from pH 2.8 to 10.5.

Before beginning the animal studies, the authors [38] determined the extent to which each carbon black adsorbed each carcinogen. Cyclohexane solutions consisting of 200 mg of each carcinogen were added to varying amounts of each black, and cyclohexane was added to yield 150-ml volumes. The resulting suspensions were filtered, and the filtrates were combined with enough cyclohexane to yield 2,000-ml volumes. The filtrates were analyzed and the difference between the amount of the carcinogen recovered in the filtrate and that taken originally yielded the amount of carcinogen adsorbed by carbon in the filter residue and was used in animal studies. Each carcinogen was tested separately on Harlan stock rats or albino Swiss mice. Adsorbed or unadsorbed 20-methylcholanthrene was injected sc in single 2-mg doses with olive oil as the vehicle. Adsorbed or unadsorbed p-dimethylaminoazobenzene, mixed with polished rice to yield 0.06% dietary concentrations, was fed ad libitum to rats. In both cases, control groups treated

with carbon black alone were used. Animals were killed at the end of the studies, and all organs were examined grossly and microscopically.

Von Haam et al [38] reported that the degree to which carbon blacks adsorbed the carcinogens studied depended on the physical properties of the carbon black. In general, carbon blacks with large total surface areas adsorbed far more carcinogen than did those with small surface areas. Average particle diameter was an ineffective indicator of adsorption rate. Because of their findings on three small-surface-area carbon blacks that differed mainly in pH, the authors suggested that high pH may enhance adsorption.

Results of the animal studies [38] substantiate these findings. In tests with 20-methylcholanthrene, 13 of 24 rats (54%) injected with unadsorbed carcinogen developed spindle-cell sarcomas within 4-8 months. Sarcoma yields in three groups administered methylcholanthrene adsorbed onto three small-surface-area blacks were 66, 29, and 16%, respectively. The authors considered the 16% sarcoma yield alone to indicate adsorption, and a second adsorption test using this carbon black showed that only 20% of the carcinogen was eluted in 4 weeks. The latency period of tumor formation was 7-8 months in rats treated with carcinogen adsorbed onto this carbon black. None of the carbon blacks alone produced tumors. Von Haam and associates [38] reported similar results in feeding studies with p-dimethylaminoazobenzene. These studies showed that, while unadsorbed p-dimethylaminoazobenzene produced a 58% tumor yield in 24 rats, carcinogen adsorbed to 3 small-surface-area carbon blacks produced only 1 tumor in 72 rats (4%) after over 10 months of feeding. Similarly, dietary concentrations of up to 18% carbon blacks alone caused no tumors or other effects.

Von Haam et al [38] concluded that the carbon blacks were not carcinogenic by themselves, and, despite tumor induction in some instances, that adsorbed carcinogens lost their biologic potency. They stated that tumor induction in animals treated with adsorbed carcinogens could be related to elution of free carcinogen by the solvent vehicle or to incomplete adsorption related to physicochemical properties of individual carbon blacks. The total doses of p-dimethylaminoazobenzene administered were not reported; species differences were not delineated; and the possible role of route of administration on observed results was not considered.

Shabad et al [32], in 1972, reported the results of an unpublished investigation of the effects of sc administration of carbon black with benzpyrene conducted by Linnik in 1969. Carbon black with 29-nm particle diameters was administered sc to 46 mice of unspecified age and sex in 125-mg doses with 1 mg of adsorbed benzpyrene. A second group of mice was similarly given 1 mg of benzpyrene adsorbed on 145 mg of carbon black particles with diameters of 80 nm. Eighteen mice given benzpyrene alone in sc 1-mg doses served as the controls. Seventeen months after the injections, mice from all groups were killed and examined for tumor development.

Of 18 control mice, 15 developed tumors of various unspecified types [32]. One of the 46 mice that received 125 mg of carbon black with 1 mg of benzpyrene developed a hemangiosarcoma and squamous-cell keratinizing skin cancer. None of the rats that received 145 mg of carbon black developed tumors. The differences in tumor induction between the experimental and control groups were statistically significant ($P<0.01$). The authors believed that the adsorption of benzpyrene on carbon black prevented tissue contact, thus either minimizing or eliminating the carcinogenic properties.

(d) Metabolism and Elution Studies

There is still some controversy on whether polycyclic organic material can be eluted from carbon black and thus made available for carcinogenesis in the body. Neal and coworkers [43], Nau et al [30], Kutscher et al [44], and Falk et al [45] have studied this, but with conflicting results. Pylev et al [34] compared the retention of 3,4-benzpyrene in the body when adsorbed on carbon black to that when it was free.

In 1962, Neal et al [43] studied the elution of polycyclic components from channel and furnace blacks and from several commercial rubber formulations containing 10-20% carbon black by weight. The eluting agents used were: (a) biologic fluids: human blood plasma, artificial intestinal fluid, and artificial gastric fluid; (b) cottonseed oil; (c) food juice components: aqueous citric acid at pH 3.85, 3% aqueous acetic acid, 3% aqueous sodium bicarbonate, and 3% aqueous sodium chloride; and (d) whole "sweet" homogenized milk. Rubber test sheets, prepared with furnace or channel blacks were cured between sheets of aluminum foil at 292 F for 20-35 minutes. For elution with the biologic fluids, a 2.5 g sample of channel or furnace black was covered with 50 ml of the eluting fluid, maintained at 28 C for 120.5 hours, then at 37 C for next 60 hours, and was shaken intermittently during the period. The suspension was centrifuged and the supernatant extracted with benzene. The benzene extract was scanned in a spectrophotometer for PAH's. In another experiment, eluting oil produced by covering rubber sheets with cottonseed oil for 7 days at 59 C was chromatographed using an alumina-silica gel column. Significant parts of the column material were removed and eluted with methanol, which was then evaporated, and the residue was dissolved in benzene and scanned for polycyclic components. A separate lot of 30-sq in rubber sheets was covered with each of the food juice components for 6 days at 59 C. The eluent was then evaporated and the residue taken up in benzene. The benzene extract was scanned for polycyclic components. Similarly, 200 g of rubber test sheets were eluted with whole homogenized milk for 7 days at 138 F to determine whether fat in the milk would elute polycyclic material from the carbon black used in the rubber. The milk was then extracted with ethyl ether and petroleum benzine, and the extract was taken up in benzene and chromatographed on silica gel and aluminum oxide. Significant portions of the column material were eluted with methanol and taken up in benzene to determine their polycyclic content. Throughout the testing, scans of standard polycyclic hydrocarbons were run as controls and to determine the sensitivity of the elution procedure.

Results showed that there was no significant elution of polycyclic matter from channel and furnace blacks by human blood plasma, artificial gastric fluid, or artificial intestinal fluid [43]. Similarly, food juice components, cottonseed oil, and homogenized milk failed to elute any significant amounts of polycyclic hydrocarbons from test rubber sheets containing 10-20% carbon black. Comparison of benzene extracts of gastric fluid with and without added carbon black revealed that carbon black removed some component of the gastric fluid rather than releasing some of its own components. Also, artificial gastric fluid eluted no detectable concentrations of polycylic hydrocarbons from channel black to which significant amounts of benzpyrene were added; this was attributed by the authors to the extensive adsorption potential of the carbon black.

In 1976, Nau et al [30] presented the results of a study on the physiologic effects of thermal carbon black on mice, guinea pigs, hamsters, and monkeys. When extracted with hot benzene for 24 hours, the fine thermal carbon black used in these studies showed the presence of coronene, o-phenylene pyrene, 1,12-benzperylene, 3,4-benz(a)-pyrene, fluoranthene, pyrene,

1,2-benz(e)pyrene, and 1-methylpyrene. To study the elution of these benzene-extractable components from the thermal carbon black, the authors incubated three physiologic fluids, synthetic gastric juice with and without cottonseed oil, synthetic intestinal juice, and human blood plasma at 37 C for 60 hours and at 28 C for 120 hours. Analysis by UV spectrophotometer showed no detectable elution of the adsorbed components by the tested physiologic fluids.

Falk et al [45], in 1958, reported the results of an experiment on the elution of polycyclic hydrocarbons from a commercial carbon black with an average particle size of 500 nm known to contain a number of adsorbed polycyclic hydrocarbons. Quantities of 50 and 100 mg were incubated at 37 C for 1.5-192 hours with 25 or 50 ml of sterile human plasma, with continuous shaking for 60 or 90 minutes during the incubation. At the end of incubation, carbon black was separated from the plasma either by filtration or centrifugation. The separated carbon black was then extracted three or four times with hot acetone to remove the adsorbed polycyclic hydrocarbons, while the plasma was extracted with ether. The carbon black and plasma extracts were chromatographed separately on activated alumina. The eluents from the columns were scanned for 3,4-benzpyrene, pyrene, fluoranthene, a substance identified only as "compound X," 1,2-benzpyrene, 1,12-benzperylene; anthanthrene, and coronene by spectrophometry and by fluorospectrophotometry to differentiate between 3,4-benzpyrene and 1,12-benzperylene. Control specimens were run through the same procedure using saline instead of human plasma.

Pyrene, fluoranthene, "compound X," and 1,2-benzpyrene were more easily eluted by plasma than were 3,4-benzpyrene, 1,12-benzperylene, anthanthrene, and coronene [45]. With prolonged incubation, the percentage of polycyclic hydrocarbons recovered both in carbon black and plasma decreased, but the authors offered no explanation for this. None of the polycyclic material was eluted by saline. Falk et al noted that incubation of carbon black with human plasma for 1.5-192 hours revealed that the degree of elution of the polycyclic hydrocarbons by plasma paralleled their elution by nonpolar solvents (such as petroleum ether) and ether from activated alumina. However, no data were presented to verify this conclusion.

Kutscher et al [46], in 1967, reported the elution of 3,4-benzpyrene by bovine serum and albumin and globulin fractions of human serum. Three types of carbon black, namely Corax L (particle size 28 nm), Degussa MT (particle size, 400 nm), and Degussa 101 (particle size 115 nm), were charged with 11-21 mg of 3,4-benzpyrene/g of carbon black. Approximately 0.25 or 0.5 g of Corax L and 0.25 g each of Degussa MT or Degussa 101 were incubated with 25 ml of bovine serum at 37 C for 0.25-166, 0.25-60, and 0.25-60 hours, respectively. In a second experiment, samples of 0.01-0.05 g of Corax L containing 0.16-0.89 mg of 3,4 benzpyrene were incubated with approximately 0.05 g of human serum fractions of albumin, alpha, beta or gamma globulins at 37 C for 100-127 hours. In both the experiments, at the end of each incubation period a sample of the incubation mixture was centrifuged or filtered to remove the carbon black, and the supernatant or filtrate was extracted with benzene and analyzed for 3,4-benzpyrene by fluorescence spectroscopy.

Of the three carbon blacks tested, Corax L required 7 hours of incubation with bovine serum when the first traces of eluted benzpyrene appeared in the serum, while Degussa MT and Degussa 101 required less than 15 minutes. The elution of benzpyrene increased with the incubation period and reached a maximum of 10, 13, and 20%, respectively for Corax L, Segussa 101, and Degussa MT. This maximum was reached within 60 hours for Corax L, and 4-6 hours for Degussa 101 and Degussa MT. Of the human serum fractions tested, albumin was the only fraction capable of

eluting the benzyprene. No quantitative data were given to support this conclusion. This investigation, however, supports the finding of Falk et al [45], who found that human plasma eluted PAH's from carbon black.

Kutscher et al [44] also tested the ability of rat lung tissue, in vitro, to elute 3,4-benzopyrene from Corax L. Benzopyrene (0.1 g) was added to the carbon black (5 g) and various amounts of the resulting mixture incubated with lung tissue preparations. Lung tissues with and without blood and in water, physiologic sodium chloride, or potassium hydroxide solutions were used. Potassium hydroxide and sodium chloride solution alone did not elute the benzopyrene from the carbon black. However, when lung tissue, either fresh or after incubation with sodium chloride solution, was tested benzopyrene was eluted, after 15 hours with the fresh tissue and after 100 hours (the first time carbon black was tested) with tissue incubated with sodium chloride. Lung tissue treated with water also eluted benzopyrene from the carbon black after 15 hours but the benzopyrene was detected in the water insoluble parts of the tissue and not in the water soluble fraction. The authors had performed this study to determine if lung tissue fluid could elute benzopyrene as well as blood plasma which had been shown to elute benzopyrene by other investigators.

In 1976, Creasia et al [47] conducted studies to evaluate in vivo elution of 3,4-benzpyrene from carbon particles (nut shell charcoal) in the respiratory tract of mice. The results showed that while 50% of the 3,4-benzpyrnene disappeared by 36 hours from the lungs of those given the carcinogen adsorbed on 15-30 μm carbon particles, 50% 3,4-benzpyrene disappeared within 1.5 hours when administered as 0.5-1.0 μm as free crystals. Thus, the retention of 3,4-benzpyrene adsorbed on carbon black in the lung was more than 20 times higher than that of the unadsorbed 3,4-benzpyrene. In contrast, pulmonary clearance of 50% of the carbon particles was achieved only about the 7th day, thus indicating an elution of 3,4-benzpyrene from the carbon. The elution rate of the carcinogen was approximately 15% each day. In another experiment, animals given 3,4-benzpyrene as 0.5 μm to 1.0-μm crystals adsorbed carbon particles of 0.5-1.0μm size or carbon particles of 15-30μm size cleared 50% of the carcinogen from their lungs in less than 2 hours, 1.5 days, and 4-5 days, respectively. The investigators described as the possible reasons for relatively low carcinogenicity the rapid clearance of small-sized particles, and hence, a residence time too short for tumor induction, and release of insufficient carcinogen because of tight binding to the larger size particles.

In 1977, Creasia [48] reported the effect of the stage of respiratory infection on the elution of 3,4-benzpyrene from carbon (nut shell charcoal) particles in the respiratory tract of mice. Seven groups of 30, 12- to 15-week-old, specific pathogen free, female mice were given an intranasal inoculation of PR8 influenza viruses. A group of 30 uninfected mice received an intratracheal insufflation of 103Ru-labeled carbon particles coated with 3,4-benzpyrene in the ratio of 1:2; another group of 30 receiving benzpyrene alone served as controls. Three groups of infected mice received similar doses of 3,4-benzpyrene adsorbed on carbon within 0.5 hour or at 7 or 21 days after the inoculation. At the same intervals three groups of mice were administered 3,4-benzpyrene alone, for comparison. The results indicated that the rate of elution of benzpyrene from carbon particles increased during the acute stage of infection and was not different from that of uninfected controls when measured either 1 week before or 2 weeks after the acute stage of infection. This might be a significant factor to consider in assessing the potential carcinogenic risk from PAH's adsorbed on carbon black.

Bokov et al [49] studied the distribution and elimination of carbon black injected into the lungs by intratracheal insufflation. The thermal black which was used in the study had a diameter of 230 nm, a surface area of 25 sq m/g, and a volatile content of 2.36%. Forty-four white rats were used in the study. The test animals received single injections of 50 mg of carbon black suspended in 0.5 ml of a physiologic solution containing 100 U of penicillin; control animals receveived only 0.5 ml of solution and 1,000 U of penicillin. Unstated numbers of animals were killed at various time intervals from immediately after the injection to 12 months later; tissues were sectioned, stained, and examined microscopically. Immediately after the injection, carbon black was found in the lumens of all bronchi and in some of the alveolae. Some alveolae contained desquamated cells. Carbon black was again found in the bronchi and alveolar but also in some pulmonary lymph vessels 1.5 to 22 hours after the injection. Lobar and lobar-confluent pneumonia was also observed. After 2 months, there was no carbon black in the bronchi or alveoli but it was observed in the alveolar macrophages, pulmonary stroma, lymph vessels and lymph nodes. Sections made 3-7 months after the injection contained decreasing amounts of carbon black in the lymph vessels and increasing amounts in the lymph nodes. Although at 9.5 months carbon black was still observed in the stroma of the lungs, by the end of 12 months, none of the lung sections contained carbon black and only small amounts were seen in the nodes. The authors concluded that carbon black was eliminated through the bronchi and lymph system but up to 12 months were required for elimination. They also observed collogen fibers that they believed indicated initial sclerosis.

Pylev et al [34], in 1969, presented the results of a study on the rate of elimination of tritiated 3,4-benzpyrene after intratracheal administration. The benzpyrene was given to hamsters with and without carbon black. In all experiments, female cream-coated or golden hamsters, weighing 80-150 g each, were used. In the first experiment, 35 animals received intratracheal injections of 5 mg of tritiated benzpyrene (36 microcuries/mg), and 27 others received 5 mg of tritiated benzpyrene with 1 mg of furnace black (90% particle size 26-160 nm). The injected material was always suspended in aminosol vitrum (contained 10% amino acids and low-molecular-weight peptides obtained by enzymatic hydrolysis of animal proteins in water) and Tween 80 and administered in a 0.2-ml dose to anesthetized hamsters. A third group received crocidolite with benzpyrene. Of 109 hamsters, 31 died before the end of the experiment. The report did not state how many animals in each of the three groups died, other than mentioning that the third group had several deaths. Three and 6 hours and 1, 3, 7, 14, 21, and 35 days after the intratracheal administration, three hamsters from each group were killed with an overdose of ether, and their lungs, liver, and kidneys were removed and prepared appropriately for radioactivity determination.

In a second experiment [34], 70 female cream-coated or golden hamsters, weighing 130-150 g each, were used [34]. The number of hamsters in each group was not given. The three treatment groups were similar to those in the first experiment, except that the specific activity of the tritiated 3,4 benzpyrene used was 20 microcuries/mg. Twenty-eight hamsters died, but there was no indication of how many were in each group. Of the 12 survivors that received benzpyrene alone and 14 that received benzpyrene plus carbon black, 2 or 3 of each group were killed by decapitation 3, 7, 14, 21, and 28 days after the intratrachael administration; their lungs, liver, and kidneys were removed and prepared for determination of amount of radioactive 3,4-benzpyrene present.

All animals in both experiments [34] had severe difficulty in breathing during the first few hours after intratracheal benzpyrene injection. These signs disappeared in 3 days in the hamsters receiving benzpyrene alone or with carbon black. Examination of the lungs at autopsy showed lobar pneumonia, primarily in the left lung. Within 3 hours after the administration, 54 and 55%

of the administered tritiated 3,4-benzpyrene were lost from the lungs of hamsters receiving benzpyrene alone or with carbon black, respectively. Both groups progressively lost the radioactivity from their lungs, and on the 14th day only 0.67% and 0.37% of the total administered dose remained in these same groups; this decreased to 0.04% and 0.25% by 35 days after benzpyrene administration. Thus, retention of radioactivity was significantly higher (no P value) in the hamsters given labeled benzpyene with carbon black than in those given benzpyrene alone. Similarly, the livers of animals that received carbon black with benzpyrene retained a higher percentage of the total administered dose on day 28 than did those from hamsters that received only benzpyrene. These differences were slight but were seen throughout the observation period. Kidney analyses showed no differences in the radioactivity retained in these organs of the animals in the two groups up to 21 days, but by day 28 the group that received carbon black retained a higher percentage of the administered labeled benzpyrene than did the group that received benzpyrene alone.

According to Pylev et al [34], the results suggested that the elimination pattern for the radioactivity from the lungs, presumably reflecting that of benzpyrene or its metabolites, occurred in two distinct phases: an initial rapid elimination during the first 2 weeks, which was not much influenced by carbon black, and a slower elimination starting in the 3rd week. During this second slow phase, although virtually all the benzpyrene had been eliminated from the lungs, the animals receiving carbon black and labeled benzpyrene retained significantly more radioactivity than did those given tritiated benzpyrene alone. The authors attributed the difference to the particulate nature of the carbon black, which could adsorb benzpyrene and hence prolong its retention in the lungs.

Pylev et al [34] also studied changes in lung macrophage number, elimination of radioactivity through macrophages, and the radioactivity of blood, feces, and urine after a single intratracheal administration of tritiated benzpyrene alone, with carbon black, or with crocidolite. Fifty-two older female hamsters of unspecified age and weight were divided into groups that were treated the same as those in the radioactivity retention studies. Three hours and 1, 7, 14, and 21 days after the intratracheal administration, three hamsters from each group were killed by decapitation. Macrophages were removed from the lungs of each animal by washing with saline, and the remaining radioactivity of the lungs was measured. Six hours after benzpyrene administration, hamsters receiving benzpyrene alone had lost 61% of the total administered radioactivity, whereas those receiving the tritiated benzpyrene adsorbed to carbon black had lost 55%. On the 21st day after administration, animals receiving benzpyrene alone or with carbon black retained 0.11 and 0.18%, respectively, of the administered radioactivity. The authors believed that these results suggested that carbon black carrying benzpyrene had penetrated the lung tissue. However, unless the lungs were washed completely free of macrophages, this conclusion may not be valid.

In a fourth experiment, 64 female hamsters, weighing 80-150 g each, were divided into 3 groups, which were treated the same as those in the first 2 experiments, using tritiated benzpyrene with a specific activity of 35.5 microcuries/mg [34]. On days 1, 7, 14, and 21 after the benzpyrene administration, 1 ml of blood was taken from three hamsters of each group. Three animals from each group were killed on day 1 and two animals each on days 7, 14, and 21. Ten hamsters not given any test materials were killed and their lung macrophages recovered to obtain normal values. Blood samples and macrophages were appropriately prepared and their radioactivities measured. Three hamsters from each group kept in separate metabolic cages were used to obtain 24-hour urinary and fecal samples on days 3, 7, 14, 21, and 36 after treatment; the radioactivity of the feces

and urine samples was measured. Blood analyses revealed no differences in radioactivity elimination until after day 7. On days 14 and 21, hamsters receiving benzpyrene alone retained more of the total administered label in their blood than did those receiving benzpyrene with carbon black. There were no differences in urine radioactivity between the two groups throughout the observation period. On day 14, the hamsters receiving benzpyrene adsorbed on carbon black had less radioactivity in their feces than did those receiving benzpyrene alone. The reverse was true on day 36; the fecal and urinary excretion patterns of labeled benzpyrene were similar in the two groups. Pylev et al did not explain why the blood of the animals receiving benzpyrene and carbon black retained less radioactivity on days 14 and 21 than did the blood of those receiving benzpyrene alone. It is possible that these differences in blood radioactivity were related to the higher retention of the labeled benzpyrene or its metabolites in the lungs of the hamsters that received carbon black with the tritiated benzpyrene.

On day 7, more lung macrophages were recovered from hamsters receiving benzpyrene with carbon black than from those receiving benzpyrene alone [34]. However, the radioactivity/macrophage on days 7, 14, and 21 was much higher in the hamsters that had received benzpyrene alone. The authors concluded that the presence of carbon black increased macrophage activity, but they offered no explanation for the lower radioactivity of each macrophage in the animals receiving benzpyrene plus carbon black. This could be caused by a dilution effect; animals receiving carbon black contained a greater number of macrophages.

Similar retardation in the clearance of the 3,4-benzpyrene from lungs of hamsters was described by Henry and Kaufman [35], in 1973, who administered it intratracheally by coating on carbon, aluminum oxide, or ferric oxide of four particle size ranges (0.5-1, 2-5, 5-10, and 15-30 μm. Clearance rates determined at eight intervals during 10-30,000 minutes after the intratracheal instillation showed that the carcinogen was cleared much more slowly from lungs of carbon-treated animals, and that there was positive correlation between particle size and retention rate.

Correlation of Exposure and Effect

Effects of both short-term and long-term occupational exposure to carbon black have been found in workers producing furnace, thermal, and channel blacks (Table III-1). None of these reports on the health effects of carbon black presented exposure concentrations, but a few listed the total dust concentrations of the work atmosphere. The concentrations of total dust ranged from as low as 8.2 mg/cu m [25] to as high as 1,000 mg/cu m [13]. These reports showed that the effects of carbon black exposure are chiefly on the respiratory system [12-15,17,18,25] but effects were also evident on the skin [13,15,19], oral mucosa [26], and heart [13,15]. One study [18] noted a higher incidence of pneumoconiosis in channel black workers than in thermal or furnace black workers. No other reports of effects on humans from carbon black exposure differentiated or compared the effects of the three types of carbon black.

The pulmonary involvement reported in a number of these studies was characterized by coughing, difficulty in breathing, and pains in the chest and near the heart in carbon black workers [14,15]. Some of these workers also complained of headaches, general weakness, malaise [14,15], and decreased senses of smell and hearing [13]. Lung diseases encountered in the carbon black workers, in descending order of prevalence, were pneumoconiosis [12,14,15,17,18,25], pneumosclerosis or pulmonary fibrosis [12-14,15,25], bronchitis [13,14,18,25], emphysema [14],

and tuberculosis [12,18]. The finding of tuberculosis in carbon black workers might suggest that the exposure to carbon black predisposed the workers to this bacterial disease. However, no evidence was presented that the incidence of the disease in carbon black workers was greater than that in the general population. In some cases, structural changes in the lungs were accompanied by functional changes in pulmonary dynamics [14,15,18,25].

In comparison to the adverse health effects produced by carbon black, nuisance aerosols reportedly have little effect on lungs and do not produce significant organic disease or toxic effects when exposures are kept under reasonable control [50]. The lung tissue reaction caused by inhalation of nuisance aerosols had the following characteristics: the architecture of the air spaces remains intact, collagen is not formed to a significant extent, and the tissue reaction is potentially reversible. Since pulmonary fibrosis is encountered in workers subjected to dust exposure during carbon black production [12-15,25], and since an increased concentration of hydroxyproline (an important component of collagen) in the lungs of animals exposed to carbon was found [18], carbon black seems to be more than simply a nuisance aerosol.

Effects on the respiratory system similar to those encountered in carbon black workers have been demonstrated in both short-term and long-term animal experiments following inhalation or intratracheal introduction of carbon black [18,28,30,31]. These effects are summarized in Table III-2. Carbon black accumulated in various regions of the upper and lower respiratory tract in both mice and monkeys exposed to carbon black (85 mg/cu m of channel black or 56 mg/cu m of furnace black for up to 7.1 years; 53 mg/cu m of thermal black for 3 years) [28,30]. Although no impairment of pulmonary function was noted in the monkeys exposed to channel, furnace, or thermal black, their lungs showed lesions analogous to those found in workers exposed to carbon black, eg, centrilobular emphysema, thickening of the alveolar walls, and occasional cellular proliferation. In one of these reports [28], it was noted that channel black penetrated more readily into the interstitial spaces of the lungs than did furnace black. This is the only report of effects of carbon black on laboratory animals that revealed differentiating characteristics between the biologic effects of furnace black and those of channel black. This experimental evidence for pulmonary fibrosis seems to confirm the occasional reports of pneumoconiosis and fibrosis in workers in the carbon black industry.

Although dermal effects of carbon black exposure have been less frequently reported, three reports have been identified. Capusan and Mauksch [19] reported the 5-year incidence of skin diseases in workers producing carbon black by large-scale sooting of a wick in a petroleum lamp burning hydrocarbon and naphthene (cycloparaffin) wastes. Of these workers, 53-86% had specific dermatoses, and 7-16% of the workers had nonspecific dermatoses. Komarova [15] found diseases of the skin in workers engaged in furnace black production, although these were not elaborated. The dust concentration in this work environment reportedly exceeded the MPC of 10 mg/cu m in 75% of the samples. In another study, Komarova [13] noted that, of more than 80 workers exposed to dust at 10-1,000 mg/cu m during packaging of carbon black, 92% complained of skin irritation.

In animal experiments, direct application of suspensions of carbon black did not reveal any observable changes [30,39]. However, in the inhalation studies conducted by Nau et al [28], mice exposed to furnace black at 56 mg/cu m for up to 1.65 years showed varying degrees of skin atrophy or hyperplasia, fibrosis of the dermis, or both. In mice exposed to channel black at 85 mg/cu m of channel black for up to 1.69 years, subcutaneous edema was found more consistently.

In contrast, excessive concentrations of nuisance aerosols caused injury to skin by chemical or mechanical action per se or by the rigorous skin cleansing procedures necessary for their removal [50].

In one report on the effects of carbon black exposure on oral mucosa, Smolyar and Granin [26] examined the oral mucosa of 300 carbon black workers who had been exposed to active furnace black (particle size 0.3-0.4 μm). They found that 24 had keratosis and 36 had leukoplakia. These incidences of keratosis and leukoplakia were 242 and 125% higher, respectively, than those of the unexposed controls and had a significance of $P<0.003$. Keratosis and hyperkeratosis were found primarily in areas where carbon black accumulated, such as in the lip mucosa, transient folds, cheeks, gums, and tongue, whereas leukoplakia was frequently encountered in the corners of the mouth and cheeks but rarely on the tongue and lower lip. The authors considered these lesions pretumorous and attributed them to exposure to carbon black dust and anthracene oils in the workers' environment. By "pretumorous," the authors undoubtedly referred to the commonly accepted belief that leukoplakia and probably keratosis may in a small but significant number of cases develop into malignancies. As has been reviewed in another criteria document on coal tar products [51], occupational exposure to PAH's, such as are contained in such mixtures as anthracene oils, may cause keratosis and leukoplakia. In their report [26], Smolyar and Granin also presented animal studies in which mice exposed at concentrations of carbon black similar to those encountered in the work environment had similar pretumorous oral mucosal lesions, but they did not present actual values. Although the production of such pretumorous lesions was not described following exposures to nuisance aerosols, excessive concentrations of nuisance aerosols reportedly injured the mucous membrane by chemical or mechanical action [50].

Myocardial dystrophy [13] and unspecified cardiovascular changes [15] were noted in a few workers exposed to carbon black. Komarova [13] found that, of more than 80 workers exposed at 10-1,000 mg/cu m of dust and at 5-120 mg/cu m of carbon monoxide during packaging of carbon black, 50% had signs of myocardial dystrophy. In another study, Komarova [15] also noted cardiovascular diseases in workers engaged in the production of furnace blacks, where dust concentrations of 75% of the samples exceeded the MPC of 10 mg/cu m. Animal toxicity studies revealing changes in the heart following carbon black exposure were presented by Nau et al [28,30]. The ECG's of monkeys exposed to channel black 85 mg/cu m for 0.55-0.82 years or to furnace black at 56 mg/cu m for 1.37 years revealed right atrial and right ventricular strain [28]. In comparison, monkeys exposed to thermal black at 53 mg/cu m for 3 years showed right ventricular, septal, and, to a lesser degree, left ventricular hypertrophy [30]. Mice exposed to furnace black at 56 mg/cu m or to channel black at 85 mg/cu m for 0.55 years had a slightly increased heart-to-body weight ratio (0.61 and 0.56 for furnace and channel groups, respectively, compared with 0.51 for controls). In the workers with myocardial dystrophy, there were high concentrations of carbon monoxide. Whether this was a factor in the causation of the heart changes is difficult to comment on without knowing more about what the authors meant by dystrophy and how it was studied. However, it seems appropriate because of this observation and the finding of ECG changes in monkeys to proceed on the belief that carbon black exposure may lead to heart changes. It is important that appropriate research be undertaken to resolve this point.

Although no carbon black studies on human exposure have investigated the possible effects on the liver, spleen, or kidneys, one study [28] using laboratory animals found that carbon black did affect these organs. In these experiments, mice exposed to furnace black at 56 mg/cu m or to channel black at 85 mg/cu m for up to 1.65 years showed changes in the liver, kidneys, and

spleen. Carbon black was present within the Kupffer cells of the livers of a few of the exposed animals, while in the kidneys the phagocytic cells containing carbon black were found around the proximal convoluted tubules and the glomeruli. The spleen, kidneys, and liver of the exposed mice had an increased incidence of amyloidosis. The kidneys of the exposed mice also showed cortical scarring and fibrosis. However, such changes in the liver, spleen, or kidneys were not reported in mice exposed to thermal black at 53 mg/cu m. These findings have not been confirmed by other investigations, so the possibility of their having arisen from intercurrent disease needs to be settled by further investigation. Furthermore, there appears to be some confusion as to whether the concentrations are correctly expressed as mg/cu m or mg/cu ft in the original article.

Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

There were four reports [20-22,26] found on cancer in humans related to carbon black exposure. Maisel et al [20] reported the case of a 53-year-old research chemist who handled a number of commercial and experimental carbon blacks for 11 years and developed parotid duct carcinoma [20]. During this period, he literally ate and breathed carbon black. Maisel et al [20] concluded that the parotid duct cancer could have been produced by carbon black. The authors considered their conclusion reinforced by the presence of squamous-cell metaplasia, a probable precancerous lesion, and the presence of a black material (presumably carbon black) in the left parotid gland. They conceded, however, that the black material found in the parotid duct was not analyzed for either polycyclic material or carbon black. It is also possible that, during the course of his career, the chemist was exposed to a number of other chemicals that might have acted as initiators, promoters, or synergists in the overall carcinogenic response. Hence, no definite conclusion can be drawn from this case report on the etiologic significance of carbon black in parotid duct carcinoma. However, as already indicated, there were methodologic deficiencies in these studies.

The studies of Smolyar and Granin [26] of the USSR, however, revealed that the incidences of pretumorous lesions such as keratosis and leukoplakia in the oral mucosa of carbon black workers were 242 and 125% higher, respectively, than they were in the unexposed control workers. This points out a possible role by carbon black in the production of parotid duct carcinoma. Smolyar and Granin also showed that pretumorous oral mucosal lesions, such as keratosis, can be produced experimentally by exposing rats and mice to carbon black, which probably contains PAH's derived from the starting material (anthracene oil) [27].

Ingalls and his collaborators performed three epidemiologic studies of cancer among employees of the Cabot Corporation [21-23]. These three studies neither prove nor disprove that carbon black is a carcinogen. There is a suggestion upon comparing the morbidity for carbon black workers with those for other workers that carbon black may be a leukemogen. This possibility raises at least suspicion that an excess risk of disease may be associated with exposure to carbon black.

While these reports do not give substantial evidence of carcinogenicity, the suggestion of carcinogenicity is more strongly supported by findings from animal experiments, discussed below, and by the finding of PAH's associated with many samples of carbon black.

In a number of studies conducted by Nau and coworkers [28,30,39,41,52], administration of whole carbon black (furnace, thermal, or channel) by oral, inhalation, dermal, or sc routes did

not produce cancer in mice. However, when benzene-extractable materials from channel and furnace blacks containing the carcinogenic components were administered to mice by skin painting [39] or feeding [41], malignant tumors were produced. These studies also showed that, when mice ingested methyl cholanthrene, a known carcinogen, adsorbed on benzene-extracted carbon black, they either had a lesser incidence of carcinomas of the gastrointestinal tract than did the mice receiving the same amount of methyl cholanthrene alone, or they had no carcinomas there. Also, when methyl cholanthrene or 3,4-benzpyrene adsorbed on benzene-extracted carbon black was administered by skin painting, the carcinogenicity of these substances was either reduced or eliminated when compared with the two carcinogens not adsorbed on carbon black. Similar conclusions were reached by Shabad et al [32], who reviewed the unpublished investigations of Linnik. In these investigations, sc administration of benzpyrene adsorbed on carbon black showed that the carcinogenicity of benzpyrene was minimized or eliminated compared with the carcinogenicity of free benzpyrene that was not adsorbed on carbon black. Such decreases in the carcinogenicity of methyl chloranthrene and 3,4-benzpyrene were believed by Nau et al [41,39] and by Shabad et al [32] to indicate that carbon black adsorbs these substances so firmly that either they are not released at all or they are released so slowly that they are ineffective as carcinogens.

Falk et al [45] showed that incubation of 50 and 100 mg of a commercial carbon black with 25 or 50 ml of sterile human plasma for 1.5-192 hours eluted varying amounts of pyrene, fluoranthene, compound X, 1,2-benzpyrene, 3,4-benzpyrene, 1,12-benzperylene, anthanthrene, and coronene. The studies of Kutscher et al [46] using bovine serum and human serum fractions for elution of 3,4-benzpyrene from three types of carbon blacks confirmed the findings of Falk et al [45]. In these studies 10, 13 and 20% of the adsorbed benzpyrene was eluted from carbon blacks of 28-, 115-, and 400-nm particle diamaters, respectively, by bovine serum. Also, these investigators noted that, of the four human serum fractions tested, only albumin eluted the adsorbed benzypyrene from carbon black. Creasia [48] reported that, if 3,4-benzpyrene-coated carbon particles were introduced into the respiratory tract of mice during the acute stage of respiratory infection by PR8 influenza viruses, the rate of benzpyrene elution from the carbon particles was increased. However, when benzpyrene-coated particles were introduced either 1 week before or 2 weeks after the acute stage of infection, the rate of elution was not different from that of the uninfected controls. Neal et al [43] found that incubation of channel and furnace blacks and several commercial rubber formulations containing 10-20% carbon black by weight, with human blood plasma, artificial intestinal fluid, artificial gastric fluid, whole milk, cottonseed oil, or food juice components (aqueous solutions of citric acid, acetic acid, sodium chloride, or sodium bicarbonate) failed to elute any polycyclic hydrocarbons adsorbed on these materials.

Shabad et al [32] found that six intratracheal administrations of 10 mg of channel black with 0.1 mg of adsorbed benzpyrene in rats produced lung neoplasms (9.6% of which were squamous-cell carcinomas) in 40% at 16 months while 24% of those receiving the benzpyrene adsorbed on thermatomic black had lung tumors at 10 months. Although no lung cancers were observed in the latter group, reticulosarcoma of the peribronchial and perivascular lymphoid tissue was detected in 22%. The rats in this study that received six intratracheal doses of 0.1 mg of benzpyrene alone had neither tumors nor precancerous lesions. In a somewhat similar experiment Pylev [33] found that of 68 rats given six intratracheal doses of 10 mg of channel black with 0.1 mg of adsorbed 3,4-benzypyrene, 44 developed inflammatory or pretumorous changes in their lungs within 6 months. Of these, 11 were described as having had diffuse hyperplasia and proliferation of the epithelium of the small and medium bronchi, diffuse hyperplasia and proliferation of the peribronchial mucous glands in 10, focal growth of the bronciular epithelium

with signs of planocellular metaplasia in 6, focal growth of the bronchiolar epithelium without cellular metaplasia in 12, and 5 cases with adenomatous growths. The 15 rats that received six intratracheal doses of 0.1 mg of benzpyrene did not develop any changes in their lungs. A similar increase in the incidence of lung carcinomas was observed by Farrell and Davis [36] after intratracheal administration of 3,4-benzpyrene with particulate carriers such as carbon, aluminum oxide, or ferric oxide. Pylev et al [34], in studying the elimination of tritiated 3,4-benzpyrene given intratracheally to hamsters with or without carbon black, found that, in the presence of carbon black, lungs of the former group retained significantly more radioactivity than did those of the latter at 28 days, although the amount retained was only a very small percentage of the total administered dose. Pylev [33] noted a similarly prolonged retention of 3,4-benzpyrene adsorbed in channel black in the lungs of rats given this substance intratracheally. Similar retardation in the clearance of 3,4-benzpyrene adsorbed on carbon from the lungs of hamsters was described by Henry and Kaufman [35] following intratracheal administration.

Thus, although carbon black by itself has not been shown to cause cancer, the carcinogenicity of the benzene extracts of carbon black has been well documented. These reports on the carcinogenicity of the polycyclic hydrocarbons adsorbed on the carbon blacks, their elutability by human plasma, and the ability of carbon black to enhance retention of known carcinogens indicate that occupational exposure to carbon black poses a significant carcinogenic hazard depending on the amount of the adsorbed PAH's and their ability to be freed from carbon black. This risk might be enhanced under certain conditions of the work environment, such as elevated temperatures or presence of solvents that facilitate the desorption of these carcinogens from carbon black. Other situations such as respiratory infections or other conditions of health of the employee that might increase the elution of the adsorbed PAH's from carbon black are likely to increase the risk of cancer. Although several papers [45,46,48] have emphasized the importance of elutability of adsorbed PAH's from carbon black as a criterion of carcinogenicity of the contaminated carbon black, there is no reason to suppose that all the PAH is cryptically located. So long as there is some appreciable affinity between the PAH and some component of the cellular membrane, simple contact of the particle of contaminated carbon black with the membrane should suffice for transfer of a fraction of the adsorbed PAH from carbon black to the membrane. The importance of elutability in carcinogenicity of PAH contaminated carbon blacks is probably quantitative rather than qualitative. It also needs to be noted that elutability is a function not only of relative adsorptive nature of competing materials but also of relative amounts of each. Elutability is not to be ignored as a factor contributing to the carcinogenicity of carbon blacks contaminated with PAH's but should not be regarded as the only important determinant of this type of toxic action.

No reports on humans or animals suggesting a mutagenic or teratogenic potential of carbon black and its extracts and their effects on reproduction have been found.

TABLE III-1

EFFECTS OF EXPOSURE TO CARBON BLACK ON HUMANS

Workers			Exposure			Observed Effects	Reference
No.	Age	Sex	Carbon Black Type/ Process	Concentration (mg/cu m)	Duration (yr)		
80	—	—	—	10-1,000*	—	Skin irritation, bronchitis, pneumosclerosis, myocardial dystrophy	13
643	—	—	Furnace	>10 in 75% of areas samples*	—	Bronchitis, pneumosclerosis, pneumoconiosis	15
35	38.8	M	(Thermal)	8.2-8.5	12.9	Pneumoconiosis, pulmonary fibrosis, bronchitis	24
52	45-60	M	Channel, furnace	8.4-24*	10-38	Pneumoconiosis	17
89	—	—	—	—	<5->17	Pneumoconiosis, fibrofocal pulmonary tuberculosis, pulmonary fibrosis	12
1	53	M	Channel, furnace, thermal, others	—	11	Squamous-cell metaplasia of left parotid duct and gland	20
66	35-40	M&F	—	—	3->19	Pneumoconiosis, pneumosclerosis, bronchitis, emphysema.	14
357	—	—	Furnace channel, thermal	—	>6	Pneumoconiosis, bronchitis, weakness in autonomic nervous system	18
—	—	—	Sooting of a wick	—	—	Stigmata with fissured hyperkeratosis, tatooing, eczema, pruritus	19
300	—	—	Furnace	—	—	Keratosis, leukoplakia	25

*Measured as total dust concentration

TABLE III-2

EFFECTS OF EXPOSURE TO CARBON BLACK ON ANIMALS

Route of Exposure	Species	Number, Sex, and Age	Type of Carbon Black	Exposure Concentration and Duration	Observed Effects	Reference
Inhalation	Monkey	—	Channel	85 mg/cu m* × 13,000+ hr	Emphysema, right atrial and ventricular strain	28
"	"	—	Furnace	56 mg/cu m* × 13,000+ hr	"	28
"	"	12	Thermal	53 mg/cu m × 5,784 hr	Emphysema, right ventricular, septal, left ventricular hypertrophy	30
"	Mouse	132 M 10 wk	Channel	85 mg/cu m* × 200-300 hr	Bronchopneumonia, emphysema, kidney fibrosis and cortical scarring, subcutaneous edema	28
"	"	148 M 10 wk	Furnace	56 mg/cu m* × 444-3,000 hr.	Bronchopneumonia, emphysema, atrophy, hyperplasia, fibrosis of skin	28
"	"	100	Thermal	53 mg/cu m for unspecified time	No significant lung changes	30
"	"	110	—	—	Atrophy, hyperkeratosis, desquamation, and acanthosis in buccal mucosa	26
"	Hamster	8 M 6 wk	Furnace, thermal	105-113 mg/cu m for 1,032 hr	Mild chronic inflammation of trachea and larynx	31
"	"	6 M 6 wk	"	105-113 mg/cu m for 318 hr	"	31

TABLE III-2 (CONTINUED)

EFFECTS OF EXPOSURE TO CARBON BLACK ON ANIMALS

Route of Exposure	Species	Number, Sex, and Age	Type of Carbon Black	Exposure Concentration and Duration	Observed Effects	Reference
Inhalation	Hamster	60	Thermal	106 mg/cu m × 172 d	No change in larynx, trachea, hypopharynx, or cervical esophagus	30
"	"	17 M 1.5 mo	Furnace, thermal	55-58 mg/cu m × 236 d	Edema of thyroartenoid fold in lamina propria	31
"	"	40	Thermal	53 mg/cu m × 236 d	Subepithelial changes in thyroartenoid fold consistent with edema	30
"	Guinea pig	40	"	53 mg/cu m for unspecified time	Phagocytes with carbon black in alveoli	30
"	Rat	60	—	—	Atrophy, hyperkeratosis, desquamation, and acanthosis in buccal mucosa	26
Inhalation	"	—	Furnace	240 mg/cu m for unspecified time	Enlarged emphysematous alveoli	18
or Intratracheal			"	50 mg in 1 ml rat serum	"	18
Intratracheal	"	52	Channel	10 mg and 0.1 mg adsorbed benzpyrene × 6 doses	Lung neoplasms	32
"	"	50	Thermatomic	"	Reticulosarcoma of peribronchial and perivascular lymphoid tissue	32

TABLE III-2 (CONTINUED)

EFFECTS OF EXPOSURE TO CARBON BLACK ON ANIMALS

Route of Exposure	Species	Number, Sex, and Age	Type of Carbon Black	Exposure Concentration and Duration	Observed Effects	Reference
Oral	Mice	20 MF 8 wk	Thermal	10% for 75 wk	No significant changes over controls	30
"	"	— 6-10 wk	—	10% 12-18 mo	No changes	41
"	"	30	Benzene-extracted black, oil base	207 g 18 mo	No ill effects	41
"	"	100	Benzene-extracted black, water base	182-243 g	Tumors: 4 skin tumors, 3 benign papillomas, 1 intracutaneous fibrosarcoma	41
"	"	80	—	0.261-0.509 g 12-18 mo	10/80 developed gastrointestinal tumors after being fed 0.02% benzene extract, water base	41
"	"	30	—	0.366 g 18 mo	No effects after having been fed 0.02% benzene extract, oil base	41
"	"	21	--	0.08%	2 gastrointestinal tumors and 2 leukemias after having been fed benzene extract, water base	41
"	"	22	—	0.08%	4 stomach tumors after having been fed benzene extract, oil base	41
"	"	—	Carbon black with methyl cholanthrene	123-327 g	No changes	41
"	"	—	—	18% 10 mo	No effects	38

*Nau et al [28] reported exposure concentrations as 1.6 mg/cu m for furnace black and 2.4 mg/cu m for channel black, which according to Nau [29] was incorrect and should have been reported as 1.4 and 2.4 mg/cu ft.