5. Summary of Data Reported and Evaluation

5.1 Exposure data

Polycyclic aromatic hydrocarbons (PAHs) are products of the incomplete combustion or pyrolysis of organic material. They are ubiquitous in the environment, which leads to measurable background levels of exposure in the general population. Tobacco smoke is a significant source of exposure to PAHs; in the nonsmoking, non-occupationally exposed population, diet is frequently the major source of exposure to PAHs.

High levels of occupational exposure can occur during the conversion of coal to coke and coal tar, and during the processing and use of coal-tar derived products. Industries and occupations for which exposures are reviewed in this monograph include coal gasification, coke production, coal-tar distillation, paving and roofing that involve coal tar, the use of creosote as a wood preservative, aluminium production (including anode manufacturing), carbon electrode manufacture, calcium carbide production, occupation as a chimney sweep and other exposures to soot, and thermoelectric power plants.

Occupational exposures to benzo[*a*]pyrene in these industries can be as high as 100 μg/m^3 compared with typical ambient air concentrations of a few nanograms per cubic metre. Similarly, levels of 1-hydroxypyrene, a urinary metabolite, can reach 100 μmol/mol creatinine in highly exposed workers but are generally less than 0.1 μmol/mol creatinine in people who are not exposed occupationally. The highest reported levels of exposure to benzo[*a*]pyrene by inhalation have been measured in the aluminium production industry when the Söderberg process is used. Levels of exposure to PAHs and profiles of exposure to multiple PAHs are, to a large extent, dependent on the industry, the job tasks performed within an industry, and the time period and country of exposure. Available information on dermal exposure suggests that it is a major route in many of the industries considered. Few measurements have been made of exposure to PAHs with a molecular weight greater than 300.

5.2 Human carcinogenicity data

Coal gasification

Epidemiological studies that are of sufficient size to be informative have consistently shown an excess of lung cancer associated with gas production. A large epidemiological cohort study of over 11 000 British gas production workers showed an excess incidence of lung cancer and urinary bladder cancer. A study of nearly 5000 German gas production workers showed an excess incidence of lung, stomach and colorectal cancer among gas furnace workers; the risk for lung cancer was related to duration of employment. A large

study of over 3000 Chinese gas plant workers that was only reported briefly showed an excess incidence of lung cancer among workers in the gas department. A case–control study nested within a cohort of gas and electricity production workers in France supported an association between coal gasification and the excess incidence of lung cancer. The Working Group noted that the findings are probably not explained by tobacco smoking habits, although no study fully adjusted for this.

Coke production

Most but not all of the epidemiological studies provided evidence of an excess risk for lung cancer among coke production workers. A large cohort study of coke plant workers in the USA and Canada showed an excess in mortality from lung cancer. The risk was highest in work areas close to the ovens and was especially high among workers in top-side jobs; an exposure–response trend was found. A very large study of coke plant workers in China that was only reported briefly also showed an increased risk for lung cancer. Cohort studies from France, Italy, Japan and the Netherlands supported an increased risk for lung cancer, although the studies were not fully conclusive when considered individually. Two mortality studies of coke plant workers in the United Kingdom showed no excess of lung cancer, although a record linkage study from the United Kingdom indicated an elevated risk. A case–control study among Chinese women who were exposed to coke oven emissions showed a positive exposure–response relationship after adjustment for tobacco smoking and supported an association between the excess incidence of lung cancer and coke production.

Coal-tar distillation

Two large surveillance programmes provide evidence of an increased risk for skin cancer among coal-tar distillers. Notifications of skin cancer in England during 1911–38 were analysed in relation to occupation, and more than 700 skin cancers that were attributed to exposure to coal tar among coal-tar distillers had been notified; crude mortality rates for scrotal cancer were very high among coal-tar distillers. Occupational health surveillance in a German coal-tar distillation plant identified more than 600 individuals with skin lesions during 1946–96, a third of whom also had malignant skin tumours; 20 cases of scrotal cancer were observed. More recent cohort mortality studies showed no indication of an increased risk for skin cancer, but this design is not sufficiently sensitive to identify potential risks for skin cancer. The findings for other cancer sites were inconsistent; a modest, non-significant increase in mortality was reported for lung cancer in one British and one Dutch study, and a significant excess in the incidence of buccal cavity and pharyngeal cancers was reported in a French study.

Paving and roofing with coal-tar pitch

Studies of pavers and roofers who presumably have been exposed to coal-tar pitch (and often also to bitumen) have suggested increased cancer risks in these occupations; studies of members of a roofer's union in the USA, analyses of registry-based data on pavers in the United Kingdom and roofers in the USA, and follow-up studies of cancer incidence among pavers in Finland and the Netherlands all showed an excess risk for lung cancer. Mortality from urinary bladder, laryngeal and skin (non-melanoma) cancer was increased in one of these cohorts, but this finding was not widely supported by other studies. Three case–control studies (conducted in the USA) reported a tobacco smoking-adjusted increase in the risk for lung cancer among roofers; none of these increases was statistically significant, but a meta-analysis of the case–control studies reported a statistically significant meta-relative risk.

Creosote

A number of cases of skin cancer, including scrotal cancer, have been reported among workers who had been occupationally exposed to creosote. A cohort study of wood impregnators in Norway and Sweden and a cohort study of timber workers in Finland, who had been exposed to creosote, reported a statistically significant excess incidence of non-melanoma skin cancer. A study of power linesmen in Sweden did not report any statistically significant increase in the incidence of cancer, although the risk for non-melanoma cancer was slightly increased. A nested case–control study of lung cancer among a cohort of gas and electricity workers in France reported an increased risk for exposure to creosote, with evidence of an exposure–response relationship. A cohort study of workers in the USA who had used creosote for the treatment of wood indicated the possibility of an increase in mortality from lung cancer. A study that applied a job–exposure matrix to job titles in the Swedish census and linked this to cancer incidence found an increase in the incidence of cancers of the renal pelvis and urinary bladder that was related to exposure to creosote.

Aluminium production

The first reports of risk for cancer associated with work in the aluminium production industry were made in the 1970s in the former USSR. A series of reports from Québec, Canada, showed statistically significant excess risks and positive exposure–response relationships for lung and urinary bladder cancer after adjustment for tobacco smoking. A study of an aluminium production plant in British Columbia, Canada, found statistically significant exposure-related trends in risk for both lung and urinary bladder cancer. A Norwegian cohort study showed an increase in the risk for cancer of the urinary bladder but not of the lung. In a study of multiple plants in the USA, the risk for lung cancer was close to that expected, but a statistically significant excess risk for bladder cancer was found. A study in the French aluminium industry reported excesses in the risk for cancer

of the lung and urinary bladder. In a recent meta-analysis of studies that used benzo[*a*]-pyrene as an index of exposure to PAHs, results from eight cohort studies of lung cancer and six studies of urinary bladder cancer in aluminium workers were pooled. Pooled risk estimates indicated a positive exposure–response relationship between cumulative exposure to benzo[*a*]pyrene and both urinary bladder and lung cancer.

In two studies, statistically significant increases in the incidence of lymphatic and haematopoietic cancers were reported for aluminium workers. Increased risks for pancreatic cancer were also reported in two studies.

Carbon electrode manufacture

A study of carbon electrode workers in China showed an excess risk for lung cancer and a positive exposure–response relationship between increasing exposure to carbon compounds and lung cancer risk. When the study was limited to nonsmokers, the increased risk was still observed. However, the study included both carbon electrode workers and pot-room workers in an aluminium smelter, and it is questionable how much of the excess risk may be attributed to exposures in carbon electrode manufacture. A small study of carbon electrode manufacturing workers in Japan showed an excess incidence of lung cancer. A large study of workers at a carbon product department of a plant in the USA showed no excess incidence of respiratory cancer and no exposure–response trend in internal analyses. A cohort study of two plants in France and two cohort studies from Italy provided no evidence for an increased risk for lung cancer associated with carbon electrode manufacture. A small study from Sweden based on only two cases was uninformative due to small numbers.

Calcium carbide production

One study of calcium carbide production workers showed an increased risk for cancers of the prostate and of the colon but not of the lung. The study provided little information on risk for cancer in relation to exposure to PAHs.

Chimney sweeps and other exposures to soot

A large cohort study of chimney sweeps in Sweden showed an excess incidence of cancers of the lung, oesophagus, urinary bladder and haematolymphatic system; the excess remained after adjustment for tobacco smoking and a trend in exposure–response was observed. A smaller cohort study of chimney sweeps in Germany showed excess mortality from lung cancer, and a Danish cohort study showed an excess of cancer deaths among chimney sweeps. Record linkage studies from Finland and Norway showed increased risks for lung cancer, although the results from the Finnish study were not statistically significant. A record linkage study from the United Kingdom showed no increased mortality from lung cancer. A large number of case series reported an increased risk for skin cancer, especially scrotal cancer, among chimney sweeps.

Case–control studies by cancer site

Lung

Smoking-adjusted increased risks for lung cancer were reported for several industries and for general occupational exposures to PAHs in Germany, Norway and Sweden. The two larger studies (Germany and Sweden) also found positive exposure–response relationships. A study of lung cancer in Canada found an excess risk for exposure to PAHs from any occupational source among light smokers and nonsmokers only; a Dutch study reported inconsistent results.

Other sites

Six studies of renal-cell carcinoma and exposure to PAHs were reviewed. One showed an increased risk among coke-oven workers and another study found a statistically non-significant positive association with exposure to coke. Exposure to coal tar and to coal-tar pitch was assessed in three studies of renal-cell carcinoma; a statistically significant or nearly significant increase in odds ratios was found in all three studies. Three studies investigated occupational exposures to PAHs and the incidence of renal-cell carcinoma; one was uninformative due to the small number of exposed cases and the other two found no excess risk for renal-cell carcinoma.

Among eight case–control studies of urinary bladder cancer and occupational exposure to PAHs, exposure to mixtures of coal-tar pitch, coal tar and asphalt was assessed in three, two of which found a statistically significant excess risk. Assessment of exposure based on industries or job titles gave inconsistent results for bladder cancer risks. Four studies assessed general occupational exposure to PAHs and one found a borderline significantly increased risk for cancer of the urinary bladder.

Three studies of laryngeal cancer consistently showed statistically significant associations with exposure to PAHs, as assessed from lifetime occupational history. Case–control studies of skin cancer (two studies), pancreatic cancer (three studies and one meta-analysis of four case–control studies), stomach cancer (two studies), oesophageal cancer (two studies) and prostate cancer (two studies) assessed jobs that entailed high known occupational exposure to PAHs; the results were inconsistent.

Dietary intake

Few epidemiological studies have directly investigated the association between dietary intake of PAHs and risk for cancer. The studies conducted to date have all used a questionnaire with a meat-cooking module in conjunction with a database of levels of benzo[*a*]pyrene that was used as a marker for total intake of PAHs. Three case–control studies of colorectal adenoma, a precursor of cancer, showed small to moderate increases in risk with higher estimated intake of benzo[*a*]pyrene. In contrast, there was no association with intake of benzo[*a*]pyrene in a case–control study of colon cancer. One case–control study of pancreatic cancer found a moderate increase in risk associated with

benzo[*a*]pyrene intake; no association was found in one study of prostatic cancer and non-Hodgkin lymphoma. The available information is at present too limited to draw definitive conclusions.

5.3 Animal carcinogenicity data

Studies on the carcinogenicity in experimental animals of anthanthrene, anthracene, benz[*a*]anthracene, benzo[*b*]fluoranthene, benzo[*j*]fluoranthene, benzo[*k*]fluoranthene, benzo[*a*]fluorene, benzo[*b*]fluorene, benzo[*c*]fluorene, benzo[*ghi*]perylene, benzo[*c*]-phenanthrene, benzo[*a*]pyrene, benzo[*e*]pyrene, chrysene, coronene, cyclopenta[*cd*]pyrene, dibenz[*a,c*]anthracene, dibenz[*a,h*]anthracene, dibenz[*a,j*]anthracene, dibenzo[*a,e*]fluoranthene, dibenzo[*a,e*]pyrene, dibenzo[*a,h*]pyrene, dibenzo[*a,i*]pyrene, dibenzo[*a,l*]pyrene, fluoranthene, fluorene, indeno[1,2,3-*cd*]pyrene, 1-methylchrysene, 2-methylchrysene, 3-methylchrysene, 4-methylchrysene, 5-methylchrysene, 6-methylchrysene, 2-methylfluoranthene, 3-methylfluoranthene, perylene, phenanthrene, pyrene and triphenylene were considered by previous working groups. For these compounds, only studies that were evaluated since that time are summarized below.

Acenaphthene was tested for carcinogenicity by dermal administration in two experiments in mice, both of which were considered to be inadequate for an evaluation.

2,3-Acepyrene (cyclopentano[*cd*]pyrene) was tested for carcinogenicity in one initiation–promotion study and one study of repeated dermal application in mice, both of which gave negative results.

Anthanthrene was tested for carcinogenicity on mouse skin in one initiation–promotion study that gave negative results. Anthanthrene also gave negative results when tested for carcinogenicity by intramamillary administration to rats.

Anthracene was tested for carcinogenicity on mouse skin in two experiments, one of which was an initiation–promotion study. Both gave negative results. It also gave negative results when administered by subcutaneous injection to mice in one study.

11*H*-Benz[*bc*]aceanthrylene gave positive results when tested for carcinogenicity in one initiation–promotion study on mouse skin, but gave negative results after subcutaneous injection to mice.

Benz[*j*]aceanthrylene was tested for carcinogenicity in one dermal initiation–promotion study on mouse skin and after intraperitoneal administration to mice. In both instances, highly significant increases in tumour incidence and/or in the number of tumours per animal were observed.

Benz[*l*]aceanthrylene was tested for carcinogenicity in one dermal initiation–promotion experiment in mice, in which it was positive as a tumour initiator.

Benz[*a*]anthracene was tested for carcinogenicity in a number of bioassays. It gave negative results in one study of repeated application on mouse skin and positive results in four initiation–promotion studies on mouse skin. In three assays in newborn mice, results were positive in two studies and questionable in one study, possibly due to the low dose

tested. One study of intratracheal instillation and one of buccal pouch application in hamsters and one study of intramammary administration to rats gave negative results.

Benzo[*b*]chrysene was tested for carcinogenicity on mouse skin in one initiation–promotion study that gave positive results.

No data were available to the Working Group on the carcinogenicity of **benzo[*g*]chrysene** in experimental animals.

Benzo[*a*]fluoranthene was tested for carcinogenicity in one initiation–promotion experiment in mice that gave positive results.

Benzo[*b*]fluoranthene was tested for carcinogenicity by dermal application in mice in multiple studies, by intraperitoneal injection into mice in one study and by intrapulmonary implantation into rats in one study. In all of these studies, benzo[*b*]-fluoranthene exhibited significant carcinogenic activity.

No new studies were available to the Working Group to evaluate the carcinogenicity of **benzo[*ghi*]fluoranthene** in experimental animals.

Benzo[*j*]fluoranthene was tested for carcinogenicity by dermal application in mice in four studies, by intraperitoneal injection into newborn mice in two studies and by intrapulmonary implantation into rats in one study. With the exception of one study in newborn female mice, benzo[*j*]fluoranthene exhibited significant carcinogenic activity in all of the assays.

Benzo[*k*]fluoranthene was tested for carcinogenicity by dermal application in mice in one study, by intraperitoneal injection into newborn mice in one study and by intrapulmonary implantation into rats in one study. Benzo[*k*]fluoranthene exhibited significant carcinogenic activity in the dermal and intrapulmonary assays.

No new studies were available to the Working Group to evaluate the carcinogenicity of **benzo[*a*]fluorene** in experimental animals.

No new studies were available to the Working Group to evaluate the carcinogenicity of **benzo[*b*]fluorene** in experimental animals.

Benzo[*c*]fluorene was tested for carcinogenicity by oral and intraperitoneal administration to mice; both studies gave positive results.

No new studies were available to the Working Group to evaluate the carcinogenicity of **benzo[*ghi*]perylene** in experimental animals.

Benzo[*c*]phenanthrene was tested for carcinogenicity by intraperitoneal injection into infant mice, which resulted in a substantial induction of lung tumours.

In several studies in which **benzo[*a*]pyrene** was applied to the skin of different strains of mice, benign and malignant skin tumours were observed. No skin tumours developed in mice that lacked the aryl hydrocarbon receptor ($AhR^{-/-}$ mice). In a large number of initiation–promotion studies, benzo[*a*]pyrene was active as an initiator when applied to the skin of mice.

In a series of studies in newborn and adult mice, intraperitoneal injection of benzo[*a*]pyrene increased the incidence of liver and lung tumours and, occasionally, that of forestomach and lymphoreticular tumours.

Subcutaneous injection of benzo[*a*]pyrene induced malignant tumours (mainly fibrosarcomas) at the injection site in mice, rats and hamsters. $AhR^{-/-}$ mice did not develop tumours.

Intratracheal administration of benzo[*a*]pyrene alone or mixed with particulates and suspended in saline with or without suspendents resulted in benign and malignant respiratory tumours in numerous studies in hamsters and in a few studies in rats and mice. Larger benzo[*a*]pyrene particles were generally more effective than smaller ones. Mice that lack the nucleotide excision repair gene *XPA* ($XPA^{-/-}$ mice) showed a stronger lung tumour response after intratracheal instillation of benzo[*a*]pyrene than their similarly treated $XPA^{+/+}$ and $XPA^{+/-}$ counterparts.

Following administration of benzo[*a*]pyrene by gavage or in the diet to mice and rats of different strains, increased tumour responses were found in several organs, including the lung, forestomach, liver, lymphoreticular tissue, oesophagus and tongue. Oral administration of benzo[*a*]pyrene to $XPA^{-/-}$ mice resulted in a significantly higher increase in lymphomas than that observed in similarly treated $XPA^{+/-}$ and $XPA^{+/+}$ mice. Benzo[*a*]pyrene administered by gavage to $XPA^{-/-}/p53^{+/-}$ double transgenic mice induced tumours (mainly splenic lymphomas and forestomach tumours) much earlier and at a higher incidence than in similarly treated single transgenic and wild-type counterparts. These cancer-prone $XPA^{-/-}$ or $XPA^{-/-}/p53^{+/-}$ mice also developed a high incidence of (mainly) forestomach tumours when fed benzo[*a*]pyrene in the diet.

Dose-related increases in the incidence of malignant lung tumours were found after injection of benzo[*a*]pyrene in beeswax/tricaprylin or beeswax/trioctanoin into the lung tissue of rats.

In a lifespan inhalation study in male hamsters, benzo[*a*]pyrene induced dose-related increases in the incidence of polyps, papillomas and squamous-cell carcinomas in both the upper respiratory tract (nose, larynx and trachea) and the upper digestive tract (pharynx, oesophagus and forestomach).

Repeated application of benzo[*a*]pyrene to the buccal pouch mucosa of male hamsters resulted in a high incidence of forestomach papillomas.

In rat subcutaneous tracheal grafts exposed to benzo[*a*]pyrene in beeswax, a high incidence of squamous-cell carcinomas was found. In one of 13 benzo[*a*]pyrene-exposed human bronchial grafts transplanted subcutaneously into nude mice, a squamous-cell carcinoma developed, while four other grafts developed preneoplastic epithelial changes.

In three studies in rats, benign and malignant mammary gland tumours developed after intramamillary administration of benzo[*a*]pyrene.

In three studies in mice, intracolonic instillation of benzo[*a*]pyrene induced a variety of benign and malignant tumours in various organs but no colonic tumours.

No new studies were available to the Working Group to evaluate the carcinogenicity of **benzo[*e*]pyrene** in experimental animals.

The carcinogenicity of **chrysene** was assessed in three studies in newborn mice, in three initiation–promotion studies in mice and after pulmonary implantation into rats.

Chrysene gave a positive response in two of three assays in newborn mice, in one of three initiation–promotion studies and in the pulmonary implantation study.

No new studies were available to the Working Group to evaluate the carcinogenicity of **coronene** in experimental animals.

4*H*-Cyclopenta[*def*]chrysene was tested for carcinogenicity in two initiation–promotion experiments in mice, in which a positive response was observed.

Cyclopenta[*cd*]pyrene was tested for carcinogenicity by repeated dermal exposure of mice and by intraperitoneal administration to newborn and adult mice. In all of these studies, cyclopenta[*cd*]pyrene gave a positive response.

5,6-Cyclopenteno-1,2-benzanthracene was tested for carcinogenicity in mouse skin in two similarly designed studies that were conducted in the same laboratory; both studies gave positive results.

Dibenz[*a,c*]anthracene was tested for carcinogenicity in an initiation–promotion study in mouse skin, but the results were questionable, presumably due to the low initiating doses of dibenz[*a,c*]anthracene that were used. Dibenz[*a,c*]anthracene gave negative results when administered subcutaneously to mice, and tumour incidence was not significantly increased over that observed in controls when the compound was administered intraperitoneally to newborn mice.

Dibenz[*a,h*]anthracene was tested for carcinogenicity by dermal application in mice, subcutaneous injection into mice and rats, intraperitoneal injection into mice, intrapulmonary injection into mice and rats and intramammary and intratracheal injection into rats. In the majority of these studies, dibenz[*a,h*]anthracene exhibited significant carcinogenic activity.

Dibenz[*a,j*]anthracene was tested for carcinogenicity in three studies on mouse skin, each of which showed a positive response.

No new studies were available to the Working Group to evaluate the carcinogenicity of **dibenzo[*a,e*]fluoranthene** in experimental animals.

13*H*-Dibenzo[*a,g*]fluorene was tested for carcinogenicity in two bioassays in which mice received repeated dermal applications. Both assays yielded positive results, although control groups were not included for comparison.

Dibenzo[*h,rst*]pentaphene was tested for carcinogenicity in one study in mice by subcutaneous injection and gave positive results.

Dibenzo[*a,e*]pyrene was assessed in two initiation–promotion studies on mouse skin. One of the studies gave positive results, while the other gave negative results. Dibenzo[*a,e*]pyrene gave negative results when tested for carcinogenicity by intramamillary administration to rats.

Dibenzo[*a,h*]pyrene was tested for carcinogenicity in one study on mouse skin, in three tumour initiation–promotion studies on mouse skin, by intraperitoneal injection into mice and by intramammary injection into rats. It exhibited significant carcinogenic activity in all of these studies.

Dibenzo[*a,i*]pyrene was tested for carcinogenicity in three initiation–promotion studies in mouse skin, one study of subcutaneous injection into mice, one study of

intraperitoneal administration to newborn mice, two studies of intratracheal administration to hamsters and one study of intramamillary administration to rats. All studies gave positive results.

Dibenzo[*a*,*l*]pyrene was tested for carcinogenicity in studies of single and repeated dermal application to mice, as well as several initiation–promotion studies on mouse skin; all studies gave positive results. Dibenzo[*a*,*l*]pyrene also induced oral cavity tumours when applied dermally to the tongue of hamsters, and lung tumours in mice following intraperitoneal injection. In addition to lung tumours, dibenzo[*a*,*l*]pyrene induced hepatic tumours and a variety of tumours at other sites when administered intraperitoneally to newborn mice. Multiple tumour sites were also observed following intragastric application of dibenzo[*a*,*l*]pyrene in mice. Intramamillary administration to rats also yielded positive results. Furthermore, two studies in fish demonstrated that non-mammalian species are also susceptible to dibenzo[*a*,*l*]pyrene-induced tumorigenicity.

Dibenzo[*e*,*l*]pyrene was tested for carcinogenicity in one study and in one initiation–promotion study on mouse skin, both of which gave negative results.

1,2-Dihydroaceanthrylene was tested in an early design-limited study by subcutaneous injection into mice and yielded negative results. More recently, it was tested in two intraperitoneal bioassays in newborn mice. In one assay, an increase in lung tumours was observed at the highest dose administered in males and females combined.

1,4-Dimethylphenanthrene was tested in two initiation–promotion studies in mice and gave positive results.

Fluoranthene was tested for carcinogenicity in four studies in newborn mice and in one study in mice by dermal application. All the studies in newborn mice gave positive results, whereas the study in mouse skin gave negative results.

No new studies were available to the Working Group to evaluate the carcinogenicity of **fluorene** in experimental animals.

Indeno[1,2,3-*cd*]pyrene was tested for carcinogenicity in two initiation–promotion studies in mice, both of which gave positive results, and by pulmonary injection into rats, which also yielded positive results. Indeno[1,2,3-*cd*]pyrene did not induce tumours in newborn mice following intraperitoneal injection. Indeno[1,2,3-*cd*]pyrene was administered subcutaneously to mice in an experiment that did not include control animals; sarcomas were observed.

No new studies were available to the Working Group to evaluate the carcinogenicity of **1-methylchrysene** in experimental animals.

No new studies were available to the Working Group to evaluate the carcinogenicity of **2-methylchrysene** in experimental animals.

No new studies were available to the Working Group to evaluate the carcinogenicity of **3-methylchrysene** in experimental animals.

No new studies were available to the Working Group to evaluate the carcinogenicity of **4-methylchrysene** in experimental animals.

5-Methylchrysene was tested for carcinogenicity in numerous initiation–promotion studies in mice and by intraperitoneal administration to newborn mice in one study and to adult mice in another study. All of these studies gave positive results.

No new studies were available to the Working Group to evaluate the carcinogenicity of **6-methylchrysene** in experimental animals.

2-Methylfluoranthene was tested for carcinogenicity in one study by intraperitoneal administration to newborn mice which gave positive results.

3-Methylfluoranthene was tested for carcinogenicity in one study by intraperitoneal injection to newborn male mice which gave positive results.

1-Methylphenanthrene was tested for carcinogenicity in an initiation–promotion study in mice and was negative.

Naphtho[1,2-*b*]fluoranthene was tested for carcinogenicity in one initiation–promotion experiment in mice that gave positive results.

Naphtho[2,1-*a*]fluoranthene was tested for carcinogenicity in one initiation–promotion experiment in mice that gave positive results.

Naphtho[2,3-*e*]pyrene was tested for carcinogenicity in one initiation–promotion experiment in mice and in one study by repeated dermal application in mice. The initiation–promotion study gave positive results; repeated dermal application gave negative results.

Perylene was tested for carcinogenicity by dermal application in mice (repeated dose and initiation–promotion protocols) and by intraperitoneal injection into mice. All studies gave negative results.

Phenanthrene was tested for carcinogenicity in one repeated-dose study on mouse skin and in one study of intrapulmonary injection into rats. Both studies gave negative results.

Picene was tested for carcinogenicity in an early design-limited study by dermal application in mice which gave negative results. More recently, picene was tested in three studies in mice by dermal application, two of which were initiation–promotion experiments. All three studies gave positive results. Picene has also been tested by subcutaneous injection into newborn and adult mice, and young rats. It gave positive results in mice and negative results in rats.

Pyrene was tested for carcinogenicity on mouse skin, in multiple studies in newborn mice and in A/J mice. All studies gave negative results.

No new studies were available to the Working Group to evaluate the carcinogenicity of **triphenylene** in experimental animals.

A number of studies assessed the carcinogenicity of **defined mixtures of PAHs** in different species using various treatment regimens. Examples include the co-administration of binary mixtures of strong (e.g. benzo[*a*]pyrene) and weak (e.g. benzo[*e*]pyrene) carcinogens onto mouse skin, using repeated dosing or initiation–promotion protocols, and the subcutaneous injection of binary mixtures of strong (e.g. benzo[*a*]pyrene) and weak (e.g. benzo[*e*]pyrene) or two strong (e.g. benzo[*a*]pyrene and dibenz[*a,h*]anthracene) carcinogens into mice. In some experiments, tumorigenic responses were consistent

with an additive effect. In other instances, the tumorigenic responses were less than or greater than the anticipated additive response. The reasons for these variations in tumorigenicity were not apparent. Additional experiments included the administration of multiple PAHs, including those with both strong and weak carcinogenic potential. As with the binary mixtures, the responses were varied; nevertheless, at low doses of the mixtures, greater than additive responses were observed while, at high doses, these were less than additive, perhaps due to metabolic saturation.

The carcinogenicity of a variety of **coal-tar preparations** has been assessed in various species. The carcinogenicity of solvent-refined coal distillates and their subfractions was assessed in two initiation–promotion studies in mice, both of which gave positive results. Coaltar-based paints were evaluated in one initiation–promotion study and one study by oral administration to mice; both gave positive results. Crude coal-tar preparations were assessed in two studies in mouse skin (one of which used repeated doses and the other used an initiation–promotion protocol). The study with repeated doses was inadequate for an evaluation of carcinogenicity, but the initiation–promotion study gave positive results. Coal-tar pitch was assessed by repeated application onto mouse skin in four studies, all of which gave positive results. Manufactured gas plant residues were evaluated in two studies of oral administration to mice and one study in newborn mice. All gave positive results.

5.4 Mechanism of action and other relevant data

Exposure to PAHs, most of which are associated with a solid or liquid matrix in aerosols of polluted air or food, occurs through the airways, skin and digestive tract. The bioavailabilities of individual PAHs may differ and contribute to differences in activity, particularly for those that contain five or more aromatic rings. Bioavailable fractions of PAHs are absorbed into the circulation through all three routes. Metabolic activation of lipophilic PAHs occurs primarily in the liver, but also in many other tissues, including the epithelial barriers. Although distribution through the circulatory system is widespread, slow absorption through most epithelia results in higher levels of enzymes that activate PAH substrates at the site of entry. This uneven distribution of dose is a factor that may contribute to the high propensity of PAHs to act as carcinogens at the sites where they enter the body.

PAHs are metabolized by phase I enzymes and peroxidases, which produce DNA-reactive metabolites, and phase II enzymes, which form polar conjugates. Phase I enzymes, such as cytochrome P450s, catalyse the mono-oxygenation of PAHs to form phenols and epoxides. Specific cytochrome P450 isozymes and epoxide hydrolase can form reactive diol epoxides that comprise one class of ultimate carcinogenic metabolites of many PAHs. Both cytochrome P450s and peroxidases can form radical cations by one-electron oxidation that comprise another class of ultimate carcinogenic metabolites. Further oxidation of PAH phenols leads to the formation of PAH quinones. The major cytochrome P450s that are involved in the formation of diol epoxides are 1A1, 1A2 and

1B1, while 2C9 and 3A4 play a minor role in the activation of PAHs. PAHs induce increased expression of activating cytochrome P450s via enhanced aryl hydrocarbon receptor-mediated transcription. Polymorphisms in human cytochrome P450s have been identified, some of which may be associated with increased susceptibility. Additional enzymes that may play a role in the further activation of some PAH diols include members of the aldo-keto reductase family, among which polymorphisms that influence susceptibility have been identified. Nicotinamide adenine dinucleotide phosphate:quinone oxidoreductase 1 catalyses the reduction of PAH quinones to hydroquinones which may be re-oxidized and generate reactive oxygen species. Polymorphisms in this gene have also been described.

The major phase II enzymes include the glutathione *S*-transferases, uridine 5′-diphosphate glucuronosyltransferases and sulfotransferases . The major glutathione *S*-transferases involved in the conjugation of PAH metabolites are M1, P1 and T1. Multiple polymorphisms of these as well as polymorphisms in both uridine 5′-diphosphate glucuronosyl- and sulfotransferases have been identified, some of which can modulate susceptibility to cancer.

The current understanding of the carcinogenesis of PAHs in experimental animals is almost solely based on two complementary mechanisms: those of the diol epoxide and the radical cation. Each provides a different explanation for the data observed in experimental animals.

The diol epoxide mechanism features a sequence of metabolic transformations of PAHs, each of which leads to potentially reactive genotoxic forms. In general, PAHs are converted to oxides and dihydrodiols, which are in turn oxidized to diol epoxides. Both oxides and diol epoxides are ultimate DNA-reactive metabolites. PAH oxides can form stable DNA adducts and diol epoxides can form stable and depurinating adducts with DNA through electrophilic carbonium ions. The inherent reactivities of oxides and diol epoxides are dependent on topology (e.g. bay regions, fjord regions, cyclopenta rings), and the reactivity of diol epoxides is further dependent on factors such as stereochemistry and degree of planarity. Both stable and depurinating adducts are formed primarily with guanines and adenines, and induce mutations (e.g. in *ras* proto-oncogenes) that are strongly associated with the tumorigenic process. Some mutagenic PAH diols, oxides and diol epoxides are tumorigenic in experimental animals.

One-electron oxidation creates radical cations at a specific position on some PAHs. The ease of formation and relative stabilities of radical cations are related to the ionization potential of the PAH. Additional important factors in the radical cation mechanism are localization of charge in the PAH radical cation and optimal geometric configuration, particularly the presence of an angular ring. The radical cation mechanism results in the formation of depurinating DNA adducts with guanines and adenines, which generate apurinic sites that can induce mutations in *ras* proto-oncogenes, which are strongly associated with tumorigenesis.

There is strong evidence that the diol epoxide mechanism operates in the mouse lung tumorigenesis of many PAHs evaluated in this monograph. For some PAHs, there is

strong evidence that both radical cation and diol epoxide mechanisms induce mouse skin carcinogenesis. Many of the pathways that lead to PAH carcinogenesis involve genotoxicity, and the genotoxic effects of PAHs and their metabolites were included in the overall evaluation of each PAH discussed.

The genotoxic effects of exposure to complex mixtures that contain PAHs have been studied in some populations exposed in industrial settings and in patients who undergo coal-tar therapy. Measured end-points include mutagenicity in urine and the presence of aromatic DNA adducts in the peripheral lymphocytes of exposed workers. In some studies, specific benzo[*a*]pyrene–DNA adducts have been measured. Cytogenetic effects such as micronucleus formation have also been reported.

Other mechanisms of carcinogenesis have been proposed for PAHs, but these are less well developed. The *ortho*-quinone/reactive oxygen species mechanism features enzymatic oxidation of non-K-region PAH diols to *ortho*-quinones by aldo-keto reductases, and has been studied only in in-vitro systems. These PAH *ortho*-quinones are highly reactive towards DNA; they yield DNA adducts and damage DNA. PAH *ortho*-quinones induce mutations in the *p53* tumour-suppressor gene *in vitro*; they can also undergo repetitive redox cycling and generate reactive oxygen species, which have been associated with oxidative DNA-base damage as well as the induction of pro-oxidant signals that may have consequences on growth. Reactive oxygen species can also be produced by other mechanisms such as the formation of PAH quinones through peroxidase reactions. Thus, this pathway has the potential to contribute to the complete carcinogenicity of a parent PAH.

The mechanism of meso-region biomethylation and benzylic oxidation features biomethylation of parent PAHs to methyl PAHs. Methyl PAHs are further metabolized by cytochrome P450s to hydroxymethyl PAHs that are converted into reactive sulfate ester forms that are capable of forming DNA adducts. Studies on this mechanism have been limited to subcutaneous tissues in rats that are susceptible to PAH tumorigenesis.

Several of the biological effects of PAHs, such as enzyme induction of xenobiotic metabolizing enzymes, immunosuppression, teratogenicity and carcinogenicity, are thought to be mediated by activation of the aryl hydrocarbon receptor. This receptor is widely distributed and has been detected in most cells and tissues. There is also evidence that the aryl hydrocarbon receptor acts through a variety of pathways and, more recently, that cross-talk with other nuclear receptors enables cell type-specific and tissue-specific control of gene expression. Translocation of the activated aryl hydrocarbon receptor to the nucleus may require threshold concentrations of the ligand. Various oxidative and electrophilic PAH metabolites are also known to induce enzyme systems via anti-oxidant receptor elements. The biological effects of aryl hydrocarbon receptor and anti-oxidant receptor element signalling involve a variety of cellular responses, including regulation of phase I and II metabolism, lipid peroxidation, production of arachidonic acid-reactive metabolites, decreased levels of serum thyroxine and vitamin A and persistent activation of the thyroid hormone receptor. Aryl hydrocarbon receptor signalling may result in adaptive and toxic responses or perturbations of endogenous pathways. Furthermore,

metabolic activation of PAHs produces cellular stress. This in turn activates mitogen-mediated protein kinase pathways, notably of Nrf2. The Nrf2 protein dimerizes with Maf-oncoproteins to enable binding to an anti-oxidant/electrophilic response element, which has been identified in many phase I/II and other cellular defence enzymes and controls their expression. Therefore, cellular stress may be regulated independently of aryl hydrocarbon receptor-mediated xenobiotic metabolizing enzymes.

PAHs exert many important effects on the immune system of many species. The dose and route of exposure determine the nature of the effect of specific and adaptive immune responses. Extremely limited or no data are available on many of the pure PAHs (with the exception of benzo[*a*]pyrene) and complex mixtures considered in this monograph. Studies with those PAHs that have been investigated indicate that the aryl hydrocarbon receptor plays a critical role in the activation of immunotoxic PAHs via diol epoxide mechanisms that lead to DNA interactions, cause genotoxicity and suppress immunity by p53-dependent pathways. Benzo[*a*]pyrene diol epoxide may also affect protein targets and modulate lymphocyte signalling pathways via non-genotoxic (epigenetic) mechanisms. Certain PAH metabolites, such as benzo[*a*]pyrene quinones, may be formed via cytochrome P450-dependent and -independent (peroxidase) pathways, and redox-cycling PAH quinones may exert oxidative stress in lymphoid cells. Human exposures usually involve complex mixtures of PAHs, and it is difficult to attribute the relative contributions of individual PAHs to the overall immunotoxic effects. There is some evidence that human environmental exposures to PAHs may produce immunotoxicity, but further studies are needed.

Since PAHs are ubiquitous in the environment, and concomitant exposure of humans to PAHs and ultraviolet light is inevitable, the photomutagenicity and photocarcinogenicity of these compounds are of considerable importance to human health. PAH-contaminated skin may be exposed to sunlight, which is of greatest concern in outdoor workers who handle products that contain PAHs. Such workers include roofers, tanners and road construction workers. Some commercial medicines also contain PAHs. For example, coal tar, a complex mixture of PAHs, is widely used in creams, ointments, lotions and shampoos for the treatment of psoriasis (the Goeckerman therapy). A topical application of coal tar on the skin followed by irradiation with ultraviolet light has been found to increase the risk for developing skin cancer.

PAHs must be metabolically activated in order to induce tumours. However, individuals differ in their ability to metabolize PAHs: people who are deficient in particular enzymes that activate PAHs to reactive metabolites may be at a lower risk for chemical carcinogenesis, whereas deficiencies in enzymes that detoxify reactive metabolites may increase this risk. Some of the epidemiological studies that have been conducted to date have shown positive relationships between genetic polymorphisms of drug-metabolizing enzymes and susceptibility to cancer, while others have been inconclusive. Many factors, including race, age, sex, tobacco smoking, alcohol intake and genetic factors, could induce or inhibit drug-metabolizing activities which indicates that a

complex interaction exists. Multi-gene and exposure interactions may also play a complex role in the interpretation of any increases in risk.

Newborn animals treated with benzo[*a*]pyrene or dimethylbenz[*a*]anthracene have been shown to develop higher incidences of liver and lung tumours than animals treated later in life. The age-dependent susceptibility to these two compounds may be dependent on their ability to act as mutagens. Analyses of data on a variety of chemicals for which tumour incidence following perinatal exposure was compared with that following adult exposure show that the increased susceptibility may be linked to a mutagenic mechanism of action. In addition, studies on the carcinogenicity of dimethylbenz[*a*]anthracene indicate that a potential period of increased susceptibility to mammary tumorigenesis exists during the pubertal period of development.

The available data on the effects of PAHs other than cancer are sparse, with the exception of reproductive or developmental and immunological studies. Chronic bioassays are available for benzo[*a*]pyrene, but they do not include histological analyses. Short-term studies, however, indicate that limited hepato- and nephrotoxic effects occur at high doses. Human exposure to polluted air containing mixtures of PAHs and animal studies with individual PAHs indicate that these compounds may affect the developing fetus and impair male and female reproductive performance.

Mechanistic considerations pertinent to the evaluations

In making its evaluations of the compounds below, the Working Group considered the following mechanistic data.

Benz[*j*]aceanthrylene is mutagenic in bacteria and in mammalian cells. It causes morphological cell transformation in mouse embryonic fibroblasts. K-*Ras* codon 12 mutations are found in benz[*j*]aceanthrylene-induced lung adenomas in mice. Benz[*j*]-aceanthrylene-1,2-diol, which is formed by cyclopenta-ring oxidation of the parent compound, is found in rodent liver and lung tissue. This metabolite is also formed *in vitro* in the presence of human microsomes. Benz[*j*]aceanthrylene-1,2-oxide is mutagenic in bacteria and causes malignant cell transformation in mouse embryonic fibroblasts. Benz[*j*]aceanthrylene-9,10-diol and benz[*j*]aceanthrylene-9,10-diol-7,8-oxide, which are formed via the diol epoxide pathway, are mutagenic in bacteria, cause malignant cell transformation in mouse embryonic fibroblasts and form DNA adducts in these cells. Benz[*j*]aceanthrylene-9,10-diol-7,8-oxide–DNA adducts have been found in benz[*j*]aceanthrylene-induced lung tumours in mice.

There is strong evidence that benz[*j*]aceanthrylene is activated via cyclopenta-ring oxidation and the formation of its diol epoxide.

The Working Group did not review all the mechanistic data on **benzo[*c*]phenanthrene**, but concluded that the formation of its diol epoxide as a mechanism for tumorigenesis is consistent with its activity as a mouse skin tumour initiator in a limited number of studies.

The complete sequence of steps in the metabolic activation pathway of **benzo[*a*]pyrene** to mutagenic and carcinogenic diol epoxides has been demonstrated in experimental animals, in human tissues and in humans. Following exposure, humans metabolically activate benzo[*a*]pyrene to benzo[*a*]pyrene diol epoxides that form DNA adducts: the *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide–deoxyguanosine adduct has been measured in populations (e.g. coke-oven workers, chimney sweeps) exposed to PAH mixtures that contain benzo[*a*]pyrene. The reactive *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide induces mutations in rodent and human cells. Mutations (G→T transversions) in the K-*ras* proto-oncogene in lung tumours from benzo[*a*]pyrene-treated mice are associated with *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide–deoxyguanosine adducts. Similar mutations in the K-*RAS* proto-oncogene and mutations in *TP53* were found in lung tumours from nonsmokers exposed to PAH-rich products of coal combustion that are known to contain benzo[*a*]pyrene (as well as many other PAHs). In an in-vitro study, the codons in the tumour-suppressor gene *TP53* that are most frequently mutated in human lung cancer were shown to be targets for DNA adduct formation and mutations induced by benzo[*a*]pyrene.

Cyclopenta[*cd*]pyrene induces mutation in bacteria, in mammalian cells and in various human cell lines that express cytochrome P450 1A1. It causes sister chromatid exchange and morphological cell transformation in mouse embryonic fibroblasts. Two major classes of K-*ras* oncogene mutations are found in lung adenomas from cyclopenta[*cd*]pyrene-treated mice. Cyclopenta[*cd*]pyrene-3,4-oxide is mutagenic in bacteria and in mammalian cells, and induces morphological cell transformation in mouse embryo fibroblasts. DNA adducts with deoxyguanosine and deoxyadenosine are found in the lungs of mice treated with cyclopenta[*cd*]pyrene. Cyclopenta[*cd*]pyrene-3,4-diol and 4-hydroxy-3,4-dihydro-cyclopenta[*cd*]pyrene are mutagenic in bacteria in the presence of 3′-phosphadenosine-phosphosulfate. 4-Sulfooxy-3,4-dihydrocyclopenta[*cd*]pyrene is a direct mutagen in bacteria. Human liver microsomes and recombinant human cytochrome P450 1A1, 1A2 and 3A4 metabolize cyclopenta[*cd*]pyrene at the cyclopenta ring.

There is strong evidence that activation via cyclopenta-ring oxidation is the mechanism by which cyclopenta[*cd*]pyrene is tumorigenic in mouse lung.

Dibenz[*a,h*]anthracene induces DNA damage and mutation in bacteria, DNA damage in cultured rodent and human cells, mutation and chromosomal damage in rodent cells in culture and morphological cell transformation in mouse embryonic fibroblasts. It induces sister chromatid exchange and micronucleus formation in lung cells and micronucleus formation in bone marrow and spleen erythrocytes of rats treated by intratracheal instillation. Dibenz[*a,h*]anthracene-3,4-diols (racemic mixture and the individual stereoisomers) are mutagenic in bacteria. Racemic dibenz[*a,h*]anthracene-3,4-diol induces tumours in mouse skin and lung. Dibenz[*a,h*]anthracene-3,4-diol-1,2-oxide induces morphological cell transformation in mouse embryonic fibroblasts. Racemic dibenz[*a,h*]anthracene-3,4-diol-1,2-oxide is tumorigenic in mouse skin. Dibenz[*a,h*]-anthracene is metabolized to dibenz[*a,h*]anthracene-3,4-diol by recombinant human liver cytochrome P450s and by human liver microsomes. Human skin treated with dibenz[*a,h*]-

anthracene in short-term culture shows an adduct profile that is qualitatively similar to that seen in mouse skin treated *in vivo*. There is moderate evidence that activation via the formation of the diol epoxide is the mechanism by which dibenz[*a,h*]anthracene is tumorigenic in mouse skin.

The complete sequence of metabolic activation of **dibenzo[*a,l*]pyrene** has been demonstrated in experimental animals and in human cells in culture. Dibenzo[*a,l*]pyrene is mutagenic in bacteria, in mammalian cells and in human cell lines. It causes morphological cell transformation in mouse embryonic fibroblasts. Dibenzo[*a,l*]pyrene induces Ki-*ras* mutations at codon 12 and 61 in mouse lung adenomas, and Ha-*ras* mutations at codon 61 in mouse skin papillomas. Dibenzo[*a,l*]pyrene-11,12-diol forms DNA adducts in Chinese hamster V79 cells that express recombinant human cytochrome P450 1A1 and is mutagenic in Chinese hamster V79 cells in the presence of metabolic activation systems. Recombinant human cytochrome P450 1B1, expressed in Chinese hamster V79 cells, metabolizes dibenzo[*a,l*]pyrene-11,12-diol to reactive metabolites that form dibenzo[*a,l*]pyrene–11,12-diol-13,14-oxide adducts. Dibenzo[*a,l*]pyrene-11,12-diols (racemic mixture) induce tumours in mouse skin and lung. Dibenzo[*a,l*]pyrene-11,12-diol-13,14-epoxides (racemic mixture) are mutagenic in bacteria and in mammalian cells and induce tumours in the skin and lung of mice and in breast tissue of rats.

There is strong evidence that the diol epoxide metabolic pathway is a mechanism in the induction of lung tumours in dibenzo[*a,l*]pyrene-treated mice and that the radical cation and diol epoxide metabolic pathways are mechanisms in dibenzo[*a,l*]pyrene-induced mouse skin tumorigenesis. The enzymes that metabolize dibenzo[*a,l*]pyrene to its reactive diol epoxides (cytochrome P450 1A1 and 1B1) are present in human tissues and in human mammary cells in culture. Mutations (G→T transversions) in the K-*ras* proto-oncogene in lung tumours from dibenzo[*a,l*]pyrene-treated mice are associated with *anti*-dibenzo[*a,l*]pyrene-11,12-diol-13,14-oxide–DNA adducts. Similar mutations in the K-*RAS* proto-oncogene were found in lung tumours from nonsmokers exposed to PAH-rich products of coal combustion that are known to contain dibenzo[*a,l*]pyrene (as well as many other PAHs).

5.5 Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of occupational exposures during coal gasification. There is *sufficient evidence* in experimental animals for the carcinogenicity of manufactured gas plant residues.

There is *sufficient evidence* in humans for the carcinogenicity of occupational exposures during coke production. There is *sufficient evidence* in experimental animals for the carcinogenicity of coke-oven coal-tar samples. There is *inadequate evidence* in experimental animals for the carcinogenicity of crude coal-tar preparations.

There is *sufficient evidence* in humans for the carcinogenicity of occupational exposures during coal-tar distillation. There is *sufficient evidence* in experimental animals for the carcinogenicity of solvent-refined coal distillates.

There is *sufficient evidence* in humans for the carcinogenicity of occupational exposure as a chimney sweep. There is *sufficient evidence* in experimental animals for the carcinogenicity of soot extracts. There is *inadequate evidence* in experimental animals for the carcinogenicity of soots.

There is *sufficient evidence* in humans for the carcinogenicity of occupational exposures during paving and roofing with coal-tar pitch. There is *sufficient evidence* in experimental animals for the carcinogenicity of coal-tar pitch.

There is *sufficient evidence* in humans for the carcinogenicity of occupational exposures during aluminium production.

There is *limited evidence* in humans for the carcinogenicity of occupational exposures during carbon electrode manufacture.

There is *inadequate evidence* in humans for the carcinogenicity of occupational exposures during calcium carbide production.

There is *limited evidence* in humans for the carcinogenicity of creosotes. There is *sufficient evidence* in experimental animals for the carcinogenicity of creosotes.

There is *sufficient evidence* in experimental animals for the carcinogenicity of benz[*a*]anthracene, benzo[*b*]fluoranthene, benzo[*j*]fluoranthene, benzo[*k*]fluoranthene, benzo[*a*]pyrene, chrysene, cyclopenta[*cd*]pyrene, dibenz[*a*,*h*]anthracene, dibenzo[*a*,*h*]-pyrene, dibenzo[*a*,*i*]pyrene, dibenzo[*a*,*l*]pyrene, indeno[1,2,3-*cd*]pyrene and 5-methyl-chrysene.

There is *limited evidence* in experimental animals for the carcinogenicity of anthanthrene, benz[*j*]aceanthrylene, benzo[*c*]fluorene, benzo[*c*]phenanthrene, dibenz[*a*,*c*]-anthracene, dibenz[*a*,*j*]anthracene, dibenzo[*a*,*e*]fluoranthene, 13*H*-dibenzo[*a*,*g*]fluorene, dibenzo[*a*,*e*]pyrene, fluoranthene, 2-methylchrysene, 3-methylchrysene, 4-methylchrysene, 6-methylchrysene, 2-methylfluoranthene and picene.

There is *inadequate evidence* in experimental animals for the carcinogenicity of acenaphthene, acepyrene (3,4-dihydrocyclopenta[*cd*]pyrene), anthracene, 11*H*-benz[*bc*]aceanthrylene, benz[*l*]aceanthrylene, benzo[*b*]chrysene, benzo[*g*]chrysene, benzo[*a*]fluoranthene, benzo[*ghi*]fluoranthene, benzo[*a*]fluorene, benzo[*b*]fluorene, benzo[*ghi*]perylene, benzo[*e*]pyrene, coronene, 4*H*-cyclopenta[*def*]chrysene, 5,6-cyclopenteno-1,2-benzanthracene, dibenzo[*h*,*rst*]pentaphene, dibenzo[*e*,*l*]pyrene, 1,2-dihydroaceanthrylene, 1,4-dimethylphenanthrene, fluorene, 1-methylchrysene, 3-methylfluoranthene, 1-methylphenanthrene, naphtho[1,2-*b*]fluoranthene, naphtho[2,1-*a*]fluoranthene, naphtho[2,3-*e*]pyrene, perylene, phenanthrene, pyrene and triphenylene.

Overall evaluation

Occupational exposures during coal gasification are *carcinogenic to humans (Group 1)*.

Occupational exposures during coke production are *carcinogenic to humans (Group 1)*.

Occupational exposures during coal-tar distillation are *carcinogenic to humans (Group 1)*.

Occupational exposure as a chimney sweep is *carcinogenic to humans (Group 1)*.

Occupational exposures during paving and roofing with coal-tar pitch are *carcinogenic to humans (Group 1)*.

Occupational exposures during aluminium production are *carcinogenic to humans (Group 1)*.

Occupational exposures during carbon electrode manufacture are probably *carcinogenic to humans (Group 2A)*.

Occupational exposures during calcium carbide production are *not classifiable as to their carcinogenicity to humans (Group 3)*.

Creosotes are *probably carcinogenic to humans (Group 2A)*.

Benzo[*a*]pyrene is *carcinogenic to humans (Group 1)*.

Cyclopenta[*cd*]pyrene, dibenz[*a*,*h*]anthracene and dibenzo[*a*,*l*]pyrene are *probably carcinogenic to humans (Group 2A)*.

Benz[*j*]aceanthrylene, benz[*a*]anthracene, benzo[*b*]fluoranthene, benzo[*j*]fluoranthene, benzo[*k*]fluoranthene, benzo[*c*]phenanthrene, chrysene, dibenzo[*a*,*h*]pyrene, dibenzo[*a*,*i*]-pyrene, indeno[1,2,3-*cd*]pyrene and 5-methylchrysene are *possibly carcinogenic to humans (Group 2B)*.

Acenaphthene, acepyrene (3,4-dihydrocyclopenta[*cd*]pyrene), anthanthrene, anthracene, 11*H*-benz[*bc*]aceanthrylene, benz[*l*]aceanthrylene, benzo[*b*]chrysene, benzo[*g*]-chrysene, benzo[*a*]fluoranthene, benzo[*ghi*]fluoranthene, benzo[*a*]fluorene, benzo[*b*]fluorene, benzo[*c*]fluorene, benzo[*ghi*]perylene, benzo[*e*]pyrene, coronene, 4*H*-cyclopenta-[*def*]chrysene, 5,6-cyclopenteno-1,2-benzanthracene, dibenz[*a*,*c*]anthracene, dibenz[*a*,*j*]-anthracene, dibenzo[*a*,*e*]fluoranthene, 13*H*-dibenzo[*a*,*g*]fluorene, dibenzo[*h*,*rst*]pentaphene, dibenzo[*a*,*e*]pyrene, dibenzo[*e*,*l*]pyrene, 1,2-dihydroaceanthrylene, 1,4-dimethyl-phenanthrene, fluoranthene, fluorene, 1-methylchrysene, 2-methylchrysene, 3-methyl-chrysene, 4-methylchrysene, 6-methylchrysene, 2-methylfluoranthene, 3-methyl-fluoranthene, 1-methylphenanthrene, naphtho[1,2-*b*]fluoranthene, naphtho[2,1-*a*]-fluoranthene, naphtho[2,3-*e*]pyrene, perylene, phenanthrene, picene, pyrene and triphenylene are *not classifiable as to their carcinogenicity to humans (Group 3)*.

In making the overall evaluations of benz[*j*]aceanthrylene, benzo[*c*]phenanthrene, benzo[*a*]pyrene, cyclopenta[*cd*]pyrene, dibenzo[*a*,*h*]anthracene and dibenzo[*a*,*l*]pyrene, the Working Group took into consideration the mechanistic data detailed in Section 5.4.