COKE PRODUCTION

Coke production and associated exposures were considered by previous IARC Working Groups in 1983, 1987, and 2005 (IARC, 1984, 1987, 2010). Since that time new data have become available, which have been incorporated in this *Monograph,* and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Production process

Coke was first produced commercially in England in the early eighteenth century. By the early to mid-1800s, coke was being widely produced in Europe and the United States of America as the major fuel for blast furnaces.

Coal carbonization is a process that yields metallurgical coke for use in iron-making blast furnaces and other metal-smelting processes. Carbonization entails heating the coal to temperatures as high as 1300 °C in the absence of oxygen to distill out tars and light oils. A gaseous by-product, referred to as coke-oven gas, together with ammonia, water and sulfur compounds are also removed thermally from the coal. The coke that remains after this distillation largely consists of carbon in various crystallographic forms, but also contains the thermally modified remains of various minerals that were in the original coal. These mineral residues, commonly referred to as coke ash are not combustible and are left after the coke is burned. Coke also contains part of the sulfur from the coal. Coke is principally used as a fuel, as a reducing agent and support for other raw materials in iron-making blast furnaces. A much smaller amount of coke is used similarly in cupola furnaces in the foundry industry. The carbonization by-products are usually refined within the coke plant to commodity chemicals such as elemental sulfur, ammonium sulfate, benzene, toluene, xylene and naphthalene. Subsequent processing of these chemicals produces a large number of other chemicals and materials. Coke-oven gas is a valuable heating fuel that is used mainly within steel plants, for example, to fire blast-furnace stoves, to soak furnaces for semi-finished steel, to anneal furnaces and lime kilns as well as to heat the coke ovens themselves (Kaegi *et al.*, 1993).

Coke is mostly produced from slot-type by-product coke ovens. Above the ovens is a roof system from which coal is discharged into each oven. Modern technology includes telescopic charging chutes to minimize dust emissions during charging. Many facilities also include automatic removal and replacement of the charging-hole lid. Volatile gases generated from the coal during carbonization flow to the top of the oven, into the free space and out through standpipes connected to large collecting mains that transport the gases to the by-product plant in which they are processed into various materials. Water is sprayed into the mains to cool the

Table 1.1 Concentrations of PAHs in the air and in urine of workers in coke ovens

Reference Country Year of study	Job/task	No. of subjects	No. of samples	No. of smokers	PAH	Air levels (μg/m³)		Urinary levels (μmol/mol creatinine)	
						Mean	Range	Mean	Range
Yrjänheikki *et al.* (1995) Finland 1987–90	Coke oven 4 working areas 10 working areas	160	510 dust; 90 gas	NR	 Fluorene Phenanthrene Benzo[*a*]pyrene	 0.58–24.64 0.16–18.76 0.05–10.30			
Liu *et al.* (2006) China NR	Coke oven	47	47	12	**1-Hydroxypyrene** All Non-smokers Smokers			**Median** 5.7 3.0 6.8	 1.4–12 0.6–6.9 2.6–14.5 (s)
Yang et al. (2007) China NR	Coke oven	101	101	77	Total PAH			**Mean**	
	Top	4 (20)				22.83	SD, 0.86	8.49	3.90
	Side	4 (27)				8.70	SD, 2.22	5.2 [a]	NR
	Bottom	4 (25)				6.04	SD, 1.85	1.79	3.71
	Adjunct workplaces	8 (29)				5.60	SD, 0.87	1.51	3.60
Marczynski *et al.* (2009) Germany 1999–2003	Coke oven	37	37	27	Sum of 16 PAHs 1-Hydroxypyrene Sum of hydroxy-phenanthrene Benzo[*a*]pyrene	22.5 1.0	15.9–91.0 0.4–2.5	 2.0 3.5	 1.1–3.6 2.1–7.5
Rossella *et al.* (2009) Poland NR	Coke oven/ maintenance	50/5	54	54	1-Hydroxypyrene			15.4 [b]	1.1–147.1

NR, not reported; PAH, polycyclic aromatic hydrocarbons; SD, standard deviation

[a] Read from figure

[b] Median

Conversions used for 1-hydroxypyrene: 1 μmol/mol creatinine = 1.93 μg/g creatinine = 0.013 μmol/L = 2.84 μg/L = 2.84 ng/mL.

gases and to condense out some of the tar. At the end of the coking cycle – which ranges from about 15 to 30 hours –, the coke is pushed into a hot car (quench car). The hot car may or may not have a moveable roof or partial roof to minimize gaseous and particulate emissions. The hot coke is then quenched before being dropped onto a conveyor system for transportation to a blast furnace, storage pile or out of the plant (Kaegi *et al.*, 1993; Crelling *et al.*, 2005). For a more detailed description of the coke production process and coke ovens, the reader is referred to the previous *IARC Monograph* (IARC (2010).

In 1990, total worldwide coke production was about 378 million tonnes, a production volume that had remained essentially unchanged since 1970. The former USSR was the largest coke producer (80 million tonnes), followed by the People's Republic of China (73 million tonnes), Japan (53 million tonnes) and the United States of America (USA) (27 million tonnes). Since 1970, production in the former USSR has remained in the 75–85 million tonne range, but massive shifts in production have occurred in the USA, Japan and China. Between 1970 and 1990, production in the USA decreased by more than 50% while Japanese production increased by 50%. During the same period, China increased coke production more than threefold (Kaegi *et al.*, 1993). By 1999, worldwide coke production had declined to about 326 million tonnes, of which 121 million tonnes were produced in China (Terjung, 2000).

1.2 Human exposure

Coke-oven workers are primarily exposed to polycyclic aromatic hydrocarbons (PAHs). Concentrations of PAHs in the ambient air and in urine of workers in coke ovens are summarized in Table 1.1. In addition to PAHs, coke-oven workers may be exposed to a large number of compounds, including asbestos, silica, amines, arsenic, cadmium, lead, nickel, vanadium, hydrocarbons, sulfur dioxide, sulfuric acid and aldehydes (IARC, 1984).

More than 30 studies on occupational exposure of coke-oven workers have been reported since 1983, of which six included profiles of three PAHs or more; seven others reported levels of pyrene, benzo[*a*]pyrene or both; the other studies reported composite measures (benzene-soluble fraction, cyclohexane-soluble material) or provided data on biological measurements only. A variety of sites across the coke plants were sampled, and the overall pattern (regardless of the exposure measured) was that topside workers (including lidmen, tar chasers and Larry-car operators) had the highest exposures, followed by workers by the side of the ovens (such as coke-side machine operators, bench-men, door repairers, wharf-men, quenchers, pushers and temperature controllers). Workers in other areas of the plant such as maintenance, office and control workers had the lowest exposures (Table 1.1). Modernization of coke plants, including improved control measures, can substantially reduce exposures (Quinlan *et al.*, 1995c).

2. Cancer in Humans

Occupational exposures during coke production were evaluated most recently in *IARC Monograph* Volume 92 (IARC, 2010). There was *sufficient evidence* in epidemiological studies for the carcinogenicity of occupational exposures during coke production, although the evidence was not uniform. A marked excess of lung cancer and a clear trend of increasing risk for this cancer with increasing duration of exposure was found in a large cohort study from the USA and Canada (Costantino *et al.*, 1995; see Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-13-Table2.1.pdf). In an even larger study from China there was also a marked lung-cancer excess (Wu, 1988). In cohort studies

from France (Chau *et al.*, 1993), Italy (Franco *et al.*, 1993), Japan (Sakabe *et al.*, 1975), and the Netherlands (Swaen *et al.*, 1991) increased risks for lung cancer were found consistently, although not all results were statistically significant. No excess of lung cancer was observed in three cohort studies of coke-plant workers in the United Kingdom (Buck & Reid, 1956; Davies, 1977; Hurley *et al.*, 1983), but an excess had been found in an earlier record-linkage study in the United Kingdom (Kennaway & Kennaway, 1947). A smoking-adjusted excess risk for lung cancer and a positive association with duration of exposure to coke-oven emissions was found in a population-based case–control study of Chinese women (Wu-Williams *et al.*, 1993; see Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-13-Table2.2.pdf). No further epidemiological studies of coke-oven workers have been published since the previous *IARC Monograph* (IARC, 2010).

Overall, an increased risk for lung cancer was found in three large studies, two of which showed evidence of a dose–response; one study was adjusted for smoking. A lung-cancer excess is supported by several but not all other available studies. Thus, there is evidence from epidemiological studies that lung cancer is causally associated with occupational exposures during coke production. The evidence is inadequate to allow and evaluation for cancer of the bladder and skin.

3. Cancer in Experimental Animals

Samples of tar from coke ovens were previously evaluated in *IARC Monograph* Volume 34 (IARC, 1984). No new studies have been published since then.

3.1 Skin application

Two samples were collected from a modern coke oven: a topside air-particulate sample and a coke-oven main sample. The coke-oven topside sample was found to contain 478 mg/kg benzo[*a*]pyrene (Nesnow *et al.*, 1982, 1983).

The coke-oven main sample was applied topically to groups of 40 male and 40 female SENCAR mice at doses of 0 (control), 0.1, 0.5, 1.0, 2.0 or 4.0 mg (in acetone) per mouse on a weekly basis, except for the highest dose, which was applied twice weekly at 2.0 mg per application, for 50–52 weeks. The incidence of skin carcinomas ranged from 5–98% in groups of treated mice. No carcinomas were observed in the control groups (Nesnow *et al.*, 1983).

The tumour-promoting activity of the coke-oven main sample was tested by repeated weekly dermal applications of 0 (control), 0.1, 0.5, 1.0, 2.0 and 4.0 mg (in acetone) for 34 weeks to groups of 40 male and 40 female SENCAR mice pre-treated (one week earlier) with a dermal dose of 50.5 µg benzo[*a*]pyrene. Skin papilloma incidence was reported to increase from 3–100% over the dose range of the coke-oven main sample tested. No papillomas were observed in the control groups (Nesnow *et al.*, 1983).

The tumour-initiating activity of both samples mentioned above was studied with groups of 40 male and 40 female SENCAR mice that were skin-painted once with 0 (control), 0.1, 0.5, 1.0, 2.0 or 10 mg of each sample dissolved in acetone. The 10-mg dose was administered in split doses of 2.0 mg each for 5 days. Beginning one week later, 2 µg of 12-*O*-tetradecanoylphorbol-13-acetate were administered topically, twice weekly. The incidence of skin papillomas and carcinomas was reported after six months and one year, respectively. Both the topside and main samples produced dose-related increases in both papillomas and carcinomas. For the topside sample, the papilloma incidence ranged from 10–100% and the carcinoma incidence was 0–20%, while

for the coke-oven main sample, the incidence of papillomas ranged from 31–100% and of carcinomas from 10–65%. In the control groups, the incidences of papillomas and carcinomas ranged from 5–8% and 0–5%, respectively (Nesnow *et al.*, 1982, 1983).

3.2 Inhalation

3.2.1 Mouse

The carcinogenicity of coke-oven tar (from a USA by-product coke oven) was investigated in C3H mice. In the untreated control group, all 30 mice survived for the duration of the experiment (71 weeks) and did not develop any squamous-cell tumours of the lung. A second group of 33 mice was exposed to a coal-tar aerosol at 300 mg/m^3 for two hours daily, three times weekly, during weeks 35–71 of the experiment. Five squamous-cell tumours of the lung, one of which was malignant, occurred in this group (Horton *et al.*, 1963).

In another experiment, the tar (Tar 1) from the same source as that in the study by Horton *et al.* (1963) and another tar (Tar 2) were separated into phenolic (P-Tar) and non-phenolic (N-Tar) fractions. Both tars were derived from USA by-product coke ovens. Aerosols were produced from these fractions and animals were exposed to the aerosols, separate or in combination, at 120–200 mg/m^3, three times per week for 55 weeks. Six groups of 50 male C3H/HeJ mice were treated with air only (control) or with aerosols of Tar 1, N-Tar 1, N-Tar 1 + P-Tar 1, N-Tar 1 + P-Tar 2 or N-Tar 2 + P-Tar 1. The experiment was terminated at 55 weeks. Lung tumours were recorded in animals that survived beyond 46 weeks. Lung-adenoma incidence was 0/32 (control), 12/13, 16/20, 14/19, 14/25 and 14/23, respectively. Lung-adenocarcinoma incidence was 0/32 (control), 3/13, 0/20, 1/19, 1/25, 0/23, respectively (Tye & Stemmer, 1967).

Groups of 75 CAF_1-JAX and 75 ICR-CF1 female mice were exposed for 90 days to concentrations of coal-tar aerosol of 0.2, 2.0 and 10 mg/m^3 (99% of the droplets were ≤ 5 μm in size), and were observed for a further 21 weeks. The aerosol consisted of a composite mixture of benzene/toluene/xylene fractions of coal tars collected from the effluents of several different coke ovens in the USA. Unexposed controls of each strain of mice were included in the study. Lung-tumour data were not available. The incidence of skin tumours [not further specified] was 1/61, 14/75 and 44/55, respectively, in the exposed ICR-CF1 mice, and 3/225 in the controls. In the exposed groups of CAF_1-JAX mice, the skin-tumour incidences were 0/75, 3/65 and 18/43, respectively, with 0/225 in the controls (MacEwen *et al.*, 1976). [The Working Group noted the lack of solvent controls.]

A group of 75 female ICR-CF1 mice and a group of 50 female CAF_1-JAX mice were exposed to the coal-tar aerosol described above at a concentration of 10 mg/m^3 for six hours per day, five days per week, for 18 months; unexposed controls of both strains were available. Alveologenic carcinomas were observed in 26/61 exposed ICR-CF1 mice, 27/50 exposed CAF_1-JAX mice, 3/68 ICR-CF1 controls and 8/48 CAF_1-JAX controls. The exposed and control groups did not differ in the incidence of other types of tumours, including skin tumours (MacEwen *et al.*, 1976). [The Working Group noted the lack of solvent controls.]

3.2.2 Rat

A group of 40 male and a group of 40 female CFE strain Sprague-Dawley weanling rats were exposed to the aerosol described above at a concentration of 10 mg/m^3 for six hours per day, five days per week, for 18 months; 40 male and 40 female unexposed controls were available. Among treated rats, 38/38 males and 31/38 females developed squamous-cell carcinomas of the lung. In the control groups, no such tumours were observed in 36 males and 37 females (MacEwen *et al.*, 1976). [The Working Group noted the lack of solvent controls.]

4. Other Relevant Data

4.1 Mechanistic evidence relevant to the carcinogenic hazard from occupational exposures during coke production

4.1.1 Experimental systems

Experimental studies of the effects of exposure to coke-oven emissions have been evaluated in previous *IARC Monographs* (IARC, 1984, 1987, 2010). Emissions from coke ovens were mutagenic to *Salmonella typhimurium* TA98 and TA100, both with and without exogenous metabolic activation, and in several mammalian cell systems: L5178Y mouse lymphoma $Tk^{+/-}$ cells with and without metabolic activation, Chinese hamster ovary cells (6-thioguanine resistance), and BALB/c 3T3 cells (ouabain resistance). Coke-oven emissions induced DNA strand-breakage in Syrian hamster embryo cells, and sister chromatid exchange in Chinese hamster ovary cells with and without exogenous metabolic activation. These emissions also caused morphological transformation in BALB/c 3T3 cells without activation.

PAHs are a component of coke-oven mixtures and many carcinogenic PAHs are genotoxic in *in-vitro* and *in-vivo* bioassay systems. Examples are benz[*a*]anthracene, benzo[*a*]pyrene, benzo[*c*]phenanthrene, benzo[*b*]fluoranthene, and benzo[*j*]fluoranthene (IARC, 1984). Many of the genotoxic effects induced by coke-oven emissions in experimental systems have also been found after exposure to individual carcinogenic PAHs (IARC, 1983; Osborne & Crosby, 1987; Harvey, 1991). The extent to which PAHs contribute to the genotoxic activity of coke-oven emissions is not known, but the available evidence strongly suggests that they do make a contribution. Some insight into the role of PAHs in genotoxicity and cancer associated with coke production can be obtained from DNA-adduct studies in experimental animals exposed to coke-oven emissions. In rats exposed to such emissions by inhalation one major adduct was detected by the [^{32}P]-postlabelling procedure. This adduct had the same chromatographic mobility as the major *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide-(BPDE)-N^2-deoxyguanosine adduct resulting from incubation of *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide with calf thymus DNA. This adduct was observed in DNA from lung, heart, and liver of the exposed rats. However, the autoradiograms also showed evidence of a complex mixture of unidentified aromatic adducts (Binková *et al.*, 1994). Mice topically exposed to coke-oven emissions showed some evidence of the formation of a BPDE-DNA adduct (Lewtas *et al.*, 1993). Although the studies in exposed rats and mice provided some evidence with respect to an *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide adduct, many other DNA adducts remained unidentified and their contribution to the total DNA-adduct profile cannot be ascertained. In addition, these DNA-adduct studies are dependent on the availability of fully characterized PAH-DNA adduct standards and in many [^{32}P]-postlabelling experiments only the *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide-DNA adduct was used as a reference. This adduct has been correlated with specific mutations in the oncogene, K_i-*Ras*, found in lung tumours induced by benzo[*a*]pyrene in mice (Ross & Nesnow, 1999). Moreover, K_i-*RAS* mutations are common in human lung tumours (Vineis & Caporaso, 1995).

4.1.2 Humans

As was previously reported (IARC, 1987), peripheral blood lymphocytes of coke-oven workers had increased frequencies of sister chromatid exchange (SCE) compared with age-matched controls. Also, in one study the urine of coke-oven workers was mutagenic in *Salmonella typhimurium* in the presence of an exogenous

metabolic system. Numerous subsequent studies largely confirmed these results.

In an Italian study, no differences in frequencies of chromosome aberrations and micronuclei were found in cultured lymphocytes of 92 coke-oven workers in a steel-production plant and a group of 19 controls from a non-oven plant in the same area (Forni *et al.*, 1996). In Germany, a group of 29 coke-oven workers and a control group were studied for frequencies of DNA single-strand breaks, DNA–protein crosslinks (measured with an alkaline filter-elution assay), SCE, and DNA adducts in lymphocytes. DNA strand-breaks in lymphocytes of coke-oven workers were significantly higher than in controls (Popp *et al.*, 1997). Eleven of 31 male non-smoking coke-oven workers in Poland produced urine that was mutagenic in *Salmonella typhimurium* strain YG1024 in the presence of an exogenous source of metabolic activation, compared with urine samples of 31 male non-smoking controls (Simioli *et al.*, 2004). 8-Oxodeoxyguanosine levels in white blood cells and the amount of DNA damage (measured with the comet assay) in lymphocytes were higher in 20 German coke-oven workers than in 55 controls (Marczynski *et al.*, 2002). Urinary 8-oxodeoxyguanosine concentrations were higher in 55 Taiwan, Chinaese topside coke-oven workers than in 162 side-oven workers (Wu *et al.*, 2003). In another study from Taiwan, China, elevated levels of 8-oxodeoxyguanosine in urine, micronuclei in lymphocytes, and glutathione *S*-transferase in serum were found in 47 workers exposed to coke-oven emissions, compared with the levels in 31 controls (Liu *et al.*, 2006). In a study of 49 Polish coke-oven workers the micronucleus frequency in peripheral blood lymphocytes was related to specific *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide-DNA-adduct formation in the same subject (Pavanello *et al.*, 2008a). Chinese coke-oven workers (n = 141) had higher frequencies of micronuclei, nucleoplasmic bridges, and nuclear buds compared with the values in 66 controls; the number of nucleoplasmic bridges and nuclear buds correlated with 1-hydroxypyrene concentrations in urine (Duan *et al.*, 2009).

A significant correlation was found between the concentrations of 1-hydroxypyrene and 8-oxodeoxyguanosine in urine from a group of 91 coke-oven workers in Taiwan, China, compared with 49 controls (Hu *et al.*, 2004), while a Japanese/Chinese study of 119 coke oven workers and 37 controls could not find a correlation between 8-oxodeoxyguanosine levels in leukocytes and 1-hydroxypyrene concentrations in urine (Zhang *et al.*, 2003). In a group of 37 German coke-oven workers the level of 8-oxodeoxyguanosine and the number of DNA strand-breaks (measured with the comet assay) were higher than in 48 controls (Marczynski *et al.*, 2009).

The mutant frequency at the *HPRT* locus (6-thioguanine resistance) in lymphocytes from a population of 43 Italian coke-oven workers was increased compared with the frequency in 26 non-exposed controls, but the difference was not significant. The percentages of the different types of gene alteration were also similar in exposed and non-exposed subjects, based on an analysis of mutations in 161 *HPRT* clones derived from the two groups. Only the frequency of splice mutations in mutant clones derived from coke-oven workers was significantly higher than in controls (Zanesi *et al.*, 1998). No difference in the plasma concentrations of either p53 (mutated or wild-type) or p21(WAF1) protein was found between 66 coke-oven workers and 44 controls in the Czech Republic, but significantly higher amounts of these proteins were found in the subgroup exposed to carcinogenic PAHs at concentrations of < 1 μg/m^3 compared with the group exposed to carcinogenic PAHs > 1 μg/m^3. Overall, a negative correlation between the concentration of p53 protein in plasma and personal exposure to carcinogenic PAHs was found (Rössner *et al.*, 2003). In another study from the Czech Republic, cytogenetic markers (chromosomal aberrations, SCE,

cells with a high frequency of SCE, the heterogeneity index SCE, and polymorphism of the genes *GSTM1* and *NAT2*) were evaluated in the peripheral lymphocytes of 64 coke-oven workers and 34 control subjects from the same plant. All the cytogenetic markers were significantly increased in the exposed workers compared with the control group, also when smoking status was taken into account. No effects of the *GSTM1* and *NAT2* genotypes on the cytogenetic markers were noted (Kalina *et al.*, 1998).

The effect of polymorphisms in genes involved in DNA repair was evaluated by means of the comet assay in isolated peripheral blood lymphocytes from 94 coke-oven workers in North-eastern China and 64 controls. One of the *XRCC1* genotypes, Arg399Gln, was associated with an increased frequency of micronuclei in the coke-oven workers (Cheng *et al.*, 2009).

Coke-oven workers have been extensively studied for the presence of biomarkers of exposure, in some cases with mixed results due to methodological issues, small sample size, inter-individual variability, and confounding factors, such as smoking and diet. However, there are several key studies that show clear relationships between exposures to coke-oven emissions and certain biomarkers. The literature is dominated by studies that examined *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide-DNA adducts as a biomarker of exposure. The amount of this adduct has been found to be increased in peripheral blood lymphocytes of male coke-oven workers compared with controls in several studies of different worker populations (Pavanello *et al.*, 1999a, 2004; Chen *et al.*, 2003). In some of these studies, analysis of genetic polymorphisms showed that the *GSTM1-null* detoxifying genotype and some low-activity nucleotide excision-repair (NER) genotypes were associated with higher *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide-DNA-adduct formation (Pavanello *et al.*, 1999b, 2004, 2005).

In 35 Dutch coke-oven workers a significant induction of aromatic DNA adducts in lymphocytes and of micronuclei in exfoliated urothelial cells was found compared with the levels in 37 controls (van Delft *et al.*, 2001). When 89 French coke-oven workers were compared with 18 power-plant workers with respect to *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide-DNA-adduct levels and genetic polymorphisms in the *CYP1A1*, *GSTM1* and *GSTT1* genes, higher numbers of DNA adducts were detected in individuals with the combined *CYP1A1(1/*2* or **2A/*2A)-GSTM1-null* genotype (Rojas *et al.*, 2000). In Polish coke-oven workers the influence was studied of four polymorphisms of nucleotide excision-repair genes and of *GSTM1* on *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide-DNA-adduct levels in lymphocytes and monocytes. The increase in DNA-adduct levels was significantly related to lack of GSTM1 activity and to the low nucleotide excision-repair capacity of the *XPC-PAT*$^{+/+}$ genotype (Pavanello *et al.*, 2005). In other studies by the same group, *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide-DNA-adduct levels were significantly increased in peripheral blood lymphocytes of coke-oven workers compared with controls, after adjustment for smoking status and diet (Pavanello *et al.*, 2004, 2008a). In one study from China, formation of the *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide-albumin adduct was associated with exposure to coke-oven emissions, after adjustment for smoking status (Wang *et al.*, 2007).

Based on the available evidence from studies in experimental systems, coke-oven emissions are mutagenic in bacteria and in mammalian cells, induce DNA damage, SCE, and morphological cell transformation. DNA-adduct data from experimental studies suggest that coke-oven emissions produce a complex mixture of aromatic adducts, one being identified as *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide-N^2-deoxyguanosine. Genotoxic effects of exposures to coke-oven emissions have been studied in

surrogate tissues from populations in industrial settings. Measured end-points include 8-oxodeoxyguanosine levels, DNA strand-breaks, SCE, micronuclei, chromosomal aberrations, and urinary mutagenicity. The increased 8-oxodeoxyguanosine levels reflect increased oxidative stress. This could be a result of redox cycling of PAH quinones and the damaging effects of reactive intermediates on cellular antioxidant levels (Joseph & Jaiswal, 1998; Klaunig & Kamendulis, 2004; Park *et al.*, 2009).

Chronic exposure to PAH in Polish non-smoking coke-oven workers induced both gene-specific (e.g. in the *TP53* gene) and global methylation changes in peripheral blood lymphocytes. These changes were correlated with BPDE-DNA adduct levels and micronuclei in the same subjects (Pavanello *et al.*, 2009).

4.2 Synthesis

Overall, these data strongly indicate a mutagenic/genotoxic mode of action for occupational exposures during coke production, based on experimental and human studies. The data also identify lung as a target, given the major route of human exposure, based on both experimental and human studies. There is ample mechanistic support for the respiratory carcinogenic effects of occupational exposures during coke production in humans, in part through analysis of exposure to benzo[*a*]pyrene. This is based on direct measurement of *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide-DNA adducts in peripheral blood lymphocytes (surrogate tissue) and on the identification of genotoxic effects consistent with those induced by *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide or benzo[*a*]pyrene. It is also consistent with the known carcinogenic activity of this epoxide in lung tissues in experimental animals. Moreover, the influence of *GST* polymorphisms on levels of *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide-DNA adducts is suggestive of the presence of reactive electrophilic intermediates, such as *anti*-benzo[*a*]pyrene-7,8-diol-9,10-oxide. Since coke-oven emissions are complex mixtures, these exposures could have more than one underlying mechanism of action. The fact that chronic exposure to PAH in Polish non-smoking coke-oven workers induced both gene-specific (e.g. in the *TP53* gene) and global methylation changes in peripheral blood lymphocytes, suggests an epigenetic mechanism.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of coke production. Coke production causes cancer of the lung.

There is *sufficient* evidence in experimental animals for the carcinogenicity of samples of tar taken from coke ovens.

There is strong evidence for a genotoxic mechanism underlying the effects of occupational exposures during coke production, based on both experimental and human studies.

The detection of anti-benzo[*a*]pyrene-7,8-diol-9,10-epoxide-DNA adducts in the peripheral blood lymphocytes in exposed populations suggests the participation of benzo[*a*]pyrene in the genotoxic mechanism for this exposure in humans.

Coke production is *carcinogenic to humans (Group 1).*

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