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Carbon Black

by Eileen D. Kuempel PhD and Tom Sorahan PhD

Citation for most recent IARC review

IARC Monographs Volume 93 (in press)

Current evaluation

Conclusion from the previous Monograph: Carbon black is *possibly carcinogenic to humans (Group 2B)* based on sufficient evidence in experimental animals and inadequate evidence from epidemiological studies.

Exposure and biomonitoring

Carbon black is a powdered form of elemental carbon manufactured by the controlled vapor-phase hydrolysis of hydrocarbons. Different types of carbon black have a wide range of particle sizes, surface areas per unit mass, and contents of toluene-extractable materials. Carbon black is variously known as acetylene black, channel black, furnace black, lampblack or thermal black depending on the specific process by which it is manufactured.

Occupational exposure

Some 8,000 inhalable dust measurements and 7,400 respirable dust measurements were taken in the period 1987-92 at 19 carbon black production plants as part of a European respiratory morbidity study (Gardiner et al., 1996). Arithmetic mean respirable dust exposures were shown for various job titles including process operator (0.41 mg.m.-3) and warehouse packer (0.78 mg.m-3). Estimates of occupational exposure to carbon black have been incorporated into the UK and German cohort mortality studies of carbon black production workers but not in the United States study of carbon black production workers. It seems likely that carbon black exposures in these cohorts are much higher than those found in user industries such as rubber manufacture and newspaper printing.

Environmental exposures

No data were found on environmental exposures to carbon black. The ambient fine mode particulate matter <2.5 μm in diameter (PM2.5) consists mainly of combustion-derived carbonaceous particles (fine and ultrafine sizes) with organic compounds and transition metals adsorbed on the surfaces (Stoeger et al., 2006).

Cancer in humans

(*inadequate*, Vol 93, in prep)

A Working Group from the International Agency for Research on Cancer (IARC) met in 2006 to review the available literature on cancer risks from exposure to carbon black. Three cohort studies of carbon black production workers were available, relating to plants in the UK (Sorahan et al., 2001), Germany (Wellman et al., 2006; Morfeld et al., 2006), and the USA (Dell et al., 2006). The focus of these three studies was on possible excess risks of lung cancer. Cohort studies of rubber workers exposed to carbon black were also available (e.g. Straif et al., 2000), but these studies are not considered here because of the difficulties of controlling for all potential lung carcinogens in the rubber industry.

UK carbon black production workers

The cohort study of UK carbon black production workers included follow-up details of 1,147 male manual workers employed for at least twelve months at one of the five main UK plants (Sorahan et al., 2001). The definition of the factory sub-cohorts differed but all workers were first employed before 1975; follow-up was analyzed for the period 1951-96 and expectations were based on mortality rates for the general population of England and Wales. Mortality from lung cancer was elevated (Observed 61, SMR 173, 95% CI 132 to 222), whereas mortality from all other causes combined was not (Observed 311, SMR 106, 95% CI 95 to 118). Exposures to carbon black were considerable. For example, it was estimated that process workers in the 1960s had typical exposures of 4.0-7.0 $mg.m^{-3}$ and bag packers in the 1960s had typical exposures of 15.0-20.0 $mg.m^{-3}$. Poisson regression analyses found no significant positive trends of lung cancer risks with estimated cumulative exposure (lagged or unlagged) to carbon black.

German carbon black production workers

The cohort study of German carbon black production workers included follow-up details of 1,535 male manual workers employed for at least twelve months in the period 1960-98 at a single German plant (Wellmann et al., 2006). All study subjects had to be alive on 1st January,

1976, and follow-up was analyzed for the period 1976-98. Expectations were based on mortality rates for the general population of Germany. Lung cancer mortality was significantly elevated (Observed 50, SMR 218, 95% CI 161 to 287), in contrast with mortality from all other causes (Observed 282, SMR 111, 95% CI 99 to 125). A Cox regression analysis of these data (Morfeld et al., 2006) did not find cumulative exposure (lagged or unlagged) to be positive predictors of lung cancer risk.

U.S. carbon black production workers

The cohort study of U.S. carbon black production workers included follow-up details of 5,011 workers with potential exposure to carbon black, whilst employed for at least twelve months at one of the eighteen U.S. plants (Dell et al., 2006). The definition of the factory sub-cohorts differed but all workers were first employed between the mid-1930's and the end of 2003; follow-up was analyzed for the same period. Expectations were based on mortality rates for the general U.S. population, specified by age, sex, calendar year, and race. Mortality from lung cancer was not elevated (Observed 138, SMR 97, 95% CI 82 to 115). This observed figure included 11 deaths of unknown cause (15% of the 76 deaths with unascertained cause of death). Mortality from all other causes was significantly depressed (Observed 1,188, SMR 72, 95% CI 68 to 76), suggesting a possible failure to trace all deaths, or incorrect allocation of person-years-at-risk. Work history details were not collected and, consequently, no analyses of lung cancer risks in relation to quantitative estimates of carbon black exposure have been attempted.

Recent Studies

Sorahan and Harrington (2007) updated the UK mortality study to the end of 2004. Based on serial rates for the general population of England and Wales, significantly elevated mortality was observed for lung cancer (Observed 67, SMR 146, 95% CI 113 to 185) but not for all other causes combined (Observed 426, SMR 106, 95% CI 97 to 117). There was highly elevated lung cancer mortality at two of the plants but no excess mortality at the other three plants combined. Analyses by period since leaving employment indicated elevated lung cancer risks were limited to those workers with some employment in the most recent 15 years. SMR analyses found an overall positive significant trend between lung cancer risks and cumulative carbon black exposure received in the most recent 15 years (so-called 'lugged' analysis). Poisson regression analyses provided different results depending on which variables were adjusted for. The authors concluded that carbon black, or chemicals associated with the production of carbon black, may have had an effect on late stages of lung cancer carcinogenesis at two of the plants but that no such effect was found at the other plants.

Morfeld and McCunney (2007) re-analyzed data from the German cohort but found no evidence of lung cancer SMRs declining with period since leaving employment. The same authors have now carried out further tests of the hypothesis that carbon black is a late stage human lung carcinogen, but find no suggestion of "lugged" exposures (cumulative exposures in recent years) being related to lung cancer risks (Morfeld and McCunney, 2009).

A summary of findings from the three available cohorts of carbon black production workers is shown in Table 1.

Table 1. Summary of lung cancer findings from cohort studies of carbon black production workers.

					Relationship between lung cancer risks and estimated cumulative exposure to carbon black		
Country	Obs	Exp	SMR	(95% CI)	Lifetime[a]	Lagged[b]	Lugged[c]
UK	67	45.9	146	(113 to 185)	No	no	Yes
Germany	50	23.0	218	(161 to 287)	No	no	No
USA	138	142.1	97	(82 to 115)	n/k	n/k	n/k
Total	255	211.0	121	(107 to 137)			

n/k not known
a. total
b. distant exposure.
c. recent exposure.

Cancer in experimental animals

(*sufficient*, Vol 93, in prep)

Previous Studies

Two chronic inhalation studies and two intratracheal instillation studies found significantly elevated lung cancer in rats exposed to carbon black.

Heinrich et al. (1995)
Rats (female Wistar Crl:(WI)BR) were exposed by whole-body inhalation, 18 hr/d, 5 d/wk for 24 months, to furnace black (Printex 90, primary particle size 14 nm; specific surface area 227 $\pm$ 18.8 m^2/g) at an average airborne concentration of 11.5 mg/m^3, then kept in clean air for another 6 months. At 30 months, 39/100 exposed rats had lung tumors (11 of which had benign cystic keratinizing squamous cell tumors only), whereas 1 of the 217 control (unexposed) rats had a lung tumor (adenocarcinoma).

Mice (female Crl:NMRI BR) were exposed to furnace black (Printex 90, primary particle size 14 nm; specific surface area 227 m^2/g) for 18 h/day, 5 d/wk, 13.5 months, to an average airborne concentration of 11.5 mg/m^3 (whole-body inhalation) then kept in clean air for another 9.5 months. The lung tumor incidence in the exposed mice was not significantly elevated compared to that in control (unexposed) mice, which had a high background tumor incidence (not related to carbon black exposure).

Nikula et al. (1995)

Rats (male and female Fischer 344/N) were exposed for 16 hr/day, 5 d/wk, for up to 24 months to 2.5 or 6.5 mg/m^3 furnace black (Elftex-12; particle size distribution: 1.95 µm (67%) and 0.1 µm (33%)). The tumor response was 8/213 and 25/211, respectively, in rats exposed to 2.5 or 6.5 mg/m^3, compared to 2/214 in control (unexposed) rats.

Intratracheal Instillation
Rats (female Wistar) were exposed by intratracheal instillation, once per week for 15 weeks, to furnace black Printex 90 (specific surface area 270 m^2/g; 3 mg/rat). Control rats were treated with the vehicle control (0.4 ml of 0.9% saline). At 131 weeks, 24 (65%) of the treated rats had benign and malignant lung tumors, while no tumors were observed in the control rats (Pott and Roller 1994; Pott et al., 1994).

Rats (female Wistar Crl:(WI)BR) received intratracheal instillation, once per week (approximately 1 mg/rat) for 16-17 weeks, to furnace black Printex 90 (specific surface area 270 m^2/g; primary particle size 14 nm) or Lampblack 101 (specific surface area 22 m^2/g; primary particle size 95 nm). Control rats were treated with the vehicle control (0.9% sodium chloride, 0.25% Tween 80 solution). At 27 months, the tumor incidence was 10/48 in rats treated with Printex 90 (benign and malignant), and 4/48 rats treated with lampblack 101 had benign squamous cell tumors. No lung tumors were observed in the control rats (Heinrich et al., 1994; Dasenbrock et al., 1996).

Other routes of exposure
In a study of C57B1 mice exposed by subcutaneous injection of 300 mg of furnace black containing benzo[a]pyrene, 18/46 mice developed subcutaneous sarcoma (Steiner 1954). In Wistar rats exposed by intraperitoneal injection (once per week for 4 weeks) with 20 mg of furnace black, 1 of the 35 treated rats developed an abdominal sarcoma (Pott et al., 1991).

Recent Studies

No carcinogenicity studies of carbon black in animals were found in the literature except those already reported in Monograph 93 (in press), discussed above.

Mechanisms of carcinogenicity

Carbon black appears to act like other poorly soluble low toxicity (PSLT) particles, which can elicit lung tumors in rats following prolonged exposure to sufficiently high concentrations of particles (Monograph 93 (in press); Baan 2007). Particle surface area dose was found to be most predictive of pulmonary inflammation and tumor response in rats when comparing the dose-response relationships for various types and sizes of PSLT including carbon black (Driscoll 1995; Elder et al., 2005). Compared to fine PSLT, much lower concentrations of ultrafine PSLT (e.g. 2.5, 6.5 or 11.5 mg/m^3 carbon black and ~10 mg/m^3 ultrafine titanium dioxide) were associated with impaired clearance, persistent inflammation, and malignant lung tumors in chronic inhalation studies in rats (Heinrich et al., 1995; Nikula et al., 1995). The retained particle volume, grouped by particle size, was also shown to describe the rat lung tumor responses to various PSLT administered by intratracheal instillation (Roller and Pott 2006).

Most evidence suggests that carbon black and other PSLT-elicited lung tumors occurs through a secondary genotoxic mechanism, involving chronic inflammation and oxidative stress (Knaapen et al., 2003). Experimental studies have shown that when the particle lung dose reaches a sufficiently high concentration (e.g., mass dose of ~0.5 mg fine-sized PSLT/g lung in rats), the alveolar macrophage-medicated clearance process begins to be impaired (complete impairment occurs at ~10 mg/g lung (Muhle et al., 1990)). Overloading of lung clearance is accompanied by pulmonary inflammation, leading to increased production of reactive oxygen and nitrogen species, depletion of antioxidants and/or impairment of other defense mechanisms, cell injury, cell proliferation, fibrosis, and as seen in rats, induction of mutations and eventually cancer.

Rats appear to be more sensitive to carbon black and other PSLT than other rodent species that have been tested. Fisher-344 rats had more severe and persistent lung responses (inflammation and histological changes) than those in B6C3F1 mice or F1B Syrian golden hamsters at equivalent exposure concentrations (females of each species) (Elder et al., 2005). Rats also had a greater proinflammatory response and a lower antioxidant response than mice or hamsters (Carter et al., 2006), indicating a greater oxidative stress response in rat lungs. Gallagher et al. (2003) observed dose-related progressive oxidative DNA damage in the lungs of rats exposed to carbon black.

Although studies in humans have not shown a direct link between inhaled PSLT and lung cancer, many of the steps in the mechanism observed in rats have also been observed in humans who work in dusty jobs, including increased particle lung retention and pulmonary inflammation in workers exposed to coal dust or crystalline silica (Castranova 2000; Kuempel et al., 2001; Lapp and Castranova 1993); and elevated lung cancer has been observed in some studies of workers exposed to carbon black (Sorahan and Harrington 2007), crystalline silica (Rice et al., 2001; Attfield and Costello 2004), and diesel exhaust particles (Stayner et al., 1998).

Recent studies

Recent findings have strengthened the association between inflammation and cancer (Hussain and Harris 2007; Calin and Croce 2006), and between the particle surface area dose of carbon black and other PSLT particles and the pulmonary inflammation response in mice (Stoeger et al., 2006) and rats (Duffin et al., 2007; Sager and Castranova 2009), and the proinflammatory effects in lung cells *in vitro* (Duffin et al., 2007; Hussain et al., 2009). Recent evidence suggests that in addition to a cancer mechanism involving indirect genotoxicity through inflammation and oxidative stress, nanoparticles may act as direct carcinogens (Mroz et al., 2008; Schins and Knaapen 2007), although additional research is needed in this area.

Recent finding concerning microRNA-mediated gene regulation in immune response during inflammation provide additional mechanistic information for an association between chronic inflammation and cancer (Hussain and Harris 2007). MicroRNAs, which are small gene-silencing RNAs that cause cleavage and degradation of target RNA, are involved in the innate immune response during inflammation and have been linked to the initiation and progression

of human cancer (Calin and Croce 2006). Studies to date have not investigated the role of microRNA in particle-elicited inflammation and cancer.

In an study of six different ultrafine carbon particles administered to mice (female BALB/cJ) by intratracheal instillation, the particle surface area dose correlated best with the inflammatory response (Stoeger et al., 2006). A no observed adverse effect level (NOAEL) of 20 cm^2 per mouse was observed for acute inflammation in healthy, in-bred mice. By comparison, mortality studies in humans in association with ambient fine particle air pollution have not shown any evidence of a threshold dose-response relationship (Schwartz et al., 2002), which may reflect a greater susceptibility to the effects of particulate air pollution in sensitive individuals such elderly individuals with preexisting cardiopulmonary diseases.

Duffin et al. (2007) investigated the role of particle surface area on acute pulmonary inflammation in a male Wistar rats, which were instilled with 125 µg of fine carbon black (surface area 9.9 cm^2) or nanoparticle carbon black (surface area 317 cm^2), in addition to titanium dioxide and polystyrene of different sizes (0.5 ml saline control). Rats were killed 18-24 hr later, and the number and type of cells in the lung was determine by bronchoalveolar lavage (BAL). A linear relationship between particle surface area and neutrophil cell count in BAL fluid was observed for all particle types and sizes (R^2=0.99), while no clear dose-response relationship was observed with the particle mass dose metric. *In vitro*, a linear relationship was also observed between the surface area dose of these PSLT particles and the induction of the proinflammatory cytokine IL-8.

Sager and Castranova (2009) investigated the role of particle surface area on pulmonary inflammation in male Fischer 344 rats treated with either fine or ultrafine carbon black by intratracheal instillation. The mass doses of ultrafine carbon black (primary particle diameter 14 nm; specific surface area 269 m^2/g; 0.047, 0.094, and 0.19 mg/rat) and fine carbon black (primary particle diameter 260 nm; specific surface area 8 m^2/g; 1.53, 3.06, and 6.12 mg/rat) corresponded to an equivalent surface area dose (0.031, 0.062, 0.12 cm^2 particles / cm^2 alveolar epithelial cell surface of the lungs). At each post-exposure time point (1, 7, or 42 days) and mass dose, the ultrafine carbon black was at least 65 times more potent than fine carbon black in eliciting pulmonary inflammation (as measured by neutrophil cell count in BAL fluid, relative to control (saline only) rats). When dose was expressed as particle surface area (measured by BET gas absorption technique (Brunauer et al., 1938)), the ultrafine carbon black was less than two times more potent than fine carbon black, and this difference was not statistically significant.

In an *in vitro* study of carbon black and titanium dioxide in a human bronchial epithelial cell line (16HBE14o-), Hussain et al. (2009) found that oxidative stress (production of reactive oxygen species) correlated with the BET-measured particle surface area of carbon black or titanium dioxide and with the internalized amount of nanoparticles (confirmed for titanium dioxide only by energy dispersion spectroscopy). The primary particle size of the carbon black nanoparticles was 13, 21, and 95 nm, and doses ranged from 5 to 160 $\mu g/cm^2$ (24-760 µg/ml); cells were treated for 24 hours.

In an *in vitro* study in a human epithelial cell line (A549), Mroz et al. (2008) were treated with several types and sizes of particles, including fine carbon black (primary particle diameter 260 nm) and nanoparticle carbon black (Printex 90, primary particle diameter 14 nm), at doses of 100 µg/ml. Nanoparticle carbon black and other nanoparticles tested caused single-strand DNA breaks, disruption of cell cycle kinetics, and induction of genes involved in cell signaling pathways, while fine carbon black did not. Urban dust caused both single and double-strand DNA breaks. The nanoparticles elicited reactive oxygen species, DNA damage, and activation of p53 and proteins related to DNA repair, which reportedly mimics the processes induced in irradiation carcinogenesis pathways.

Ultrafine carbon black (Printex 90) was selected as being representative of the carbon core of combustion particles in an *in vitro* study of components of particulate air pollution using two human epithelial cell lines (alveolar type II-derived A549 cells and bronchial-derived BEAS-2B cells) (Ovrevik et al., 2009). Despite different physical and chemical properties, the compounds tested showed similar responses to the positive control crystalline silica, suggesting that the generation of reactive oxygen species may be a common mechanism for all the particles tested. The predominant response was increased gene expression of the neutrophil-recruiting CXC-chemokines.

Translocation of ultrafine black (Printex 90, 14 nm diameter) from the lungs in mice following intratracheal instillation was observed by electron microscopy (Shimada et al., 2006). Particles were seen in gaps between lung epithelial cells, inside the capillary lumen in the lungs, and attached to red blood cells. This study suggests possible pathways for the distribution of ultrafine carbon black from the lungs, which may influence biological responses including in the immune system.

Biomarkers of exposure

No biomarkers of exposure were found that would be observed at lower doses than markers of early effect. For example, chest x-ray or computerized tomography may show deposits of particles in the lungs, but by the time these opacities are visible, adverse lung effects are also likely to have occurred. Markers of early effect may be more sensitive.

Biomarkers of effect

The genes involved in the early response to inhaled ultrafine carbon particles were elucidated in mice (female BALB/cJ) exposed by inhalation to ultrafine carbon particles (produced by electric spark generator from ultrapure graphite electrodes in an argon atmosphere) at an average mass concentration of 380 µg/m^3 for 4 or 24 hours (Andre et al., 2006). Upregulation of mRNA expression for immune-modulatory genes (e.g., heat shock protein) after 4 h of exposure, followed by several genes regulated by the NF-kB signaling pathway involved in oxidative stress and antioxidant response. Osteopontin, aglectin-3, and lipocalin-2 are secreted proteins observed in mice after acute inhalation to ultrafine carbon particles, which have also been observed in humans. These proteins may be useful markers for particle-induced pulmonary inflammation, although validation studies are needed.

Lung proteins involved in lung injury from ultrafine carbon black were identified in a study of ICR male mice administered 200 µg of ultrafine carbon black (Printex 90; 14 nm diameter,

surface area 254 m^2/g) and killed 24 hours later (Chang et al., 2007). Leukemia inhibitory factor receptor (LIFR) and epidermal growth factor receptor (EGFR) were associated with epithelial shedding and with vascular endothelial growth factor (EGRF) in bronchoalveolar lavage fluid.
The antioxidant cerulopasmin (Cp) was produced by lung epithelial cells.

Standard tests of oxygen diffusion capacity may provide an early marker of alveolar changes that affect gas exchange.

Research needs and recommendations

Epidemiology

Currently there is a single study of UK carbon black production workers providing strong (though novel) evidence that carbon black is a late stage human lung carcinogen. This hypothesis has been given no support whatsoever from the German study of carbon black production workers, although it would be worthwhile for an IARC Working Group to evaluate these recent studies. Ideally, at least one further test of the hypothesis that carbon black is a late stage lung carcinogen is also required. The most obvious candidate is the United States study of carbon black production workers. Attempts should be made to a) locate the 76 unascertained death certificates for this study, b) review plant-specific frequency distributions by year of hire and year of leaving employment to make sure that expected numbers of deaths are not being increased artifactually by including periods of follow-up when no deaths could have occurred, c) collect work history details and derive estimates of cumulative exposure, and d) carry out analyses of lung cancer risks in relation to "lugged" (recent) exposures. Examination of 1) possible relationships between lung cancer risks and other exposure metrics and 2) possible effects of age at exposure need to be carried out for all three published cohorts of carbon black production workers.

The cancer experience of workers at many other carbon black production factories remains unexamined, including workers at Columbian (Hannover, Germany), Hanan (Germany), Columbian (Trecate, Italy), Cabot (Ravenna, Italy), Degussa (Ravenna, Italy), Cabot (France), Cabot (Berre L'etang, France), Carbon Black Nederland (Botlek, Netherlands), Cabot (Rozenburg, Netherlands), Carbesa (Cadiz, Spain), Columbian (Santander, Spain), Cabot (Santurce, Spain), and Nordisk (Malmo, Sweden). The outcome variable could be cancer incidence, mortality, but preference would be to use an effect biomarker such as 8-OHdG with the exposure biomarkers.

Toxicology

Experimental studies are needed that improve our understanding of the mechanisms of particle-elicited lung cancer. A study examining the relationship between occupational exposure to carbon black and validated biomarkers of oxidative stress may provide information on the early biological responses relevant to particle-induced lung cancer mechanisms. These exposure-response relationships should be quantitatively compared in humans and rodents, and the role of particle size should also be examined.

Given the recent findings of an association between the production of microRNA and immune and inflammation processes (Hussain and Harris 2007), it may be useful to investigate the production of microRNA *in vitro* and *in vivo* in experimental systems with conditions equivalent to those in which inflammation and tumors were observed in rats (e.g., Elder et al., 2005; Heinrich et al., 1995; Nikula et al., 1995). Investigation of microRNA in other rodent species (mice and hamsters) could provide data on whether the microRNA responses are associated with the chronic inflammation and lung tumor responses. However, investigating a role of microRNA in particle-induced lung responses in humans may not be feasible without the availability of noninvasive or minimally invasive procedures.

Studies elucidating the role of particle size in the biological mechanism of particle-elicited carcinogenesis would be useful. Currently, there is uncertainty of whether nanoparticles can interact directly with DNA, in addition to the secondary genotoxic mechanism involving inflammation, oxidative stress, and oxidative DNA damage (Schins and Knaapen 2007).

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Styrene-7,8-oxide and Styrene

by Paolo Vineis PhD and Lauren Zeise PhD

Citation for most recent IARC review
IARC Monograph 82, 2002

Current evaluation:
Styrene is *possibly carcinogenic to humans (Group 2B)*. The Working Group found *limited evidence* in humans and *limited evidence* in experimental animals for the carcinogenicity. Evidence from mechanistic studies did not contribute in making the overall classification decision.

Styrene-7,8-oxide is *probably carcinogenic to humans* (*Group 2A*). The Working Group found inadequate evidence in humans and sufficient evidence in experimental animals for the carcinogenicity. In making the overall evaluation, the Working Group took into consideration supporting evidence that styrene-7 ,8-oxide: (i) forms covalent adducts with DNA in humans, rats and mice; (ii) induces gene mutation in bacteria and rodent cells in vitro; (iii) induces chromosomal aberrations, micronuclei and sister chromatid exchange in human cells in vitro; and (iv) induces chromosomal aberrations and sister chromatid exchange in mice in vivo.

Recent Authoritative Review
The National Toxicology Program recently finalized a review of styrene (NTP, 2008). The review covered use, exposure, and evidence for carcinogenicity from epidemiology, animal, mechanistic and other relevant studies. Except where citations are given, the discussion below relies on the NTP review. The NTP review was finalized after peer review by the "Report on Carcinogens Expert Panel for Styrene" The Panel made conclusions about the evidence for the carcinogenicity of styrene. The Panel found limited evidence of carcinogenicity in humans and sufficient evidence in animals. Major considerations in the Panel's recommendation included the established animal carcinogenicity and genotoxicity of the metabolite styrene-7,8-oxide, and the evidence for styrene-related DNA adducts and cytogenetic effects in styrene-exposed workers. In writing this summary we relied on existing authoritative reviews such as the NTP document, which has been subjected to careful peer review, exhaustive fact

A Collaboration Project between International Agency for Research on Cancer (IARC) and National Occupational Research Agenda (NORA)

IARC Technical Publication No. 42

Identification of research needs to resolve the carcinogenicity of high-priority IARC carcinogens

Views and Expert opinions of an IARC/NORA expert group meeting

Lyon, France: 30 June – 2 July 2009

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