International Carbon Black Association

PLEASE REPLY TO:

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February 27, 2012

Dr. Ruth Lunn
Director, Office of the RoC, DNTP, NIEHS
P.O. Box 12233
MD K2-14
Research Triangle Park, NC 27709
via email to lunn@niehs.nih.gov and overnight mail

RE: International Carbon Black Association's Comments on "Request for Public Comment on Nominations and Call for Additional Nominations to the Report on Carcinogens" 77 Fed. Reg. 2728 (Jan. 19, 2012).

Dear Dr. Lunn:

The International Carbon Black Association (ICBA) respectfully submits these comments on the Department of Health and Human Services' (HHS) request for comments on several substances, including carbon black, which have been nominated for possible review for future editions of the Report on Carcinogens (RoC). 77 Fed. Reg. 2728 (January 19, 2012). The ICBA recommends removal of carbon black as a candidate substance, since it does not meet the listing requirements stipulated by the National Toxicology Program RoC criteria. Details supporting this recommendation are provided below.

The members of the ICBA include companies engaged in the manufacture of carbon black in North America, South America, Europe, Africa, and Asia. The objectives of the ICBA include the funding of scientific research and studies regarding the environmental and health effects of carbon black and communicating with government agencies regarding these matters.

Manufactured carbon black is a particulate form of elemental carbon manufactured by the controlled vapor-phase pyrolysis and partial combustion of hydrocarbons. Approximately 89% of the total manufactured carbon black consumption in the United States is in the rubber industry. Within that industry, approximately 70% is used in automotive and truck tires and related tire products; and, 10% of consumption is in other automotive rubber products, such as

belts, hoses, and related accessories. The final 9% is consumed in rubber products unrelated to the automotive industry. The remaining 11% of total consumption is in non-rubber applications such as paints, inks, coatings, plastics, electrostatic discharge compounds, ultraviolet light absorption applications, and as a chemical reagent.

In comments attached hereto and also separately submitted, the Scientific Advisory Group (SAG) to the ICBA is providing detailed responses to the specific items listed in the Federal Register request, including data on current production, use patterns, and human exposure to carbon black, information about published, ongoing, or planned studies related to evaluating the potential carcinogenicity of carbon black, scientific issues important for assessing the potential carcinogenicity of carbon black, and the names of scientists with expertise or knowledge about carbon black. ICBA does, however, wish to make several important points that reiterate SAG's comments and support removal from the candidate list.

First, an increased incidence of tumors from exposure to carbon black has not been found in *multiple* animal species. *See* Listing Requirements for "Reasonably Anticipated to be a Human Carcinogen" Category. Several studies have demonstrated that laboratory rats can develop lung tumors when exposed to carbon black by inhalation or intratracheal instillation under conditions of particle lung overload. However, studies have also shown that tumors from such exposure do not form in other species such as mice and hamsters.

Second, while the International Agency for Research on Cancer (IARC) has classified carbon black as a Group 2B substance (*possibly carcinogenic to humans*), this classification is based *solely* on the observation that laboratory rats develop lung tumors under condition of "lung overload." The reliability of lung tumors induced in rats by inert, poorly soluble particles, such as carbon black, as a predictor of hazard to humans is highly questionable. The epidemiological evidence has not shown that exposure to carbon black causes a statistically significant increase in cancer risk.

Third, the Public Health Service Act requires that HHS list substances in the RoC "to which a significant number of persons residing in the United States are exposed." *See* 42 U.S.C. § 241(b)(4). Exposure to carbon black occurs primarily in the carbon black manufacturing workplace. The effects of this exposure are well studied and this exposure is small both in the number of people exposed and the concentrations to which they are exposed. ICBA has access to limited data on exposure to carbon black in downstream industries, but believes that these exposures are negligible as carbon black is bound within matrices of downstream products, thus unavailable. There is very little exposure to the general public. The potential emission of carbon black from end use products is very low because the substance is very firmly bound in the product matrix. Accordingly, because of the lack of significant exposure, a formal evaluation or consideration of carbon black for inclusion in the RoC is not justified.

Finally, important and relevant studies concerning the potential cancer risk to humans due to carbon black exposure are currently underway. The dose-response portion of the very significant US Mortality study is scheduled for completion in 2013 and will provide important data that should be considered in any evaluation of the carcinogenicity of carbon black. Thus, HHS

should not consider evaluation of carbon black for possible inclusion in the RoC without consideration of the results of these important studies.

The ICBA appreciates the opportunity to submit the foregoing comments and would be happy to address these issues further if additional information or clarification is needed.

Respectfully submitted,

[Redacted]

Jimmy W. Boyd
President, ICBA

Attachment

February 27, 2012

Dr. Ruth Lunn, Director
Office of the RoC
DNTP, NIEHS, P.O. Box 12233,MD K2–14
Research Triangle Park, NC 27709

By e-mail to: *lunn@niehs.nih.gov* and overnight mail

Dear Dr. Lunn,

On behalf of the International Carbon Black Association (ICBA, www.carbon-black.org), the Scientific Advisory Group (SAG) would like to respond to the request for comments on the nomination of carbon black for possible review for future editions of the Report on Carcinogens (77 Fed. Reg. 2728, Jan. 19, 2012). The SAG advises the ICBA on scientific studies related to protecting the health of manufacturers and users of carbon black. Since 1995, the SAG has recommended and overseen epidemiological, toxicological and exposure related assessments associated with carbon black.

In the Federal Register Notice, the National Toxicology Program (NTP) seeks comments regarding the substances being considered for review in the next Report on Carcinogens (RoC) on four topics including: (1) Data on current production, use patterns, and human exposure; (2) Information about published, ongoing, or planned studies related to evaluating carcinogenicity; (3) Scientific issues important for assessing carcinogenicity of carbon black; and (4) Names of scientists with expertise or knowledge about carbon black.

The attached document provides detailed information on each of these four points. In summary, with regard to Topic No. 1, exposure to carbon black occurs primarily in the carbon black manufacturing workplace. The effects of this exposure are well studied and this exposure is small both in the number of people exposed and the concentrations to which they are exposed. ICBA has access to limited data on exposure to carbon black in downstream industries, but believes that these exposures are minor, as to exposure and concentration, as well – a conclusion also drawn by the International Agency for Research on Cancer (IARC) in its recent review of carbon black (IARC, 2010).

With regard to Topic No. 2, the several epidemiological studies that have been performed do not show a causal link between exposure to carbon black and cancer in humans. In addition, the ICBA is currently sponsoring two epidemiological studies of workers involved in the manufacture of carbon black, including the dose-response portion of the US Mortality Study.

Regarding Topic No. 3, although IARC has classified carbon black as a Group 2B substance (possibly carcinogenic to humans), this classification is based *solely* on the observation – **in a single species** - that laboratory rats develop lung tumors under conditions of "lung overload." The reliability of lung tumors induced in rats by inert, poorly soluble particles, such as carbon black, as a predictor of hazard to humans is highly questionable.

Finally, with regard to Topic No. 4, SAG has included in this response a list of SAG scientists who have published on epidemiology, exposure, and health effects related to carbon black.

If you have any questions on the attached document, please do not hesitate to contact me.

Sincerely,

[Redacted]

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Attachment

Response to National Toxicology Program's request for comments on Carbon Black by the Scientific Advisory Group on behalf of the International Carbon Black Association

February 27, 2012

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Appendices

A. Additional exposure information
B. White Paper developed by the ICBA discussing the reasons for not classifying carbon black for carcinogenicity under Regulation (EC) No 1272/2008 (CLP Regulation)

Introduction

On behalf of the International Carbon Black Association[1] (ICBA, www.carbon-black.org), the Scientific Advisory Group (SAG) would like to respond to the request for comments on the nomination of carbon black for possible review for future editions of the Report on Carcinogens (77 Fed. Reg. 2728, Jan. 19, 2012). The SAG[2] advises the ICBA on scientific studies related to protecting the health of manufacturers and users of carbon black. Since 1995, the SAG has recommended and overseen epidemiological, toxicological and exposure related assessments associated with carbon black.

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In summary, with regard to Topic No. 1, exposure to carbon black occurs primarily in the carbon black manufacturing workplace. The effects of this exposure are well studied and this exposure is small both in the number of people exposed and the concentrations to which they are exposed. ICBA has access to limited data on exposure to carbon black in downstream industries, but believes that these exposures are minor as to exposure and concentration, as well – a conclusion also drawn by the International Agency for Research on Cancer (IARC) in its recent review of carbon black (IARC, 2010).

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Finally, with regard to Topic No. 4, SAG has included in this response a list of SAG scientists who have published on epidemiology, exposure, and health effects related to carbon black.

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[1] ICBA member companies include: Aditya Birla Group; Cabot Corporation; Continental Carbon Company; Cancarb Limited; Orion Engineered Carbon; Sid Richardson Carbon & Energy Company; and, Timcal Carbon and Graphite

[2] The SAG is comprised of a multi-disciplinary group of world-class scientists with extensive experience in carbon black-related matters. The SAG includes both ICBA member company employees and external consultants. The current members of the SAG are: Robert J. McCunney, MD, MPH, Chair (occupational medicine, epidemiology); Peter Morfeld, PhD (epidemiology, mathematics); Len Levy, PhD, FFOM, FBTS (toxicology); Hank Muranko, MPH, CIH (industrial hygiene); Ross Myerson, MD, MPH (occupational medicine); Nils Krueger, DVM (toxicology); Terry Maples, CIH (industrial hygiene); Ishrat Chaudhuri, PhD (toxicology); and, Yufanyi Ngiewih, PhD (toxicology)

1.0 Production and particle properties, uses and exposure

1.1 Production and particle properties

Manufactured carbon black (Chemical Abstract Service #1333-86-4) has been produced in the United States for over 100 years. Carbon black is an amorphous particulate form of elemental carbon manufactured by the controlled vapor-phase pyrolysis and partial combustion of hydrocarbons. Depending on the manufacturing process, carbon blacks are categorized as furnace black, lamp black, acetylene black, channel black, gas black, or thermal black. The furnace black and thermal processes are the only commercial processes operating within the United States. Different types of carbon black are characterized by the size distribution of the primary particles (nodules) and the degree of their aggregation and agglomeration, as well as their surface areas per unit mass. Except for thermal carbon black products (about 5% of total production), carbon black does not exist in the form of discrete primary particles (nodules), but consists of aggregates of aciniform particles (i.e., aggregates of rounded nodules strongly fused together in random configuration that resemble grape-like clusters) (Gray and Muranko, 2006). These aciniform aggregates constitute the smallest inseparable entities in manufactured carbon black and are hence the fundamental structural units of carbon black. However, carbon black aggregates are not readily available outside the closed reaction chamber of the manufacturing process as the aggregates rapidly form larger agglomerates held together by van der Waals forces. Carbon black agglomerates may also be compressed into even larger-sized pellets as a final step in the manufacturing process.

Carbon black is not the same as "soot" or "black carbon" which are names applied to emissions from fires and incomplete combustion of carbon-containing fuels and products in commerce (e.g., waste oil, fuel oil, gasoline fuel, diesel fuel, coal, coal-tar pitch, oil shale, wood, paper, rubber, plastics and resins, household refuse, etc.). Such emissions contain some elemental carbon but also significant quantities of organics and other compounds (Watson and Valberg, 2001).

The majority of carbon blacks currently manufactured contain small quantities (< 1%) of organic compounds, including polycyclic aromatic hydrocarbons, strongly adsorbed onto their surface. Both *in vitro* and *in vivo* studies have demonstrated that these particle-adsorbed PAHs are not bioavailable (Borm, 2005.)

Worldwide production of carbon black in 2010 was 10,712,000 metric tons (10,712 KMT) with approximately 1,375,000 metric tons (1,375 KMT) produced in the United States (Notch Consulting Group, 2011). Fifteen carbon black manufacturing plants are currently operating in the United States.

1.2 Uses

About 89% of total manufactured carbon black consumption in the U.S. is in the rubber industry. Of that, 70% goes toward automotive and truck tires, and related tire products; and, approximately 10% of consumption is in other automotive rubber products, such as belts, hoses and related accessories. The final 9% is consumed in rubber products unrelated to the automotive industry.

The remaining 11% of total production is used in non-rubber applications such as paints, inks, coatings, plastics, electrostatic discharge compounds, ultraviolet light absorption applications, and as a chemical reagent (Wang et al., 2003).

1.3 Exposure

Occupational exposure to carbon black may arise during the manufacture of carbon black and during its use in the formulations of rubber, printing ink, and paint manufacturing. Consumer exposure to carbon black is negligible because, in nearly all cases of use, carbon black is tightly incorporated into a rubber or polymer matrix and is unavailable.

1.3.1 Exposure and controls within the carbon black workplace

The main route of occupational exposure of relevance to human health is inhalation via the nose and mouth. Established in 1971, the US Occupational Safety and Health Administration (OSHA) permissible exposure limit for carbon black is 3.5 mg/m^3, measured as the total dust fraction of an 8-hour Time Weighted Average (TWA). Established in 2011, the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV®) for carbon black is 3.0 mg/m^3, measured as the inhalable dust fraction of an 8-hour TWA.

Beginning in the late 1970s extensive occupational exposure monitoring campaigns were initiated within the carbon black production industry in the US and Canada and are reported in detail, and/or summarized in the peer reviewed literature as the exposure component of epidemiology studies. Exposure studies reported in the peer reviewed literature were conducted in 1979 – 1980 (Smith and Musch, 1982), 1994-1995 (Muranko et al., 2001), and in late 2000 (Harber et al., 2003a, b). Additional industry-wide exposure studies developed data in 1882-83, 1987, 2003, 2007, and 2011. [Extensive monitoring campaigns were also conducted within the carbon black production industry in Western Europe in 1987-1989, 1991-1992, and 1994-1995 as part of a multi-center European respiratory morbidity study (Gardiner et al., 1992a, b, 1993, 1996, 2001; van Tongeren et al., 2000b).] Appendix A Table 1 summarizes industry-wide occupational exposure studies sponsored by the International Carbon Black Association. In addition to personal exposure assessments, two particle characterization studies measured the size of manufactured carbon black within the manufacturing environments in the U.S. and Europe (additional information provided in Appendix A) (Wake, 2002; Kuhlbusch, 2004, 2006).

Engineering controls designed to eliminate or reduce occupational exposure to carbon black dust to the lowest feasible level are preferred to the use of respirators or other types of personal protective equipment. Exposure data are collected: to identify operation(s) that may contribute to worker exposures; to prioritize and define control design; to establish baseline data for evaluating the effectiveness of controls; and in support of occupational epidemiology studies.

Engineering exposure controls used in the handling of carbon black dust include: (1) ventilation hoods for controlling exposures to laboratory personnel engaged in handling samples; (2) local exhaust ventilation for dusty operations, such as bagging and bag splitting; and, (3) containment of powders and dusts within sealed mixing, processing, and conveying systems. Containment systems (e.g., enclosed conveyors) are especially effective when operated under a slight negative pressure to minimize fugitive dust emissions, as are central vacuum systems to support routine housekeeping and spill containment

procedures. Effective engineering controls and good housekeeping practices are employed to ensure occupational exposures and fugitive dust are minimized

When respiratory protection is required to minimize exposures to carbon black, US manufacturing facilities follow the applicable requirements of the Occupational Safety and Health Act, 29 CFR 1910.134 (Respiratory Protection).

1.3.2 Exposure to consumers

In nearly all cases of use, carbon black is incorporated into a rubber or polymer matrix, in which carbon black is tightly bound within other materials. Indeed, IARC recognized and noted the unique nature of carbon black and the distinction between pure and bound-in-matrix carbon black (IARC, 1996):

> **"End users of these products (rubber, ink or paint) are not exposed to carbon black per se, since it is bound within the product matrix."**

IARC did not identify carbon black bound in a matrix as a potential carcinogen, but rather, based its classification of carbon black on the results of the rat studies which tested pure, unbound carbon black alone.

To evaluate carbon black's exposure profile outside the production environment, an understanding of the distinction between bound and unbound carbon black in the three largest applications is provided below: rubber, plastics/composites, and inks and toners.

1.3.2.1 Rubber

As noted above, approximately 89% of all manufactured carbon black in the U.S. is used in rubber products, of which approximately 70% are tires. In every instance in which carbon black is used in rubber, such as belts, hoses, engine mounts, weather stripping, gaskets, etc, its performance requires that it be thoroughly dispersed in the polymer so that each carbon black aggregate is surrounded and interpenetrated by tightly adsorbed elastomer. These rubber products typically contain from 1 to 40% carbon black cross-linked with a polymer matrix. In the vast majority of the products, the polymer in question is an elastomer (Donnet and Voet, 1976; Donnet et al., 1993). In fact, the phenomenon of carbon black bound in rubber has been extensively studied by industry scientists who have determined that carbon black cannot be extracted from rubber even with aggressive solvents (Donnet et al., 1993).

Ten or twenty years after a rubber product is put in service, the carbon black contained therein is still totally enclosed in rubber. If the carbon black were not distributed through the rubber, it would lose the properties for which it was added to the rubber. None of the studies on the wear of rubber products indicate any measurable amount of unbound carbon black.

1.3.2.2 Plastics/composites

In addition to its use in rubber products, carbon black is also used in composites. In the case of plastic materials, carbon black can provide pigmentation, UV absorbance to prevent degradation, and electrical conductivity. In plastics, the carbon black is likewise intimately embedded in a polymer matrix and is fully dispersed throughout that matrix. In paint coatings, the carbon black is mixed into a dissolved polymer or a latex suspension. Following drying, the carbon black is again cross-linked with polymer chains.

1.3.2.3 Inks and toners

In commerce today, inks that utilize carbon black as a pigmenting source incorporate carbon black into larger molecular complexes. These complexes into which carbon black is incorporated use proprietary polymers as their foundations for imparting desirable physical properties such as solubility, polarity, or charge. These physical properties enable the resulting ink formulations to be efficiently and accurately directed to the printing surfaces. Some specialty inks utilize either lattices or dissolved varnishes and thus are analogous to paints. The same is true of toners utilized in copy-machines and printers. These toners incorporate carbon black into molecular complexes, typically with polymer or wax foundations. The carbon black is completely encased and surrounded by the polymer and is not released on aging. Therefore, the "particles" that could be generated from these inks and toners (i.e., from either liquid or solid colorant formulations) are not unbound carbon black.

Wet toners contain carbon black in a hydrocarbon solvent and are applied to the photo conductor by a roller and bath. Wet toners are almost invariably handled by a sealed system of containers that plug into the reservoir (HSE, 1990). Exposure to inhalable dust during the use of photocopiers has been measured in the range 0.05 – 0.23 mg/m^3. The toner component was found to be less than 20% (or 0.01-0.046 mg/m^3) of the inhalable dust fraction (HSE, 1990). During normal use, the exposure to carbon black from toner is therefore not considered significant.

1.3.3 Exposure to the environment

Carbon black emissions may occur from dryer vents, transport system vents, cleanup system vents, operational upsets and to a lesser extent cleaning, spills, and fugitive leaks. In the thermal process, minor carbon black emissions occur in the form of spills from carbon handling systems. The largest thermal black producer in the world located in Alberta Canada carefully collects and weighs all spills since a carbon mass balance is required for its provincial Greenhouse Gas legislation. Approximately 1 tonne of emissions occur from various handling system dust collectors. Using the U.S. EPA ISCST3 dispersion model, local digital terrain elevation data, meteorological data, and August 2001 main stack measurements, the maximum PM10 concentration at the nearest residence of a carbon black plant (1.75 kilometers distance) was calculated to be 0.0016 mg/m^3 (24 hour average) or 0.0001 mg/m^3 (annual average) (Health Canada, 2011).

Process water from the production process is generally emitted in the form of water vapor. Liquid water releases come from wash-down streams unless the tail gases are dehumidified to increase the quality of the fuel gas. Some companies maintain total recovery systems in order to capture and re-use wash-down water for process quenching.

Releases of carbon black into the environment during the manufacture of products (preparations) and articles are considered to be substantially lower than emissions during production. Carbon black is one of the most highly visible materials used in manufacturing today. Because of this, particularly in the event of a baghouse filter failures, many manufacturers of end products/articles, together with the manufacturers of carbon black itself, have installed environmental particulate monitors to enable compliance monitoring for legislative requirements and also to identify the potential failure of filter systems before elevated emissions occur.

Finally, it should be noted that in 2011, Health Canada and Environment Canada conducted a screening assessment of carbon black and determined that carbon black does not meet either criteria of high exposure or high health hazard, and determined that no further action was needed on this substance (Canada Gazette, 2011). This human health determination was based on available evidence on carcinogenicity, mutagenicity, developmental toxicity and/or reproductive toxicity and included a thorough review of exposure, including consumer and environmental exposure (Health Canada, 2011).

2.0 Information about published, ongoing or planned studies that would provide information on carcinogenicity

This section summarizes a number of published and ongoing studies that provide information on potential carcinogenicity from exposure to carbon black. Several epidemiological studies have been performed which do not show a link between exposure to carbon black and cancer in humans. In addition, the ICBA is currently sponsoring two epidemiological studies of workers involved in the manufacture of carbon black, including the dose-response portion of the US Mortality Study. The cumulative dose-response assessment portion of this study is currently underway and would be important for NTP's consideration.

2.1 Published studies

2.1.1 Carbon black worker population

The most recent evaluation of potential cancer risks from carbon black exposure was performed by an IARC[3] Working Group in February 2006 (IARC, 2010). The Working Group noted the following key points: (1) lung cancer is the most important health endpoint to consider and (2) exposures of workers at carbon black production sites are the most relevant for an evaluation of risk. Studies conducted since the 2006 IARC review are also discussed below.

2.1.1.1 Studies reviewed in IARC 2006 evaluation

Three epidemiological studies reviewed by IARC in 2006 investigated lung cancer mortality in carbon black production plants.

1. A UK cohort study on 1,147 workers at five plants found an SMR[4] for lung cancer of 1.73 (61 cases, 0.95-CI[5]: 1.32, 2.22) (Sorahan *et al*. 2001). No trend across crudely assessed cumulative exposures, lagged up to 20 years, was noted. Elevated lung cancer SMRs were observed at two plants, and the SMRs of the other three plants were unexceptionable. Smoking data were not available for the cohort, therefore this study could not be corrected for smoking.

2. A German study on 1,528 workers at one plant estimated an SMR for lung cancer of 1.83 (50 cases, 0.95-CI: 1.34, 2.39; using regional rates) (Wellmann *et al*. 2006, Morfeld *et al*. 2006a, Buchte *et al*. 2006, Morfeld *et al*. 2006b). Like the UK study above, no positive trends with carbon black exposures were noted. The study

[3] IARC = International Agency for Research of Cancer
[4] SMR = standardized mortality ratio
[5] CI = confidence interval

identified smoking and prior exposures to known carcinogens as important risk factors that explain the major part of the excess risk.

3. A US cohort study on 5,011 workers at 18 plants calculated an SMR for lung cancer of 0.85 (127 cases, 0.95-CI: 0.71, 1.00) (Dell *et al*. 2006). Again, like the UK and German studies noted above, no trend across time since first exposure and duration of exposure was noted. Smoking data were not available for this study.

The Working Group at IARC concluded that the human evidence for carcinogenicity was inadequate (IARC, 2010).

2.1.1.2 Studies conducted since IARC 2006 evaluation

The authors of the UK study conducted an extended follow-up of their cohort and applied a novel exposure metric, known as "lugging" in an attempt to address the effect of recent exposures on lung cancer risk (Sorahan and Harrington, 2007). In contrast to lagging, a "lugging" analysis focuses on the most recent exposures. The authors hypothesized that carbon black may act as a late stage lung cancer carcinogen at plants with elevated SMRs. If the hypothesis were true, the elevated SMRs should decrease substantially after cessation of exposure and positive associations should be found with "lugged" cumulative carbon black exposure. For example, "lugging" the exposure by 15 years, means to count only exposures received during the last 15 years. The authors noted an elevation in risk of lung cancer through their novel lugging assessment only in the two UK plant cohorts that had elevated lung cancer SMRs. The authors called for repetitions of their methodology in other cohorts.

The "lugging" hypothesis was then tested in the German carbon black cohort. (Morfeld and McCunney, 2007, 2009). The hypothesis that recent exposures to carbon black are more likely to explain a lung cancer mortality excess than those received in the distant past is <u>not</u> supported by the German cohort "lugging" analysis.

One more recent study (Morfeld and McCunney 2010) performed a Bayesian bias analysis to explore all potential risk factors and confounders that may have contributed to the results. These additional investigations do not support the "lugging" hypothesis.

2.1.2 User industry studies

Carbon black is used primarily in the rubber industry; other less common uses include use in printing inks and toner manufacturing. Highlights of the recent studies follow.

2.1.2.1 Case-control studies in user populations

The relationship between workplace exposure to carbon black and lung cancer risk was examined in two large population-based case-control studies in Montreal, Canada (Parent *et al*., 1996; Ramanakumar *et al*., 2008). Interviews for Study I were conducted in 1979–1986 (857 cases, 533 population controls, 1,349 cancer controls) and interviews for Study II were conducted in 1996–2001 (1,236 cases and 1,512 controls). Detailed lifetime job histories were elicited and a team of industrial hygienists and chemists evaluated the evidence of exposure to a host of occupational substances, including carbon black. Lung cancer risk was analysed in relation to each exposure, adjusting for several potential confounders, including smoking. Subjects with occupational exposure to carbon black,

titanium dioxide, industrial talc and cosmetic talc did not experience any detectable excess risk of lung cancer. Specifically, for carbon black, the reported odds ratio(95% confidence interval) for pooled Study I and Study II for 3 exposure groups (any exposure, non-substantial exposure and substantial exposure) was 1.1 (0.95-1.5), 1.1(0.95-1.7) and 0.8 (0.4-1.5), respectively.

These further detailed investigations showed no causative link between carbon black exposure and cancer risk in humans. This view is consistent with both the IARC conclusion in 2006 and ACGIH's recent evaluation (ACGIH, 2011).

2.1.2.2 Rubber industry

Numerous epidemiological studies have been conducted in the rubber industry, which, in addition to carbon black, uses other materials including accelerators and solvents, among others. Earlier mortality studies in the rubber industry were also confounded by the presence of asbestos in the manufacturing plant. IARC concluded that there was sufficient evidence of a human cancer risk in the rubber industry, (Category 1) but no specific substance was highlighted as the causative agent. (IARC, 1982; IARC, 1987)

A review article in 1998 summarized the studies of rubber industry workers conducted since IARC reviewed the rubber industry in 1982 and updated its review in 1987 (Kogevinas et al, 1998). While excess risks of bladder cancer, lung cancer and leukemia were noted, the authors concluded that there was no information associating specific exposures, such as carbon black, with cancer risk.

Subsequently, a study of nearly 9000 German rubber workers evaluated risk of cancer associated with specific agents used in the rubber industry (Straif et al, 2000). The authors claimed their report was the first to examine exposure specific data in terms of cancer risks in the rubber industry. No causative link between carbon black and cancer risk was reported by the authors in their study of nearly 9000 workers with potential exposure to carbon black. To the contrary, the authors speculated that the lung cancer risk observed in the rubber industry workers was likely due to asbestos and talc exposure. In the study, rate ratios (RR) for low, medium and high exposures and 95% confidence intervals (CI) were calculated using Cox proportional hazards models, with the lowest exposure level used as the reference category. Exposure-response relations between exposure to asbestos and lung cancer mortality (RR(high) = 2.0, 95% CI: 0.9, 4.1) and between exposure to dust (talc and asbestos combined) and stomach cancer mortality (RR(high) = 2.7, 95% CI: 1.0, 7.1) were observed. The authors concluded that the increased mortality from lung and stomach cancer among rubber workers is associated with exposure to asbestos and dust, respectively.

A mortality study of a cohort of over 17,000 rubber tire workers in Poland showed no excess in lung cancer (Wilczynska et al, 2001). The study indicated significantly lower total mortality in the cohort (men: SMR = 72; women: SMR = 62) as compared to the general population, which is an example of a well known "healthy worker effect". The number of deaths from malignant neoplasms was also lower than expected (men: SMR = 67; women: SMR = 64). A study of a large US rubber manufacturing facility that included over 3400 workers showed no excess in lung cancer (Beall et al, 2007). In this study, employees experienced 390 deaths compared with 608 expected (SMR = 64; 95% CI = 58-71). Total cancer mortality (SMR = 75, 95%CI = 62-89) and lung cancer mortality (SMR =72, 95% CI =

53-96) were lower than expected. A mortality and cancer industry survey among relatively recently hired employees (1982-1991) in the British rubber industry showed no increase in mortality from lung cancer (Dost et al, 2007). Specifically, mortality from lung cancer was close to expectation for males (SMR = 93) and females (SMR = 70).

In summary, although the rubber industry has been associated with increases in some types of cancer, no study has implicated carbon black exposure as an explanation for these findings, including the risk of lung cancer reported in earlier rubber industry studies.

2.1.2.3 Toner industry

Another common use of carbon black is in the production of toner. Toner used in laser printers and photocopiers has commonly contained carbon black mixed with a heat sensitive polymer. These products are ubiquitous in businesses and homes all over the world. A large retrospective study of mortality among employees occupationally exposed to toner was recently reported in the medical literature. This study group included 33,671 employees of a xerographic company employed between 1960 and 1982. The group was tracked through 1999. The exposed group included employees involved in the manufacturing of toner and customer service engineers who service copiers out in the field. Standardized mortality ratios (SMRs) were calculated using the U.S. population for comparison. All cause SMRs for toner-exposed populations were 0.65 and 0.84 for white men and women respectively. SMRs for all cancers including lung cancer were lower than 1.0. There was no evidence that toner exposure increased the risk of all-cause mortality or cause-specific mortality for the 23 categories of death analyzed (Abraham et al, 2010).

2.2 On-going or planned studies in carbon black worker population

The ICBA is currently sponsoring two epidemiological studies of workers involved in the manufacture of carbon black (McCunney, *et al.* 2011). In the US, an update of the cohort mortality study reviewed by IARC in 2006 is underway (Dell *et al.,* 2006). The original cohort is being followed for additional years of vital status; the earlier version addressed vital status through 2003; this update includes follow up through 2010. In addition, a cumulative dose-response assessment is underway; each cohort member will be assigned a cumulative exposure measure. This metric will be based on a variety of factors, including quantitative exposure data, and a comprehensive review of job descriptions, duties and production process changes. As described above, published exposure data related to the manufacture of carbon black date back to 1979, which enables the investigators to have nearly 30 years of quantitative data for the dose-response assessment. In addition, plans include conducting a similar "lugging" analysis in the US cohort as noted in the discussion above of the UK and German carbon black cohorts.

Recent position papers, including a comprehensive review by The American Heart Association, have called attention to the potential role of particles in causing cardiac disease (Brook *et al*, 2010). The concern is based primarily on environmental studies. Nonetheless, to understand this potential health risk among carbon black manufacturing workers, single and combined analyses (meta regression) of the three cohorts in the US, Germany and UK are underway. As part of this effort, extended SMR and Cox regression analyses of the German, UK and US cohort will be performed including an update of follow-up in the UK and in the US. Due to privacy laws in Germany, the earlier records of the cohort evaluation were destroyed and as a result no further updates of this cohort are feasible.

Completion of the above studies is expected by the end of 2013.

3.0 Scientific Issues important for assessing carcinogenicity

IARC has classified carbon black as a Group 2B substance (possibly carcinogenic to humans). This classification, however, is based solely on the observation that rats develop lung tumors under condition of "lung overload." Further, these tumors have been observed only in a single species. The reliability of lung tumors induced in laboratory rats by inert, poorly soluble particles, such as carbon black, as a predictor of hazard to humans is uncertain. The epidemiological evidence has not shown that exposure to carbon black causes a statistically significant increase in cancer risk.

3.1 Animal toxicology studies and mechanism of rat lung overload

Carbon black is considered a chemically inert poorly soluble particle (PSP). A number of animal studies (discussed in Section 3 of the IARC Monograph on Carbon Black (IARC, 2010)) have demonstrated that rats (but not mice or hamsters) can develop lung tumors when exposed to carbon black by inhalation or intratracheal instillation under conditions of lung overload. Lung overload is described as a reaction caused by prolonged inhalation of high levels of PSPs causing delayed alveolar lung clearance and marked retention of particles.

At the International Workshop Evaluation on Particle and Fibre Toxicity (Greim et al., 2001) a consensus was reached that PSPs caused lung tumors in rats by a secondary genotoxic (inflammatory/proliferative) mechanism. The group concluded that, "Studies to date have not demonstrated primary genotoxicity of carbon black with low PAH contamination using appropriate in vitro assays. DNA adducts related to associated organic compounds so far have not been found in lung tissue from rats exposed chronically to carbon black although in the same studies adducts were found in diesel exhaust-exposed rats." This result was also seen in a study conducted by Borm et al. (2005).

Implicit in the inflammatory / proliferative mechanism is the existence of a non-linear, dose-related effect with a threshold. Particle exposures that do not overwhelm host defense mechanisms (e.g., anti-oxidants, DNA repair) and hence do not elicit inflammatory and proliferative responses, should not pose an increased risk of lung tumors in humans (Driscoll, 1996a; Driscoll et al., 1996b). Sub-chronic inhalation of 1.1 mg/m^3 (respirable) carbon black did not elicit any detectable adverse lung effects (Driscoll et al. (1996b). Results from other research groups (Carter et al., 2006; Elder et al., 2005) support this finding, and indicate a carbon black No Observed Adverse Effect Level (NOAEL) of 1 mg/m^3 (respirable). Furthermore, participants at the ILSI workshop (2000) proposed that no uncertainty (safety) factor (for rat-to-human extrapolation) was required for neoplastic and fibrogenic endpoints associated with particle exposure, because the rat appears to be more sensitive in its responses to all particle-related effects than other species, including humans.

3.2 The lung overload response in rats may not be relevant to humans

The evaluation of carbon black by IARC (1996 and 2010) and Greim et al. (2001) as a suspect carcinogen is solely founded on the observation that rats develop tumors under conditions of lung overload. The ILSI workshop (2000), which evaluated the relevance of

the rat responses to particle overload for human risk assessment, concluded that at non-overload exposures, a lung-cancer hazard did not exist. Lung tumors were not observed in mice and hamsters under similar study conditions.

Experimentally-induced lung tumors in rats occur in the alveolar and small airway regions of the lungs, unlike human lung cancers that tend to occur in epithelial cells at the bifurcations of the major airways (bronchi). These anatomical differences in site of origin of tumors adds further uncertainty in extrapolating the results in the rat studies to humans.

The lung overload reaction in rats has also been observed in a range of PSPs with low toxicity, such as titanium dioxide. Basing human lung cancer risk predictions on the rat response to the inhalation of PSP's, including carbon black, under conditions of lung overload is not a scientifically valid approach. Several independent, expert, scientific advisory groups have cautioned against using tumorigenic data from rats exposed to high ("lung overload") concentrations of insoluble particles for quantitative risk assessment. In the United States, the Presidential / Congressional Commission on Risk Assessment and Risk Management (CRARM, 1997) noted that the response of rat lungs to high concentrations of inhaled PSP's (specifically carbon black and titanium dioxide) are not likely to be predictive of human cancer risks. For diesel exhaust, the Clean Air Scientific Advisory Committee (CASAC, 1995 and 1998), a peer-review group for the U.S. Environmental Protection Agency (EPA), has commented on two drafts of the EPA´s Health Assessment Document on Diesel Exhaust. On both occasions, CASAC emphasized that the data from lung-overloaded rats are not relevant for human risk assessment. Likewise, the Health Effects Institute (1995) also has concluded that rat data should not be used for assessing human lung-cancer risk from diesel-exhaust exposure.

Within the framework of the European REACH Regulations, specifically the Classification, Labeling and Packaging (CLP) Regulation- Guidance for Specific Target Organ Toxicity – Repeated Exposure (STOT RE) (CLP, 2011), the issue of lung overload is discussed under the heading "Mechanisms not relevant to humans". The CLP regulation states that '**Substance – induced species specific mechanisms of toxicity, i.e. demonstrated with reasonable certainty to be not relevant for human health, shall not justify classification**'. In its *Screening Assessment for Carbon Black*, Health Canada (2011) states, "The available toxicity studies were conducted at high carbon black exposure levels resulting in a particle overload state in the lung, while the effects of exposure to lower levels of carbon black have not been examined fully. The relevance of rat particle-overload pulmonary toxicity to humans has yet to be elucidated." Appendix B includes a document developed by the ICBA on the reasons for not classifying carbon black as a carcinogen under the European Union CLP regulation.

In conclusion, the evaluation of carbon black as a suspect carcinogen (possibly carcinogenic to humans, Group 2B) by IARC is based *solely* on the observation that rats develop lung tumors under conditions of "lung overload." These tumors have been observed only in a single species. The reliability of lung tumors induced in rats by inert, poorly soluble particles, such as carbon black, as a predictor of hazard to humans is highly questionable. Overall, the epidemiological evidence, discussed elsewhere, from well-conducted investigations has not shown that exposure to carbon black causes a statistically significant increase in cancer risk.

4.0 Names of scientists knowledgeable about carbon black

The Scientific Advisory Group (SAG) of the International Carbon Black Association (ICBA) consists of scientists knowledgeable about potential health implications of exposure to carbon black. Many of these scientists have published on carbon black and potential health effects. Selected publications are noted below.

All of the SAG scientists listed below have agreed to participate in the NTP process in any way that can be helpful. In addition to the scientists listed below, you can also contact Dr. Robert McCunney for additional references of scientists not affiliated with the SAG.

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Selected Carbon Black Publications by SAG Members (member names noted in bold below)

1. **McCunney RJ**, **Muranko H,** Valberg P. "Carbon Black" in Patty's Industrial Hygiene and Toxicology 3rd edition, 2000

2. **Morfeld P,** Büchte S, Wellmann J, **McCunney R**, Piekarski C. Lung cancer mortality and carbon black exposure: Cox regression analysis of a cohort from a German carbon black production plant J Occup Environ Med 2006; 1230-41

3. Büchte S, **Morfeld P,** Wellman J, Bolm-Audorff U, **McCunney R**, Piekarski C. Lung cancer mortality and carbon black exposure – A nested case-control study at a German carbon black production plant J Occup Environ Med 2006;48:1242-52

4. **Morfeld P**, Buechte S, **McCunney R**, Piekarski C. Lung cancer mortality and carbon black exposure-uncertainties of SMR analyses in a cohort study at a German carbon black production plant. J Occup Environ Med 2006;48:1253-64

5. **Morfeld P, McCunney RJ**. Carbon black and lung cancer-testing a new exposure metric in a German cohort Am J Ind Med 2007; 50: 565-567

6. **Morfeld P, McCunney RJ** Carbon black and lung cancer – testing a novel exposure metric by multi-model inference Am J Ind Med 2009; 52: 890-899

7. **Morfeld P, McCunney RJ** Bayesian bias adjustments of the lung cancer SMR in a cohort of German carbon black production workers J Occup Med Toxicol. 2010 Aug 11;5:23

8. **McCunney, RJ, Morfeld P, Levy L, Muranko H** Carbon black research recommendations Environ Health Perspect 2011; 119: A332-A333

9. **McCunney RJ**, **Muranko H,** Valberg P, **Morfeld P**. "Carbon Black" in Patty's Industrial Hygiene and Toxicology 4th edition, 2011 (in press)

10. Gray CA, **Muranko H**. (2006). Studies of robustness of industrial aciniform aggregates and Agglomerates - Carbon Black and Amorphous Silica: A review amplified by new data. JOEM 48(12), 1279-1290

11. Harber P, **Muranko H,** Solis S, Torossian A, and Merz B (2003a). Effect of Carbon Black Exposure on Respiratory Function and Symptoms. J Occup Environ Med **45(2)**, 144-155

12. Harber P, **Muranko HJ**, Shvartsblat S, Solis S, Torossian A and Oren T (2003b). A Triangulation Approach to Historical Exposure Assessment for the Carbon Black Industry. J. Occup Env Med 45(2), 131-143

13. **Muranko HJ,** Hethmon TA, Smith, RG. (2001). "Total" and respirable dust exposures in the U.S. carbon black manufacturing industry. Amer Ind Hyg Assoc J 62:57-64

14. Kerr, SM, **Muranko, HJ**, Vincent, JH (2002). Personal sampling for inhalable aerosol exposures of carbon black manufacturing industry workers. J Applied Occup Env Hyg 17(10) 681-692.

15. **Levy LS** (1996) Differences between rodents and humans in lung tumor response - lessons from recent studies with carbon black. Inhal Toxicol, 8 (suppl), 125-138

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19. IEH (1999) IEH Report on Approaches to Predicting Toxicity from Occupational Exposure to Dust (Report R11), Compiled and edited Shuker L & **Levy L,** Leicester, UK, MRC Institute for Environment and Health

20. IARC (1996) IARC Monographs on Evaluation of Carcinogenic Risks to Humans, Vol 65, Printing Processes and Printing Inks, Carbon Black and Some Nitro Compounds, Lyon, France, International Agency for Cancer Research (Contribution by **Levy L as Invited Expert to IARC Working Group**)

21. IARC (2010) IARC Monographs on Evaluation of Carcinogenic Risks to Humans, Vol 93, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 93 Carbon Black, Titanium Dioxide, and Talc, Lyon, France, International Agency for Cancer Research (**Contribution by Levy L as Invited Expert to IARC Working Group)**

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Appendix A. Additional Exposure Information

This appendix provides summary information for personal exposure assessment studies (Table 1), and a summary of particle characterization measurements conducted in carbon black manufacturing environments in the US and Western Europe. Over 9000 time-weighted average personal breathing zone samples have been collected at North American carbon black manufacturing facilities between 1979 and 2011 to support epidemiology studies, evaluate the effectiveness of exposure controls, and to assess compliance with occupational exposure limits. A general overview of these studies is presented in Table 1. In addition, two particle characterization studies to assess potential exposure to ultrafine/nano-sized particles are summarized in this appendix.

Table 1: North American and European Respirable, Inhalable and "Total" Dust Carbon Black Average Exposure Values by Sampling Campaign.

Study year	Respirable mg/m^3	Inhalable mg/m^3	"Total" dust mg/m^3
North American Studies (Smith and Musch, 1982; Muranko et al., 2001; Harber et al., 2003a,b)			
1979-1980 (n=1,564 "total", 387 respirable)	0.11 GM	nm	0.46 GM
1982-1983 (n= 973 "total")	Nm	nm	Nc
1987 (n= 577 "total")	Nm	nm	0.47 GM
1993-1995 (n=1,004 "total", 1,056 respirable)	0.15 AM 0.07 GM	nm	0.59 AM 0.20 GM
2000-2001 (n= 1010 inhalable, 1010 respirable)	0.26 AM	1.29 AM 0.66 GM	0.46 AM 0.22 GM
2003 (n=426)	Nm	1.47 AM 0.73 GM	0.49 AM 0.25 GM
2006-2007 (n=523)	Nm	1.84 AM 0.87 GM	0.62 AM 0.29 GM
2010-2011 (n=447)	Nm	1.52 AM 0.80 GM	0.51 AM 0.27 GM
European Studies (Gardiner et al., 1992a,b; 1996; van Tongeren, 2000a,b)			
1987-1989 (n= 1,316 inhalable, 1,297 respirable)	0.40 AM 0.21 GM	1.52 AM 0.57 GM	Nm
1991-1992 (n=3,454 inhalable, 2,950 respirable)	0.35 AM 0.18 GM	0.81 AM 0.37 GM	Nm
1994-1995 (n= 3,245 inhalable, 3,157 respirable)	0.24 AM [0.13] GM	0.57 AM [0.29] GM	Nm

nm = not measured; nc = overall descriptive statistics were not calculated; [ ]= data from van Tongeren, 2000a; AM = arithmetic mean; GM = geometric mean; n = sample number. "Total" designates dust collected with traditional 37-mm closed-faced filter cassette.

Summary of ultrafine particle characterization studies

Kuhlbusch et al. (2001, 2004) conducted field measurements at three carbon black manufacturing plants (two European and one US) over two-week periods in the year 2000 and compared the particle characteristics of emissions in the bag filling area to diesel exhaust particles derived from tailpipe emissions (dilution tunnels) and to particles from ambient air. The particle size and chemical composition of carbon black particles found in bag filling areas of the three plants were different from those characteristic of either tailpipe or ambient particles collected near busy streets. Carbon black particles released from bag filling activities had a size distribution starting at about 0.4 micron d_{ae} (d_{ae} = aerodynamic diameter) with two dominant modes (maxima) at 1-2 micron d_{ae} and at > 8 micron d_{ae} (the larger size mode went beyond the particle size range investigated). Although ultrafine particle emissions were measured in workplace sampling locations in two of the three plants, the data showed that these particles were generally not carbon black, but could be attributed, for instance, to diesel- or propane-powered forklift emissions, as well as butane-fueled heaters. Measured diesel-soot particle diameters were mainly below 0.2 micron. Diesel soot contained a significant amount of organic carbon as well as inorganic compounds. The elemental carbon, as a percentage of total carbon, averaged 55% (range, 15- 75%) for tailpipe emissions and 45% (range 28-54%) for ambient air sites. In contrast, the elemental carbon percentage in carbon black bag filling areas averaged 85%. With respect to the reactor and pelletizing areas, Kuhlbusch and Fissan (2006) concluded that "no carbon black is released in the reactor and pelletizing areas (as UFP or PM10) from the closed production lines under normal operating conditions".

Wake et al. (2002) investigated the number of particles with a diameter between 16.5 and 805 nm inside (bagging area) and outside a U.K. carbon black manufacturing plant. Particle numbers within the bagging area were much lower than that measured outside, which, according to the study authors, was probably due to particles emitted from road vehicles. Median particle diameter in the bagging area ranged between 51 and 599 nm. Elemental carbon analysis was not performed as part of this survey, thus it is unclear whether carbon black contributed to these nano-size range exposures.

Appendix B. White Paper developed by the ICBA discussing the reasons for not classifying carbon black for carcinogenicity under Regulation (EC) No 1272/2008 (CLP Regulation)

International Carbon Black Association

*Recommendation for No Classification of Carbon Black for Carcinogenicity**

**(according to the Criteria of EU (Official Journal of the EU, No L 110 A/ 60, 4.5.93)*

Note: Regulation (EC) No 1272/2008 (CLP Regulation) is based on the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) and is implementing the provisions of the GHS within the EU.

A. Epidemiology

The most recent evaluation of possible human cancer risks due to carbon black exposure was performed by an IARC[a] Working Group in February 2006 (Baan *et al*. 2006). The Working Group identified lung cancer as the most important endpoint to consider and exposures of workers at carbon black production sites as the most relevant for an evaluation of risk.

Three epidemiological studies were undertaken to investigate lung cancer mortality in carbon black production plants and these were considered in great detail by IARC:

A UK cohort study on 1,147 workers at five plants (Sorahan *et al*. 2001) found an SMR[b] of 1.73 (61 cases, 0.95-CI[c]: 1.32, 2.22) but no trend across crudely assessed cumulative exposure, lagged up to 20 years. Elevated lung cancer SMRs were observed at two plants, the SMRs of the other three plants were unexceptionable. A German study on 1,528 workers at one plant (Wellmann *et al*. 2006, Morfeld *et al*. 2006, Buechte *et al*. 2006, Morfeld *et al*. 2006) estimated an SMR = 1.83 (50 cases, 0.95-CI: 1.34, 2.39) but could not find any positive trends with carbon black exposures. However, the German study identified smoking and prior exposures to known carcinogens as important risk factors that could explain the major part of the excess risk. A US cohort study on 5,011 workers at 18 plants (Dell *et al*. 2006) calculated an SMR = 0.85 (127

[a] IARC = International Agency for Research of Cancer
[b] SMR = standardized mortality ratio
[c] CI = confidence interval

cases, 0.95-CI: 0.71, 1.00) and found no trend across time since first exposure and duration of exposure.

The Working Group at IARC concluded that the human evidence for carcinogenicity was ***inadequate*** (Baan *et al*. 2006).

Since this IARC 2006 evaluation, an extended follow-up of the UK study by Sorahan and Harrington (2007) applied a novel exposure metric ("lugging") while hypothesizing that carbon black may act as a late stage lung cancer carcinogen at plants with elevated SMRs. If so, the elevated SMRs of lung cancer should decrease substantially after cessation of exposure and positive associations should be found with "lugged" cumulative carbon black exposure ("lugging" the exposure by 15 years, say, means to count only exposures received during the last 15 years). Sorahan and Harrington 2007 observed both phenomena in those (and only those) two UK plant cohorts that had elevated lung cancer SMRs. In their paper, the authors asked for repetitions of their surprising finding in an independent study. Morfeld and McCunney 2007 thus tested the hypothesis of Sorahan and Harrington 2007 in the German study. Neither a decreasing SMR after cessation of exposure was observed nor a positive relationship with "lugged" cumulative carbon black exposure although the German cohort showed a clearly elevated lung cancer SMR. Therefore, Morfeld and McCunney 2007 were unable to lend support to the new hypothesis proposed by Sorahan and Harrington.

More recent studies have also been published. (Morfeld and McCunney, 2009 and 2010). In a detailed analysis of the German carbon black cohort, additional analysis was conducted to address potential "lugging" effects. As noted above, "lugging" is a term introduced by Sorahan and Harrington (2007) to account for the most recent exposures with respect to health risk. Methods such as Bayesian analysis were employed to explore all potential risk factors and confounders that may have contributed to the results. These additional studies provide further support for the lack of a significant increased risk of cancer as a result of working in the carbon black industry.

The relationship between workplace exposure to carbon black and lung cancer risk was examined in two large population-based case-control studies carried out in Montreal, Canada (Parent *et al*., 1996; Ramanakumar *et al*., 2008). Interviews for Study I were conducted in 1979–1986 (857 cases, 533 population controls, 1,349 cancer controls) and interviews for Study II were conducted in 1996–2001 (1,236 cases and 1,512 controls). Detailed lifetime job histories were elicited and a team of hygienists and chemists evaluated the evidence of exposure to a host of occupational substances, including CB. Lung cancer risk was analysed in relation to each exposure, adjusting for several potential confounders, including smoking. Subjects with occupational exposure to CB, titanium dioxide, industrial talc and cosmetic talc did not experience any detectable excess risk of lung cancer.

Overall, as a result of these further detailed investigations, no causative link of carbon black exposure and cancer risk in humans has been demonstrated. This view is consistent with the IARC evaluation in 2006.

B. Toxicology

Summary of Animal Data

In numerous studies, rodents, particularly rats, have been exposed by inhalation to carbon black. Based on the results from these studies a number of conclusions may be drawn.

First, prolonged inhalation of high levels of carbon black causes delayed alveolar lung clearance and marked retention of particles. This phenomenon is described as "lung overload" (IARC, 1996; Mauderly, 1996) and is common for a range of respirable insoluble dusts of low toxicity. The sequelae to these high lung burdens in rats include sustained inflammation, which leads to a range of changes in pro- and anti-inflammatory biochemical parameters (found in the BAL), epithelial hyperplasia, and pulmonary fibrosis.

Second, rats are more sensitive to the effects of carbon black overload than other species (mice, hamsters), with female rats having more pronounced reactions than male rats (ILSI, 2000). In long-term studies, only female rats were prone to a significant increase in the development of lung tumours. The lowest carbon black concentration used in a chronic inhalation study where lung tumours were induced was 2.5 mg/m^3, with rats being exposed for 16 hours/day, 5 days/week for 2 years (Mauderly *et al*, 1994). However, mice exposed to 11.6 mg/m^3 carbon black for 18 hours/day, 5 days/week for 13.5 months and observed for a further 9.5 months did not exhibit an increase in lung tumours (Heinrich *et al*, 1995).

In primates (Nikula *et al*., 1997) and in humans (Mauderly, 1996), there are clear differences in particle deposition, clearance patterns, and tissue reactions, when compared to rats. These differences underline the uniqueness of the rat tumour development under conditions of lung overload and raise questions as to the validity of interspecies extrapolations of particle effects from rats to humans. In further support of the uniqueness of the rat response to particle overload are findings with another inert insoluble particle, namely TiO_2. In a recent study, Bermudez, *et al* (2004) exposed female rats, mice, and hamsters to aerosol concentrations of 0.5, 2.0, or 10 mg/m^3 uf-TiO_2 particles for 6 h per day and 5 days per week for 13 weeks. Animals were kept up to 52 weeks post-exposure. Mice and rats had similar retained lung burdens at the end of the exposures, when expressed as mg uf-TiO_2/mg dry lung, whereas hamsters had retained lung burdens that were significantly lower. Pulmonary inflammation was seen in rats and mice exposed to 10 mg/m^3 as well as progressive epithelial and fibro-proliferative changes. Importantly, these lesions became more pronounced with increasing time post-exposure. However, epithelial, metaplasia, and fibro-proliferative changes were not seen in either mice or hamsters. Under conditions wherein the lung uf-TiO_2 burdens were equivalent, rats developed a more severe inflammatory response than mice. A severe, persistent neutrophilic inflammatory response in the rat lung was believed to result in the development of progressive epithelial and fibro-proliferative changes. These data are consistent with the results of a companion study using inhaled pigmentary (fine mode) TiO_2 (Bermudez, *et al.*, 2002) and demonstrate that the pulmonary responses of rats exposed to ultrafine particulate concentrations likely to induce pulmonary overload are different from the effects measured in similarly exposed mice and hamsters. Overall, these results remarkably parallel the interspecies findings seen in the Oberdoerster interspecies study with carbon black and further emphasise the uniqueness of the rat lung in its pathophysiological

response (including neoplasia) to overload from inhaled poorly soluble inert particles such as carbon black.

Data on coal miners provides the best available human evidence with which to explore lung overload questions. Using eight studies conducted between 1956 and 1986 from a total of 1,225 miners in the US and UK, Mauderly (1994) converted the lung burden of coal dust into units of specific lung burden and showed that long-term coal miners commonly accumulated dust burdens in the range of 7 to 14 mg per g lung. This value indicates that the dust burdens in heavily exposed human lungs are in the same range as, or greater than, the heavily exposed experimental animals seen in chronic bioassays. In spite of these high lung burdens, coal dust exposure does not cause a significant increase in lung cancers among miners (IARC, 1996). This reasoning, although quite compelling, does not preclude the possibility that total particle surface area and particle number are also parameters pertinent to biological outcomes.

Third, results from genotoxicity studies suggest a direct association of mutation with inflammation and its sequelae in rat lung tumour development. Lung inflammation leads to the production of reactive oxygen species, and these mutational lesions seen in the *ex vivo hprt* assay can be prevented by experimental treatment with antioxidants (Driscoll, *et al*. 1997). This study demonstrated that the increase in mutation frequency is caused by oxidative damage alone, typical of a secondary genotoxic mechanism.

The prevailing scientific consensus is that rat lung tumours induced by inert, poorly soluble particles (PSP's), such as carbon black, arise out of a background of chronic and persistent inflammatory changes; the corollary being that if these changes are avoided, then the tumours will not occur. In this respect, the studies of Driscoll, *et al.* (1996 a) are of particular relevance because exposure to 1.1 mg/m^3 of respirable carbon black particles did not evoke inflammatory or mutational changes to female rats. A no observed adverse effect level (NOAEL) of 1 mg/m^3 (respirable) carbon black has been supported by more recent rodent findings by Oberdoerster, Driscoll, and colleagues (Carter *et al.*, 2006; Elder *et al.*, 2005; Driscoll, *et al*., 2002).

Exposure protocols in experimental studies and relevance to occupational exposure

Exposure patterns and particle characteristics in experimental animal studies do not mimic conditions in the occupational environment. The duration of carbon black exposure in the chronic studies ranged from 16 to 18 hours per day, which does not simulate the workplace. Prolonged exposure does not give the animals the normal recovery period for lung clearance. This is explained by the fact that rat studies are only hazard studies and not risk based studies.
In contrast to the animal exposures, workplace exposure assessments in contemporary carbon-black manufacturing operations in Europe and in North America reveal typical 8-hour TWA exposures to well below 0.5 mg/m^3 respirable dust. In addition, industry workplace exposures are to large-size carbon black agglomerates that represent only part of the total dust (12 - 73%) exposure, with the remainder of workplace exposure being to non-carbon-black constituents. Thus, for both particle size and aerosol composition, workplace exposure characteristics are different from what has been used in the animal studies. Therefore, from a risk perspective (risk = hazard x exposure) the validity of studies showing rat tumour development under conditions of lung overload is unclear.

Mechanism of tumour development in rats and species differences

1. Lung overload

The development of lung tumours occurs only in rats under lung overload conditions (IARC, 1996; Mauderly, 1996). Neither other rodents, such as mice and hamsters, nor humans develop lung tumours under similar conditions of lung overload from PSP's. The evidence to support this contention has been addressed above in the section summarising the most relevant experimental animal studies. All the interspecies investigations point to the same conclusion regarding the uniqueness of a very specific pathophysiological process operating in the rat, particularly the female rat, leading to the formation of primarily alveogenic tumours. The development of lung tumours at lung overload exposures is triggered by the inability of rats to effectively clear the particles from their lungs and a sustained inflammatory process.

2. Role of primary genotoxic effects caused by PAH's

The proposed mechanism of tumour induction in rats is not primary genetic damage caused by the particle. Numerous mutagenicity assays with carbon black showed no inherent particle genotoxicity. All carbon blacks are insoluble in water, biological fluids, and organic solvents. Soot particles generally contain a high percentage of tarry material, with large amounts of adsorbed PAH's. In contrast, only traces amounts of organic compounds are adsorbed on carbon black (typically less than 1,000 ppm or 0.1%) (Watson and Valberg, 2001). At these low levels, organic compounds are tightly bound to carbon black particles, and extensive solvent extraction procedures are needed to remove them. In a recent study, Borm and co-workers (2005) tested three carbon black particle exposure levels (1, 7, 50 mg/m^3) of Printex 90 and one concentration (50 mg/m^3) for Sterling V, as well as a sham exposure group specifically for PAH-DNA adduct forming properties. F344 rats were exposed by inhalation for 13 weeks and then DNA was extracted from whole lung DNA immediately after exposure. The lungs of the rats for DNA analysis were not lavaged but the vascular system was perfused. DNA was extracted and used to determine oxidative DNA damage. To determine whether PAHs were available and subsequently transformed into DNA-binding metabolites, lungs of three animals from each exposure group

were analysed for DNA adducts, immediately after exposure. No adducts were found in DNA from lung homogenates isolated immediately after 13 weeks of inhalation of up to 50 mg/m^3 of Printex 90 and Sterling V, which resulted in lung burdens of 4.9 mg and 7.6 mg, respectively. Lung DNA from rats following inhalation of carbon black showed no "spots" relating to PAH-DNA adduct formation compared to sham-exposed animals.

Donaldson and co-workers (1998) postulate in their review on particle-mediated lung injury, that there is no evidence to support carbon black particles having direct mutagenic activity. They noted that diesel exhaust, carbon black and titanium dioxide (TiO_2), caused similar levels of overload tumours (Heinrich *et al*. 1995), despite the fact that the extractable organic component was 40% for diesel exhaust, 0.04% for carbon black and 0% for TiO_2. The results of Gallagher *et al*. (1994) support the findings of Heinrich and co-workers, because no PAH-DNA adducts were detected in rats with overload carbon black tumours. Examinations by Bond and co-workers (1990) and Wolff and co-workers (1990) showed similar results. Donaldson and co-workers (1998) concluded that the particles themselves cause recruitment of inflammatory cells, which release respiratory burst-derived oxidants and that these oxygen free radicals could induce mutations in particle-exposed lung of rats.

3. Role of secondary genotoxic effects caused by Reactive Oxygen Species

The lack of association between the inherent genotoxic activity of PSP's and the development of rat lung tumours after chronic inhalation exposure implies a secondary mechanism for this response. At an international workshop organized by the German Research Council / DFG (Deutsche Forschungsgemeinschaft) on particle and fibre evaluation (Greim *et al.*, 2001), it was generally agreed that tumours in rat experiments are caused by a secondary, inflammatory / proliferative mechanism as opposed to direct genotoxicity. Lung overload leads to sustained inflammation, release of various biological mediators and oxidative stress. In addition to carbon black, high exposure levels of titanium dioxide (250 mg/m³) (Lee *et al*., 1985) and talc (10 or 20 mg/m³) (Hobbs *et al*., 1994) cause lung tumours in rats. Thus, the lung tumour response to inhaled inert particles observed in female rats is not particle specific.
"Particle overload" is the key factor leading to the development of tumours in rats, and it appears that oxidative stress is the primary event / mechanism critical for tumour pathogenesis. The susceptibility of the rat may reside in the fact that rat lungs show a far greater induction of several key pro-inflammatory processes and less induction of anti-inflammatory processes than other species (Driscoll and Carter, 1999).

At and below carbon black concentrations of approximately 1 mg/m³ (respirable), it is highly unlikely that rats, other rodents, or humans are at risk for developing lung cancer (Oberdörster and Yu, 1997; Driscoll *et al*., 1995, 1996 a; ILSI [International Life Sciences Institute] Risk Science workshop, 2000). At the DFG workshop (Greim *et al.*, 2001), the consensus was that preventing lung inflammation will prevent the development of lung tumours.
Evidence for an effect threshold has been demonstrated in that sub-chronic inhalation of 1.1 mg/m³ respirable carbon black did not elicit inflammation or increases in *hprt* mutation frequency in epithelial cells (Driscoll *et al*., 1996 a). In rats, a lung-tumour threshold has also been

demonstrated for diesel-exhaust exposure (Valberg and Crouch, 1999). More recently, sub-chronic inhalation of carbon black over a range of concentrations has confirmed the absence of inflammatory responses following repeated exposures to 1 mg/m^3 (Carter *et al.*, 2006; Elder *et al.*, 2005; Driscoll *et al.*, 2002). Thus, 1mg/m^3 of respirable-sized carbon black represents a clear NOAEL for even the most sensitive of inflammatory markers in the most sensitive of test organisms, the female rat.

Conclusions, Animal Studies

At the DFG International Workshop Evaluation on Particle and Fibre Toxicity (Greim *et al.*, 2001) a consensus was reached regarding the tumorigenic properties of inert, PSP's. The participants generally accepted that PSP's caused lung tumours in rats by a secondary genotoxic (inflammatory/proliferative) mechanism. The group concluded that, *"Studies to date have not demonstrated primary genotoxicity of carbon black with low PAH contamination using appropriate in vitro assays. DNA adducts related to associated organic compounds so far have not been found in lung tissue from rats exposed chronically to carbon black, although in the same studies adducts were found in diesel exhaust-exposed rats."*

Implicit in the inflammatory / proliferative mechanism is the existence of a non-linear, dose-related effect with a threshold. That is, particle exposures that do not overwhelm host defence mechanisms (*e.g.,* anti-oxidants, DNA repair) and hence do not elicit inflammatory and proliferative responses, should not pose an increased risk of lung tumours in humans (Driscoll, 1996 b; Driscoll *et al.,* 1996a). Using a meta-analysis approach, Valberg and Crouch (1999) demonstrated that the incidence of lung tumours was not elevated in rats with less than an average 0.6 mg/m^3 continuous lifetime exposure to diesel exhaust particles. Therefore, the use of linear models for dose-response extrapolation from "lung overload" conditions is not appropriate and should be replaced with non-linear models incorporating a threshold.

Driscoll *et al*. (1996 b) have demonstrated that sub-chronic inhalation of 1.1 mg/m³ (respirable) carbon black did not elicit any detectable adverse lung effects. The results from Oberdörster's and Driscoll's research groups (Carter *et al.*, 2006; Elder *et al.*, 2005; Driscoll *et al.*, 2002) support this finding, with a carbon black NOAEL of 1 mg/m³ (respirable). Furthermore, participants at the ILSI workshop (2000) proposed that no uncertainty (safety) factor (for rat-to-human extrapolation) was required for neoplastic and fibrogenic endpoints associated with particle exposure, because the rat appears to be more sensitive in its responses to all particle-related effects than other species, including humans. The evaluation of carbon black by IARC (1996 and 2006) and Greim *et al.* (2001) as a suspect carcinogen is solely founded on the observation that rats develop tumours. The ILSI workshop (2000), which evaluated the relevance of the rat responses to particle overload for human risk assessment, concluded that at non-overload exposures, a lung-cancer hazard did not exist.

Furthermore, experimentally-induced lung tumours in rats occur in the alveolar and small airway regions of the lungs, unlike human lung cancers that tend to occur at the bifurcations of the major airways (bronchi), further questions the appropriateness of extrapolating the results in the rat studies to humans.

Basing human lung cancer risk predictions on the rat response to the inhalation of PSP's, including carbon black under conditions of lung overload is not valid. Several independent, expert, scientific advisory groups have cautioned against using tumorigenic data from rats exposed to high ("lung overload") concentrations of insoluble particles for quantitative risk assessment. In the United States, the Presidential / Congressional Commission on Risk Assessment and Risk Management (CRARM, 1997) noted that the response of rat lungs to high concentrations of inhaled, PSP's (specifically carbon black and titanium dioxide) are not likely to be predictive of human cancer risks. For diesel exhaust, the Clean Air Scientific Advisory Committee (CASAC, 1995 and 1998), a peer-review group for the U.S. Environmental Protection Agency (EPA), has commented on two drafts of the EPA´s Health Assessment Document on Diesel Exhaust. On both occasions, CASAC emphasized that the data from lung-overloaded rats are not relevant for human risk assessment. Likewise, the Health Effects Institute (1995) also has concluded that rat data should not be used for assessing human lung-cancer risk from diesel-exhaust exposure.

C. Recommendation for Classification of Carbon Black according to EU Criteria:

Although lung tumours are induced in rats when exposed to carbon black, it is generally acknowledged that these tumours are produced because of a phenomenon known as "lung overload". When exposed to a poorly soluble particle such as carbon black in high concentrations, laboratory rats cannot adequately clear carbon black from their respiratory tract, so lung tumours are induced by a secondary non-genotoxic mechanism. Lung tumours were not observed in mice and hamsters under similar study conditions. The relevance of the rat tumour data to human risk assessment is highly questionable (ILSI, 2000). Thus, based on these findings and the guidance from authoritative bodies, the ICBA and the Carbon Black REACH Consortium have reached the opinion that it is not appropriate to classify carbon black as "Category 2 Carcinogen" under the GHS/CLP Regulation. In support of this opinion, it should be noted that in the CLP Guidance for Specific Target Organ Toxicity – Repeated Exposure (STOT RE) (CLP, **2011),** the issue of lung overload is mentioned under section 3.9.2.5.3 Mechanisms not relevant to humans (CLP Annex 1, 3.9.2.8.1.(e)) as 'The relevance of lung overload in animals to humans is currently not clear and is subject to continued scientific debate'. Also section 3.9.2.8 (e) **of the GHS/CLP regulation** states that 'Substance – induced species specific mechanisms of toxicity, i.e. demonstrated with reasonable certainty to be not relevant for human health, shall not justify classification'. **Further,** Section 3.6.1.1 of the GHS/CLP regulation states "Substances which

have induced benign and malignant tumours in well performed experimental studies on animals are considered also to be presumed or suspected human carcinogens **unless** there is strong evidence that the mechanism of tumour formation is not relevant for humans." The ACGIH® has also designated carbon black a category A3 carcinogen, Confirmed Animal Carcinogen with Unknown Relevance to Humans. This designation by the ACGIH® is consistent with the ICBA and the Carbon Black REACH Consortium conclusion not to classify carbon black.

In conclusion, the evaluation of carbon black as a suspect carcinogen is based solely on the observation that rats develop lung tumours under condition of "lung overload". The reliability of lung tumours induced in rats by inert poorly soluble particles, such as carbon black, as a predictor of hazard to humans is uncertain. Overall, the epidemiological evidence from well-conducted investigations has not shown that exposure to carbon black has a carcinogenic potential for humans.

Therefore, we recommend that no classification of carbon black is required based on the fact that data from rat lung overload studies, as described above and fully discussed in our statement, cannot be extrapolated to humans.

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