International Carbon Black Association

Recommendation for No Classification of Carbon Black for Carcinogenicity

Statement of Overall Conclusions

Carbon Black (CB) should not be classified for carcinogenicity according to the criteria of the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). This recommendation is also valid for GHS implementation by different regulatory regions such as the EU (Regulation (EC) No 1272/2008 (CLP)), United States 2012 OSHA Hazard Communication Standard (29 CFR 1910.1200) and the Canadian Hazardous Products Regulation (HPR) 2015. Human health studies show that exposure to carbon black does not increase the risk of carcinogenicity. Studies in laboratory animals show that lung tumours are induced in rats as a result of repeated exposure to inert, poorly soluble particles like carbon black and other poorly soluble particles. Rat tumours occur are a result of a secondary non-genotoxic mechanism associated with the phenomenon of lung overload. This is a species-specific mechanism that has questionable relevance for classification in humans. Thus, a carcinogenicity classification for CB is not warranted.

GHS Classification System for Carcinogenicity

The categories for classification and labelling of carcinogenic substances under GHS are summarized in Table 1.

Table 1 Classification Criteria for Carcinogenicity under GHS

GHS, Chapter 3.6.2.1
Category 1: Known or presumed human carcinogens *The placing of a substance in Category 1 is done on the basis of epidemiological and/or animal data.*
Category 2: Suspected human carcinogens *The placing of a substance in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1. Based on strength of evidence together with additional considerations, such evidence may be from either limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.*

The following sections discuss data from epidemiological and animal studies on carbon black. Based on weight of evidence from these data, carbon black is not classified as a carcinogen under GHS.

A. Epidemiology

The most recent evaluation of possible human cancer risks due to carbon black exposure was performed by an IARCa 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. These studies were considered in great detail by IARC:

A UK cohort study on 1,147 workers at five plants (Sorahan et al. 2001) found an SMRb of 1.73 (61 cases, 0.95-CIc: 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 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).

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

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.

An update and extension of the retrospective mortality study of US carbon black workers evaluated a cohort of 6634 workers employed in the carbon black industry dating back to the 1930s (Dell et al. 2015). The mortality follow-up was extended until December 31, 2011, and a quantitative assessment of individual cumulative exposure to inhalable carbon black dust conducted. The results showed no increase in lung cancer or any other malignancy in either the total or inception cohorts: Lung cancer mortality was decreased in comparison to state-specific reference rates (184 observed deaths, SMR = 0.77; 0.95-CI: 0.67 to 0.89), and for all cancers (512 observed deaths, SMR=0.79, 0.95-CI: 0.72–0.86). Internal exposure-response analyses showed no convincing link between carbon black exposure and lung cancer mortality. In summary, the authors of the study concluded: *"Regardless of whether exposure was based on lagged, lugged, or total cumulative estimates, no consistent association was seen with lung cancer or non-malignant respiratory disease."*

A meta-regression analysis based on three cohorts was conducted to quantify the relationship between CB exposure and lung cancer mortality. A 10 mg/m^3.year increase in cumulative exposure to carbon black was associated with a non-statistically significant relative risk decrease of 1% (RR = 0.99; 95% CI: 0.87 – 1.13) for lung cancer mortality. No positive exposure-response relationship was observed between carbon black exposure and mortality from lung cancer. (Yong et al. 2019).

Excess mortalities were reported for diseases of the blood-forming organs and peritoneal and unspecified digestive organ cancers. No biological plausibility or mechanism can be discerned for these endpoints, but the excesses may easily be explained by false positive findings due to the large number of comparisons performed (Morfeld 2016).

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 and 2010.

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; IARC, 2010, Mauderly, 1996) and is common for a range of respirable insoluble dusts of low toxicity (ECHA, 2017b). 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 bronchoalveolar lavage fluid), epithelial hyperplasia, and pulmonary fibrosis.

Second, rats are more sensitive to the effects of carbon black overload than other species (mice, hamsters) (Driscoll & Borm 2020), with female rats having more pronounced reactions than male rats (ILSI, 2000). 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. Lung toxicity and respiratory effects as well as particle retention kinetics, inflammation, and histopathology were examined in female rats, mice, and hamsters exposed for 6 hours per day; 5 days per week for 13 weeks to high surface area carbon black (HSCb) at doses of 0, 1, 7, and 50 mg/m3. A group of rats was also exposed to 50 mg/m3 of a low surface area carbon

black (LSCb). Following exposure and 3- and 11-months recovery periods, animals were evaluated for measurements of lung burdens and lung and nasal histopathology (Elder et al. 2005), (Santhanam et al. 2008). Prolonged retention was found in rats exposed to mid- and high-dose HSCb and to LSCb, but LSCb was cleared faster than HSCb. Retention was also prolonged in mice exposed to mid- and high-dose HSCb, and in hamsters exposed to high-dose HSCb. Lung inflammation and histopathology were more severe and prolonged in rats than in mice and hamsters.

In further support of the uniqueness of the rat response to particle overload are findings with another inert insoluble particle, namely TiO_2. Bermudez, *et al.* (2004) exposed female rats, mice, and hamsters to aerosol concentrations of 0.5, 2.0, or 10 mg/m^3 ultrafine-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 ultrafine-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 ultrafine-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. These studies with TiO_2 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 coalmine 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. A more recent update on coal's potential to cause lung cancer concluded that "*the weight of the scientific literature suggests that coalmine dust does not increase lung cancer risk." (McCunney and Yong, 2022)*

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 other rodent findings by Oberdörster, 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 (Mauderly *et al*. 1994; Heinrich *et al.* 1995), which does not simulate the workplace. Prolonged exposure causes undue stress to the animals as it does not give the animals the normal recovery period for lung clearance.

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 generally to large-size carbon black agglomerates that represent only part of the total dust 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, the applicability to human risk assessment of studies showing rat tumour development under conditions of lung overload is unclear.

Mechanism of tumour development in rats and species differences

The development of lung tumours occurs only in rats under lung overload conditions (IARC, 1996; IARC 2010; 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 conclusion 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.

Bevan and colleagues, in their 2018 review paper on poorly soluble particles, lung cancer and lung overload, noted that one of the key differences in humans compared to rats is in the processing of inhaled particles. While in humans, particles migrate to and are sequestered in the interstitium, in the rat, the particles accumulate in the alveolar lumen. They concluded that *"A different particle lung translocation pattern compared to rats make humans less sensitive to developing comparable lung overload conditions and appears to also preclude tumour formation, even under severe and prolonged exposure conditions. Evidence continues to suggest that the rat lung model is unreliable as a predictor for human lung cancer risk."* In reaching this conclusion, the researchers examined several studies, including studies regarding lung cancer in coal miners, carbon black production workers, and titanium dioxide production workers. These studies of workers who are chronically exposed to indicated that there is not a lung cancer excess among this population and that these

materials do not cause the same inflammatory outcome in humans as they do in rats. This publication was largely built on and updated the findings of a 2013 Task Force convened by the European Centre for Ecotoxicology and Toxicology of Chemicals that likewise concluded that the rat is unique in developing lung tumours under chronic inhalation overload exposures to PSLTs (ECETOC 2013).

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. 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.,* antioxidants, 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.

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.

In 2020, an international panel of particles scientists and experts in the fields of Chemicals regulation, toxicology and epidemiology discussed the relevance of rat lung tumour data for PSLTs, including carbon black (Driscoll and Borm 2020). Their consensus views were: "*In summary, the Expert Panel thoughtfully considered the current state of the science for PSLT and reached agreement on several matters relevant to PSLT toxicology, hazard classification and risk assessment. Specifically, the Expert Panel: (1) outlined an experimental process for determining if a material should be considered as poorly soluble and low toxicity; (2) agreed the rat is a sensitive test species for PSLT inhalation toxicology and supported continued use of the rat for PSLT inhalation toxicology studies; (3) recommended that future studies focus on defining thresholds for inflammation and inflammation be used as a critical endpoint for OEL setting**; (4) agreed rat lung cancer occurring only under conditions of lung particle overload, in the absence of corroborating data from other species, should not be interpreted to imply a cancer hazard for humans and, (5) were in consensus that rat lung tumours under lung particle overload are not relevant to health hazard or risk under non-overload exposure conditions."*

In 2021, Health Canada considered a classification of carcinogenicity for carbon black. However, after reviewing animal and human data on carbon black carcinogenicity, Health Canada determined that there are deficiencies in the design of the rat studies, including the high dose levels used which caused lung overload. They also noted that the conclusion of epidemiological studies on carbon black workers has been negative or equivocal. Thus, Health Canada determined ***"that there is***

insufficient evidence to conclude that carbon black meets the classification criteria of a category or subcategory of the Carcinogenicity health hazard class."

Consistent with the above is the judgement of the European Court of Justice (ECJ) on a TiO_2 cancer classification (CWS Powder Coatings v Commission, Case number T-279/20, ECJ 2022). The ECJ annulled the carcinogenic classification of TiO_2 because of errors made by ECHA and the Commission in the interpretation and translation of the results seen for TiO_2 in rats to humans. According to criteria developed by ECHA for overload studies, studies with effects (tumours) occurring under severe or excessive overload would preclude them for use in hazard identification. Interpreting the ECJ ruling, had ECHA applied the rules for its criteria correctly, ECHA would not have concluded that TiO_2. meets the criteria of a category or subcategory of the Carcinogenicity health hazard class. It is worth noting that carbon black cancer studies in rats have shown very similar activity (severe overload) to TiO_2, and a similar argument to disregard the rat tumour studies also applies to carbon black.

C. Recommendation for Classification of Carbon Black according to GHS 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). A review by ECETOC (2013) also concluded that the rat represents a unique model with regard to lung neoplastic responses under conditions of lung overload. In 2018, this conclusion has been updated and reconfirmed (Bevan et al. 2018). In 2020, a panel of experts reaffirmed the conclusion that the rat is an especially sensitive test species for testing poorly soluble substances like carbon black (Driscoll and Borm, 2020). They agreed that rat lung cancer occurring only under conditions of lung particle overload, in the absence of corroborating data from other species, should not be interpreted to imply a cancer hazard for humans. Further, they arrived at the conclusion that rat lung tumours under lung particle overload are not relevant to health hazard or risk under non-overload exposure conditions in humans. Lastly, tumours in the rat occurring under excessive overload are not relevant for hazard identification (ECHA 2017b).

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 for a category or subcategory of the Carcinogenicity health hazard class under the GHS Regulation.

In support of this opinion, it should be noted that in the EU CLP Guidance on the Application of the CLP Criteria (ECHA, 2017), 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 3.9.2.8.1 (e) of 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". **Further,** Section 3.6.1.1 of the 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. More recently, Health Canada reached the conclusion ***"that there is insufficient evidence to conclude that carbon black meets the classification criteria of a category or subcategory of the Carcinogenicity health hazard class."***

The United States 2012 OSHA Hazard Communication Standard's (29 CFR 1910.1200) (HCS) section on carcinogenicity is consistent with GHS, except that it provides classifiers with the option of relying on the classification listings of IARC and National Toxicology Program (NTP) to make classification decisions regarding carcinogenicity, rather than applying the criteria themselves. Using IARC and NTP listings for carcinogen classification is provided as an option. It is not mandatory. Therefore, the weight of evidence evaluation shown in this document is also acceptable under HCS.

In conclusion, the evaluation of carbon black as a suspect carcinogen (GHS Cat 2) 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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