



# International Carbon Black Association

## *Specific Target Organ Toxicity - Repeated Exposure: Recommendation for No Classification of Carbon Black*

### Statement of Overall Conclusions

According to the Criteria of the United Nations Globally Harmonized System of Classification and Labelling of Chemicals (GHS), Carbon Black (CB) should not be classified for Specific Target Organ Toxicity - Repeated Exposure (STOT-RE). This recommendation is also valid for GHS implementation by different regulatory regions such as the EU (Regulation (EC) No 1272/2008 (CLP, 2021)), United States 2012 OSHA Hazard Communication Standard (29 CFR 1910.1200) and the Canadian Hazardous Products Regulation HPR (SOR/2015-17). Although CB produces pulmonary irritation, cellular proliferation, fibrosis and lung tumours in the rat under conditions of pulmonary overload, there is ample evidence to demonstrate that this response is principally a species-specific response that is not relevant to humans. Thus, a STOT - RE classification for CB is not warranted.

### GHS Classification System

The categories for classification and labeling of substances causing STOT – RE under GHS are summarized in Table 1.

**Table 1:** Classification Criteria for STOT – RE under the GHS

GHS, Chapter 3.9
Category 1: <i>Substances that have produced significant toxicity in humans, or that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to produce significant toxicity in humans following repeated exposure.</i>
Category 2:

*Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following repeated exposure.*

Classification under GHS for STOT - RE depends upon the availability of reliable evidence that repeated exposures to the substance have produced a consistent and identifiable toxic effect in humans or in experimental animals. Toxicologically significant changes are considered to be those that have affected the function or morphology of a tissue/organ, or have produced serious changes to the biochemistry or hematology of the organism and these changes are relevant for human health. All significant health effects that can impair function, reversible and irreversible, immediate and/or delayed are included. If available, human data should be the primary source of evidence for this hazard class.

Assessment should take into consideration not only significant changes in a single organ or biological system but also generalized changes of a less severe nature involving several organs. The information required in order to evaluate specific target organ/systemic toxicity comes either from repeated exposure in humans (e.g. epidemiology studies, workplace exposures, etc.) or from studies conducted in experimental animals. The standard animal studies in rats or mice that provide this information are 28 day, 90 day or lifetime studies (up to 2 years) that include hematological, clinico-chemical and detailed macroscopic and microscopic examination to enable the toxic effects on target organs to be determined.

In the case of dust particles, GHS guidance values for exposure concentrations are given in Table 2. Classification in either Category is based on significant toxic effects observed in 90-day repeated-dose toxicity studies in experimental animals.

**Table 2:** Guidance values to assist in STOT-RE Category 1 and 2 Classifications for dust exposures

	Concentration (mg/l)
Category 1	0.02
Category 2	0.02 - 0.2

Substances are classified as STOT-RE by expert judgment on the basis of the weight of all the evidence available, including the use of recommended guidance values that take into account the duration of exposure and the dose/concentration that produced the effect(s). There are a number of conditions under which no classification is necessary. For insoluble particles such as CB, toxic effects in animal inhalation experiments are caused by the “lung overload phenomenon” (Levy 1995, 1996; Warheit et al, 1997; Bevan et al, 2018). The rat is the most sensitive species to lung overload from particles. Species specific differences are demonstrated in various mechanistic animal studies (ILSI, 2000). It has been demonstrated, with reasonable certainty, that lung overload conditions in the rat are not relevant for human health and, therefore, results based on these data do not justify classification. Moreover, in regard to the Guidance values shown in Table 2 above, all poorly-soluble particles, most of which can be considered to be of

no-or very low toxicity would require classification, which would defeat the objective of the classification system.

## Supporting Information

### A. Epidemiology of Malignant and Non-Malignant Respiratory Diseases and CB Exposure

#### Summary of human data on possible malignant disease

An evaluation of possible human cancer risks due to CB exposures was performed by an IARC Working Group in February 2006 (IARC, 2006). The Working Group identified lung cancer as the most important endpoint to consider and exposures at CB production sites as the most relevant for an evaluation.

Three major cohort epidemiological studies were performed in the UK, USA and Germany to investigate lung cancer mortality in CB production plants:

A UK cohort study on 1,147 workers at five plants (Sorahan *et al.* 2001) found a standardised mortality ratio (SMR) of 1.73 (61 cases, 0.95-confidence interval (CI): 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.* 2006a, Buechte *et al.* 2006, Morfeld *et al.* 2006b) estimated an SMR = 1.83 (50 cases, 0.95-CI: 1.34, 2.39) but could not find any positive trends with CB 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 (Morfeld *et al.* 2006a). 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 in years.

The working group at IARC concluded that the evidence in humans for the carcinogenicity of CB was *inadequate* (IARC, 2006).

Since this IARC 2006 evaluation, in an extended follow-up of the UK study, Sorahan and Harrington (2007) applied a novel exposure metric (“lugging”) while hypothesizing that CB may act as a late-stage lung 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 CB exposure (“lugging” the exposure by 15 years 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. The authors asked for repetitions of their surprising findings in independent settings. 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 CB 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 generated by Sorahan and Harrington (2007)).

Additional studies have also been published (Morfeld and McCunney (2009 and 2010)). In a detailed analysis of the German CB 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 CB industry.

The relationship between workplace exposure to CB 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.*”

Excess mortalities were reported only 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 2016a). Further analysis of the mortality studies in a comprehensive meta-analysis also

showed no excess of malignancies-including those of the lungs- among workers exposed to carbon black (Yong et al, 2019).

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

### **Summary of human data on non-malignant disease**

There are several occupational studies available in which the non-malignant respiratory effects of CB have been investigated in CB production workers.

A large multi-center European study was performed by Gardiner *et al.* (1993) with a follow-up consisting of two separate phases (Gardiner *et al* 2001). Phase I of the study covered the period 1987-1989, phase 2 the period 1991-1992, and phase 3 the period 1994-1995. The final analysis for Phase 1 was based on 1742 employees from 15 plants (81% response rate); for phases 2 and 3 the final analyses were based on 2324 workers (19 plants), and 1994 workers (16 plants), with an overall response rate of greater than 90%. Results from phases 2 and 3 had higher worker participation rates; increased exposure measurements and greater precision due to new job titles and exposure categories; and were therefore considered more reliable than the Phase 1 data.

Results of the first phase of the study by Gardiner indicated an overall good respiratory health of the study population with a low prevalence of pneumoconiotic change (0.3%) without progression in subsequent follow-up. Mean prevalence of respiratory symptoms were considered by the authors to be generally low and typical of industrial populations. No significant impairment in lung function was found. However, statistical analyses revealed a trend of increasing prevalence of respiratory symptoms and a decline in lung function scores that related to recent (not cumulative) exposure to respirable CB. There was no relation between these health outcomes and the inhalable dust exposures.

In Phases 2 and 3, exposures dropped considerably as compared to Phase 1; the arithmetic means for exposures to inhalable dust across all plants were 0.77 mg/m<sup>3</sup> (range 0.07-7.41), and 0.57 mg/m<sup>3</sup> (range 0.11 - 3.26) in Phases 2 and 3 respectively. The mean prevalence of respiratory symptoms were reported to be lower in Phase 3 compared with Phase 2, both being lower than for phase 1. Logistic regression analysis showed a relationship between symptoms and cumulative smoking; weaker, but statistically significant relations were found for some symptoms with CB exposures (chronic bronchitis, sputum production in phase 2, cough and cough with sputum production in phases 2 and 3). Methodological limitations in the administration of the questionnaire however limit the conclusions that can be drawn about the reported symptoms.

Spirometry results revealed a good standard of respiratory function. However, there were statistically significant relationships between current and cumulative exposures and declines in forced expiratory volume in 1 second (FEV<sub>1</sub>) and other parameters, suggestive of obstructive effects. The findings were consistent and similar across Phases 2 and 3. However, the degree of the effect was clinically insignificant.

The authors estimated that based on the cumulative exposure measures for inhalable CB in Phase 3, the expected decrements after 40 years employment with a mean (8-hr TWA) exposure of  $1 \text{ mg/m}^3$  would be 48 ml (95% CI 1-91ml) for FEV<sub>1</sub>.

These predictions suggest that after 40 years exposure to  $1 \text{ mg/m}^3$  (8-hr TWA) there would be no effects of CB exposure on forced vital capacity (FVC), slight effects on FEV<sub>1</sub>, and negligible effects on the FEV<sub>1</sub>/FVC ratio.

Using multiple regression analyses of the data from the US study, Harber *et al.* (2003) found a consistent relationship between cumulative CB exposure and small reductions in FEV<sub>1</sub>, but not with other spirometry parameters. The estimated slopes were minus 2 ml FEV<sub>1</sub> per  $\text{mg}\cdot\text{year}/\text{m}^3$  of cumulative "total" dust exposure and minus 0.7 ml FEV<sub>1</sub> per  $\text{mg}\cdot\text{year}/\text{m}^3$  of cumulative exposure for the inhalable fraction. The modeling of the data indicated that for non-smoking males, exposure to inhalable CB for a working lifetime (40 years) at 1, 2 and  $3.5 \text{ mg/m}^3$  (8hr TWA) would lead to mean decreases in FEV<sub>1</sub> of 48, 91 and 169 ml, respectively (beyond the decreases caused by age; for comparison, the average age-related decline in FEV<sub>1</sub> in adult males is about 30 ml per year). Recent exposures, typically much lower than historical exposures, were not demonstrated to be associated with these effects.

Harber *et al.* (2003) report that heavy cumulative exposures of CB were associated with a small increase in self-reported chronic bronchitis symptoms in non-smokers. These symptoms were not reported in smokers and ex-smokers, and there were no increases of the other listed symptoms on the questionnaire; namely, chronic sputum and dyspnea. Table 6 of Harber *et al.* (2003) described elevated prevalence of symptoms (chronic bronchitis) in the highest exposure pentile which is comparable to an exposure to inhalable dust of  $138 \text{ mg}\cdot\text{years}/\text{m}^3$  or to an average concentration over 40 years of exposure at  $(138\text{mg}\cdot\text{years}/\text{m}^3)/(40 \text{ years}) = 3.5 \text{ mg/m}^3$ . Based on the occurrence of bronchitis, which is the most sensitive human health effect after carbon black exposure, the American Conference of Governmental Industrial Hygienists (ACGIH) developed a Threshold Limit Value – time weighted average (TLV-TWA) for carbon black of  $3 \text{ mg/m}^3$  (inhalable) (ACGIH 2011).

Results from a cross-sectional study on CB production workers performed by Kuepper *et al.* (1994, 1996a,b) provided no clear evidence for an effect of CB on lung function. Exposure measurements revealed that the mean levels of respirable and total inhalable dust were  $0.58$  and  $1.08 \text{ mg/m}^3$ , respectively. However, no information on respiratory symptoms was provided.

A cross sectional study of rubber workers from Iran suggested that workers exposed to levels of CB estimated to be twice above the current TLV, had a higher rate of respiratory symptoms and lung function changes (Neghab *et al.*, 2011). There were 72 workers and 69 controls; exposure levels to CB exceeded  $6 \text{ mg/m}^3$  (inhalable fraction).

A meta-analysis of potential cardiac risks among carbon black workers showed no increase in mortality (Morfeld *et al.*, 2016b).

## ***Conclusion***

In exposed CB production workers, repeated inhalation exposure to CB can cause non-clinical decrements in pulmonary function, increases in respiratory symptoms, and, possibly chest film changes. Based on data from a large European multi-centre study covering 19 plants in 7 countries (UK, 2 plants; France, 3 plants; Germany, 5 plants; Holland, 2 plants; Italy, 3 plants; Spain, 3 plants; and Sweden, 1 plant), predictions suggest that after 40 years exposure to 1.0 mg/m<sup>3</sup> (inhalable fraction, 8-hr TWA) there would be minimal effects on lung function parameters. It has been estimated that exposure to a working lifetime of 40 years to inhalable CB at 1, 2 and 3.5 mg/m<sup>3</sup> (8-hour TWA) would lead to mean decreases in FEV<sub>1</sub> of 48, 91 and 169 ml, respectively. This may be compared to the average age-related FEV<sub>1</sub> in adult males of about 1,200 ml over this 40-year period. This equates to an additional 4% loss in FEV<sub>1</sub> when exposed to 1 mg/m<sup>3</sup> over 40 years. A study of production workers in North America covering 22 plants (Canada, 2 plants; United States, 20 plants) yielded comparable respiratory function results for 1 mg/m<sup>3</sup> 40-year working-life exposures (FEV<sub>1</sub>, 28 ml decrease).

## **B. Toxicology**

### **Rodent toxicity data based on repeated inhalation exposure**

Several repeated-dose studies evaluating inhalation exposure to carbon black are available. Particle retention kinetics, inflammation, and histopathology were examined in female rats, mice, and hamsters exposed for 13 weeks to high surface area CB (Printex 90, HSCb, primary particle size 17 nm, MMAD 1.2 - 2.4 µm) at doses of 0, 1, 7, and 50 mg/m<sup>3</sup>. Rats were also exposed to 50 mg/m<sup>3</sup> low surface area CB (Sterling V, LSCb, MMAD 0.6 - 0.9 µm). Groups of animals were sacrificed immediately after 13 weeks of exposure, and after 3 and 11 months of recovery for bronchoalveolar lavage analysis, as well as for measurements of lung burdens and lung histopathology (Elder *et al.* 2005). 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, and both were similar in rats exposed to mid-dose HSCb and LSCb. The results show that hamsters have the most efficient clearance mechanisms and least severe responses of the three species tested. The results from rats also show that particle surface area is an important determinant of target tissue dose and, therefore, effects. From these results, a sub-chronic No Observed Adverse Effect Level (NOAEL) of 1 mg/m<sup>3</sup> respirable HSCb can be assigned to female rats, mice, and hamsters.

A thorough sub-chronic inhalation study was performed by Driscoll *et al.* (1996) in male Fischer 344 rats using respirable CB. Groups of male rats were exposed to 0, 1.1, 7.1 or 52.8 mg/m<sup>3</sup> Monarch 880 (furnace black) for 13 weeks (6 hr/d, 5 d/week). The primary particle size was 16 nm, with a MMAD of 0.88 µm, and a specific surface area of 220 m<sup>2</sup>/g. Groups of animals were sacrificed immediately after 13 weeks of exposure, and after 3 and 8 months of recovery for bronchoalveolar lavage analysis, as well as for measurements of lung burdens and lung histopathology. No pathological or biochemical changes were found in the lungs at 1.1 mg/m<sup>3</sup> (NOAEL), but there were clear dose-related increases in both biochemical and cellular markers of lung damage at the mid- and

high exposure levels. By 8 months, there was substantial clearance of the CB retained in the lungs in the low exposure group, moderate clearance in the mid-exposure group and very little clearance in the high exposure group. Histopathology revealed particle-containing macrophages located in the alveolar and alveolar duct regions of the lungs of rats exposed to 1.1 mg/m<sup>3</sup>. In contrast, in rats exposed to 7.1 mg/m<sup>3</sup> there was evidence of inflammation characterized by accumulation of neutrophils and macrophages within the alveolar spaces. There was also evidence for focal and random areas of mild epithelial hyperplasia and mild interstitial fibrosis. Exposure to 52.8 mg/m<sup>3</sup> showed more pronounced epithelial hyperplasia and fibrosis. Fibrosis was greatest after the 8 month recovery period.

In an inhalation study investigating the effects of agglomeration on toxicity of carbon black, Lim et al (2012) reported no changes in body weight, cytokine levels in the bronchoalveolar lavage (BAL) fluid or blood biochemical and hematological parameters following nose only exposure of male rats to approximately 9 mg/m<sup>3</sup> carbon black for 90 days.

### **Mechanism of the Rat Lung Response to Particle Overload**

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

**First**, prolonged inhalation of high levels of CB 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. Currently, these particles, including CB, are described as poorly-soluble particles of low toxicity (PSLTs). The sequelae to these high lung burdens in rats include inflammation, which leads to a range of changes in pro- and anti-inflammatory biochemical parameters (found in bronchoalveolar lavage fluid), epithelial hyperplasia, and pulmonary fibrosis.

**Second**, rats are more sensitive to the effects of CB overload than other species; with female rats having more pronounced reactions than male rats (ILSI, 2000). The lowest CB concentration used in a chronic inhalation study where lung tumours were induced was 2.5 mg/m<sup>3</sup>, with rats being exposed for 16 hours/day, 5 days/week for 2 years (Nikula *et al.* 1995). However, mice exposed to 11.6 mg/m<sup>3</sup> CB 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 (Bevan *et al.* 2018). In an Expert Workshop held in 2020 (Driscoll and Borm 2020) amongst a panel of highly experienced scientists and regulators, consensus was reached on several points regarding lung overload. As stated in the paper “Key outcomes included: a functional definition of PSLTs; agreement the rat is a sensitive model for PSLT inhalation toxicology; identifying lung inflammation as a critical endpoint for PSLT risk assessment; and, agreement that rat lung cancer occurring only under



conditions of lung particle overload does not imply a cancer hazard for humans under non-overloading exposures.”

Data on coal miners provide 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 in 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, 1997). 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 as it is generally accepted that the pathogenicity (including tumour induction) in rats of inhaled particles is more closely related to total particle surface area rather than mass and coal dust has a large proportion of large particles.

**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, such as CB, 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) are of particular relevance because exposure to 1.1 mg/m<sup>3</sup> of respirable CB particles did not evoke inflammatory or mutational changes to female rats. A NOAEL of 1 mg/m<sup>3</sup> (respirable) CB has been supported by additional rodent findings (Carter *et al.* 2006, Elder *et al.* 2005).

To summarize, the major rodent interspecies differences in lung responses to inhaled CB particles are: 1) the pulmonary clearance of CB particles was significantly faster in hamsters vs. rats or mice; 2) exposures to higher concentrations of CB produced particle overload in the lungs of both rats and mice; 3) the pulmonary cellular and tissue responses to particle overload were different in the rats when compared to similarly exposed mice – i.e., rats developed greater and sustained lung inflammatory responses and significantly more intensive epithelial and fibro-proliferative responses.

Other poorly soluble, low toxicity dusts cause similar impaired pulmonary clearance and inflammation at high doses in the rat (ILSI, 2000; Mauderly, 1996; Donaldson, 2000). In a study comparing 14 inhalation studies with chemically different particulate materials

(including synthetic amorphous silica, cerium oxide, barium sulfate, titanium dioxide and several pigments), Weber *et al* (2023) found that all investigated substances caused similar lesions. For most substances, 1 mg/m<sup>3</sup> of respirable particulate matter was established as the borderline for adverse morphological changes after the 90-day exposure period. Possible reversibility was demonstrated when recovery groups are included in the study especially allowing the differentiation between regeneration or progressing of inflammatory changes during the recovery period. It was concluded, that the major driver of toxicity is not an intrinsic chemical property of the particle but a particle effect.

In Chapter 3.9 on STOT-RE, GHS rev 10 (<https://unece.org/sites/default/files/2023-07/GHS%20Rev10e.pdf>) states “*Specific target organ toxicity – repeated exposure refers to specific toxic effects occurring after repeated exposure to a substance or mixture. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed and not specifically addressed in chapters 3.1 to 3.7 and 3.10 are included.*”[underline added]. PSLTs, such as talc, titanium dioxide and carbon black cause non-specific particle effects from accumulating in the lung. These effects are not specific to the individual chemistry of the substance, and therefore should not be classified for STOT-RE.

### **Pulmonary Response in Mammalian Species Other Than Rodents**

In studies reported by Nikula *et al.* (1997, 2001), it is proposed that the intrapulmonary particle retention patterns and tissue reactions in rats may not be predictive of pulmonary retention patterns and tissue responses in either primates or humans. Male cynomolgus monkeys and F344 rats were exposed for 7 hours/day, 5 days/week for 24 months to diesel exhaust (2 mg/m<sup>3</sup>), coal dust (2 mg/m<sup>3</sup>), or diesel exhaust and coal dust combined (1 mg/m<sup>3</sup> each) and were subsequently examined histopathologically (Nikula *et al.* 1997). In all exposed groups, monkeys retained a similar amount or more particulate material in the lungs than did rats. Rats retained a greater proportion of the particulate material in the alveolar ducts and alveoli, whereas monkeys retained a greater proportion of particulate material in the interstitium. Rats, but not monkeys, had significant alveolar epithelial hyperplastic, inflammatory, and septal fibrotic responses to the retained particles.

In a subsequent study, Nikula *et al.* (2001) evaluated the influence of exposure concentration or dose on the distribution of particulate material within the lungs of rats and humans. In this study the investigators used morphometric methods to assess the influence of exposure concentration on particle retention by evaluating histological lung sections from rats and humans. The rats had been exposed for 24 months to diesel exhaust at 0.35, 3.5, or 7.0 mg/m<sup>3</sup>. The human subject groups included: 1) nonsmokers who did not work as miners; 2) nonsmoking coal miners who worked under the current standard of 2 mg dust/m<sup>3</sup> for 10-20 years; and 3) nonsmoking coal miners who worked under the former standard of <10 mg dust/m<sup>3</sup> for 33 to 50 years. The distribution of retained particles within the lung compartments was markedly different between species. In all three groups of rats, 82 to 85% of the retained particulate material was located in

the alveolar and alveolar duct lumens, primarily in macrophages. In humans, 57, 68, and 91% of the retained particulate material, respectively, was located in the interstitium of the lung in the three aforementioned study groups. The authors concluded: “These results show that chronically inhaled diesel soot is retained predominantly in the airspaces of rats over a wide range of exposures, whereas in humans, chronically inhaled particulate material is retained primarily in the interstitium. In humans, the percentage of particles in the interstitium is increased with increasing dose (exposure concentration, years of exposure, and/or lung burden). This difference in distribution may bring different lung cells into contact with the retained particles or particle-containing macrophages in rats and humans and, therefore, may account for differences in species response to inhaled particles.” A comprehensive review on translational toxicology focusing on dust exposure and on carbon black as one example was published in Morfeld *et al.* 2015.

## **Summary of Animal and Human Data and Implications for STOT - RE Classification**

The rat is a uniquely sensitive species in its pulmonary responses to sub-chronic or chronic exposures to high doses of inhaled low solubility dusts, leading to inflammation, the development of fibro-proliferative effects, and eventually lung tumor formation. These responses are not observed or measured in similarly exposed mice or hamsters. The pulmonary effects observed in rats, including inflammatory and fibrotic responses, are also not observed in large mammals such as nonhuman primates and humans. It has also been clearly demonstrated through epidemiology studies of CB-exposed workers that there is no causative link between CB exposure and the risk of non-malignant respiratory disease in humans. It is noted that in the CLP Guidance for Specific Target Organ Toxicity – Repeated Exposure (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 3.9.2.8.1 (e) states that ‘Substance – induced species specific mechanisms of toxicity substance, i.e. demonstrated with reasonable certainty to be not relevant for human health, shall not justify classification’. For these reasons, the STOT - RE classification is not justified for CB.

## **Recommendation for No Classification of Carbon Black for STOT - RE**

CB should not be classified under the GHS classification of STOT - RE for effects on the lung. The rat is recognized as a uniquely sensitive species in its pulmonary responses to inhaled low solubility dusts such as CB under conditions of pulmonary particle overload. The pattern of pulmonary effects in the rat following such exposures includes inflammation and fibrotic responses that are not observed in other rodent species, nonhuman primates or humans under similar exposure conditions. Overall, the epidemiological evidence from well-conducted investigations has shown no causative link between CB exposure and the risk of non-malignant respiratory or malignant disease in humans.

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