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Respirable Crystalline Silica: Rationale For Classification According to the CLP\* Regulation and within the Framework of the Globally Harmonised System (GHS) of Classification and Labelling of Chemicals.

Summary Report based on the Review and Hazard Assessment of the Health Effects of Respirable Crystalline Silica (RCS) Exposure to inform Classification and Labelling under the Global Harmonised System: Overview Report. (Borm P, Brown T, Donaldson K, Rushton L 2009) and based on the Review of the Literature of the Health Effects of Occupational Exposure to Crystalline Silica: Silicosis, Cancer and Autoimmune Diseases (Brown T, Rushton L 2009).

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\* CLP = Regulation (EC) No 1272/2008 on the Classification, Labelling and Packaging of substances and mixtures

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## **1. Introduction**

A globally harmonized system of classification and labelling of chemicals (GHS), developed under the auspices of the United Nations, has been proposed for use by regulatory bodies throughout the world (UN 2009[34]). In Europe, the GHS criteria have been introduced as a new regulation, the Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures (EU 2008[15], EU 2008[13], EU 2008[14]), the CLP Regulation for short. Article 5 of the CLP Regulation (EU 2008[15]) requires each Manufacturer/Importer on the EU market to classify the substances (and mixtures) they manufacture/import in the EU. Also, Title V of the CLP Regulation (EU 2008[15]) requires from 1 December 2010 that substances within one month of placing on the market, which meet the criteria for classification as hazardous according to the CLP Regulation, or substances subject to registration under REACH (regardless of classification or otherwise) must be notified to the classification and labelling inventory of the European Chemicals Agency (ECHA).

EUROSIL (European Association of Industrial Silica Producers) commissioned an independent scientific hazard assessment review of the health effects of respirable crystalline silica (RCS) exposure to determine its classification and labelling under the new classification and labelling scheme (Borm et al. 2009[3] and Brown and Rushton 2009[5]). The present report, also commissioned by EUROSIL, is a documented summary supporting an industry decision to classify respirable crystalline silica - and its species respirable quartz, respirable cristobalite and respirable tridymite - according to the requirements of GHS (UN 2009[34]) and the CLP Regulation (EU 2008[15]). The rationale is based on the reports by Borm et al. 2009[3] and Brown and Rushton 2009[5] while referring to additional literature. The responsibility to classify correctly crystalline silica according to the GHS/CLP Regulation (UN 2009[34], EU 2008[15]) lies with the industry.

## **2. GHS/CLP classification approach**

### **2.1 GHS/CLP substance and mixture definition: reducing ambiguities**

GHS (UN 2009 - 3<sup>rd</sup> version[34])<sup>1</sup> is a classification system of substances or mixtures of substances with respect to adverse effects on people and environment. The term substance refers to chemical elements and their compounds in the natural state or obtained by any production process. The term mixture refers to a mixture or solution composed of two or more substances in which they do not react (cp. 1.1.1, 1.2, 1.3.2.1.1 in GHS Part 1 Introduction, UN 2009[34]).

GHS establishes a globally harmonised scheme for hazard communication. More specifically, this implies the introduction of hazard classifications and categories, hazard pictograms, signal words, hazard statements, and precautionary statements. For hazards impacting human health, distinctions are made between effects occurring after single or short term exposures (e.g., acute toxicity) and those that arise following multiple or chronic exposures. Furthermore, differences in the severity of health effects are accounted for by assigning classifications to different categories – e.g. classification of acute toxicity under CLP has four categories. This document considers Specific Target Organ Toxicity, Repeated Dose (STOT Re) and Carcinogenicity.

It should be noted that human data can be used to assign a substance or mixture into category 1 or 2 with respect to carcinogenicity but usually only into category 1 with respect to specific organ toxicity following repeated exposure (Chapters 3.6 and 3.9 in GHS Part 3 Health Hazards with exceptional cases described in Chapter 3.9.2.6, UN 2009[34]). Note further that even if adverse effects are seen in animal studies or in-vitro tests, no classification is needed if the mechanism or mode of action is not relevant to humans (1.3.2.4.9.4 in GHS Part 1 Introduction, UN 2009[34]). Moreover, it is important to note that mixtures can be classified as a whole when data are available for the complete mixture rather than being based on hazardous components. This procedure is in particular valid when evaluating the endpoints Carcinogenicity and STOT RE (Chapters 3.6 and 3.9 in GHS Part 3 Health Hazards, UN

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<sup>1</sup> The EU CLP Regulation has integrated the UN GHS 2<sup>nd</sup> Revised Version. The integration the UN GHS 3<sup>rd</sup> Revised Version will take place via ATP in 2011. However there are no changes in the 3<sup>rd</sup> Revised Version that impact on the endpoints discussed in this document.

2009[34]). According to CLP test data on mixtures may be used for classification of carcinogens when demonstrating effects that have not been established from the evaluation based on the individual ingredients (Chapter 3.6.3.2.1, EU 2008[15]). Finally, note that the definition of a mixture does not imply that all substances that are mixed have to be hazardous *per se*.

The GHS criteria suffer from some ambiguities. The following conflicting applications of the GHS criteria appear relevant to highlight. If circumstances are detected in which crystalline silica behaves as a hazard

- a) Crystalline silica itself may be classified as such (ignoring the specific circumstances) or
- b) Adverse health effects due to crystalline silica may occur only when crystalline silica is the outcome of a production process and/or shows specific physico-chemical properties, bioavailability and/or is above a cut-off value/concentration limit in a mixture (cp. 1.3.2.4.5.1, 1.3.3.2 in GHS Part 1 Introduction, UN 2009[34]). Thus, a classification may be restricted to silica dust or to respirable silica dust or to respirable silica dust with additional properties (e.g., a concentration or percentage of crystalline silica above a limit in the respirable mixture of silica dust and other dusts and air).

Therefore, the GHS documentation (UN 2009[34]) leaves ambiguities how to define the substance/mixture under consideration. However, the CLP Regulation (EU 2008[15]) and ECHA Guidance to the CLP Regulation [8] are helpful. The CLP Article 8.6 specifies that “Tests that are carried out for the purposes of this Regulation shall be carried out on the substance or on the mixture in the form(s) or physical state(s) in which the substance or mixture is placed on the market and in which it can reasonably be expected to be used”. In addition, the ECHA Guidance to the CLP Regulation ([8], Chapter 1.2.3.2, p. 40) mentions that “for human health, different forms (e.g. particle sizes, coating) or physical states may result in different hazardous properties of a substance or mixture in use” and therefore they may be classified differently.

## 2.2 GHS/CLP carcinogenicity classification system: reducing ambiguities

Other difficulties exist beyond those of defining the substance/mixture under consideration - in particular when different health endpoints and a specific mode of action obviously play a role when evaluating the carcinogenicity of a substance/hazard. A recent review (McGregor et al. 2010[24]) provided clarification on some of these points and this is expanded further below.

The CLP Regulation EU 2008[15] replaces the former classification and labelling system under Directive 67/548/EEC (EEC 1967[9] , EEC 1983[10], EEC 1991[11]). The categories for classification and labelling of carcinogenic substances under the former Dangerous Substances Directive (DSD) and the new CLP Regulation are summarized in Table 1.

**Table 1:** Comparison of Classification Criteria for Carcinogenic Substances under EU Directive 67/548/EEC and CLP Regulation (EC)

<b>EU Directive 67/548/EEC (DSD), Annex VI, Section 4.2.1</b>	<b>GHS, Chapter 3.6 / CLP Regulation Annex VII</b>
<b>Category 1:</b> <i>Substances known to be carcinogenic to man.</i>	<b>Category 1A:</b> <i>Known to have carcinogenic potential in man.</i>
<b>Category 2:</b> <i>Substances that should be regarded as carcinogenic to man.</i>	<b>Category 1B:</b> <i>Presumed to have carcinogenic potential for humans.</i>
<b>Category 3:</b> <i>Substances that may cause concern for man owing to possible carcinogenic effects.</i>	<b>Category 2:</b> <i>Suspected human carcinogen.</i>

A category 1 (DSD) or 1A (GHS/CLP) indicates adequate human evidence for carcinogenicity. Generally, a weight-of-evidence approach determines further categorization into Categories 2 or 3 (DSD) or Categories 1B or 2 (GHS/CLP). In the case of a Category 2 assignment in the former DSD system, adverse results from two animal species are required or clear carcinogenicity in a single species with supporting data. This is similar to the requirements for Category 1B in the GHS/CLP system but with the recognition that “limited”<sup>2</sup>

<sup>2</sup> Limited evidence as defined by IARC. Limited human data would suggest a causal relationship of exposure to cancer in humans but with bias or confounding data reducing the confidence in the data. Limited animal data may suggest (i) evidence is based on a single experiment, (ii) questions of adequacy or interpretation from positive animal studies, and (iii) the agent causes increases in only benign tumors or lesions with uncertain neoplastic potential, or of neoplasms occurring at high incidences in certain strains.

evidence of carcinogenicity in humans and experimental animals may be sufficient for a Category 1B classification. However, no practical difference can be seen between Category 1A and 1B (McGregor et al. 2010[24], p. 279). A DSD Category 3 classification recognizes that tumor-inducing effects from adequate studies may be insufficient for a DSD Category 2 classification or that a substance has been inadequately investigated and that further experimentation is needed. In the case of insufficient evidence from existing studies, the classification in Category 3 would remain provisional until additional testing was performed. A GHS/CLP Category 2 classification recognizes limited suggestive evidence of carcinogenicity from animal or human studies combined with a weight of evidence from other experimental data. The classification categories in both the DSD and GHS/CLP systems correlate closely with IARC (International Agency for Research on Cancer) Group 1, 2A and 2B classifications (e.g., Baan 2007[2]). Despite these correlations some distinctions can be identified (McGregor et al. 2010[24], p.280). However, these distinctions appear to be of only limited relevance to this approach of categorizing crystalline silica.

Both of these classification systems recognize a weight-of-evidence approach to support the final classification. Under the GHS/CLP system, requirements for no classification are not clearly defined but consideration should be given to the mode of action and potency (McGregor et al. 2010[24]). In particular, the authors of this review strongly recommended classifying substances and mixtures while considering the carcinogenic potency although this is not definitely defined as a criterion in the GHS/CLP documentation (McGregor et al. 2010[24], p. 257, 258, 262). Furthermore, they argued as follows:

*“For non-genotoxic compounds, potency would be taken into consideration in an evaluation of any primary toxicity underlying carcinogenicity, for example hepatic necrosis, chronic inflammation of the lung, and proximal tubular damage. When such toxicity occurs at doses below those causing carcinogenicity, there should be no requirement to classify for carcinogenicity, because classification of the primary toxicity would ensure adequate protection also against carcinogenicity” (McGregor et al. 2010[24], p. 263).*

## 2.3 GHS/CLP classification system for Specific Target Organ Toxicity (STOT) following repeated exposure (RE)

The categories for classification and labelling of substances causing specific target organ toxicity after repeated exposure according to GHS and the CLP Regulation are summarized in Table 2.1 and 2.2. This is largely analogous to the R48 Danger of serious damage to health by prolonged exposure.

**Table 2.1:** Classification Criteria for Specific Target Organ Toxicity (STOT) – Repeated Exposure Under the GHS

<b>GHS, Chapter 3.9</b>	
<b>Category 1:</b>	<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>
<b>Category 2:</b>	<i>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.</i>

**Table 2.2:** Classification Criteria for Specific Target Organ Toxicity (STOT) – Repeated Exposure Under the CLP Regulation:

<i>Table 3.9.1 – Annex I of the CLP Regulation</i>	
<b>Categories for specific target organ toxicity-repeated exposure</b>	
Categories Criteria	
<b>Category 1</b>	<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. Substances are classified in Category 1 for target organ toxicity (repeat exposure) on the basis of:</i> <ul style="list-style-type: none"> <li><i>— reliable and good quality evidence from human cases or epidemiological studies; or</i></li> <li><i>— observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations. Guidance dose/concentration values are provided below (see 3.9.2.9), to be used as part of a weight-of-evidence evaluation.</i></li> </ul>
<b>Category 2</b>	<i>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. Substances are classified in category 2 for target organ toxicity (repeat exposure) on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations. Guidance dose/concentration values are provided below (see 3.9.2.9) in order to help in classification. In exceptional cases human evidence can also be used to place a substance in Category 2</i>



Classifications under GHS and CLP for STOT (Repeated Exposure, STOT RE) depend 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. It is recognized that human data will be the primary source of evidence for this hazard class. The classifications are abbreviated as STOT RE1 and STOT RE 2 in the following.

### **3. Rationale to classify respirable crystalline silica (RCS)**

#### **3.1 The substance/mixture of interest**

Dust is defined as solid particles of a substance or a mixture suspended in a gas (usually air) (UN 2009[34]). The respirable fraction is the mass fraction of inhaled particles penetrating to the unciliated airways (CEN EN 481[6]). Investigation of the effects of crystalline silica in both the epidemiological and toxicological literature has focused on the respirable fractions after repeated exposure (see overview by Borm et al. 2009[3], p. 17). The epidemiological studies analysed and identified long-term occupational dust exposures as potential health effect causes and, furthermore, emphasized the respirable fraction (if crystalline silica is addressed directly) - even when studying endpoints like COPD or autoimmune diseases (Brown and Rushton 2009[5], Chapter 3.1.3, p.5-26, Chapter 3.5, p. 94-122). All animal inhalation experiments were performed with repeated exposure to respirable crystalline silica dust (IARC 1997[19]). Scientific committees who evaluated the health effects of crystalline silica dust exposure also focused on the respirable fraction (Greim 1999[16], HSE 2002[18], SCOEL 2002[29]). There is no evidence that specific health effects due to crystalline silica dust exposure are caused by other dust fractions, by other occurrences of crystalline silica, or by other routes of exposure to crystalline silica (Greim 1999[16]). Thus, the substance of relevance to classification is respirable crystalline silica (RCS). This is the case whether it is present alone or when present in a mixture.

### **3.2 Silicosis hazard**

Epidemiological studies and animal experiments showed positive dose-response relationships beyond doubt between occupational RCS and silicosis. An overview of epidemiological morbidity studies (X-ray studies) demonstrating this definite relationship was given by Brown and Rushton 2009[5], Chapter 3.2, p. 27-31. These authors also accumulated evidence from mortality investigations: epidemiological support of a pronounced dose-response relationship based on cause-of-death data was given by Mannetje et al. 2002[21] and Hedlund et al. 2008[17]. Inhalation experiments with rats showed a clear-cut fibrogenic pulmonary response after respirable quartz dust exposure: a pivotal study demonstrating this association was Muhle et al. 1991[27]. In contrast to all other endpoints with potential causal relationships to RCS - like COPD, autoimmune diseases or lung cancer - the dose-response association between respirable crystalline silica dust exposure at the workplace and silicosis prevalence/incidence/mortality is the most pronounced and specific one (Brown and Rushton 2009[5]). In conclusion, no other non-malignant health effect due to RCS is as specific and so clearly linked to RCS as silicosis.

### **3.3 Carcinogenicity**

The most relevant and controversial medical endpoint to be considered is the potential cancer risk due to respirable crystalline silica dust exposure (IARC 1997[19], Donaldson and Borm 1998[7], Soutar et al. 2000[30]). A potential cancer risk is limited to lung cancer occurrence (Straif et al. 2009[33]). Brown and Rushton 2009[5] listed epidemiological studies dealing with other cancers than lung cancer but judged that there is no evidence for a causal impact of crystalline silica dust exposure on these endpoints (Chapter 3.4, p.94; Chapter 6.1.4, p. 154). Accordingly, Borm et al. 2009[3] restricted their report on carcinogenic effects to lung cancer only (Chapter 3.4, p.6-10). Thus, the cancer endpoint of interest with a view to a GHS/CLP classification and to be evaluated in this report is identified as lung cancer.

### **3.4 Lung cancer risk**

Brown and Rushton 2009[5] investigated extensively the epidemiological evidence of a link between crystalline silica dust exposure and lung cancer risk in occupational settings (Chapter 3.3, p.31-93). Although they listed a couple of limitations (Brown and Rushton 2009[5], Chapter 5.3, p. 142-144 and Borm et al. 2009[3], Chapter 4.3, p.10) these authors identified the pooled cohort study by Steenland et al. 2001[32] as a pivotal investigation (Chapter 5.3, p. 143). Steenland and co-workers judged ([32]), p. 781) that RCS is a weak lung carcinogen in comparison to other established carcinogens such as chromium, nickel, cadmium and arsenic, when measured by mass in the air (cp. Brown and Rushton 2009[5], p. 150). Indeed, lung cancer excess risks were convincingly demonstrated in this pooled cohort study only under high ( $\geq 6 \text{ mg/m}^3$ -years) cumulative exposures to RCS (Brown and Rushton 2009[5], Fig. 4, p. 151 and see the discussion by Borm et al. 2009[3], Chapter 4.3, p.10). Assuming a working life of 40 years, RCS concentrations have to be higher than  $0.15 \text{ mg/m}^3$  to fulfil this condition. Pukkala et al. 2005[28] argued in favour of a threshold of at least  $0.2 \text{ mg/m}^3$  (p.106). Accordingly, the lung cancer standardized mortality ratio showed a small excess of only 20% (SMR=1.2, 0.95-confidence limits: 1.1-1.3) in Steenland et al. 2001[32], Table 2 - without taking the potential upward bias due to smoking into account (Steenland and Greenland 2004[31]). In these studies, the role of silicosis as a potential intermediate confounder has not been accounted for (see section 3.5). Thus, lung cancer excess risks were convincingly demonstrated only under rather high occupational exposures to RCS. This means that further considerations are necessary to decide whether a cancer classification is warranted (McGregor et al. 2010[24]).

### **3.5 Heterogeneity of lung cancer risks**

The lung cancer excess risk due to RCS is heterogeneous across industries (IARC 1997[19], Attfield and Kuempel 2008[1], Miller et al. 2007[25], Morfeld et al. 2005[26]). Generally, results from epidemiological studies of industrial cohorts indicate that differences are found in the magnitude of the relationship between silica exposure and several of the health outcomes reviewed between industries (Brown and Rushton 2009[5], Chapter 6.2, p.155). Although some indications were given at a higher potency of respirable cristobalite dusts in comparison to respirable quartz dusts - see the specific impact of the Californian cristobalite study as

described by Borm et al. 2009[3], Chapter 4.3, p.10 and the comparison of the lung cancer risk in diatomaceous earth workers compared to the risk in the granite and industrial sand industries (Brown and Rushton 2009[5], Chapter 6.2, p.155) - no convincing distinction can be made between these species of crystalline silica with a view to health effects. This is so, because toxicological studies that have compared different species of crystalline silica gave no evidence that one of these species is more active than others. All studies indicate that the activity (generation of ROS, inflammatory response, cellular uptake, DNA-damage, cytokine release) is very much determined by the surface and this can be influenced by physical and/or chemical treatments (Borm et al. 2009[3], Chapter 6.2, p.16). However, a more than 10-fold variation in potency among commercial quartzes (flours) was demonstrated, and similar differences in activity among quartz sampled at the workplace (Borm et al. 2009[3], Chapter 7, p.18).

### **3.6 Mode of action**

The mode of action how RCS causes lung cancer is indirect via inflammation (Greim 1999[16], SCOEL 2002[29] and confirmed by Borm et al. 2009[3], Chapter 5.3, p.11-13). A potential direct genotoxicity can only be produced *in vitro* at levels of RCS exposure far beyond the exposures necessary to cause inflammation (Borm et al. 2009[3], Chapter 5.4, p.13, 14). Throughout the studies, the lowest level of significant DNA damage was found to be 40  $\mu\text{g}/\text{cm}^2$  which is equivalent to a dose significantly above (50-fold) any amount of RCS that was demonstrated to cause fibrotic events *in vivo* (Borm et al. 2009[3], Chapter 7, p.17). Moreover, RCS particles do not enter the nucleus of the cells, and *in vivo* no quartz particles are found in epithelial cells (Borm et al. 2009[3], Chapter 7, p.17).

### **3.7 Silicosis and lung cancer**

Silicosis is a primary effect of excess exposure to RCS (section 3.1) and silicosis is a result of inflammation in the lung. Excess lung cancer risks are obvious among silicotics (Brown and Rushton 2009[5], Chapter 5.3.4, p.147-149). However, the actual mechanistic causal role of silicosis in the development of lung cancer remains to be clarified (Brown and Rushton 2009[5], Chapter 6.2, p.155). Perhaps silicosis is a biomarker of susceptibility: to lung

carcinogens in general, or to lung damage, including lung cancer. If it is a marker of susceptibility then one would expect a clear-cut association between silicosis and lung cancer, as has been found, even if crystalline silica itself is not carcinogenic (Erren et al. 2009[12], p. 1000). Importantly, this lung cancer risk appears to be restricted to subjects who contracted silicosis: Erren et al. 2009[12] demonstrated in a meta analysis that there is no evidence that non-silicotics among workers exposed to respirable crystalline silica suffer from elevated lung cancer risks, in particular after taking smoking habits into account.

### **3.8 Role of silicosis in lung cancer risk reduction**

Based on considerations of mode of action and lung cancer risk in crystalline silica exposed workers with or without silicosis (see Chapter 3.5 of this report) Greim 1999[16], SCOEL 2002[29] and HSE 2002[18] argued that minimizing silicosis risk would also minimize lung cancer risk due to RCS. This point of view was recently discussed and emphasized by Brown 2009[4], taking stopping of smoking into account as an additional intervention strategy. On practical grounds, therefore, minimizing silicosis risk will also minimize or even eradicate lung cancer risk due to RCS.

### **3.9 Mixed dusts**

Occupational exposures to crystalline silica dust are almost never pure dust exposures to crystalline silica. Dust exposures at the workplace are almost always mixed and include varying mass percentages of respirable crystalline silica - but usually no analyses are performed that clarify the role of the components (Brown and Rushton 2009[5]). Coal mine dust exposure is an exception: a recent review of the role of quartz in coal mine dust concluded that a silicosis risk – beyond the pneumoconiosis risk due to respirable coal mine dust exposure – is expected to occur at quartz dust contents within the respirable mixed dust of 10 % or higher (McCunney et al. 2009[23], see also the letter exchange about silicosis in coal mining: Laney and Attfield 2009[20], McCunney et al. 2009[22]).

In conclusion, a relevant silica–silicosis effect can be assumed to occur after repeated exposure to mixed respirable dusts with mass percentages greater than 10 % respirable

crystalline silica. Thus, mixed respirable dusts at the workplace (consisting of crystalline silica particles and poorly soluble particles of no other specific toxicity) should be classified according to their respirable silica content if the mass percentage exceeds 10 %.

### **3.10 Conclusions for Classification**

#### **3.10.1 STOT Classification**

A clear dose-response was demonstrated for silicosis/pulmonary fibrosis in epidemiological investigations and in animal studies after repeated exposure to RCS. Therefore a classification of STOT RE 1 is indicated for RCS.

Mixed respirable dusts may be classified according to the respirable crystalline silica content applying the mixture rule of the CLP regulation (EU 2008[15], Annex 1, Table 3.9.4) or the rule of the GHS (UN 2009[34], Table 3.9.3, Note 1).<sup>3</sup>

However, the mixture may be evaluated on its own. By reference to the case of coal mine dust (see Chapter 3.8) a classification may just be necessary if the mass percentage of respirable crystalline silica exceeds 10%. No classification appears to be required if the respirable crystalline silica content is below 10%.

#### **3.10.2 No Classification for Carcinogenicity**

Lung cancer excess risk is demonstrated only under rather high occupational exposures to RCS which is heterogeneous across industries. Although some hints are given at a higher potency of respirable cristobalite dusts in comparison to respirable quartz dusts no convincing distinction can be made between these forms of crystalline silica with a view to health effects.

However the lung cancer excess risk is restricted to subjects who contracted silicosis. It has also been accepted that minimising the silicosis risk will also minimize lung cancer risk due to RCS. This observations support the suggested mode of action that RCS may produce lung cancer indirectly via inflammation. A potential direct genotoxicity can only be indicated at levels of RCS exposure far beyond the exposures necessary to cause inflammation.

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<sup>3</sup> Whereas the classification of the mixture is mandatory if the concentration is above 1% and up to 10% according to CLP but optional according to GHS.

In conclusion, there is no requirement to classify RCS as a carcinogen if silicosis is used as the pivotal endpoint for classification.

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