Brussels, 3 May 2019

Re: Comments on the Proposal for Harmonised Classification & Labelling (CLH) of Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica as STOT RE 2 – H373

Technical Names:	HMDZ surface-treated SAS (Synthetic Amorphous Silica); AEROSIL® R 812 S
EC Number:	272-697-1
CAS Number:	68909-20-6

Dear Sir or Madam,

The Members of the Association of Synthetic Amorphous Silica Producers, *ASASP*, a Cefic Sector Group, hereby take the opportunity to provide input to the public consultation on the proposed hazard classification of Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica (EC No. 272-697-1), i.e. AEROSIL® R 812 S, in the following abbreviated as 'HMDZ surface-treated SAS', as STOT RE 2 (H373) by the French Competent Authority.

During a careful review of the CLH proposal, ASASP realised that not all critical and up to date information pertaining to the inhalation hazard of HMDZ surface-treated SAS may have been considered by the French Competent Authority during their report drafting. ASASP requests for including the more recent information that was not presented in the original active biocide application for HMDZ surface-treated SAS under the Biocidal Products Directive 1998/8 for considering the French CLH proposal. Full references are provided in the accompanying reference list.

General comment

The French Competent Authority justifies its proposal to classify HMDZ surface-treated SAS as STOT RE 2 (H373) based on effects reported for a 90-day rat inhalation toxicity study with AEROSIL® R 974, which was carried out by the contract laboratory TNO (TNO, 1987). AEROSIL® R 974 is a hydrophobic synthetic amorphous silica (SAS) and has been surface-treated with dichlorodimethylsilane (DDS). In 1991, based on material from the original study, TNO reported slight to moderate increase of lung collagen content with signs of focal interstitial fibrosis, granuloma like lesions and septal cellularity in the lungs of rats after inhalation exposure to AEROSIL® R 974 (Reuzel *et al.*, 1991). The French Competent Authority considered these findings to meet the classification criteria for STOT RE 2 (H373). No further data or information was presented in the CLH Report for supporting the classification proposal.

Recently, a re-analysis of the lung tissue slides of the original TNO study was conducted by an expert pathology working group (PWG). This was carried out according to the current criteria for pathology assessment (EPL, 2016; Weber *et al.*, 2018). This re-analysis clearly demonstrated that focal interstitial fibrosis, an irreversible disease, was not present in the lungs of the AEROSIL® R 974 exposed rats at any point in time. The study pathologist of the original TNO study, Dr. Ruud Woutersen, agreed with the outcome of the PWG's re-evaluation of the original lung slides in a subsequent statement (Woutersen, 2017).

The effects observed with AEROSIL® R 974 represent markers of typical inflammatory responses of the rat lung after continued high exposures to particles, which may persist over a long time (ECETOC, 2006). Ultimately, all effects of AEROSIL® R 974 were fully reversible and cannot be termed adverse according to WHO/IPCS definitions (WHO, 2004). Accordingly, the conditions that would trigger a STOT RE 2 classification as detailed in Paragraph 3.9.2.7.3 (Annex I) of the CLP Regulation (EC, 2008) and related ECHA guidance documents (ECHA, 2017) have not been met. ASASP thus disagrees with the French Competent Authority's interpretation of the TNO study and their conclusion that the effects observed in this study meet the CLP STOT RE 2 (H373) classification criteria.

ASASP also points out that, in addition to the incomplete interpretation of the TNO (1987) study, the CLH report does not consider the value of existing animal inhalation studies with similar SAS materials or epidemiological studies done in SAS production plants. The CLP Regulation requires the consideration of the weight of evidence of all relevant information pertaining to the hazard of a substance including physico-chemical properties, animal data or occupational exposure data. In particular, regarding HMDZ surface-treated SAS, the key information requiring consideration when assessing repeated dose toxicity via the inhalation route is

- **SAS is rapidly cleared from the lung**. SAS is soluble under physiological conditions and therefore has little persistence in the lung. Clearance occurs by hydrolysis or phagocytosis by alveolar macrophages.
- **No intrinsic toxicity of SAS**. There is no indication of systemic toxicity following repeated inhalation of SAS including AEROSIL® R 974 at the sole exposure concentration of 34.7 mg/m^3.
- **Effects induced in the lung by SAS-inhalation are reversible, hence adaptive and not adverse**. Numerous inhalation toxicity studies have been conducted with hydrophilic and hydrophobic SAS, including AEROSIL® R 974. All SAS grades show a similar pattern of toxicity during inhalation toxicity studies, representing an adaptation of the lung to high and sustained particle exposure (e.g., transient increases in inflammation, markers of cell injury, and lung collagen content; macrophage accumulation). Both, hydrophilic and hydrophobic SAS do not induce progressive fibrosis in the lung. Hence, all effects are limited and fully reversible with no severe consequences on organ function.

- **Epidemiological studies demonstrate absence of effects of worker exposure to SAS on lung function**. SAS have a long history of production and use. No indication of pneumoconiosis or other exposure-related pulmonary diseases were observed in epidemiological studies. The particle sizes of commercial SAS handled do not penetrate the lung.

Considering all information, it is obvious to ASASP that HMDZ surface-treated SAS does not warrant a classification for specific target organ toxicity following repeated inhalation exposure. The proposal for a classification as STOT RE 2 (H373) by the French Competent Authority is neither based on a thorough evaluation of all available as well as up to date scientific information pertaining to the inhalation toxicity of SAS materials, nor on the appropriate consideration of the CLP criteria for a STOT RE 2 (H373) classification.

More detail, in particular with regard to the re-evaluation of the Reuzel study by the PWG, is provided in the section 'specific comments'. ASASP hereby explicitly refers to the expert reviews conducted and submitted to this public consultation by Professors W. Dekant and L. Levy.

Specific comments

1. Inhalation toxicity study with AEROSIL® R 974 used to read-across to HMDZ surface-treated SAS (AEROSIL® R 812 S)

Since there are no repeated dose inhalation toxicology studies available for HMDZ surface-treated SAS (AEROSIL® R 812 S, CAS No. 68909-20-6), the CLH report justified its classification proposal based on a 90-day inhalation toxicity study of AEROSIL® R 974, an analogous hydrophobic synthetic amorphous silica (SAS) conducted by the contract laboratory TNO (1987) and later published by the study investigators Reuzel *et al*. (1991).

In this inhalation study, rats were exposed for 6 hours per day and 5 days per week over a period of 13 weeks to a control atmosphere (sham), 3 concentrations of AEROSIL® 200 (pyrogenic SAS) at 1.3, 5.9, and 31 mg/m^3, as well as one concentration of AEROSIL® R 974 (surface-treated pyrogenic SAS) at 34.7 mg/m^3, one concentration of Sipernat®22 S (precipitated SAS) at 34.9 mg/m^3, and one concentration of a crystalline silica, quartz (58.5 mg/m^3) as a positive standard (TNO, 1987). The results of this study have also been published (Reuzel *et al*., 1991). The test report stated that a OECD test guideline 413 comparable study was conducted in compliance with GLP.

AEROSIL® R 974 is the only surface-treated amorphous silica tested in this study and consists of very small constituent (primary) particles[1] (with a nominal size of 12 nm which form aggregates and agglomerates with a size distribution range of 1 to well above 100 µm). For each type of SAS and sample concentration, 5 groups of 10 rats per sex and per were exposed to the afore mentioned test levels. One group was sacrificed after 13 weeks of exposure and 4 groups were observed for recovery, persitence, or delayed occurrence of lesions until 13, 26, 39 and 52 weeks after exposure. Clinical signs, body weight, haematology, biochemistry, urinalyses, organ weights, retention of test material in the lungs and the regional lymph nodes, collagen content of the lungs and gross and microscopic pathology were determined.

Regarding the testing of AEROSIL® R 974 following deviations/differences from the test guideline were observed:

- AEROSIL® R 974 was only tested at one concentration, which was selected based on the results of a previous 2-week inhalation toxicity study;

[1] In the initial particle formation step, primary particles with dimensions below 100 nm are formed by growth of SAS monomers (SiO_2 units). Within a short time (milliseconds up to minutes depending on the process), these primary particles covalently bond to form indivisible units, called aggregates, which have no physical boundaries among the primary particles. Primary particles do not exist as such in the product as placed on the market.

- The size of the constituent (primary) particles could not be measured[2] due to their electrostatic charge. Instead, their size was calculated with a nominal size of 12 nm by the arithmetic mean of transmission electron microscopy;
- No ophthalmologic examinations were performed;
- Histopathology was performed on all organs/tissues but with particular attention to nose larynx, trachea, hilus and mediastinal lymph nodes, and lungs;
- Collagen (as hydroxyproline) and silica content were determined in lungs and regional lymph nodes.

In its study assessment, the French Competent Authority identified the following effects of AEROSIL® R 974 on the lung:

- Increased lung weight noted at the end of the exposure period but normal after a recovery period of 3 months;
- Swollen and/or spotted lungs and irregular surface of the lung in some animals at the end of exposure and after 13 weeks;
- Accumulation of alveolar macrophages in most males and females after observation periods of 13, 26 and 39 weeks but not after 52 weeks of recovery;
- Intra-alveolar accumulation of granular material, cellular debris and leucocyte infiltration observed at the end of the exposure period but not found any more after 13 weeks of recovery and longer;
- Granuloma-like lesions seen in all animals at the end of the exposure period and after an observation period of 13 weeks. These lesions did not show fibroblastic activity and hyalinization in the granulomas. This lesion decreased in incidence and was not found any more after an observation period of 52 weeks;
- Increase in lung collagen observed in males and females at the end of the exposure period. Although the differences gradually decreased during the recovery period, they remained statistically significant after observation periods of 13 and 39 weeks;
- Some signs of focal interstitial fibrosis observed in 3/5 male rats after 13 weeks of the recovery period and in 1/5 male rat after 26 weeks of recovery period (not statistically significant);
- Increased septal cellularity still present in a few animals after an observation period of 52 weeks (very slight degree);
- Alveolar bronchiolisation in 2/10 males after the exposure period and in 1/5 at 13 week post-exposure (not statistically significant);
- High amount of silicon detected in the lungs and lymph nodes of males and females at the end of the exposure period and after observation periods of 13 and 26 weeks.

[2] Furthermore, quantitative measurement of the particle size distribution of primary particles is technically very challenging as it may exhibit high variability due to different number counts and/or different image analysis protocols

Silicon was still present in lymph nodes of one male at the end of the observation period;

- Nasal inflammatory signs such as nasal irritation, focal necrosis and rhinitis and slight degeneration of the olfactory epithelium, were also reported.

In its evaluation of the Reuzel (1987) study, the French Competent Authority stated the following:

"*In conclusion, the lung was the major target organ after exposure to AEROSIL® R 974. All the observed effects are characteristic of an inflammation and were reversible. They completely disappeared at the end of the one-year recovery period, except septal cellularity which was still present in 2 animals of each sex.*

The effects could be mainly related to a pulmonary overload and no dose-response relationship could be established. Similar phenomenon in the generation of an alveolar inflammation was observed in preliminary 14-day study in rats (III6.3.3). This supports the conclusions that lung is the target organ after exposure to amorphous silica.

No study with a second non-rodent species was available. It is acknowledged that rats have a more protective upper respiratory surface area compared to human, the observed effects in rat lungs lead to consider that human lungs and especially alveolar part, could be more severely exposed to silica. Rat remains the most suitable species to predict lung toxicity."

2. Re-evaluation of the lung lesions in rats after exposure to AEROSIL® R 974

Re-evaluation of the lung histopathology slides

In 2016, the histopathological slides from the Reuzel (1987) study were submitted for re-evaluation according to current diagnostic criteria and terminology and International Nomenclature and Harmonization of Diagnostic Criteria (INHAND) nomenclatures (EPL, 2016). This was performed at AnaPath GmbH (AnaPath, 2016), Switzerland, by Dr Klaus Weber using the PathData system Version 6.2e2 (PDS Pathology Data Systems AG, Switzerland).

For this reason, all previously haematoxylin and eosin (HE)–stained slides of the toxicity study (more than 28 years old) were de-coverslipped and re-stained by HE owing to the fading of the original staining. The slides were coverslipped again for histopathological evaluation. The evaluation of the re-stained sections of the lungs was performed according to current standards under GLP conditions. For the re-evaluation, there were only slides available from males at the scheduled 13-week sacrifice and sections from both sexes after 13 and 52 weeks of recovery. The results of this re-evaluation were published by Weber *et al*. in 2018. All non-neoplastic findings were graded on a severity scale from 1 to 5 (i.e., minimal, slight, moderate, marked, and severe). For group comparison, mean grades on lesions were calculated by the PathData System as sum of grades in groups divided by the number of affected individuals. Fisher's exact test was performed on all data. The trend test for non-neoplastic lesions (Armitage test) was applied comparing the findings after the 52-week recovery sacrifice, between controls and AEROSIL® R 974 groups.

Peer review of the histopathology slides by the Pathology Working Group (PWG)

Following the re-evaluation, a PWG was assembled. The PWG review was performed according to the procedures recommended in the EPA Pesticide Regulation (PR) Notice 94-5: "Requests for Reconsiderations of Carcinogenicity Peer Review Decisions Based on Changes in Pathology Diagnoses" (EPA, 1994) and in compliance with GLP requirements. Since there were only a few reported differences between sexes, the PWG examined coded HE-stained slides only from male rats without knowledge of treatment group or previous diagnosis.

The PWG focused on:

- Presence or absence of (persistent) fibrosis in the lungs; *and*
- Reversibility of the induced lesions (increased alveolar macrophages/macrophage aggregates, interstitial inflammation, granulomatous inflammation, type II pneumocyte hyperplasia, alveolar/bronchiolar hyperplasia, foreign material).
- Related to the point of full reversibility, it was unclear what the discussed term 'increased septal cellularity' stands for. Increased cellularity represent either an inflammatory infiltrate, or macrophage type II proliferation, or alveolar/bronchiolar hyperplasia. None of these findings were noted in the Peer Review or during the PWG-process at an increased incidence and/or severity in animals after 52 weeks of recovery. In contrast, all findings noted were consistent with normal background incidences in rats at these ages.

There were up to nine sections per lung and per animal available for examination, and of these just only one section, containing tissue from the left lung was selected for the PWG review. During the review process of the PWG, additional sections were selected for discussion when necessary. The PWG examined slides containing lung sections from the first five male rats in each exposure group at each sacrifice interval.

Results of the re-evaluation and the PWG review

During the re-evaluation of the original sections, several degenerative and inflammatory lesions were recorded in all test item treated as well as in the control groups. Daily inhalation of AEROSIL® R 974 at 34.7 mg/m^3 for 13 weeks did not cause any irreversible changes including fibrosis in the lungs over the recovery period of 52 weeks and there was no significant difference between treated and control groups. In contrast, a high level of multifocal fibrosis was recorded in quartz-treated rats.

The evolution of the lesions seen in rats exposed to atmospheric concentrations of AEROSIL® R 974 is summarized in Table 1.

Table 1: Incidence and mean severity of findings in the lungs of rats exposed to AEROSIL® R 974 at 34.7 mg/m^3 for 13 weeks.

Lung lesions observed	***Sex***	***Incidence (mean severity)***					
		Sham *(control atmosphere)*			***Treated***		
		13 wks	***13 wks recovery***	***52 wks recovery***	***13 wks***	***13 wks recovery***	***52 wks recovery***
Number of rats evaluated	M	9	5	10	10	5	10
	F	-	5	10	--	5	8
Perivascular infiltration	M	7/9(1.6)	2/5(1.5)	4/10(1.0)	8/10(1.5)	1/5(1.0)	0
	F	-	1/5(1.0)	2/10(1.0)	-	2/5(1.5)	2/8(1.0)
Alveolar macrophages	M	2/9(1.0)	1/5(1.0)	4/10(1.0)	10/10(2.7)*	2/5(1.0)	2/10(1.0)
	F	-	1/5(1.0)	4/10(1.0)	-	3/5(1.0)	1/8(1.0)
Macrophage aggregations	M	2/9(1.0)	0	1/10(1.0)	10/10(1.4)*	2/5(1.0)	0
	F	-	0	1/10(1.0)	-	1/5(1.0)	0
Pneumocyte type II hyperplasia	M	0	0	1/10(1.0)	9/10(1.9)*	0	0
	F	-	0	0	-	0	0
Interstitial inflammation	M	3/9(1.3)	1/5(1.0)	2/10(1.0)	1/10(2.0)	0	0
	F	-	0	0	-	0	0
Granulomatous inflammation	M	0	0	0	10/10(3.5)*	5/5(2.8)*	0
	F	-	0	0	-	3/5(2.0)	0
Cleft granulomas	M	0	0	0	1/10(1.0)*	0	0
	F	-	0	0	-	0	0
Granulomas, alveolar bronchiolar junctions	M	0	0	0	9/10(3.4)*	5/5(3.4)*	0
	F	-	0	1/10(1.0)	-	5/5(2.8)*	0
Fibrosis	M	0	0	1/10(1.0)	0	0	0
	F	-	0	0	0	0	0
Hyperplasia, alveolar bronchiolar	M	0	0	1/10(3.0)	2/10(1.0)	0	0
	F	-	0	0	-	0	0

*Statistically significantly different from control group (Fisher's exact test).

From Table 1 the statistically significant lesions in the males at the end of the 13-week exposure period (i.e., alveolar macrophages, macrophage aggregations, pneumocyte type II hyperplasia, granulomatous inflammation, cleft granulomas and granulomas of alveolar bronchiolar junctions) recovered after 13 weeks of post exposure observation except for granulomatous inflammation in males and granulomas of alveolar bronchiolar junctions in males and females. The only lesions that were observed after 52 weeks of recovery were minimal presence of alveolar macrophages in males (2/10 vs 4/10 in the sham control group), minimal perivascular infiltration in females (2/8 vs 2/10 in the sham control group) and minimal presence of alveolar macrophages in females (1/8 vs 4/10 in the sham control group), all lesions with an incidence that is normally observed in rats of that age. During re-evaluation and PWG review, fibrosis (defined as an observable increase in the amount or abnormal location of collagen in lung parenchyma with an occurrence in alveolar septa, interstitium, and pleura, resulting in disruption of the normal lung architecture) was not seen after the 13-week exposure period, and after 13 weeks of recovery. The PWG confirmed the absence of an induced fibrosis in this study. In contrast, slight to moderate fibrosis was diagnosed in all quartz-treated animals. It is of note that the study pathologist of the original TNO study, Dr. Ruud Woutersen, concurred with the outcome of the PWG's re-analysis of the original lung slides (Woutersen, 2017).

3. Discussion

The French Competent Authority justified its proposal for classification of HMDZ surface-treated SAS as STOT RE 2 (H373) as follows:

"*A classification STOT RE 2 H373 (May cause damage to organs through prolonged or repeated exposure) according to the CLP regulation is proposed for pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide ; based on the slight to moderate significant increase of the lung collagen content with signs of focal interstitial fibrosis, on the granuloma-like lesions and on septal cellularity (still present at 52 weeks of recovery) after inhalation exposure to AEROSIL® R 974.*

Even if the majority of these effects were reversible during the one-year recovery period, it is considered that the time necessary for the reversibility is relatively important compared to the duration of the exposure.

According to the CLP regulation (1272/2008), these findings meet the following criteria for classification STOT RE 2: "significant functional changes in the central or peripheral nervous systems or other organ systems, including signs of central nervous system depression and effects on special senses (e.g. sight, hearing and sense of smell) (criteria b) or multi-focal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity (criteria e)."

The PWG review demonstrated that after a recovery period of 52 weeks following exposure of rats to AEROSIL® R 974 at 34.7 mg/m^3 for 13 weeks, the lung lesions observed at the end of the exposure period were completely cleared and that the pathology profile of the lungs was comparable to that of control rats of that age. The PWG further stated that no fibrogenesis (reversible) or fibrosis was observed in the rats exposed to AEROSIL® R 974. Since HMDZ surface-treated pyrogenic SAS and AEROSIL® R 974 are both hydrophobic surface-treated SAS, HMDZ surface-treated pyrogenic SAS should also not be considered as producing irreversible lesions in the lung after continuous exposure to levels up to 34.7 mg/m^3 for 13 weeks.

The effects observed with AEROSIL® R 974 are typical hallmarks of inflammation responses of the rat lung to continued high levels of particle exposures (foreign body reactions), whichmay persist of over a long time (ECETOC, 2006). All effects were fully reversible and cannot be termed adverse according to WHO/IPCS definitions (WHO, 2004). The argument that '*Even, if the majority of these effects were reversible during the on-year recovery period, it is considered that the time necessary for the reversibility is relatively important compared to the duration of the exposure*' is not consistent with regulatory guidance and the results of the re-evaluation. Reversibility is an important aspect regarding adversity. As all effects induced by inhalation of AEROSIL® R 974 were completely resolved within a period of 52 weeks after exposure as stated by the pathology reevaluation, these transient effects are not adverse effects that should serve as basis for classification.

In addition to the incomplete interpretation of the Reuzel study, the CLH report does not consider the wealth of existing animal inhalation studies with similar SAS materials or epidemiological studies in SAS production (Morfeld *et al*., 2014; Taeger *et al*., 2016). The CLP Regulation requires the consideration and weight of evidence of all relevant information pertaining to the hazard of a substance including physico-chemical properties, animal data or occupational exposure data. In particular, with regard to HMDZ surface-treated SAS, the key information that requires consideration when assessing repeated dose toxicity via the inhalation route is

- **SAS is rapidly cleared from the lung**. SAS is soluble under physiological conditions and therefore has little persistence in the lung. Clearance occurs by hydrolysis or phagocytosis by alveolar macrophages.
- **No intrinsic toxicity of SAS**. There is no indication of systemic toxicity following repeated inhalation of SAS including AEROSIL® R 974 at the sole exposure concentration of 34.7 mg/m^3.
- **The effects induced in the lung by SAS-inhalation are reversible, hence adaptive and not adverse**. Numerous inhalation toxicity studies have been conducted with hydrophilic and hydrophobic SAS including AEROSIL® R 974 have been conducted. No evidence for systemic toxicity following repeated inhalation of these grades were observed. All SAS show a similar pattern of toxicity in these studies representing an adaptation of the lung to a sustained high particle exposure (e.g., transient increases in inflammation, markers of cell injury, and lung collagen; macrophage accumulation).

Both, hydrophilic and hydrophic SAS are not involved in progressive fibrosis in the lung. Hence, all effects are limited and fully reversible with no severe consequences on organ function.

- **Epidemiological studies demonstrate absence of effects of worker exposure to SAS on lung function**. SAS have a long history of production and use. Epidemiological studies did not provide evidence for pneumoconiosis or other exposure-related pulmonary disease in SAS exposed workers (Merget *et al.*, 2002; Morfeld *et al*., 2014; Taeger *et al*., 2016). There is no study that provides evidence for the inhalation carcinogenicity of synthetic amorphous silica to humans (Merget *et al*., 2002). These studies are overwhelmingly negative. The particle sizes of commercial SAS to which workers are exposed at the workplace do not penetrate the lung.
- **Lung Load**. It is noteworthy that there is currently no possibility to translate effects observed in lungs of rats to the human situation. The extremely high doses cause an overcharge of the lungs. The alveolar lumen of rats is much smaller than those of human. Whereas in extreme cases one reactive alveolar macrophage may fill the lumen of a small rat alveolus completely this is not the case in human lungs. This causes an overcharge of rat alveoli with subsequent reactive and inflammatory sequelae, whereas human lung alveoli might be cleared easier by emigration of macrophages and coughing. In summary, based on the morphological differences and in absence of any mathematical model, as well as the extremely high doses in the rat study compared to working exposure, the conclusions drawn by such study is deemed to be arbitrary.

4. Conclusion

ASASP rejects the French Competent Authority's interpretation of the TNO study and their conclusion that the effects observed in this study meet the CLP STOT RE 2 (H373) classification criteria.

The CLH report did not take into accout the most recent and up to date data on inhalation toxicity of the substance. According to current criteria for pathology assessment, the only available subchronic inhalation study with AEROSIL® R 974 did not demonstrate the occurance of focal interstitial fibrosis and displayed complete reversibility of all observed lung lesions (AnaPath, 2016; ELP, 2016; Weber *et al*., 2018). Moreover, the CLH proposal is also considered incomplete, because it does not take into account all additional available scientific information pertaining to the inhalation toxicity of SAS materials.

The available information from animal inhalation toxicity and human exposure studies paired with the known toxicokinetic characteristics of synthetic amorphous silica, including hydrophobic DDS surface-treated SAS 'AEROSIL® R 974' and HMDZ surface-treated SAS does not warrant a classification as STOT RE 2 (H373). The effects observed in the available animal inhalation study with AEROSIL® R 974 are not adverse and fully reversible. The material does

not cause organ damage or dysfunction (i.e., no progressive fibrosis of the lung or systemic toxicity have been observed) and effects should be considered as an adaptive response by the rat to a prolonged exposure to a high particle concentration. The CLP Regulation states that H373 should not be applied when toxicological changes are the result of an adaptative response or where a species-specific mechanism of toxicity has been demonstrated (EC, 2008; ECHA, 2017).

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