Committee for Risk Assessment

RAC

Annex

Records

of the targeted consultation following receipt of new information on the actute inhalation toxicity of

Silanamine, 1,1,1-trimethyl-N- (trimethylsilyl), hydrolysis products with silica

Pursuant to Article 77(3)(c) of Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals

EC Number: 272-697-1
CAS Number: 68909-20-6

A77-O-0000007327-71-01/F

Adopted

8 June 2023

ANNEX 2 RECORDS OF THE TARGETED CONSULTATION FOLLOWING RECEIPT OF NEW INFORMATION ON THE ACTUTE INHALATION TOXICITY OF SILANAMINE, 1,1,1-TRIMETHYL-N- (TRIMETHYLSILYL), HYDROLYSIS PRODUCTS WITH SILICA; PYROGENIC, SYNTHETIC AMORPHOUS, NANO, SURFACE TREATED SILICON DIOXIDE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Following a request to review the RAC opinion pursuant to Article 77(3)(c) of Regulation (EC) No 1907/2006 and receipt of new information provided by Industry addressing the classification for acute inhalation toxicity of Silanamine as adopted by RAC on 5 December 2019, an ad hoc consultation on the harmonised classification and labelling of Silanamine, 1,1,1-trimethyl-N- (trimethylsilyl), hydrolysis products with silica; pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide was launched from 23 January 2023 to 6 February 2023.

Comments provided during this consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Substance name: Silanamine, 1,1,1-trimethyl-N- (trimethylsilyl), hydrolysis products with silica; pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide
EC number: 272-697-1
CAS number: 68909-20-6

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	United States of America	Synthetic Amorphous Silica and Silicate Industry Association (SASSI)	Industry or trade association	1
Comment received				
SASSI is aligned with ASASP's comments for the Targeted Public Consultation for HMDZ-treated synthetic amorphous silica (see attached) and fully supports its conclusions that HMDZ-treated SAS does not warrant a classification as an acute toxicant. Recent assessments by Canadian Regulatory Authorities should also be considered by ECHA. See https://www.canada.ca/en/environment-climate-change/services/evaluating-existing-substances/screening-assessment-silanamine-trimethyl-trimethylsilyl-hydrolysis-silica-tmss.html#toc15 ECHA note – An attachment was submitted with the comment above. Refer to public attachment SASSI Comments Silanamine 230203.pdf				

RAC's response
Thank you for your comment. Please see the response to comment no. 14. The recent assessment by Canadian authorities (2022) does not specifically address the acute inhalation toxicity hazard.

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	Germany	Eurocolour e.V.	Please select organisation type..	2
Comment received				
The Association Eurocolour e. V. would like to support the comments of the Association of Synthetic Amorphous Silica Producers (ASASP) in its opinion based on new results of studies. The comments provided by ASAPS are in the attachment. Eurocolour e. V. is the umbrella association for the manufacturers of pigments, dyes, fillers, frits, ceramic and glass colours, and ceramic glazes in Europe. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 20230206 ASASP comments to Silanamine final.pdf				
RAC's response				
Thank you for your comment. Please see the response to comment no. 14.				

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	Belgium	ASASP (Association of Synthetic Amorphous Silica Producers) Cefic Sector Group	Industry or trade association	3
Comment received				
The Association of Synthetic Amorphous Silica Producers (ASASP), a sector group of Cefic, would like to share its comments to the Targeted Public Consultation for substance HMDZ-treated synthetic amorphous silica (SAS). The Association of Synthetic Amorphous Silica Producers is a sector group of the European Chemical Industry Council (Cefic) and represents the major producers of synthetic amorphous silica (SAS) in Europe. ASASP is a non-profit organisation established in 1992 dedicated to promoting the safe use and benefits of SAS to society. Please find attached ASASP (Association of Synthetic Amorphous Silica Producers) comments and experts statement in the zip file. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 20230203 ASASP comments to HMDZ-treated SAS final.zip				
RAC's response				
Thank you for your comment. Please see the response to comment no. 14.				

ANNEX 2 RECORDS OF THE TARGETED CONSULTATION FOLLOWING RECEIPT OF NEW INFORMATION ON THE ACTUTE INHALATION TOXICITY OF SILANAMINE, 1,1,1-TRIMETHYL-N- (TRIMETHYLSILYL), HYDROLYSIS PRODUCTS WITH SILICA; PYROGENIC, SYNTHETIC AMORPHOUS, NANO, SURFACE TREATED SILICON DIOXIDE

Date	Country	Organisation	Type of Organisation	Comment number
26.01.2023	Germany		Individual	4
Comment received				
CAS No. 68909-20-6 is termed synthetic amorphous silica surface treated with hexamethyldisilazane (HMDZ-SAS). HMDZ-SAS is a low-density particulate material with a hydrophobic surface and is commercially used as non-respirable agglomerates with a mass median aerodynamic diameter (MMAD) of app. 80 µm. Significant shear stress is required to break down the agglomerates into particles in the respirable range (MMAD less than 10 µm) for inhalation toxicity testing. The small particles generated by shear stress readily re-agglomerate when shear stress is absent. HMDZ-SAS (AEROSIL® 812) induced lethality in a 4-hour inhalation exposure in rats at 500 mg/m3. The derived four-hour LC50 may mandate classification of HMDZ-SAS as Acute Tox Cat 2 (fatal if inhaled). However, the particle characteristics of HMDZ-SAS and observations with similar particles suggested suffocation due to airway occlusion as a cause of lethality.				
RAC's response				
Thank you for your comment. Please see the response to comment no. 14.				

Date	Country	Organisation	Type of Organisation	Comment number
29.01.2023	Switzerland		Individual	5
Comment received				
Frozen sections, which are important for examining a dust in the nasal cavity, were made at my laboratory (AnaPath Services GmbH). The reason was that likely with formalin-fixed material the blockage could be flushed out of the hollow organ, and, therefore, a standard treatment for the production of the tissue sections was not suitable. Thereafter, we performed an EDX analysis in order to demonstrate that the material that stuck in the the nasal cavity was identical with the test item (based on Si). Si was not at all detected in the lungs. In nasal cavieties, there was no further lesion. In lungs, however, there were indicators for asphyxia (hemorrhage, acute necrosis, acute emphysema). Hence, it has been proven that a mechanical blockage of the nasal cavity and not a toxic effect caused death. The anatomy and physiology of the respiratory system of rats (also other laboratory species) and humans are not comparable. Of highest importance is that rodents are obligatory nasal breather and, therefore, suffocates when the nasal passages are blocked. The results of this study has been published.				
RAC's response				
Thank you for your comment. RAC agrees that the findings in the new study are consistent with suffocation due to obstruction of nasal cavity. RAC also agrees that this mode of action is not relevant to humans. Nevertheless, the evidence of non-relevance is less clear for the lower airways, where occlusion by test material was observed in some earlier studies (e.g. Cabot, 2000).				

Date	Country	Organisation	Type of Organisation	Comment number
24.01.2023	Germany		Individual	6
Comment received				
Thanks reopening the discussion and sharing the data that conclusively show the mode of action in the animals. This now gives regulators the chance to avoid a classification which				

contributes only little or nothing to human safety. Sticking to classification of clearly relevant effects is an urgent need to ensure a proper-working hazard warning system.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
06.02.2023	Belgium	Silicones Europe (a sector group of Cefic)	Industry or trade association	7
Comment received				
Silicones Europe (SiE), a sector group of Cefic (the European Chemical Industry Council), representing all major silicone producers in Europe, is aligned with the position of ASASP (Association of Synthetic Amorphous Silica Producers) related to the harmonised classification of Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica. SiE support submission of the paper to the RAC and as part of the on-going targeted public consultation.				
RAC's response				
Thank you, please see the response to comment no. 14.				

Date	Country	Organisation	Type of Organisation	Comment number
06.02.2023	Japan	Japan Inorganic Chemical Industry Association	Industry or trade association	8
Comment received				
Based on the new studies, it is clear that the lethal effect in rats was initially caused by physical obstruction in the inhalation system, and not by the intrinsic toxicity of the substance tested. Clinical signs and findings in the lung were caused by such initial physical effects. As the OECD Guidance specifically warns that physical obstruction should not be misdiagnosed as a toxic effect, a classification as an acute toxicant of HMDZ-treated SAS is unwarranted. Consequently, JICIA kindly requests that the current RAC opinion on the classification for acute inhalation toxicity of this substance as Acute Tox. 2; H330 be revised. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2023-02_JICIA public comment (FINAL).pdf				
RAC's response				
Thank you for your comment. Please see the response to comment no. 14.				

Date	Country	Organisation	Type of Organisation	Comment number
04.02.2023	United Kingdom		Individual	9
Comment received				
My attention has been drawn to this targeted consultation regarding the acute classification of Aerosil® R 182 based on a rat inhalation study provided by ECHA in this				

consultation and I would like to make two comments. The first in relation to the interpretation of this specific study and the second of a more general, but important animal welfare nature, for the testing of materials that can agglomerate in the nasal cavities of obligate nasal breathers, such as the rat, causing blockage with eventual physical suffocation/asphyxiation.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Wessely et al. 2022.pdf

RAC's response

Thank you, please see the response to comment no. 20.

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	Germany	SASforREACH GbR	Industry or trade association	10

Comment received

SASforREACH GbR, the industry consortium for the REACH registration of Synthetic Amorphous Silica and Silicates, would like to provide its comments to the targeted public consultation for Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl), hydrolysis products with silica; pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide (CAS # 68909-20-6).

Please find our comments in the attachement as well as corrisponding corrigenda for both sections of the mechanistic study.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment SASforREACH Documents.zip

RAC's response

Thank you for your comment. Please see the response to comment no. 14.

Thank you also for the corrigenda to the test reports of the new study and the technical pre-test. The changes have no impact on the assessment.

As to the earlier studies, these have been evaluated by RAC and taken into account in a weight-of-evidence assessment.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	United States of America	Synthetic Amorphous Silica and Silicate Industry Association (SASSI)	Industry or trade association	11

Comment received

The current RAC opinion on the classification for acute inhalation toxicity of this substance as Acute Tox. 2, H330 should be revised.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment SASSI Comments Silanamine 230203.pdf

RAC's response

Thank you, noted.

Date	Country	Organisation	Type of Organisation	Comment number
27.01.2023	Belgium	IMA-Europe	Industry or trade association	12
Comment received				
IMA-Europe supports the assessment and comments made by the Association of Synthetic Amorphous Silica Producers (ASASP). We would like to repeat that the a CLP classification address the intrinsic properties of a substance. Death by suffocation due to a physical blockage of the rat upper respiratory tract by agglomeration of particles is not an intrinsic property and shall thus not trigger a classification for the acute inhalation endpoint.				
RAC's response				
Thank you for your comment. Please see the response to comment no. 14.				

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	Germany	Eurocolour e.V.	Please select organisation type..	13
Comment received				
In fact, the results of SAS for REACH's new mechanistic study submitted by ASAP to RAC demonstrate that HMDZ-treated SAS is not an acute toxicant by inhalation via a relevant mode of action. The final results of the study have confirmed that the cause of animal death is suffocation, a physical effect due to the presence of foreign materials and not due to an intrinsic (i.e. substance-specific) toxic effect. For this reason, HMDZ-treated SAS does not warrant a classification as acute toxicant and we ask that the current RAC opinion on the classification for acute inhalation toxicity of this substance as Acute Tox. 2; H330 should be revised. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 20230206 ASASP comments to Silanamine final.pdf				
RAC's response				
Thank you for your comment. Please see the response to comment no. 14.				

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	Belgium	ASASP (Association of Synthetic Amorphous Silica Producers) Cefic Sector Group	Industry or trade association	14
Comment received				
The Association of Synthetic Amorphous Silica Producers (ASASP), a sector group of Cefic, would like to share its comments to the Targeted Public Consultation for substance HMDZ-treated synthetic amorphous silica (SAS). The results of SASforREACH Consortium's new mechanistic study (shared in this				

consultation) demonstrate that HMDZ-treated SAS is not an acute toxicant by inhalation via a relevant mode of action. The study confirms a physical blockage of the rat upper respiratory tract by agglomerated HMDZ-treated SAS as cause of death by suffocation, and not due to intrinsic toxicity of the particle. In addition, such a physical blockage is not relevant for humans due to anatomical differences between rat and human respiratory tracts.

For these reasons, ASASP concludes that HMDZ-treated SAS does not warrant a classification as acute toxicant and therefore the current RAC opinion on the classification for acute inhalation toxicity of this substance as Acute Tox. 2; H330 should be revised.

The intention of this study was to clarify whether lethality in connection with low density hydrophobic particles is caused by physical obstruction or an intrinsic effect (such as systemic toxicity or disturbance of function or the physiology of the alveoli by interaction with the surfactant or membranes). As the guidelines for acute inhalation toxicity assessment (OECD 403 and 436) only require counting dead animals and a macroscopic examination of the surfaces of the organs in the abdominal and thoracal cavity, causes for lethality were not assessed in previous studies.
This new study differs from previous studies conducted following standard OECD protocols as additional physical, biological and histopathological parameters have been included to clarify the above question. The mechanistic study comprises:
- physico-chemical characterisation of the generated aerosol and the exposure atmospheres in the test system (stability, particle concentration, change in the particle size distribution over time). The aerosol generation is crucial for the correct execution of acute inhalation toxicity testing and to determine the highest technical feasible aerosol concentration with no or maximum acceptable altering;
- examination of the entire respiratory tract pathology including proximal nose and nasal cavities (for this purpose a new preparation and examination method was developed)
- thorough histopathological examination of organs that are known to be sensitive to suffocation
- blood oxygen monitoring
The aim was to clarify the origin of the effects described in former acute inhalation studies. Furthermore, "bottlenecks" for particles in the rat upper respiratory tract (e.g. nasal cavities) were not examined in the existing studies, while in this study, for the first time the entire respiratory tract including proximal nose and nasal cavities were examined.

Animal vs Humans
In the attached experts statement (Annexe1 and 2), experts have investigated the human relevance of the observed lethality of HMDZ-treated SAS in acute toxicity testing using inhalation exposure in rats.
The result of the investigation is that suffocation effects on rats cannot be transferred to humans, because the anatomy of the rat respiratory tract differs from the human: mainly monopodial branching of airways, smaller ventilatory unit volume, smaller alveolar size and lower average number of cells per alveolus (Miller, Mercer and Crapo, 1993). The new mechanistic study shows that the OECD 403 and 436 Guideline limit test concentrations (5000 mg/m3) for acute toxicity studies for CLP classifications are too high for hydrophobic low-density particles. In fact, much lower technical feasible aerosol concentrations can lead to physical obstruction effects in rats, but are not reflective of what could happen in humans. Contrary to humans, the rat is an obligatory nose breather; while fixed in a tube for four hours during acute inhalation studies, the rat can neither protect its nose by fur nor can it physically clean it.

Conclusion
A complete physical obstruction of the proximal nose (nasal cavities) has been proven by histopathology as cause of mortality, due to suffocation. Clinical signs such as preterminal gasping and macroscopical findings in the lung (i.e. congestion, edema, acute emphysema and petechiae) are secondary effects resulting from obstruction of the nasal cavity at 500mg/m³. This should not be misdiagnosed as a toxic effect, as stated in OECD Guidance 39 (2018) para 51: "At very high concentrations, dry powder aerosols …tend to form conglomerates in the proximal nose causing physical obstruction of the animals' airways (e.g., dust loading) and impaired respiration which may be misdiagnosed as a toxic effect".

The final results of the study have confirmed that the cause of animal death is suffocation, a physical effect due to the presence of foreign materials and not due to an intrinsic (i.e. substance-specific) toxic effect. For this reason, HMDZ-treated SAS does not warrant a classification as acute toxicant and we ask that the current RAC opinion on the classification for acute inhalation toxicity of this substance as Acute Tox. 2; H330 should be revised.

Please find attached ASASP (Association of Synthetic Amorphous Silica Producers) comments and experts statement in the zip file.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 20230203 ASASP comments to HMDZ-treated SAS final.zip

RAC's response

Thank you for your comments.

RAC appreciates the new acute inhalation toxicity study with HMDZ-treated SAS, which represents a valuable contribution to the existing dataset, in particular due to the thorough characterisation of the test atmosphere, careful examination of upper airways for the presence of test material, as well as histopathological examination of a wide range of respiratory and non-respiratory tissues.

On the other hand, the use of only a single exposure concentration, which caused 100% mortality, is considered a drawback of this study. Testing at multiple concentrations, even with a lower number of animals per concentration, would have provided valuable additional information.

Still, RAC agrees that marked deposition of test material in the nasal cavity, the lung histopathology and lack of lesions in other tissues are collectively indicative of suffocation as the main cause of death in the new study. RAC also agrees that obstruction of nasal cavity by dust observed in rats is of no human relevance.

As part of the current re-assessment, RAC has also examined the reports of the earlier acute inhalation toxicity studies with hydrophobic surface-treated fumed silicas. Three of these earlier studies included histopathological examination. One of them (Cabot, 2000) is considered relevant for the mode of action discussion due to thorough examination of the whole respiratory tract. This study showed marked test substance deposition in the nasal cavity, larynx, bronchi and bronchioles, as well as some inflammation. The LC_{50} from this study (between 0.52 and 1.12 mg/l) in the range of Category 3. The MMAD was lower than in the new study.

Unlike the situation with nasal cavity (and possibly larynx), lack of human relevance of lower respiratory tract effects has not been convincingly demonstrated. Although there are factors decreasing the concern (e.g. larger diameter of lower airways in humans), this is counterbalanced by the lower filtering capacity of human nose and the possibility of oral breathing in humans. Thus, the effect in study Cabot (2000) can be partly attributed to a potentially human-relevant MoA.

The propensity of HMDZ-treated SAS to obstruct respiratory tract is primarily related to a combination of hydrophobicity, low solubility and low density of the particles. RAC is of the view that this effect, observed in standard studies, may still be considered an intrinsic property in line with its definition in the Guidance on the application of the CLP criteria (section 1.1.3). However, this is partly a regulatory issue, not entirely in the remit of RAC.

The particle size distribution may vary between individual HMDZ-treated SAS products. According to the report from the pre-test (Stintz and Wessely, 2022), Aerosil R812 has a median (geometric) particle size of about 75 µm (corresponding to MMAD of ca. 20 µm) under low shear intensity (freefall shaft). It cannot be excluded that HMDZ-treated SAS products with a lower MMAD exist on the market or will be developed in the future.

In summary, suffocation is considered the main cause of death in the new study. However, considering also the findings of the older studies at higher concentrations and different MMAD in a weight of evidence assessment, RAC agreed on no classification due to inconclusive data.

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	Japan	Japan Business Machine Information System Industries Association (JBMIA)	Industry or trade association	15
Comment received				
JBMIA would like endorse the comments submitted by The Association of Synthetic Amorphous Silica Producers (ASASP). The new study report (Fraunhofer ITEM Study No. 02 G 21 009) clearly shows that the cause of animal death is suffocation, a physical effect due to the presence of foreign materials and not due to an intrinsic (i.e. substance-specific) toxic effect. In addition, such a physical blockage is not relevant for humans due to anatomical differences between rat and human respiratory tracts. For this reason, HMDZ-treated SAS does not meet the requirements for acute toxicity classification. JBMIA kindly ask that the current RAC opinion on the classification for acute inhalation toxicity of this substance as Acute Tox. 2; H330 should be revised. ECHA note – An attachment was submitted with the comment above. Refer to public attachment JBMIA Comments on the HMDZ treated silica.pdf				
RAC's response				
Thank you for your comment. Please see the response to comment no. 14.				

Date	Country	Organisation	Type of Organisation	Comment number
26.01.2023	Germany		Individual	16
Comment received				
The results of a recent acute inhalation toxicity studies with detailed assessment of particle deposition in the entire respiratory tract confirm that the upper airways of rats exposed to HMDZ-SAS are blocked by deposited particulate material. Mortality is thus due to suffocation. The blocking of the upper respiratory tract in rats is initiated by the rapid re-agglomeration of HMDZ-SAS and an interaction of the formed agglomerates with liquids on the surface of the airways. These forms large and viscous droplets due to the inhalation of a very large number of low-density particles. As only intrinsic properties of substances are relevant to classification, the observed lethality is not due to an intrinsic toxic property of HMDZ-SAS, but due to a physical effect of the deposited particles. Thus, the effect should not be used for classification. The observations in the recent study confirm the caveats regarding lethal effects by physical obstruction of airways after inhalation of high particle loads described in OECD guidance 39. Besides the absence of an intrinsic property of HMDZ-SAS to cause lethality under the condition of an acute inhalation exposure study, the observed lethality due to physical obstruction of the nasal cavity in rats after exposures to determine a LC50 has no human relevance. This is due to differences in breathing patterns and airway structures. Rats are obligate nose-breathers and blockade of the nasal passage will result in asphyxia. In contrast, humans are both nose and mouth breathers, specifically under stress. Therefore, blockade of the nasal passages will not result in asphyxia since mouth breathing remains possible in humans. The upper airways in rats and humans also show major differences regarding airway geometry (shape of nasoturbinate and maxilloturbinate) and diameter. These influence air flow characteristics, location and amount of particle deposition, and tendency for blocking of airways. Basic laws of fluid dynamics of particulate containing air in low diameter tubing predict a very low airflow in rats exactly at the site of airway blockade seen with HMDZ-SAS. The low airflow promotes re-aggregation and deposition of HMDZ-SAS on the moist surfaces of the airways that results in blockade of the airways in rats. In humans, such low airflows are not predicted, and deposition will not occur at these sites. In addition, the much wider airways of humans require formation of larger droplets. These cannot form due to absence of moisture on the surface of an already deposited particle film. If particles inhaled at high concentrations reach the lower airways in humans, the major structural differences will also result in different outcomes and blocking of the lower airways in humans is considered as highly unlikely. Therefore, lethality due to physical obstruction of airways under conditions of assessing an LC50 should not be used in classification and labeling.				
RAC's response				
Thank you for your comment. Please see the response to comment no. 14.				

ANNEX 2 RECORDS OF THE TARGETED CONSULTATION FOLLOWING RECEIPT OF NEW INFORMATION ON THE ACTUTE INHALATION TOXICITY OF SILANAMINE, 1,1,1-TRIMETHYL-N- (TRIMETHYLSILYL), HYDROLYSIS PRODUCTS WITH SILICA; PYROGENIC, SYNTHETIC AMORPHOUS, NANO, SURFACE TREATED SILICON DIOXIDE

Date	Country	Organisation	Type of Organisation	Comment number
01.02.2023	Germany	SASFORREACH Consortium GbR	Industry or trade association	17

Comment received

In already existing acute inhalation studies with different synthetic amorphous silicas including Silanamine, 1,1,1-trimethyl-N- (trimethylsilyl), hydrolysis products with silica; pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide provided reasonable suspicion that the observed mortality is due to suffocation associated with the extremely high particle numbers/high substance volumes administered (ECETOC, 2006).
To get a more profound scientific basis the new comprehensive study (OECD TG 436, GLP, rats, nose-only + comprehensive aerosol characterization work + detailed histopathological examination of the respiratory tract + detection of test substance in the lungs + analysis of blood oxygen concentration) has been performed to investigate the acute inhalation toxicity of Aerosil® 812 under well-defined conditions and to clarify the Mode of Action (MoA) of observed toxicity to understand the relevance for (human) hazard definition and classification needs.
The results of the study are conclusive and confirm the initial hypothesis.
1. Strong shearing forces are necessary to achieve a respirable particle fraction (Mass Median Aerodynamic Diameter, MMAD > 4 µm) which is requested by the OECD TG 436. This particle size differs significantly from the commercial product and in which it can be reasonably be expected under normal handling and use conditions.
2. The specific behavior of this respirable particle fraction in the test chamber and in the respiratory tract of the test animals (deagglomeration, agglomeration; deposition behavior) leads to the observed health effects
3. Therefore the toxicological effects are clearly related to this specific artifical generated fraction and they are not an intrinsic property of the product as placed on the market
4. The cause of morbidity/mortality (MoA) in all test animals is asphyxia by physical obstruction of the upper respiratory tract
5. This MoA is not a specific intrinsic property of the substance but a purely physical effect, only. It is the result of the extreme load of the rodent lung with particulate material/substance volume.

Due to the two aspects summarized above (differences in particle sizes of commercial product vs test aerosol; unspecific, physical Mode of Action) a classification of the product based on acute inhalation toxicity test data is not indicated and is not in line with CLP guidelines.

ECETOC (2006). "Synthetic Amorphous Silica (CAS No. 7631-86-9)". JACC No. 51. ISSN-0773-6339-51

Extract from the CLP regulation concerning relevance of data for hazard classification:
• "The information shall relate to the forms or physical states in which the substance is placed on the market and in which it can be reasonable be expected to be used"
• „The information/data shall examined to ascertain whether it is adequate, reliable and scientifically valid for classification.“
• "Tests that are carried out for the purpose of this regulation shall be carried out on the substance or on the mixture in the form(s) of physical state(s) in which the substance or mixture is placed on the market and in which it can be reasonably be expected to be used."

<confidential>
RAC's response
Thank you for your comment. Please see the response to comment no. 14.

Date	Country	Organisation	Type of Organisation	Comment number
01.02.2023	Japan	<confidential>	Company-Importer	18
Comment received				
The current RAC opinion on the classification for acute inhalation toxicity should be revised because it is not intrinsic properties of this substance. The observed lethality was thought to be due to suffocation. Let me explain using an example. In Japan, rice cake is eaten by a lot of people, celebrating a new year. Some people die because the rice cake is choked in their throad, but it is not intrinsic properties of rice cake. Some manufactures of rice cake voluntary print this risk on the package, and this food is still sold. For this substance, the risk may have to be written on SDS, but acute toxicity classifcation is not necessary.				
RAC's response				
Thank you for your comment. Please see the response to comment no. 19.				

Date	Country	Organisation	Type of Organisation	Comment number
24.01.2023	Germany		Individual	19
Comment received				
Death of animals in acute inhalation toxicity studies due to blockage of the respiratory tract by particle deposition is not an intrinsic property of the substance and not of direct relevance to humans. Based on several statements in the CLP regulation and guidance only intrinsic properties are intended to be subject to CLP regulation. The current RAC opinion of this substance must be revised accordingly.				
RAC's response				
Thank you for your comment. According to the CLP guidance (1.1.3), intrinsic hazards are "the basic properties of a substance or mixture as determined in standard tests or by other means designed to identify hazards." RAC acknowledges that the mortality in acute inhalation toxicity studies with hydrophobic surface-treated SAS is related to the physico-chemical properties of undissolved particles rather than to toxic properties of the dissolved form. RAC is of the view that the definition of "intrinsic hazard" in the CLP guidance does not exclude use of particle-related effects observed in standard studies for classification. Nevertheless, this is a regulatory issue, partly beyond the remit of RAC.				

Date	Country	Organisation	Type of Organisation	Comment number
04.02.2023	United Kingdom		Individual	20
Comment received				
I became aware of this study, described in the consultation, at a conference on particles and health which I co-chaired in London in October 2021 (https://www.particlesandhealth.org/) where two papers were presented which addressed this study and these findings and were later published (Kruger et al. 2022 and Wessely et al. 2022). Further details of these studies are now available as a full report (Acute Nose-Only Inhalation Study in Wistar Rats with the Synthetic Amorphous Silica Aerosil® R182),				

kindly supplied by ECHA in this targeted consultation but, it simply provided further detailed post-mortem examination of the 5 rats and helpful histopathological information confirming that the rats died of asphyxiation caused by the test material agglomerating in the nasal cavities, causing blockage and thus not progressing into the lungs, as evidenced by the histopathology. The finding of extensive petechial haemorrhaging on the surface of the lung are a manifestation of the rats physically struggling to try to move air in and out the airways and lungs and the marked pressure changes in the thoracic cavity, caused by this violent muscular movement. This is clearly not an intrinsic toxicological property of the tested material, nor even a general inert particle effect as seen where respirable poorly-soluble low-toxicity materials are able to induce inflammatory effects and "lung overload" The results are thus not relevant for acute testing classification according to OECD Test Guideline 436 for the tested material Aerosil® R 812 and thus, the current classicisation of Acute Tox 2 (H330: "fatal if inhaled") is inappropriate and not warranted.
My second concern is the more general one of the need to test such materials, even of respirable size, that have the tendency to agglomerate in the nasal cavity, at the concentrations required by the current OECD guidance, which may cause blockage in the nasal cavities and, in obligate nasal breathers, cause suffocation and death by asphyxiation. This unnecessary suffering is an urgent animal welfare concern and has been highlighted in detail by these study findings and is something that would seem to require urgent ECHA/OECD attention as there may be many other low-toxicity inert particles, with a tendency to agglomerate, that might cause similar effects when so tested.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Wessely et al. 2022.pdf

RAC's response

Thank you for your comments. RAC agrees that obstruction of the airways is a plausible explanation of the deaths in the new study (Krueger *et al*. 2022). Please see the response to comment no. 14.

Date	Country	Organisation	Type of Organisation	Comment number
03.02.2023	Germany	SASforREACH GbR	Industry or trade association	21

Comment received

SASforREACH concurs with the comments submitted by ASASP (The Association of Synthetic Amorphous Silica Producers, a sector group of CEFIC):

The classification of the aforementioned HMDZ-treated SAS as Acute Tox 2, inhalation as well as STOT RE2, inhalation is not warranted.

The conducted mechanistic OECD TG 436 study clearly shows that lethality of the rats is not based on intrinsic properties of Silanamine, 1,1,1-trimethyl-N-(trimethylsi¬lyl), hydrolysis products with silica; pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide, but on physical properties of the particles, which could also be expected to be established for any material of similar density, hydrophobicity and particle size.
With regards to the results of the mechanistic study, SASforREACH comments as fol-lows:
The animal part of the mechanistic study was conducted according to OECD TG 436 in order to comply with an internationally accepted standard. The goal of the OECD TG 436 test was not to determine the lethal concentration of particles in air, but to explain

unambiguously the pathological reason for the lethality upon exposure. The mechanistic study contains two sections:

Section 1: describes the dispersion and (re)-agglomeration behaviour of powders, including HMDZ-treated SAS. (Wessely et al. 2022)
Section 2: investigates the actual mechanism for the lethal outcome in test according to OECD TG 436. (Krueger et al. 2022)

The mechanistic study (including pathological results) clearly concludes on the reason of death to be suffocation due to agglomerated hydrophobic particles in the nasal cavities. An intrinsic chemical toxicity can thus be ruled out. It additionally justifies the Klimisch 3 rating applied to the existing studies on Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl), hydrolysis products with silica; pyrogenic, synthetic amorphous, nano, surface treated silicon dioxide in the REACH dossier. Thus, these studies should be disregarded for any assessment.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment SASforREACH Documents.zip

RAC's response

Thank you for your comment. Please see the response to comment no. 14.

As to the earlier studies, these have been evaluated by RAC and taken into account in a weight-of-evidence assessment.

PUBLIC ATTACHMENTS
1. 2023-02_JICIA public comment (FINAL).pdf [Please refer to comment No. 8]
2. Wessely et al. 2022.pdf [Please refer to comment No. 9, 20]
3. SASforREACH Documents.zip [Please refer to comment No. 10, 21]
4. SASSI Comments Silanamine 230203.pdf [Please refer to comment No. 1, 11]
5. 20230206 ASASP comments to Silanamine final.pdf [Please refer to comment No. 2, 13]
6. 20230203 ASASP comments to HMDZ-treated SAS final.zip [Please refer to comment No. 3, 14]
7. JBMIA Comments on the HMDZ treated silica.pdf [Please refer to comment No. 15]