Synthetic Amorphous Silica and Silicate Industry Association

Association of Synthetic Amorphous Silica Producers

September 11, 2017

Dr. Patrick N. Breysse, Director
Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
Environmental Toxicology Branch
1600 Clifton Road, NE, Mail Stop F-57
Atlanta, GA 30333

RE: Toxicological Profile for Silica, Draft for Public Comment, April 2017

Dear Dr. Breysse:

The Synthetic Amorphous Silica and Silicate Industry Association (SASSI) is a nonprofit organization incorporated in the District of Columbia as a 501(c)(6) entity on July18, 2007 by eight founding members. Key tenets of SASSI's mission focus on furthering the understanding of synthetic amorphous silica and silicate health and safety data within the industry, monitoring the regulation of synthetic amorphous silica and silicate by government, educating the public and government on the views of the industry, and consulting and cooperating with officials and agencies on matters having an industry-wide significance.

All of the member companies of SASSI are also members of the European organization, The Association of Synthetic Amorphous Silica Producers (ASASP), a Sector Group within The European Chemical Industry Council (CEFIC). ASASP has currently 10 members representing the majority of synthetic amorphous silica (SAS) producers in Europe. As a Sector Group, formed in 1992, ASASP provides a forum to address industry-wide questions arising during production related activities as well as ecotoxicity, toxicology and regulatory matters related to synthetic amorphous silica. Its mission is to ensure that members' views are made known to other technical groups and organizations, official bodies and national and international authorities, especially those involved in framing regulations. ASASP operates under EU competition law and according to CEFIC competition law guidelines.

Consistent with our mission, the members of SASSI and ASASP would like to take this opportunity to comment on the April 2017 *Toxicological Profile for Silica-Draft for Public Comment.*

We would first like to reference SASSI's June 22, 2015 comment letter to ATSDR on the February 12, 2015 *Federal Register* notice regarding the development of a toxicological profile on Silica CASRN 7631-86-9. At that time, we inquired about the selection of silica and asked to be assured that the Profile would focus on the crystalline forms of silica (CASRNs 14464-46-1/14808-60-7/15468-32-3) and not synthetic amorphous silica(SAS). We assumed silica (7631-

86-9) was included as one of the 275 hazardous substances on the Priority List of Hazardous Substances on the basis of the well-documented human health concerns related to crystalline silica. We asked that ATSDR clearly identify the polymorphs of concern (crystalline forms) in its Profile, and clearly and explicitly exclude the SAS polymorphs. Included in our correspondence was an attached reference publication that was intended to provide a clear understanding of the SAS polymorphs and as a reference to the relevant toxicological properties of these materials: European Centre for Ecotoxicology and Toxicology of Chemicals (ECOTOC) Joint Assessment of Commodity Chemicals (JACC)No. 51 on "Synthetic Amorphous Silica (CAS No. 7631-86-9)". We did not receive a response to our letter and we noted that the JACC No. 51 report was not referenced in the April 2017 Profile.

Regarding the April 2017 Draft, we offer the following comments:

General comments:

1. As noted in our June 22, 2015 letter, we recommended a clear differentiation of the polymorphs of silica, including a clear distinction between natural amorphous silica and synthetic amorphous silica. (Note in the attached documents: (1) February 1, 2016 letter to SASSI: ACGIH clearly differentiated "Calcium silicate, synthetic nonfibrous" from "Calcium silicate, naturally occurring as Wollastonite". (2) Addressing a similar issue with OSHA regarding the "Occupational Exposure to Respirable Crystalline Silica Final Rule" issued in 2016, we received confirmation that they would be diligent in differentiating between crystalline and amorphous silica.)

2. We propose subdividing the document into three sections, clearly separating the polymorphs and allowing for a clearer delineation of the differences in health effects between these categories:

- Crystalline silica (quartz, cristobalite and tridymite)
- Natural amorphous silica (diatomite, calcined, flux calcined, fused silica)
- Synthetic amorphous silica (pyrogenic, precipitated, gel, colloidal)

3. We noted the absence of references to a significant volume of recent, publicly available sets of data (especially for SAS), and would like to provide those references for your consideration in the revision of the Draft:

- OECD WPMN disseminated dossier on SAS (NM-2XX serie) (http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2016)23&doclanguage=en)
- REACH dossier data/Dissemination Report (https://echa.europa.eu/de/registration-dossier/-/registered-dossier/15556)
- Fruijtier-Pölloth, C. (2016). The safety of nanostructured synthetic amorphous silica (SAS) as a food additive (E 551). Arch Toxicol. doi:10.1007/s00204-016-1850-4

- Fruijtier-Pölloth, C. (2012). The toxicological mode of action and the safety of synthetic amorphous silica - A nanostructured material. Review Article. Toxicology 294, Issues 2-3, 61- 79
- ECETOC JACC Report No. 51 "Synthetic Amorphous Silica" (http://www.ecetoc.org/wp-content/uploads/2014/08/JACC-051.pdf)
- Taeger, D., McCunney, R., Bailer, U., Barthel, K., Küpper, U., Brüning, T., Morfeld, P., Merget, R. (2016). Cross-sectional study on non-malignant respiratory morbidity due to exposure to synthetic amorphous silica. J Occup Environ Med. 58 (4): 376-84
- Morfeld, P., Taeger, D., Mitura, H., Bosch, A., Nordone, A., Vormberg, R., McCunney, R., Merget, R. (2014). Cross sectional study on respiratory morbidity in workers after exposure to synthetic amorphous silica at five German production plants. J Occup Environ Med. 56 (1): 72-78

4. We suggest the following revisions (in red) and consideration of SASSI and ASASP comments:

Page 1: Silica is both a naturally occurring compound and one that can be manufactured synthetically. Naturally occurring silica is widespread in the environment. It is of particular concern in areas adjacent to crystalline silica mining, processing, and transporting facilities.

Page 1: If you are exposed to silica, many factors determine whether you'll be harmed. These include, the type and form of silica, the size of the silica particles, how much you are exposed to (dose), how long you are exposed (duration), how often you are exposed (frequency), and how you are exposed (route of exposure).

Page 2: Available data in humans and laboratory animals are not sufficient to demonstrate a causal relationship between oral exposure to a-silica and any adverse effect outcome. **[SASSI/ASASP comment: Given the widespread FDA and EPA/USDA approvals, including use as food and feed additives, GRAS notices, Drug Excipient use, and as FIFRA crop use inert ingredients, we believe that there are a sufficient number of oral studies available to demonstrate safety. Please see the study reference list provided.]**

Page 3: No health effects are shown to occur in humans from eating food or drinking water contaminated with c-silica or a-silica or from exposure of the skin to these compounds. **[SASSI comment: This implies a-silica is only found in food as a contaminant, when in fact there are many FDA approved uses of a-silica in food applications, as noted in the previous comment.]**

Page 3: People may be exposed to silica through their diet. Some types of a-silica compounds are used ~~as~~ in USDA and EPA approved pesticides that are applied to crops and are used near food handling and preparation areas due to their extremely low toxicity. A-Silica is approved for use~~d~~ in food packaging; however, there is no evidence that migration from the packaging into the ~~therefore~~ food is ~~expected to be an important~~ a source of exposure to silica. ~~for most people.~~ **[SASSI/ASASP comment: The absence of migration of synthetic amorphous silica is**

already known and documented in these two references: (1) *Investigation into the migration potential of colloidal silica from food packaging plastics into food*, Bott et al. 2015 (https://www.ivv.fraunhofer.de/content/dam/ivv/en/documents/Forschungsfelder/Produktsicherheit-und-analytik/Migration_potential_of_colloidal_silica_from_food_packaging_plastics_into_food.pdf): "At a detection limit of 0,1 mg silica per kg food (simulant) no migration of colloidal silica was detected…From the findings it can be concluded that nano-particulate SAS in general would not migrate into food when it is incorporated into a polymer matrix." ;(2) *Critical review of the migration potential of nanoparticles in food* , Störmer, A., Bott, J., Kemmer, D., Franz, R., Trends in Food Science & Technology (2017), doi: 10.1016/j.tifs.2017.01.011.]

Page 3: The most important route of exposure to c-silica and a-silica is through air containing these compounds. Only very small particles of silica, less than 5 microns, are more likely to be deposited in the lungs. Small amounts of silica compounds deposited in the lungs may be coughed up and swallowed. Once in your body, silica compounds remain for long periods of time in the lungs and tissues surrounding the lungs. Some silica is distributed to the kidneys and the lymphatic system, an important part of the immune system. Silica compounds are not broken down by the body. Small amounts of silica compounds leave the body in the urine. **[SASSI/ASASP comment: There is no differentiation in these comments between a-silica and c-silica regarding the significant differences in persistence of the materials in the body. The differences between c-silica and a-silica must be considered, as this paragraph is only relevant for c-silica. Synthetic a-silica shows a high dissolution in physiological media, which leads to a fast elimination from the respiratory tract and elimination via urine.]**

Page 3: Health effects of c-silica and a-silica in people are found in workers exposed for long periods of time (typically ≥10 years) or with extremely heavy exposure over a short period of time (acute silicosis**). [SASSI/ASASP comment: As stated on page 4 of the profile "Only c-silica, no other chemical, including a-silica, causes silicosis." Silicosis is not observed for SAS. New epidemiological data clearly indicates low level of toxicity.]**

Page 4: Other than acute lung effects, no other effects associated with inhaled a-silica have been ~~established~~ demonstrated.

Page 5: For workers exposed to c-silica compounds, periodic x-rays and tests for lung function are recommended to look for abnormalities. Workers should also be evaluated for tuberculosis, kidney function, and autoimmune diseases. **[SASSI/ASASP comment: We believe these recommendations are only intended for exposure to c-silica. Ref: Taeger, D., McCunney, R., Bailer, U., Barthel, K., Küpper, U., Brüning, T., Morfeld, P., Merget, R. (2016*). Cross-sectional study on non-malignant respiratory morbidity due to exposure to synthetic amorphous silica*. J Occup Environ Med. 58 (4): 376-84 comes to a different conclusion concerning periodic x-rays in case of synthetic a-silica.]**

Page 10: Although quantitative data are not available, water containing diatomite fragments and quartz particles is a potential source of exposure for the general population. **[SASSI/ASASP**

comment: Although we believe it to be accurate why use quartz and diatomite in the following sentence rather than c-silica and a-silica?]

Page 11: …very few studies evaluating the adverse effects of oral amorphous silica in animals have been conducted. **[SASSI/ASASP comment: We suggest review of Takizawa publication Takizawa Y, Hirasawa F, Noritomi E, Aida M, Tsunoda H, Uesugi S. 1988. *Oral ingestion of Syloid to mice and rats and its chronic toxicity and carcinogenicity.* Acta Medica et Biologica 36:27-56.) and the OECD and JACC summaries.]**

Page 11: Available animal studies either do not identify adverse effects at the doses tested or do not provide sufficient data to determine the toxicological significance of observed effects (e.g., changes in organ weights in the absence of histopathological changes). **[SASSI/ASASP comment: for a-silica, reference JACC No. 51, page 87-91: "Many studies examining the effects of oral administration of SAS to rats have been conducted… The results of the acute oral toxicity studies indicate a very low order of toxicity of SAS: no signs of toxicity were observed at doses of up to 5,000 mg SiO_2/kgbw. No difference was found between LD_{50} values for the various types of SAS studied."]**

Page 11: No association between dermal exposure and adverse effects has been ~~reported~~ demonstrated**.** **[SASSI/ASASP comment: For a-silica, reference JACC No. 51, page 91-92: "There was no indication of systemic adverse effects related to SAS in any test. It is concluded that SAS is not toxic by the dermal route."]**

Page 13: Relative to the abundance of data on crystalline silica, few studies have evaluated the effects of inhaled silica. **[SASSI/ASASP comment: This sentence implies that a-silica may have similar adverse health effects to c-silica but has not been studied, when in fact it has been demonstrated that a-silica is a substance of low toxicity. Due to the serious adverse health effects of c-silica, studies on c-silica are warranted, while they are not for a-silica.]**

Page 16: Although all a-silica polymorphs have not been evaluated for acute respiratory toxicity, results of acute inhalation studies in rats indicate that the biological activity of a-silica varies between polymorphs. **[SASSI/ASASP comment: It should be clarified if this statement relates to the comparison of hydrophilic to hydrophobic a-silica. Also, it is not clear what is meant by "biological activity". Reference JACC no. 51, Section 8.1]**

Page 17: …there is considerable uncertainty regarding identification of NOAEL or LOAEL values that could serve as the basis of development of inhalation MRLs, as values based on a single a-silica polymorph may not apply to all forms of a-silica. **[SASSI/ASASP comment: Concerning synthetic a-silica, a comprehensive data set exist concerning inhalation toxicity. There is no difference in the general toxicological behavior of synthetic a-silica in the lungs (inflammation, fast elimination, reversibility of effects, no progressive lung injury). NOAELs (respirable fraction) from animal tests are in the same range. Only gradual differences can be observed. Reference: JACC Report No. 51, Section 8.1.4: "Numerous acute inhalation toxicity studies have been conducted on both hydrophilic**

and hydrophobic SAS. For hydrophilic SASs, LC_{50} values are higher than the highest technically achievable concentrations. The mortality observed with hydrophobic SAS is due to suffocation associated with the extremely high particle numbers administered and not with any intrinsic toxicity of the SAS tested."]

Page 17: …no information on the effects of oral amorphous silica in humans was identified, and available animal studies either do not identify adverse effects at the doses tested or do not provide sufficient data to determine toxicological significance of observed effects. Therefore, available data for amorphous silica are insufficient to derive oral MRLs for amorphous silica for any duration. **[SASSI/ASASP comment: We suggest review of Takizawa publication and the OECD and JACC summaries.]**

Pages 102-105: **[SASSI/ASASP comment: Rather than a repetition of copy/paste for the various sections, we suggest placing the animal study result/discussion first, followed by the human studies.]**

Page 184: Section 3.4 Toxicokinetics: **[SASSI/ASASP comment: reference JACC Report No. 51, Section 7: Kinetics and Metabolism]**

Page 198: The oral database for chronic-duration exposure to a-silica is limited to a single 24-month study in rats (Lewinson et al. 1994). In this study, the only administered dose level of 100 mg/kg/day was identified as a NOAEL for a lack of systemic effects. The reliability of this study is low due to small animal groups (20/sex), lack of concurrent control, and use of a single dose level that did not approach the MTD. Considering the limitations of the available data, well-designed chronic toxicity studies of a-silica may provide evidence to establish a LOAEL and critical effects for long-term oral exposure. **[SASSI/ASASP comment: Reference current information: Fruijtier-Pölloth, C. (2016). *The safety of nanostructured synthetic amorphous silica (SAS) as a food additive (E 551)*. Arch Toxicol. doi:10.1007/s00204-016-1850-4 and JACC No. 51]**

Pages 233-239: Sections 5.1, 5.2, 5.3 and 5.4: **[SASSI/ASASP comment: We would strongly suggest that each of the Sections 5.1, 5.2, 5.3 and 5.4 be further divided to distinguish between crystalline and amorphous silica, and, as needed, a distinction be made between synthetic and naturally occurring amorphous silica.]**

Pages 233-235: Section 5.1: **[SASSI/ASASP comment: The distinction between crystalline and amorphous silica is not clear and the section lacks any detail on naturally occurring amorphous silica versus synthetic forms. Also, the comment on the bottom of page 235 that silica gel is hydrous silica composed of interconnected particles of 2-10 nm is not a sufficient description of the material, and does not take into account or describe the formation of agglomerates and aggregates.]**

Page 236 - Section 5.2: **[SASSI/ASASP comment: Data on amorphous silica imports and exports is available via the EPA's Chemical Data Report (CDR) database.]**

Page 236 - Section 5.3: **[SASSI/ASASP comment: The distinction between crystalline and amorphous silica is not clear and the section lacks any specific distinction between naturally occurring amorphous silica and synthetically manufactured amorphous silica, e.g. the statement on the high purity of synthetic silica (page 235) is followed immediately by a sentence detailing a naturally occurring form of amorphous silica.]**

Page 253- Section 6.5, 6.6 or 6.7: **[SASSI/ASASP comment: The absence of migration of synthetic amorphous silica is already known and documented in these two references: (1) *Investigation into the migration potential of colloidal silica from food packaging plastics into food*, Bott et al. 2015: "At a detection limit of 0,1 mg silica per kg food (simulant) no migration of colloidal silica was detected…From the findings it can be concluded that nano-particulate SAS in general would not migrate into food when it is incorporated into a polymer matrix." ;(2) *Critical review of the migration potential of nanoparticles in food* , Störmer et al. 2017.]**

Page 277- Section 8: **[SASSI/ASASP comment: (1) There are a number of references to EPA regulation (e.g. Hazardous Air Pollutant or Designated as a Hazardous Substance in Accordance with Section 311…) with the listing being "no data"; in most cases these should be changed to "Not Listed". (2) For FDA in Table 8.1, only silicon dioxide EAFUS are listed but there are no citations of various FDA approvals (e.g., 160.105, 172.230, 172.480, 173.340…); (3) For USDA citations, please refer to the Nov 12, 2010 Technical Evaluation Report Complied by the USDA National Organic Program; (4) Although references are made in the document to the use of silica as a pesticide there is no reference to the regulation, EPA Inert ingredient 40 CFR 152.25(f) per 40 CFR 180.950(e).]**

We appreciate your consideration of our comments and concerns. We are open to meeting with you and discussing any opportunity to assist ATSDR in completing a comprehensive and accurate review of Silica/SAS.

Please contact me to determine how we can support the efforts of your organization.

Sincerely yours,

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