Data Supplement

Alkyl Amide MIPA

MCI-MI

Palm Tree-derived Ingredients

Paraben

Pomegranate

Silica and Silicates

CIR EXPERT PANEL MEETING
APRIL 8-9, 2019

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Alice Akinsulie, Scientific Writer/Analyst
Date: March 29, 2019
Subject: Wave 2 – Alkyl Amide MIPA

On March 28, 2019, new data regarding the method of manufacture of the Alkyl Amide MIPA ingredients were received. According to a supplier, MIPA fatty acid alkanolamides are generally manufactured by the reaction of a fatty acid source (i.e., free fatty acids; fatty acid methyl esters or triglycerides) with monoisopropanolamine at elevated temperatures. Residuals include free monoisopropanolamine (≤ 2%), free fatty acid source (≤ 5%) and traces of glycerol if triglycerides are used as feedstock (≤ 5%). The relevant data has been attached herein and is labeled as *AlkylA042019_W2_data1*.

The Council also provided information on composition, physical and chemical properties, and acute toxicity on Cocamide MIPA (*AlkylA042019_W2_data2*). According to the summary data, oral administration of Cocamide MIPA resulted in an LD_{50} value > 2000 mg/kg in rat and dermal LD_{50} > 2000 mg/kg in rabbit. This submission contained limited information on the acute toxicity study. Since there was a lack of detail to the study, does the Panel recommend adding these data to the safety assessment?

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Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: March 28, 2019

SUBJECT: Alkyl Amide MIPA Ingredients

Anonymous. 2019. Method of manufacture MIPA fatty acid alkanolamides.

The REACH registration of the following substances has been completed. The respective REACH name, EC# and weblink to the REACH registration are provided below:

Amides, C8-10 (even-numbered), N-(2-hydroxypropyl) ('C8-10 MIPA FAA'; EC# 915-384-3; https://echa.europa.eu/de/registration-dossier/-/registered-dossier/25083)

Amides, C8-18 (even-numbered) and C18-unsatd., N-(2-hydroxypropyl) ('C8-18 & C18unsatd. MIPA FAA'; 'Cocoamide MIPA'; EC# 931-596-9; https://echa.europa.eu/de/registration-dossier/-/registered-dossier/13560)

Isostearic acid monoisopropanolamide ('IsoC18 MIPA FAA'; EC# 431-540-9; https://echa.europa.eu/de/registration-dossier/-/registered-dossier/2879/1)

March 2019

Method of Manufacture MIPA Fatty Acid Alkanolamides (FAA)

MIPA FAA are generally manufactured by the reaction of a fatty acid source (i.e., free fatty acids; fatty acid methyl esters or triglycerides) with monoisopropanolamine at elevated temperatures. The fatty acid source determines the alkyl chain distribution. Given the natural origin of the fatty acids, the alkyl chains are even numbered. Typical impurities/residues contained in MIPA FAA are free monoisopropanolamine (≤ 2%), free fatty acid source (≤ 5%) and glycerol if triglycerides are used as feedstock (≤ 5%).

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Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: March 22, 2019

SUBJECT: Cocamide MIPA

Anonymous. 2018. Summary information: Cocamide MIPA.

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August 2018

Summary Information: Cocamide MIPA

Composition

Cocamide MIPA	96% minimum
Monoisopropylamine	2% maximum
Methanol	<1%

Physical and Chemical Properties

Physical State	Solid
Form	Pastilles
Color	White

Melting point/freezing point	126 °F (52.22 °C)
Initial boiling point and boiling range	302 °F (150 °C)
Flash point	>201.0 °F (>93.9 °C) Pensky-Martens Closed Cup
Evaporation rate	Estimated slower than ethyl ether

Acute Toxicity

Dermal LD50 Rabbit	>2000 mg/kg
Oral LD50 Rat	>2000 mg/kg

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett, Senior Scientific Writer/Analyst
Date: March 29, 2019
Subject: Re-review of the Safety Assessment on MCI/MI – Wave 2

Enclosed is the Council's concentration of use survey results for MCI/MI *(mcimi042019wave2_data1* and *mcimi042019wave2_data2*) and an updated use table. The new table contains the 2019 survey results and the use table information from the original report, which was not included in the information that was posted on March 15. Currently, Industry reports that MCI/MI (3:1) is used at up to 7.5 ppm in leave-on products and at up to 15 ppm in rinse-off products. In reviewing the data for 2019, the Panel should be aware that concentrations of use were not reported for several products categories that were reported to have current uses in the VCRP database. These categories include those that are considered to be leave-on products, such as eye makeup preparations and several that fall under skin care preparations (specifically face, neck, body, and hand preparations and moisturizers).

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Table 1. Current (2019) and historic (1986) frequency and concentration of use according to duration and type of exposure for Methylisothiazolinone and Methylchloroisothiazolinone[1-3]

	# of Uses 2019	*# of Uses 2019*	*Max Conc of Use 2019 (ppm)*	*# of Uses 1986*	*Max Conc of Use 1986 (%)*
	Methylchloroisothiazolinone*	**Methylisothiazolinone***	**MCI/MI¥**	**MCI/MI**	**MCI/MI‡**
Totals†	**5137**	**6037**	**0.000019-15**	**381**	**≤0.1-1**
Duration of Use					
Leave-On	480	1042	0.075-7.5	137	≤0.1-1
Rinse Off	4521	4849	0.15-15	244	≤0.1-1
Diluted for (Bath) Use	136	146	0.000019	NR	NR
Exposure Type					
Eye Area	32	60	NR	8[d]	≤0.1-1[d]
Incidental Ingestion	NR	1	NR	NR	NR
Incidental Inhalation-Spray	11; 192[a]; 112[b]	14; 470[a]; 286[b]	0.075-7.5; 7.4-7.5[a]	5[a]; 95[b]	≤0.1-1[a,b]
Incidental Inhalation-Powder	1; 112[b]; 2[c]	1; 286[b]; 2[c]	NR	95[b]	≤0.1-1[b]
Dermal Contact	3486	4163	0.000019-15	178[d]	≤0.1-1[d]
Deodorant (underarm)	NR	NR	NR	NR	NR
Hair - Non-Coloring	1567	1780	0.5-15	203[e]	≤0.1-1[e]
Hair-Coloring	68	68	0.15-11	[e]	[e]
Nail	1	4	NR	NR	NR
Mucous Membrane	2981	3099	0.000019-15	8	≤0.1-1
Baby Products	11	16	12	NR	NR

NR = Not reported. S = Survey underway

* MCI and MI are reported separately in the VCRP database. While it is likely that all MCI totals are for MCI/MI, there is no way to verify this information.

† Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

¥ No wipe products were reported.

‡ Concentrations were reported as general ranges in 1986.

[a.] It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.

[b.] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

[c.] It is possible these products may be powders, but it is not specified whether the reported uses are powders.

[d.] Eye and facial makeup preparations were reported together in the original safety assessment. The reported number was only accounted for in the eye area exposure

[e.] Non-coloring and coloring hair preparations, except for non-coloring shampoos, were reported together in the original safety assessment. The reported number was only accounted for in the non-coloring hair products.

References

1. Elder RL. Final Report on the Safety Assessment of Methylisothiazolinone and Methylchloroisothiazolinone. *JACT*. 1992;11(1):75-128.

2. U.S. Food and Drug Administration Center for Food Safety & Applied Nutrition (CFSAN). Voluntary Cosmetic Registration Program - Frequency of Use of Cosmetic Ingredients. College Park, MD: 2019.

3. Personal Care Products Council. 2019. Concentration of Use by FDA Product Category – MCI/MI (ratio approximately 3:1).

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Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: March 25, 2019

SUBJECT: Concentration of Use Information: MCI/MI

Concentration of Use by FDA Product Category – MCI/MI (ratio approximately 3:1)

FDA Product Category	Rinse-Off/Leave-On*	Maximum Concentration of Use (ppm MCI/MI)
Baby shampoo	Rinse-off	12
Bubble baths	Rinse-off	0.000019
Colognes and toilet waters	Leave-on	0.075
Hair conditioners	Rinse-off	0.82-15
Hair sprays Aerosol Pump spray	 Leave-on Leave-on	 7.5 7.5
Permanent wave	Rinse-off	7.5
Rinses (non-coloring)	Rinse-off	11
Shampoos (non-coloring)	Rinse-off	0.5-15
Tonics, dressings and other hair grooming aids	Rinse-off Leave-on	7.5 7.4
Other hair preparations	Rinse-off	7.5-12
Hair tints	Rinse-off	0.4
Hair rinses (coloring)	Rinse-off	11
Hair shampoos (coloring)	Rinse-off	0.15-6
Other makeup preparations	Leave-on	0.021
Bath soaps and detergents	Rinse-off	3.4-15
Other personal cleanliness products	Rinse-off Leave-on	12.9 7.5
Shaving cream	Rinse-off	0.19-4.5
Other shaving preparations	Rinse-off	14.9
Skin cleansing (cold creams, cleansing lotions, liquids and pads)	Rinse-off	4-15

*For each product category, the survey asked if the product was a rinse-off or leave-on product, or if it was a wipe product. No wipe products were reported.

Information collected 2018-2019
Table prepared March 25, 2019

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: March 29, 2019
Subject: Wave 2 Data on Palm Tree-derived Ingredients

A summary of a human repeated insult patch test (HRIPT) on a face and neck product containing 3% Euterpe Oleracea Pulp Powder that was received from the Council is summarized below and attached (*palmtr042019data4.pdf*) for the Panel's review.

An HRIPT involving a face and neck product containing 3% Euterpe Oleracea Pulp Powder was performed using 214 subjects.[1] Testing occurred over a 6-week period. During induction, a 2 cm x 2 cm occlusive patch containing the product (0.2 ml or 0.2 g) was applied for 24 h to the infrascapular area of the back (to the right or left of midline) or to the upper arm. This procedure was repeated for a total of 9 induction applications, and sites were evaluated at 48-h intervals. For 24-h patch applications on Fridays, sites were evaluated on the following Monday (i.e., 72 h after patch application). The evaluation of sites after the 9th patch application was followed by a 10- to 15-day non-treatment period, after which (at week 6) the challenge phase was initiated. A challenge patch was applied for 24 h to a new test site, and reactions were scored at 24 h, 48 h, and 72 h after patch application. Definite erythema and damage to the epidermis, but no edema, were observed (at 5th induction evaluation) in 1 subject. Thereafter, the product was applied to a new site and reactions were not observed for the remainder of the induction period or during the challenge phase. The authors concluded that there was no evidence of sensitization to the product tested in this study.

1. TKL Research. 2010. Repeated insult patch test of a face and neck product containing 3% Euterpe Oleracea Pulp Powder. Unpublished data submitted by the Personal Care Products Council on March 4, 2019.

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Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: March 4, 2019

SUBJECT: Euterpe Oleracea Pulp Powder

TKL Research. 2010. Repeated insult patch test of a face and neck product containing 3% Euterpe Oleracea Pulp Powder.

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[redacted]

REPEATED INSULT PATCH TEST

Face + neck product containing 3%
Euterpe Oleracea Pulp Powder

[redacted]

[redacted]

CONDUCTED FOR:

[redacted]

DATE OF ISSUE:

April 29, 2010

[redacted] [redacted]

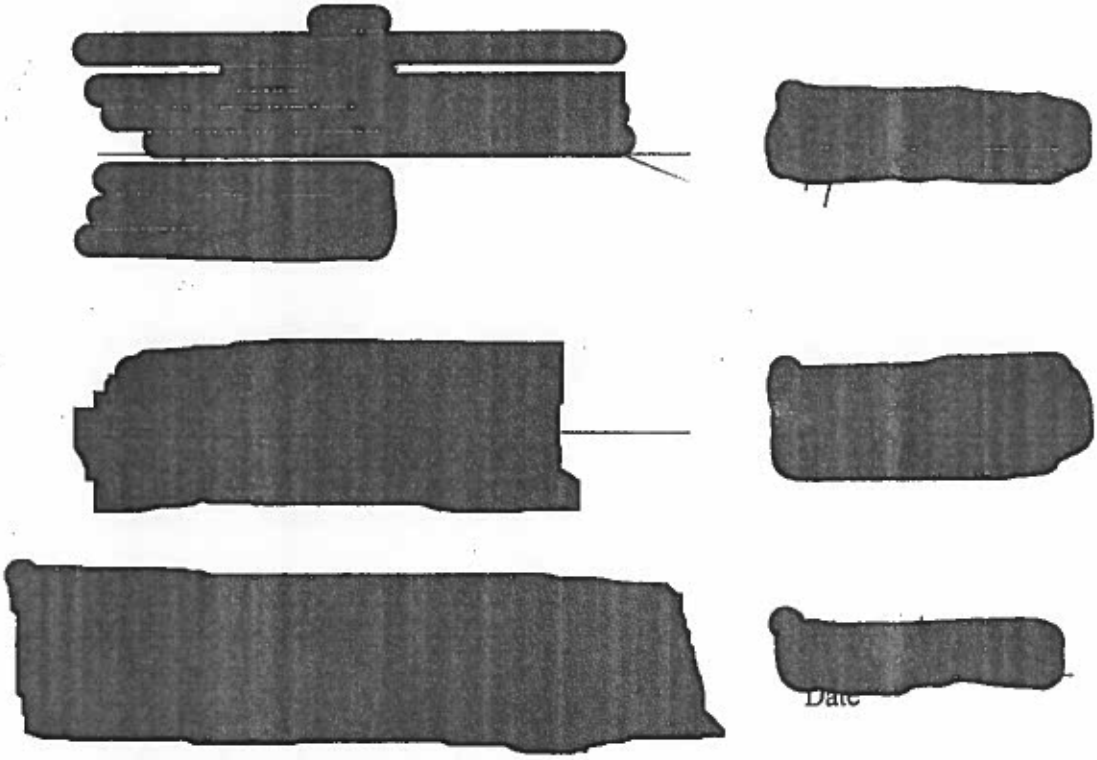
TABLE OF CONTENTS

APPENDICES

[redacted]

SIGNATURES

This study was conducted in compliance with the requirements of the protocol and [redacted] Operating Procedures, and in the spirit of GCP ICH Topic E6.[1] The report accurately reflects the raw data for this study.



STATEMENT OF QUALITY CONTROL

The Quality Control Unit of the Dermatological Safety Department conducted a 100% review of all study-related documents. The protocol was reviewed prior to the start of the study, and the medical screening forms and informed consent documents were reviewed in-process of the study. The regulatory binder and study data were reviewed post-study to ensure accuracy. The study report was reviewed and accurately reflects the data for this study.

[1] ICH Topic E6 "Note for guidance on Good Clinical Practices (CPMP/ICH/135/95)" – ICH Harmonised Tripartite Guideline for Good Clinical Practices having reached Step 5 of the ICH Process at the ICH Steering Committee meeting on 1 May 1996.

[redacted]

SUMMARY

One (1) study material, Formula No. [redacted] was evaluated neat to determine its ability to sensitize the skin of volunteer subjects with normal skin using an occlusive repeated insult patch study. Two hundred fourteen (214) subjects completed the study.

One subject on [redacted] showed definite erythema, no edema and damage to epidermis (+D) at the 5th Induction reading to the product. The subject was patched with the product at a new site following the reaction. The subject showed no reaction (-) at the new site for the rest of the Induction phase and also showed no reaction (-) at Challenge.

Under the conditions employed in this study, there was no evidence of sensitization to Formula [redacted]

[redacted]

1.0 OBJECTIVE

The objective of this study was to determine the ability of the study material to cause sensitization by repeated topical applications to the skin of humans under controlled patch study conditions.

2.0 RATIONALE

Substances that come into contact with human skin need to be evaluated for their propensity to irritate and/or sensitize. Once an appropriate pre-clinical safety evaluation has been performed, a reproducible, standardized, quantitative patch evaluation procedure must be used to demonstrate that a particular material can be applied safely to human skin without significant risk of adverse reactions. The method herein employed is generally accepted for such a purpose.

Repeated insult patch evaluation is a modified predictive patch study that can detect weak sensitizers that require multiple applications to induce a cell-mediated (Type IV) immune response sufficient to cause an allergic reaction. Irritant reactions may also be detected using this evaluation method, although this is not the primary purpose of this procedure. Results are interpreted according to interpretive criteria based upon published works, as well as the clinical experience of TKL Research, Inc. These interpretive criteria are periodically reviewed and amended as new information becomes available.

3.0 STUDY DESIGN

3.1 STUDY POPULATION

A sufficient number of subjects were enrolled to provide 200 completed subjects. In the absence of any sensitization reactions in this sample size (200 evaluable subjects), a 95% upper confidence bound on the population rate of sensitization would be 1.5%.

3.1.1 Inclusion Criteria

Individuals eligible for inclusion in the study were those who:

1. were males or females, 18 to 70 years of age, in general good health;
2. were free of any systemic or dermatologic disorder which, in the opinion of the investigative personnel, would have interfered with the study results or increased the risk of adverse events;
3. were of any skin type or race, providing the skin pigmentation would allow discernment of erythema;
4. had completed a medical screening procedure; and
5. had read, understood, and signed an informed consent agreement.

3.1.2 Exclusion Criteria

Individuals excluded from participation in the study were those who:

1. had any visible skin disease at the study site which, in the opinion of the investigative personnel, would have interfered with the evaluation;

2. were receiving systemic or topical drugs or medication which, in the opinion of the investigative personnel, would have interfered with the study results;
3. had psoriasis and/or active atopic dermatitis/eczema;
4. were females who were pregnant, planning to become pregnant during the study, or breast-feeding;
5. had a known sensitivity to cosmetics, skin care products, or topical drugs as related to the material being evaluated; and/or
6. were participating in another study or had been recruited to participate in another study concurrently.

3.1.3 Informed Consent

A properly executed informed consent document was obtained from each subject prior to entering the study. The signed informed consent document is maintained in the study file. In addition, the subject was provided with a copy of the informed consent document (see Appendix III).

3.2 DESCRIPTION OF STUDY

3.2.1 Outline of Study Procedures

Subjects participated in the study over a 6-week period involving 3 phases: (1) Induction, (2) Rest, and (3) Challenge. Prior to study entry, the subjects were screened to assure that they met the inclusion/exclusion criteria. Informed consent was obtained. Each subject was provided with a schedule of the study activities. All subjects were told to avoid wetting the patches and were asked not to engage in activities that caused excessive perspiration. They were instructed to notify the staff if they experienced any discomfort beyond mild itching or observed any adverse changes at the patch sites, while on the study or within 2 weeks of completing the study.

The Induction Phase consisted of 9 applications of the study material and subsequent evaluations of the patch sites. Prior to application of the patches, the sites were outlined with a skin marker, eg, gentian violet. The subjects were required to remove the patches approximately 24 hours after application. They returned to the facility at 48-hour intervals to have the sites evaluated and identical patches applied to the same sites. Patches applied on Friday were removed by subjects after 24 hours. The sites were evaluated on the following Monday, ie, 72 hours after patch application.[2] Following the ninth evaluation, the subjects were dismissed for a rest period of approximately 10-15 days.

Subjects who were absent once during the induction phase received a make-up (MU) patch at the last induction visit. The MU applications were graded 48 hours later at the MU visit, or were recorded as N9G (no ninth grading).

The Challenge Phase was initiated during the sixth week of the study. Identical patches were applied to sites previously unexposed to the study material. The patches were removed by subjects after

[2] A Monday or Friday holiday could result in evaluation at 96 hours after patch application.

24 hours and the sites graded after additional 24-hour and 48-hour periods (ie, 48 and 72 hours after application). Rechallenge was performed whenever there was evidence of possible sensitization.

To be considered a completed case, a subject must have had 9 applications and no fewer than 8 subsequent readings during induction, and a single application and 2 readings during challenge. Only completed cases were used to assess sensitization.

3.2.2 Study Flow Chart

WEEK 1

DAY	ACTIVITIES
1*	Staff obtained informed consent, reviewed completed medical screening form, applied patches
2	Subject removed patches
3	Staff graded sites, applied patches
4	Subject removed patches
5	Staff graded sites, applied patches
6	Subject removed patches

WEEK 2

DAY	ACTIVITIES
1	Staff graded sites, applied patches
2-6	Same as Week 1

WEEK 3

DAY	ACTIVITIES
1-6	Same as Week 2

WEEK 4

DAY	ACTIVITIES
1	Staff graded sites; applied make-up (MU) induction patches, if required
2	Subject removed MU patches
3	Staff graded MU induction sites at MU visit
2-7	Rest period

WEEK 5

DAY	ACTIVITIES
1-7	Rest period

* Study flow starting with Week 1, Day 1, was altered when enrollment occurred on Wednesday or Friday. Study flow could be altered if a holiday occurred during the study.

WEEK 6

DAY	ACTIVITIES
1	Staff applied patches
2	Subject removed patches
3	Staff graded sites
4	Staff graded sites

3.2.3 Definitions Used for Grading Responses

The symbols found in the scoring scales below were used to express the response observed at the time of examination:

SYMBOL		REACTION
-	=	No reaction
?	=	Minimal or doubtful response, slightly different from surrounding normal skin
+	=	Definite erythema, no edema
++	=	Definite erythema, definite edema
+++	=	Definite erythema, definite edema and vesiculation

SPECIAL NOTATIONS

E	=	Marked/severe erythema
S	=	Spreading of reaction beyond patch site (ie, reaction where material did not contact skin)
p	=	Papular response > 50%
pv	=	Papulovesicular response > 50%
D	=	Damage to epidermis: oozing, crusting and/or superficial erosions
I	=	Itching
X	=	Subject absent
PD	=	Patch dislodged
NA	=	Not applied
NP	=	Not patched (due to reaction achieved)
N9G	=	No ninth grading

3.2.4 Evaluation of Responses

All responses were graded by a trained dermatologic evaluator meeting TKL's strict certification requirements to standardize the assignment of response grades.

[redacted]

4.0 NATURE OF STUDY MATERIAL

4.1 STUDY MATERIAL SPECIFICATIONS

[redacted]

4.2 STORAGE, HANDLING, AND DOCUMENTATION OF STUDY MATERIAL

Receipt of the material used in this study was documented in a general logbook, which serves as a permanent record of the receipt, storage, and disposition of all study material received by TKL. On the basis of information provided by the sponsor, the study material was considered reasonably safe for evaluation on human subjects. A sample of the study material was reserved and will be stored for a period of 6 months. All study material was kept in a locked product storage room accessible to clinical staff members only. At the conclusion of the clinical study, the remaining study material was discarded or returned to the sponsor and the disposition documented in the logbook.

4.3 APPLICATION OF STUDY MATERIAL

All study material was supplied by the sponsor. Material was applied in an amount proportionate to the patch type or as requested by the sponsor, generally 0.2 mL or g or an amount sufficient to cover the 2 cm x 2 cm patch. The patches were applied to the infrascapular area of the back, either to the right or left of the midline, or to the upper arm.

4.4 DESCRIPTION OF PATCH CONDITIONS

Material evaluated under occlusive patch conditions is applied to a 2 cm x 2 cm Webril pad attached to a non-porous, plastic film adhesive bandage (3M medical tape). The patches are secured with hypoallergenic tape (Micropore), as needed.

Material evaluated under semi-occlusive patch conditions is applied to a 2 cm x 2 cm Webril pad. The pads are affixed to the skin with hypoallergenic tape (Micropore).

5.0 INTERPRETATION

Sensitization is characterized by an acute allergic contact dermatitis. Typical sensitization reactions begin with an immunologic response in the dermis resulting in erythema, edema formation, and secondary epidermal damage (vesiculation), sometimes extending beyond the patch site and often accompanied by itching. Sensitization reactions tend to be delayed. The reaction typically becomes evident between 24 and 48 hours, peaks at 48-72 hours and subsequently subsides. The reaction is often greater at 72 hours than at 48 hours. The severity of the reaction is generally greater during the challenge phase of a Repeated Insult Patch Test (RIPT) than that seen during induction.

Irritant reactions are characterized as a non-immunologic, localized, superficial, exudative, inflammatory response of the skin due to an externally applied material. The typical initial reaction does not develop much edema or vesiculation but results in scaling, drying, cracking, oozing, crusting, and erosions. The reaction is usually sharply delineated, not spreading beyond the patch

[redacted]

site. Irritant reactions are typically evident by 24 hours and diminish over the next 48-72 hours. Removal of the offending agent results in gradual improvement of the epidermal damage. The reaction seen at 72 hours is, therefore, less severe than that seen at 48 hours. Finally, the severity of the reaction experienced in the challenge phase is generally similar to that seen during induction.

If the results of the study indicate the likelihood of sensitization, the recommended practice is to rechallenge the subjects who have demonstrated sensitization-like reactions to confirm that these reactions are, indeed, associated with the product. Our preferred rechallenge procedure involves the application of the product to naïve sites, under both occlusive and semi-occlusive patch conditions. Use of the semi-occlusive patch condition helps to differentiate irritant and sensitization reactions. Generally speaking, if a product is a sensitizer it will produce a similar reaction under both occlusion and semi-occlusion. Whereas, if the product has caused an irritant reaction, the reactions will be less pronounced under the semi-occlusive condition.

6.0 DOCUMENTATION AND RETENTION OF DATA

The case report forms (CRFs) were designed to identify each subject by subject number and initials, and to record demographics, examination results, adverse events, and end of study status. Originals or copies of all CRFs, correspondence, study reports, and all source data will be kept on hard-copy file for a minimum of 5 years from completion of the study. [redacted] provided a secure environment with burglar/fire alarm systems, camera detection and controlled temperature and humidity. [redacted]

7.0 RESULTS AND DISCUSSION

Two hundred thirty-four (234) subjects between the ages of 18 and 70 were enrolled and 214 subjects completed the study (see Tables 1 and 2 in Appendix I and Data Listings 1 and 2 in Appendix II).

The following table summarizes subject enrollment and disposition.

Number enrolled:		234
Number discontinued:		20
Lost to follow-up:	5	
Voluntary withdrawal:	14	
Protocol violation: (Psoriasis)	1	
Number completed:		214

Source: Table 1, Appendix I

There were no adverse events reported on either study.

[redacted]

One subject (No. 082) on [redacted] showed definite erythema, no edema and damage to epidermis (+D) at the 5th Induction reading. The subject was patched with the product at a new site following the reaction. The subject showed no reaction (-) at the new site for the rest of the Induction phase and also showed no reaction (-) at Challenge.

A summary of response data is provided in Table 3, Appendix I. Individual dermatological response grades are provided in Data Listing 3 and residual readings in Data Listing 3A, Appendix II.

8.0 CONCLUSION

Under the conditions employed in this study, there was no evidence of sensitization to Formula No. [redacted]

9.0 REFERENCES

Schwartz L, Peck SM. The patch test in contact dermatitis. Publ Health Pep 1944; 59:2.

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Stotts J. Planning, conduct and interpretation of human predictive sensitization patch tests. In:Drill VA, Lazar P, eds. Current Concepts in Cutaneous Toxicity. New York: Academic Press, 1980: 41-53.

Griffith JF. Predictive and diagnostic testing for contact sensitization. Toxicol Appl Pharmacol, Suppl 1969; 3:90.

Gerberick GF, Robinson MK, Stotts J. An approach to allergic contact sensitization risk assessment of new chemicals and product ingredients. American Journal of Contact Dermatitis 1993; 4(4): 205-211.

[redacted]

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MEMORANDUM

To: CIR Expert Panel and Liaisons

From: Jinqiu Zhu, PhD, DABT, ERT - Toxicologist
Priya Cherian - Scientific Writer/Analyst

Date: March 29, 2019

Subject: Wave 2 Data on Parabens

Enclosed is the new data summary in response to the comments from the Women's Voices for the Earth (WVE), received on March 12 and 25, 2019.

Of the 14 recent papers submitted by WVE, three studies have already been included in the Draft Final Amended Report *parabe042019FAR*, including Harley *et al* 2018 (paper #2 in WVE's comments, similarly hereinafter), Samarasinghe *et al* 2018 (#5) and Kolatorova *et al* 2018 (#6). Eight studies, i.e., Ashrap *et al* 2018 (#3), Philippat *et al* 2019 (#8), Li *et al* 2019 (#9), Liu *et al* 2019 (#10), Quirós-Alcalá *et al* 2019 (#11), Pollack *et al* 2018 (#12), Martinez *et al* 2019 (#13) and Jiang *et al* 2019 (#14), were published (or the full text was available) after the data cut-off date of the April Panel meeting. The three remaining studies, including Bellavia *et al* 2018 (#1), Wu *et al* 2018 (#4) and Yang *et al* 2018 (#7), were previously identified in the published literature and ordered, but not received prior to the mail date for Panel meeting materials.

Also, two recent systemic review papers were published in *Dermatitis* since the last meeting on parabens, titled "Paraben Toxicology" and "Parabens: Contact (Non) Allergen of the Year." Therein, the authors noted:

- "Based on currently available scientific information, claims that parabens are involved in the genesis or propagation of these controversial and important health problems are premature." [1]
- "Parabens remain one of the least allergenic preservatives available. The unsubstantiated public perception of paraben safety has led to its replacement in many products with preservatives having far greater allergenic potential."[2]

The papers summarized below include one in vitro study, two biomonitoring studies (Table 1), and seven epidemiological studies (Table 2), all of which will be added to the safety assessment after the Panel meeting. The Panel should carefully review the new data summary, with particular focus on the potential impacts of parabens on human health. The Panel should determine whether current risk calculations provide adequate safety margins in consideration of the updated biomonitoring and epidemiology data.

Effects on Human Trophoblast Cells

Butylparaben

Human trophoblast cells, HTR8/SVneo, were exposed to Butylparaben at 50, 100, 200, and 400 µM.[3] Butylparaben inhibited cell proliferation and induced both apoptosis and endoplasmic reticulum stress at all doses. Butylparaben promoted the production of intracellular reactive oxygen species, increased Ca^{2+} concentration, and induced mitochondrial membrane depolarization. Butylparaben also inhibited the activation of PI3K/AKT pathways including AKT, ribosomal protein S6, P70 S6 kinase, and glycogen synthase kinase 3b. In addition, ERK1/2 activity was involved in Butylparaben-mediated signal transduction in HTR8/SVneo cells. The author claimed that exposing human trophoblast cells to Butylparaben diminished normal physiological activity, leading to apoptosis and problems with early placental development.

Table 1. Biomonitoring

Test Substance(s)	Species/ Strain	Sample Type/Test Population-Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
Methylparaben Ethylparaben Propylparaben Butylparaben Benzylparaben 4-Hydroxybenzoic Acid heptylparaben	Human	143 healthy, premenopausal women (aged 18 - 44)	Aggregate exposures (undefined sources)	- Participants were free of known chronic health conditions, and not using hormonal contraception who were recruited at the University at Buffalo research center from 2005 to 2007; - Participants attended up to 8 clinic visits for up to two menstrual cycles of study; urine samples were selected at key menstrual cycle phases; - Reproductive hormones levels timed to key periods of variability across the menstrual cycle were measured, including E2, progesterone, LH and FSH; - Urine samples were spiked with ^{13}C-labelled and analyzed by HPLC-MS/MS; the LOD was 1 mg/dL; - Using the hierarchical principal component analysis approach, paraben factor consists of Methylparaben, Ethylparaben, Propylparaben and Butylparaben	- All individuals had levels of Methylparaben and 4-Hydroxybenzoic Acid above the LOD; - Benzylparaben and heptylparaben were below the LOD for > 45% and were excluded in the analyses; - In a single-chemical model, 4-Hydroxybenzoic Acid was associated with increased FSH 0.07 (95% CI: 0.01, 0.13); parabens were not associated with LH; - The paraben factor was significantly associated with increased E2 0.21 (95% CI: 0.15, 0.28) as well as increased progesterone 0.32 (95% CI: 0.23, 0.41)	[4]
Methylparaben Ethylparaben Propylparaben Butylparaben	Human	1003 pregnant women (aged 18 - 40)	Aggregate exposures	- Participants, enrolled in the PROTECT project, were recruited at seven prenatal clinics and hospitals throughout Northern Puerto Rico during 2010–2016 (14 ± 2 weeks of gestation); - The questionnaire was administered at each urine sample collection to gather data on self-reported product use: bar soap, cologne/perfume, colored cosmetics, conditioner, deodorant, fingernail polish, hair cream, hairspray/hair gel, laundry products, liquid soap, lotion, mouthwash, other hair products, shampoo, and shaving cream; - The questionnaire contained yes/no questions about the use of different products in the 48-h preceding urine sample collection, in addition to questions on the usual frequency (not at all,<once/month, 1–3 times/month, once/week, few times/week, every day); - The participants were also asked to report the specific brand of the product; - Urine samples were analyzed by solid-phase extraction HPLC-MS/MS; - The LODs were 1.0 µg/L for Methylparaben, and 0.1 µg/L for Propylparaben and Butylparaben; all paraben concentrations were adjusted for SG	-Detectable paraben concentrations among pregnant women were prevalent and tended to be higher than levels measured in women of reproductive age from the general US population; - Trends were observed for increasing concentration of four parabens with increasing age categories; - Decreasing temporal trends were observed for all parabens in the study population from 2011 to 2016; - Exposure to parabens varied by location, sex, age, race, and ethnicity; - GM concentration at first visit for Butylparaben was statistically higher than later visits in the study; - Higher paraben concentrations were found among women who reported using cosmetics and lotion	[5]

EARTH=Environment and Reproductive Health; E2= 17β-estradiol; FSH=Follicle stimulating hormone; GM= Geometric mean; LH= Luteinizing hormone; LOD= Limit of detection; PROTECT= Puerto Rico Testsite for Exploring Contamination Threats

Table 2. Epidemiological studies of parabens

Ingredient(s)	Population/ Geographical Area	Study/ Diagnosis Years	Methods and Limitations	Findings	OR, β, or MPC (95% C.I.)*	Reference
			Prospective Studies			
Methylparaben Propylparaben Butylparaben	241 pregnant women (between 18 and 45 years) from the Massachusetts General Hospital Fertility Center in Boston	Subjects recruited from 2005 to 2015	- Used data on women who had completed at least one in vitro fertilization cycle, and provided at least one urinary sample during 1st or/and 2nd trimester; - Blood glucose levels were assessed as a continuous outcome during the 2nd trimester of pregnancy (median: 27 weeks gestation) through a 1-h non-fasting, 50-g GLT used as the first step in screening for GDM; - Women with glucose levels >140 mg/dL as having abnormal GLT; - Urine samples were collected during the 1st and 2nd trimesters of pregnancy (median: 7 and 21 gestation weeks, respectively); - When two urine samples were available (about 80% of measurements), the geometric mean of the SG-adjusted concentrations was used as a measure of trimester-specific urinary paraben; - All models were adjusted for the following confounders: maternal age, pre-pregnancy BMI, total physical activity, race, smoking status, education level, infertility diagnosis, number of fetuses, previous IVF, previous intrauterine insemination; - The LODs were 1.0 μg/L for Methylparaben, and 0.2 μg/L for Propylparaben and Butylparaben; all paraben concentrations were adjusted for SG; - Methylparaben, Butylparaben, and Propylparaben were evaluated separately or simultaneously as a chemical mixture; linear regression models or BKMR method were applied Limitations - Only evaluated continuous glucose levels; - The analysis did not include other chemicals that may be associated with glucose levels, e.g., phthalates	- 1st trimester Butylparaben and Propylparaben urinary concentrations were associated with glucose levels in a pregnancy cohort of women at high risk of GDM Association between Pregnancy Glucose Levels and the 1st trimester Parabens Mixture (4th vs. 1st quartiles) Methylparaben Propylparaben Butylparaben Association between Pregnancy Glucose Levels and the 2nd trimester Parabens Mixture (4th vs. 1st quartiles) Methylparaben Propylparaben Butylparaben	β Coefficient (Adjusted) 13.1 (-7.9, 34.0) ***-22.3 (-43.2, -1.4)*** **12.5 (0.9, 24.2)** β Coefficient (Adjusted) -4.8 (-19.8,10.3) 1.2 (-13.6,16.0) **11.2 (0.2, 22.3)**	6
Methylparaben Ethylparaben Propylparaben Butylparaben Benzylparaben	850 pregnant women (between 20 to 44 years) at Wuhan Women and Children Medical and Healthcare Center in Hubei Province, China.	2014-2015	- Maternal urine samples collected at the first, second, and third trimesters during pregnancy; - Paraben concentrations were analyzed by UPLC–MS/MS; the LODs were 0.01 ng/mL for Ethylparaben and Benzylparaben and 0.05 ng/mL for Methylparaben, Propylparaben and Butylparaben; - Urinary paraben concentration was adjusted for the SG; - Birth and early childhood weights and heights were normalized to z-scores by applying WHO child growth standards specified by sex and age Limitations: - Pregnancy exposure is limited by low to moderate interclass correlation coefficients, indicating the temporal variability of paraben concentrations throughout pregnancy; - The information regarding collection conditions of urine samples, e.g., the hour of sampling and time since last void, were not considered in the analyses; - Without collecting data on lactational or other sources of	- Results suggested negative associations between prenatal paraben exposure and fetal and childhood growth; - The third trimester may be the window of susceptibility Association of Urinary Paraben Concentrations with Weight Z-score at Birth (All, n=850) Methylparaben Ethylparaben Propylparaben Butylparaben Benzylparaben Association of Urinary Paraben Concentrations with Weight Z-score at Birth (Male, n=446)	β Coefficient -1.83% (-4.75%, 1.09%) ***-2.82% (-5.11%,- 0.53%)*** -1.51% (-3.84%, 0.82%) 0.14% (-13.11%, 13.40%) -0.65% (-19.24%, 7.13%) β Coefficient	7

			paraben exposure during early childhood, which may also influence growth during childhood		Methylparaben Ethylparaben Propylparaben Butylparaben Benzylparaben	-0.47%(-4.58%, 3.65%) ***-3.61% (-6.74%,- 0.48%)*** -0.70% (-3.90%, 2.51%) -0.81% (-19.12%, 17.49%) -5.29% (-24.02%, 13.43%)
Methylparaben Ethylparaben Propylparaben Butylparaben	473 mother–son pairs from the EDEN cohort study, the obstetrical departments of the university hospitals of Nancy and Poitiers, France	2003-2006	- Placental and birth weight were obtained at birth from hospital maternity records; - Concentrations of parabens were measured in a single spot urine sample collected during pregnancy; - All paraben concentrations were adjusted by creatinine Limitations: -The high frequency of missing placental weight led to an underrepresentation of mother–son pairs; - A delay in the weighing of the placenta after delivery may lead to a lower weight estimate; - Missed other placental characteristics, such as placental diameter, thickness, shape, and vascularization, etc.	- A positive association between the sum of parabens and placental weight		[8]
Methylparaben Ethylparaben Propylparaben Butylparaben Benzylparaben	1087 pregnant women at Wuhan Women and Children Medical Care Center in Wuhan, China.	2014-2015	- The random spot urine samples were collected between 8 and 16 weeks of gestation (on average 13 weeks); - Only included the first delivery records for women who had two separate deliveries; - Standard face-to-face interviews were conducted to collect retrospective information about sociodemographic characteristics (maternal age and education) and lifestyle habits during pregnancy (smoking, passive smoking, and alcohol consumption); - Paraben concentrations were analyzed by HPLC–MS/MS; The LODs were 0.01 ng/mL for Ethylparaben and Benzylparaben, and 0.05 ng/mL for Methylparaben, Propylparaben and Butylparaben; - Urinary paraben concentration was adjusted for the SG; the total concentrations of parabens Σparabens = [1×Methylparaben+16.7×Ethylparaben+83.3×Propylparaben+250×Butylparaben]; Benzylparaben was excluded for the calculations due to the low detection rate; - GDM was assessed by 75-g OGTT; women were diagnosed with GDM according to the IADPSG recommendations Limitations: - The interviews were conducted at delivery, which was after the diagnosis of GDM and might resulted in recall bias; - The information on the family history of diabetes was self-reported, and thus pregnant women with a family history of diabetes and type 2 diabetes may not be totally excluded; - Information on food consumption was not collected, which may be related to GDM risk or paraben levels; - The paraben concentrations measured at one spot time may not accurately reflect paraben exposure	- A total of 103 (9.5%) women were diagnosed with GDM; - The detection rate of urinary Methylparaben, Ethylparaben and Propylparaben is >90%, while Butylparaben and Benzylparaben were detected in less than 50% urine samples; - There was no evidence of associations between urinary Methylparaben or Propylparaben and GDM; - After adjustment for potential confounders, including maternal age, education, maternal pre-pregnancy BMI, parity, and cadmium levels, urinary Ethylparaben was associated with GDM Ethylparaben < 0.24 μg/L 0.24-0.54 μg/L 0.54-1.93μg/L ≥ 1.93 μg/L p_{trend} **=0.051**	**RR(adjusted)** 1.00 1.12 (0.63, 2.01) 1.11 (0.64, 1.93) 1.70 (1.02, 2.82)	[9]
Methylparaben Ethylparaben Propylparaben Butylparaben Benzylparaben	478 mother-child pairs at Wuhan Women and Children Medical Care Center in Wuhan, China.	2014-2015	- Three spot urine samples collected in the first (13.0 ± 1.2 weeks), second (23.6 ± 3.4 weeks) and third (36.1 ± 3.3 weeks) trimester during pregnancy; - Paraben concentrations were analyzed by UPLC–MS/MS; - Urinary paraben concentration was adjusted for the SG; - At the age of around 24 months, the participating children were given the BSID assessments, which provided two main scales: the	- Butylparaben and Benzylparaben were detected less frequently (< 50%) of urine samples and were not included in the statistical analysis; - In the adjusted models, each 2-fold increase in average prenatal paraben concentration was significantly associated with lower MDI scores		[10]

			MDI to assess cognition, language and social development, and the PDI to assess gross (crawling, sitting, walking) and fine (isolation of fingers, grasping) motor skills; - The paraben sum (Σparabens) was calculated by the sum of molar concentrations of five parabens; - To examine windows of vulnerability to exposure during pregnancy, generalized estimating equations were used to examine the relationships of parabens concentrations over trimesters with BSID results to jointly evaluate the exposure-outcome relationships at each trimester; - All models were adjusted for the following confounders: maternal education (≤ high school, college, or ≥ bachelor's degree), child sex, passive smoking during pregnancy as well as maternal age and pre-pregnancy BMI	among girls [**−1.08 (95% CI: −2.10, −0.06)** and **−1.51 (95% CI: −2.69, −0.32**) for Methylparaben and Σparabens, respectively]; - The association was not statistically significant among boys; - In trimester-specific analyses, increasing parabens was associated with lower girls' MDI only in the second trimester; - The results suggested that prenatal exposure to parabens may be associated with impairment in child cognitive abilities at 2 years	
Cross-sectional Studies					
Methylparaben Ethylparaben Propylparaben Butylparaben	696 pregnant women at the Women and Children's Medical Care Center of Wuhan City in Hubei province, China	2012-2014	- GDM was diagnosed on the basis of the fasting plasma glucose level after overnight fasting and 1 h and 2 h plasma glucose levels after having 75-g OGTTs; the cut-off values were 5.1, 10.0 and 8.5 mmol/L, respectively; - Face-to-face interviews were conducted within 3 days before or after delivery to collect information on lifestyle habits and sociodemographic characteristics; - Prepregnancy BMI was calculated as self-reported weight before pregnancy divided by the square of height; Participants were classified into underweight, normal weight and overweight/obese by prepregnancy BMI based on the criteria for Asian populations by the WHO; the cut-off values for underweight and overweight/obese were 18.5 and 23.0 kg/m^2, respectively; - Urinary paraben concentrations were analyzed with UPLC-MS/MS Limitations: - Only one measurement of parabens before delivery, while GDM was diagnosed in the middle of pregnancy; - The urine samples were collected within three days of delivery and the exact time of sample collection was not recorded; - One spot urine sample was sufficient to capture the exposure profiles during a period of time; - Die and exercise information of the pregnant women was limited, both of which were important factors associated with GDM; - Weighting coefficients in the calculation equation of summed estrogenic activity were derived from in vitro experiments, which cause biases when applied into human studies; - Limited number of overweight/obese pregnant women in the study population	- No statistically significant association between parabens and GDM was found in the overall population; - Among the overweight/obese pregnant women, significant non-linear associations of Propylparaben and the summed estrogenic activity of parabens with GDM were found, with adjusted ORs of 3.47 (95% CI: 1.28, 9.42) and 2.87 (95% CI: 1.07, 7.73) for GDM in the second tertile of urinary Propylparaben (0.17–0.93 ng/mL) and the summed estrogen activity, respectively	[11]
Methylparaben Ethylparaben Propylparaben Butylparaben	450 children with asthma and 4023 children with asthma prevalence (between 6 and 19 years) from US NHANE Survey (2005-2014).	2005-2014	- Paraben exposure measurements were conducted on a random one-third subsample of participants 6 years of age and older; - Urinary paraben concentration was adjusted for the creatinine; LODs were 1.0 μg/L for Methylparaben and Ethylparaben and 0.2 μg/L for Propylparaben and Butylparaben; - Participants or their caregivers completed a questionnaire relevant to medical conditions of asthma; for current asthma, the comparison group was children who never received an asthma diagnosis or who reported formerly having asthma; - Logistic regression models were analyzed to examine associations	- An increased prevalence odds of reporting emergency department visits was observed for every 10-fold increase in Methylparaben and Propylparaben concentrations among boys with asthma 2.61 (95% CI, 1.40-4.85) and 2.18 (95% CI, 1.22-3.89), respectively; - Associations remained after adjusting for other phenolic compounds previously linked to respiratory outcomes (e.g., triclosan, bisphenol A, and 2,5-dichlorophenol);	[12]

	between urinary paraben biomarker concentrations and each outcome of interest Limitations: - Cause-effect relationship between paraben exposures and outcomes of interest cannot be elucidated through cross-sectional design; - Paraben concentrations only reflected recent rather than long-term exposures; - Analyses were limited by the variables available in this national survey	- No other dimorphic effects of exposure by sex were observed

*** Bolded text** was used to highlight statistically significant increases; ***Italicized text*** was used to highlight statistically significant decreases

BKMR=Bayesian kernel machine regression; BMI= Body mass index; BSID= the Bayley Scales of Infant Development; EARTH=Environment and Reproductive Health; EDEN = Etude des Déterminants pré et postnatals du développement et de la santé de l'Enfant; PFR: Placental–to–birth weight ratio; GDM= Gestational diabetes mellitus; GLT= Glucose loading test; IADPSG= International Association of Diabetes and Pregnancy Study Groups; IVF= In vitro fertilization; LOD= Limit of detection; MDI= Mental developmental index; MGH= Massachusetts General Hospital; NHANE: National Health and Nutrition Examination; PDI= Psychomotor development index; SG= Specific gravity; OGTTs= Oral glucose tolerance tests; WHO= World Health Organization

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett, Senior Scientific Writer/Analyst
Date: March 29, 2019
Subject: Draft Safety Assessment on *Punica granatum*-Derived Ingredients – Wave 2

Enclosed is an update from Council on the ingredient Punica Granatum Extract, along with updated concentration of use data (*pomegr042019wave2_data1* and *pomegr042019wave2_data2*); an updated use table follows this memo. Earlier, the Council noted that Punica Granatum Extract was incorrectly defined as an extract of "the whole plant" in the *Dictionary*. The Council now reports that Punica Granatum Extract has been deleted from the *Dictionary*, and that several member companies have reported that previous concentration of use survey results should now fall under the Punica Granatum Fruit Extract (primarily) or Punica Granatum Pericarp Extract entries. Not all manufacturers have responded to the request for updated concentration of use, so another update to this data is possible in the future and, currently, the concentration of use from those companies that have not yet responded remain under the Punica Granatum Extract entry in the use table. The 312 frequency of use entries in the VCRP for Punica Granatum Extract are expected to remain in the database until manufacturers update their submissions. No timeframe has been provided as to when labels on store shelves will change.

Table 1. Frequency (2019) and concentration (2017) of use according to duration and type of exposure for *Punica granatum*-derived ingredients.[30,31]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Punica Granatum Extract*		**Punica Granatum Bark Extract**		**Punica Granatum Flower Extract**		**Punica Granatum Fruit Extract**	
Totals[†]	**312**	**0.00001-0.13**	**13**	**NR**	**5**	**0.0001**	**172**	**0.0000002-0.1**
Duration of Use								
Leave-On	219	0.00001-0.13	12	NR	4	NR	118	0.0000002-0.1
Rinse Off	92	0.0001-0.00085	1	NR	1	0.0001	52	0.000005-0.1
Diluted for (Bath) Use	1	NR	NR	NR	NR	NR	2	0.0005
Exposure Type								
Eye Area	20	0.001	1	NR	NR	NR	20	0.000005-0.018
Incidental Ingestion	13	NR	NR	NR	NR	NR	2	0.0005-0.02
Incidental Inhalation-Spray	2; 73[a]; 62[b]	0.00001-0.001; 0.00001-0.003[a]	2[a]; 8[b]	NR	2[b]	NR	33[a]; 48[b]	0.00002-0.0005; 0.00002-0.02[a]
Incidental Inhalation-Powder	7; 62[b]	0.02-0.1[c]	8[b]	NR	2[b]	NR	48[b]	0.005; 0.0002-0.1[c]
Dermal Contact	238	0.001-0.13	10	NR	4	NR	151	0.0000002-0.1
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	0.0005
Hair - Non-Coloring	53	0.00001-0.1	2	NR	1	0.0001	15	0.00002-0.1
Hair-Coloring	8	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	0.00001-0.001
Mucous Membrane	24	NR	NR	NR	NR	NR	17	0.0005-0.02
Baby Products	2	NR	1	NR	NR	NR	NR	0.000005
	Punica Granatum Fruit Juice		**Punica Granatum Fruit Water**		**Punica Granatum Juice Extract**		**Punica Granatum Pericarp Extract**	
Totals[†]	**86**	**0.0001-0.1**	**15**	**NR**	**6**	**0.005**	**5**	**0.0000002-0.1**
Duration of Use								
Leave-On	68	0.01-0.1	9	NR	3	NR	4	0.0000002-0.005
Rinse Off	18	0.0001	6	NR	2	0.005	1	0.01-0.1
Diluted for (Bath) Use	NR	NR	NR	NR	1	NR	NR	NR
Exposure Type								
Eye Area	9	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	3	NR	NR	NR	NR	NR	3	NR
Incidental Inhalation-Spray	27[a]; 23[b]	NR	9[a]	NR	1[a]; 1[b]	NR	1[b]	0.00002; 0.00002-0.005[a]
Incidental Inhalation-Powder	23[b]	0.01	NR	NR	1[b]	NR	1[b]	NR
Dermal Contact	75	0.01-0.1	15	NR	5	0.005	2	0.0000002-0.01
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	8	0.0001	NR	NR	NR	NR	NR	0.00002-0.1
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	8	NR	NR	NR	2	NR	3	NR
Baby Products	NR	NR	NR	NR	1	NR	NR	NR

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Table 1. Frequency (2019) and concentration (2017) of use according to duration and type of exposure for *Punica granatum*-derived ingredients.[30,31]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Punica Granatum Seed		**Punica Granatum Seed Extract**		**Punica Granatum Seed Powder**			
Totals†	**3**	**NR**	**1**	**0.01-0.3**	**6**	**0.01**		
Duration of Use								
Leave-On	3	NR	1	0.01-0.3	4	NR		
Rinse Off	NR	NR	NR	NR	1	0.01		
Diluted for (Bath) Use	NR	NR	NR	NR	1	0.01		
Exposure Type								
Eye Area	NR	NR	1	NR	NR	NR		
Incidental Ingestion	NR	NR	NR	0.11	NR	NR		
Incidental Inhalation-Spray	3[a]	NR	NR	NR	2[a]; 2[b]	NR		
Incidental Inhalation-Powder	NR	NR	NR	NR	2[b]	NR		
Dermal Contact	3	NR	1	0.01	6	0.01		
Deodorant (underarm)	NR	NR	NR	NR	NR	NR		
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR		
Hair-Coloring	NR	NR	NR	NR	NR	NR		
Nail	NR	NR	NR	0.3	NR	NR		
Mucous Membrane	NR	NR	NR	0.11	1	0.01		
Baby Products	NR	NR	NR	NR	NR	NR		

NR = Not reported.

* Uses are reported in the VCRP and concentration of use survey under this non-INCI name

† Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

[a.] It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.

[b.] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

[c.] It is possible these products may be powders, but it is not specified whether the reported uses are powders.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: March 25, 2019

SUBJECT: Updated Concentration of Use Information: Pomegranate-Derived Ingredients

Trade names associated with the INCI name Punica Granatum Extract (defined as an extract of the "whole plant") have been reassigned based on the plant part from which they are derived (Punica Granatum Fruit Extract or Punica Granatum Pericarp Extract). The INCI name Punica Granatum Extract has been deleted from the Dictionary.

Companies reporting use of Punica Granatum Extract (defined as an extract of the "whole plant") to the PCPC survey were asked to identify the plant part from which the ingredient is derived. The clarifications received (updated table attached) also indicate that the ingredient under the Punica Granatum Extract is derived from fruit or pericarp.

Concentration of Use by FDA Product Category – Pomegranate-Derived Ingredients*

Punica Granatum Extract (defined as an extract of the "whole plant"; deleted from the Dictionary)
Punica Granatum Bark Extract
Punica Granatum Bark/Fruit Extract
Punica Granatum Callus Culture Extract
Punica Granatum Flower Extract
Punica Granatum Fruit Extract
Punica Granatum Fruit Juice
Punica Granatum Fruit/Root/Stem Powder
Punica Granatum Fruit/Sucrose Ferment Filtrate
Punica Granatum Fruit Water
Punica Granatum Juice Extract
Punica Granatum Leaf Cell Extract
Punica Granatum Peel Extract
Punica Granatum Pericarp Extract
Punica Granatum Seed
Punica Granatum Seed Cell Culture Lysate
Punica Granatum Seed Extract
Punica Granatum Seed Powder

Ingredient	Product Category	Maximum Concentration of Use
Punica Granatum Extract	Eye lotions	0.001%
Punica Granatum Extract	Hair conditioners	0.00024%
Punica Granatum Extract	Hair sprays Aerosol Pump spray	 0.00001% 0.00001%
Punica Granatum Extract	Shampoos (noncoloring)	0.0001-0.00085%
Punica Granatum Extract	Tonics, dressings and other hair grooming aids	0.00001-0.003%
Punica Granatum Extract	Other hair preparations (noncoloring)	0.1%
Punica Granatum Extract	Foundations	0.001%
Punica Granatum Extract	Face and neck products Not spray Spray	 0.1% 0.001%
Punica Granatum Extract	Body and hand products Not spray	 0.02%
Punica Granatum Extract	Moisturizing products Not spray	 0.13%
Punica Granatum Flower Extract	Rinses (noncoloring)	0.0001%
Punica Granatum Flower Extract	Shampoos (noncoloring)	0.0001%
Punica Granatum Fruit Extract	Baby lotions, oils and creams Not powder	 0.000005%
Punica Granatum Fruit Extract	Other bath preparations	0.0005%
Punica Granatum Fruit Extract	Eyeliners	0.000005%
Punica Granatum Fruit Extract	Eye shadows	0.018%
Punica Granatum Fruit Extract	Eye lotions	0.00005-0.0022%
Punica Granatum Fruit Extract	Eye makeup removers	0.000005%
Punica Granatum Fruit Extract	Other eye makeup preparations	0.00005-0.0005%
Punica Granatum Fruit Extract	Colognes and toilet waters	0.0005%
Punica Granatum Fruit Extract	Hair conditioners	0.00025-0.1%

Punica Granatum Fruit Extract	Hair sprays Aerosol Pump spray	 0.0003% 0.00002%
Punica Granatum Fruit Extract	Shampoos (noncoloring)	0.0005-0.1%
Punica Granatum Fruit Extract	Tonics, dressings and other hair grooming aids	0.00002-0.02%
Punica Granatum Fruit Extract	Blushers	0.0001%
Punica Granatum Fruit Extract	Face powders	0.005%
Punica Granatum Fruit Extract	Foundations	0.0025%
Punica Granatum Fruit Extract	Lipstick	0.0005-0.02%
Punica Granatum Fruit Extract	Makeup bases	0.0005%
Punica Granatum Fruit Extract	Makeup fixatives	0.00005%
Punica Granatum Fruit Extract	Basecoats and undercoats	0.00001-0.001%
Punica Granatum Fruit Extract	Nail polish and enamel	0.00007%
Punica Granatum Fruit Extract	Bath soaps and detergents	0.0005-0.0043%
Punica Granatum Fruit Extract	Deodorants Not spray	 0.0005%
Punica Granatum Fruit Extract	Shaving soap	0.01%
Punica Granatum Fruit Extract	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0001-0.02%
Punica Granatum Fruit Extract	Face and neck products Not spray	 0.001-0.1%
Punica Granatum Fruit Extract	Body and hand products Not spray	 0.0002-0.02%
Punica Granatum Fruit Extract	Moisturizing products Not spray	 0.0002%
Punica Granatum Fruit Extract	Night products Not spray	 0.0005-0.1%
Punica Granatum Fruit Extract	Paste masks and mud packs	0.00005%
Punica Granatum Fruit Extract	Skin fresheners	0.0001%
Punica Granatum Fruit Extract	Other skin care preparations	0.0000002-0.01%
Punica Granatum Fruit Extract	Indoor tanning preparations	0.001-0.005%
Punica Granatum Fruit Juice	Hair conditioners	0.0001%
Punica Granatum Fruit Juice	Face powders	0.01%
Punica Granatum Fruit Juice	Foundations	0.1%
Punica Granatum Fruit Juice	Makeup bases	0.1%
Punica Granatum Fruit Juice	Makeup fixatives	0.1%
Punica Granatum Juice Extract	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.005%
Punica Granatum Pericarp Extract	Hair conditioners	0.1%
Punica Granatum Pericarp Extract	Hair sprays Pump spray	 0.00002%
Punica Granatum Pericarp Extract	Shampoos (noncoloring)	0.1%
Punica Granatum Pericarp Extract	Tonics, dressings and other hair grooming aids	0.00002%
Punica Granatum Pericarp Extract	Skin cleansing (cold creams, cleansing	0.01%

	lotions liquids and pads)	
Punica Granatum Pericarp Extract	Other skin care preparations	0.0000002%
Punica Granatum Pericarp Extract	Indoor tanning preparations	0.005%
Punica Granatum Seed Extract	Blushers	0.01%
Punica Granatum Seed Extract	Lipstick	0.11%
Punica Granatum Seed Extract	Cuticle softeners	0.3%
Punica Granatum Seed Powder	Other bath preparations	0.01%
Punica Granatum Seed Powder	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.01%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

Information collected in 2017

Table prepared December 14, 2017

Updated March 22, 2019: Identification of plant part (fruit or pericarp) for some companies reporting use of Punica Granatum Extract (defined as an extract of the "whole plant" – a name that has been deleted from the Dictionary)

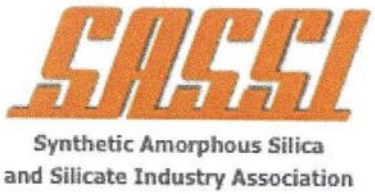
Cosmetic Ingredient Review

Commitment & Credibility since 1976

Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett, Senior Scientific Analyst/Writer
Date: March 29, 2019
Subject: Draft Tentative Amended Safety Assessment of Silica and Silicate Ingredients – Wave 2

The Synthetic Amorphous Silica and Silicate Industry Association (SASSI) has provided numerous data files regarding particle size distributions of various samples of silica products (*silica042019wave2_data1* through *silica042019wave2_data20*). CIR staff is seeking guidance from the Panel on what data are useful for inclusion in the safety assessment and what data need further clarification from SASSI. The SASSI letter also provides additional feedback: a 2008 report by SASSI on Silica on particle size distribution in relation to nanoscale materials, and a summary of the findings from this submission and the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Joint Assessment of Commodity Chemicals No. 51 on "Synthetic Amorphous Silica (CAS No. 7631-86-9)" (JACC51) that discusses how Silica forms aggregates and agglomerates and the related particle sizes (*silica042019wave2_data21* and *silica042019wave2_data22*, respectively). Both of these latter documents were previously reviewed by the Panel when Silica and Hydrated Silica were originally review; they are being included here as a refresher.



Cosmetic Ingredient Review
1620 L St. N. W. Suite 1200
Washington D. C. 20036

March 11, 2019

Dr. Bart Heldreth, Ph.D., Executive Director, CIR

Comments from the
Synthetic Amorphous Silica and Silicate Industry Association
To
Cosmetic Ingredient Review
Dr. Bart Heldreth, Director and the Expert Panel
on
Post Meeting Announcement: Cosmetic Ingredient Review Expert Panel

149th Meeting (December 3-4, 2018) – Findings of December 7, 2019:

Insufficient Data Announcement: Silica & Silicates

Dear Dr. Heldreth,

In response to the Expert Panel request for data listed in the "Post Meeting Announcement, Cosmetic Ingredient Review Expert Panel 149th Meeting (December 3-4, 2018) – Findings/December 7, 2018: Insufficient Data Announcement Silica & Silicates", the members of the Synthetic Amorphous Silica and Silicate Industry Association (SASSI) would like to take this opportunity to provide analytical data related to particle size distribution on a number of synthetic amorphous silica and silicate (SAS) products manufactured by our member companies that may be used in cosmetic applications.

The following tables, scans and summary documents provide particle size distribution results for a number of our products:

Company A:

Company A: Sample A	Free Flow, Rheology and suspension in a spray	Horiba
Company A: Sample B	Free Flow, Rheology and suspension in a spray	Horiba
Company A: Sample C	Powder-to-cream, Dry water, Dry Glycerin, Powder Shampoo, Hair styling, Powder lipstick	Horiba
Company A: Sample D	Eyeshadow	Horiba
Company A: Sample E	Powder-to-cream, Dry water, Dry Glycerin, Powder Shampoo, Hair styling, Powder lipstick	Horiba
Company A: Sample F	Free Flow, Rheology and suspension in a spray	Horiba
Company A: Sample G	Eyeshadow	Horiba
Company A: Sample H	Free Flow, Rheology and suspension in a spray	Horiba
Company A: Sample I	Free Flow, Rheology and suspension in a spray	Horiba
Company A: Sample J	Carrier	Beckman Coulter
Company A: Sample K	Carrier	Beckman Coulter
Company A: Sample L	Carrier	Beckman Coulter
Company A: Sample M	Carrier	Beckman Coulter
Company A: Sample N	Carrier	Beckman Coulter
Company A: Sample O	Carrier	Beckman Coulter
Company A: Sample P	Carrier	Beckman Coulter
Company A: Sample Q	Carrier	Beckman Coulter
Company A: Sample R	Carrier, ultra soft face powder	Beckman Coulter
Company A: Sample S	Free Flow and Absorption of moisture and odor	Horiba LS960
Company B: Sample T		Helos

				Volume based quantiles		
Sample U	Type	Sample preparation	Equipment and Software	D10	D50	D90
				in µm	in µm	in µm
BET 193 m^2/g, QC data	pyrogenic SAS, polydisperse, fractal system	dry powder, GRADIS dispersing system	He-Ne-Laser for optical spectroscopy (HELOS, GRADIS, Sympatec, Germany); feeding to disperser unit by electromagnetic sieve vibrator (Model EMS 750, TOPAS, Germany)	430,9	681,7	965.7

Company C:

	Percent less than 2um	D10 (microns)	D50(microns)	D90 (microns)	D98 (microns)	Chemical Composition
Sample V	1.6	3	6	12	16	SiO2>99.6%
Sample W	1.6	3	6	12	16	SiO2>99.6%
Sample X	0.7	3	6	13	20	SiO2>99.6%
Sample Y	4.6	3	6	14	19	SiO2>99.6%
Sample Z	3.8	3	5	10	14	SiO2>99.6%
Sample AA	0	80	135	210	260	SiO2>99.6%
Sample BB	0	180	340	590	750	SiO2>99.6%
Sample CC	0	85	275	580	795	SiO2>99.6%
Sample DD	0.2	5	14	50	75	SiO2>99.6%
Sample EE	0	7	17	45	70	SiO2>99.6%

As noted in our earlier correspondence, in 2007 and 2008 SASSI provided references that contain comprehensive descriptions of the physical and chemical properties of SAS, including particle size data. These publications include the European Centre for Ecotoxicology and Toxicology of Chemicals (ECOTOC) Joint Assessment of Commodity Chemicals No. 51 on "Synthetic Amorphous Silica (CAS No. 7631-86-9)" and the US EPA's Nanoscale Material Stewardship Program-Basic Program report from SASSI "NMSP Voluntary Submittal Package for Synthetic Amorphous Silica (CAS# 7631-86-9)". The entire document is on-line at:

www.epa.gov/opt/nano/sassi.pdf. We also provided a PDF copy to CIR. We believe these documents contain relevant information that should be referenced by the Expert Panel.

Excerpts from JACC51 and the NSMP Report related to particle size distribution are captured in the embedded file: PSD Data JACC51 & NSMP Report.doc

As it relates to health and safety hazards, studies have shown that the SAS materials described in the summary data provided here are "essentially non-toxic." (ref: JACC 51: Executive Summary: "In humans, SAS is essentially non-toxic by mouth, skin or eyes, and by inhalation. Epidemiology studies show little evidence of adverse health effects due to SAS. Repeated exposure (without personal protection) may cause mechanical irritation of the eye and drying/cracking of the skin.") We acknowledge that ingredient particle size information is needed to assess the safety of workers involved in SAS manufacturing and, where applicable, in the manufacture of cosmetic products but we question whether ingredient particle size is helpful or not for assessing the safety of cosmetic products as used by consumers, since particle sizes of finished cosmetic products are not the same as the particle size of ingredients (as previously reported by Personal Care Product Council).

We would also ask for clarification on the scope (40 ingredients) of the review of silica and silicates as outlined in the notice. Many of these materials were not in the scope of the "Safety Assessment of Silica and Related Cosmetic Ingredients" issued on Sept. 25, 2009, and in fact several of the materials on the list were the subject of separate safety assessments. Many of these materials have compositions and physico/chemico structures significantly different from SAS compounds and may not have the same safety profiles. As has been the case in the past relating to amorphous and crystalline silica, we are concerned about possible confusion over the results of the assessment unless they are sufficiently explicit.

We are open to discussing any opportunity to assist CIR in completing a comprehensive and accurate review of synthetic amorphous silica. Please contact me to determine how we can support the efforts of your agency.

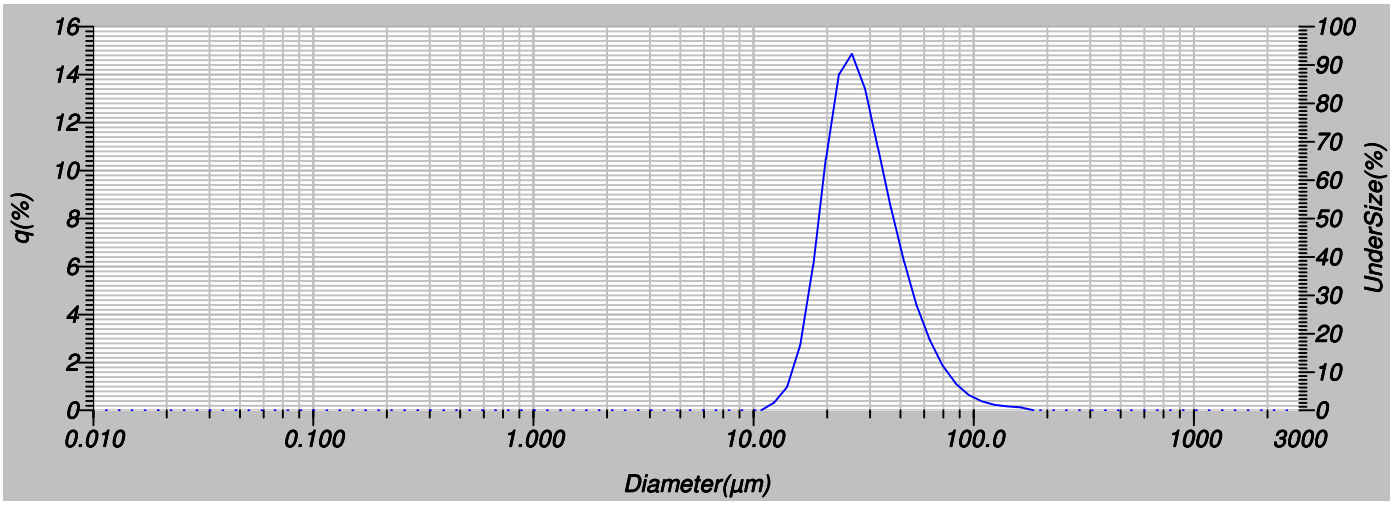
We look forward to your response.

Sincerely yours,

David A. Pavlich
Association Manager
Synthetic Amorphous Silica and Silicate Industry
116 Countryside Drive
South Russell, OH 44022
440-897-8780

HORIBA Laser Scattering Particle Size Distribution Analyzer LA-950

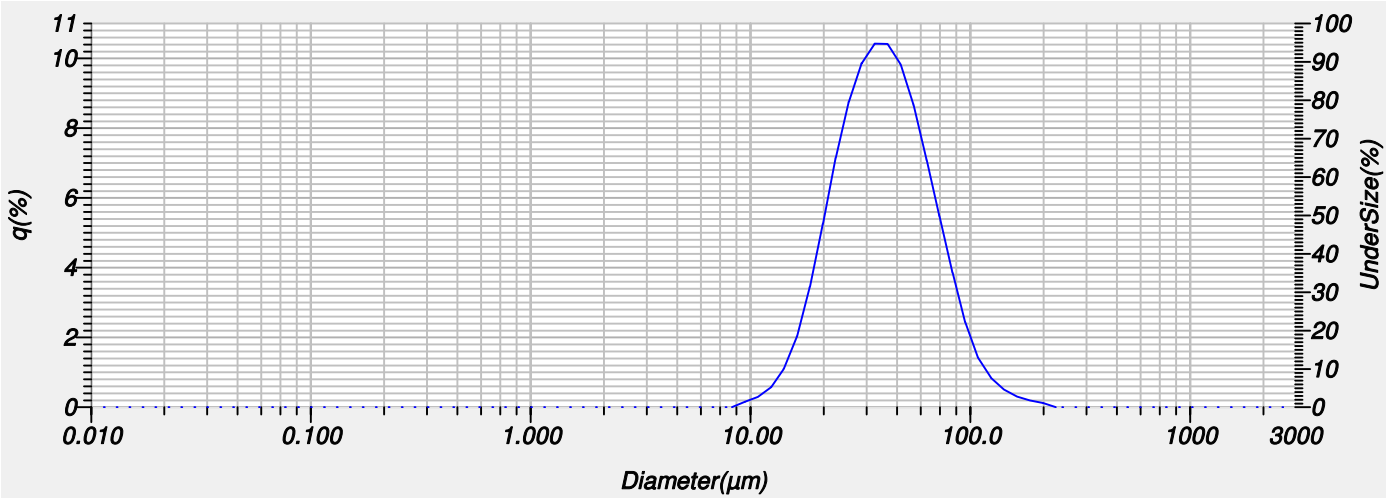
Sample Name	:	Sample A	Median Size	: 30.11218(µm)
Lot Number	:	201405220929973	Mean Size	: 34.51494(µm)
ID#	:		Std.Dev.	: 16.7031(µm)
Transmittance(R)	:	88.0(%)	Geo.Mean Size	: 31.6169(µm)
Transmittance(B)	:	89.2(%)	Geo.Std.Dev.	: 1.4920(µm)
Circulation Speed	:	3	Mode Size	: 27.8678(µm)
Agitation Speed	:	1	Span	: 1.1405
Ultra Sonic	:	OFF	D(v,0.1)	: 19.90790(µm)
Form of Distribution	:	Manual	D(v,0.5)	: 30.11218(µm)
Distribution Base	:	Volume	D(v,0.9)	: 54.25110(µm)
Refractive Index (R)	:	[Fumed SiO2(1.459 - 0.000i),DI water(1.330)]		
Refractive Index (B)	:	[Fumed SiO2(1.459 - 0.000i),DI water(1.330)]		



No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)	UnderSize(%)
1	0.011	0.000	0.000	26	0.339	0.000	0.000	51	10.097	0.000	0.000	76	300.518	0.000	100.000
2	0.013	0.000	0.000	27	0.389	0.000	0.000	52	11.565	0.000	0.000	77	344.206	0.000	100.000
3	0.015	0.000	0.000	28	0.445	0.000	0.000	53	13.246	0.312	0.312	78	394.244	0.000	100.000
4	0.017	0.000	0.000	29	0.510	0.000	0.000	54	15.172	0.978	1.290	79	451.556	0.000	100.000
5	0.020	0.000	0.000	30	0.584	0.000	0.000	55	17.377	2.681	3.971	80	517.200	0.000	100.000
6	0.022	0.000	0.000	31	0.669	0.000	0.000	56	19.904	6.012	9.983	81	592.387	0.000	100.000
7	0.026	0.000	0.000	32	0.766	0.000	0.000	57	22.797	10.478	20.462	82	678.504	0.000	100.000
8	0.029	0.000	0.000	33	0.877	0.000	0.000	58	26.111	14.003	34.465	83	777.141	0.000	100.000
9	0.034	0.000	0.000	34	1.005	0.000	0.000	59	29.907	14.860	49.325	84	890.116	0.000	100.000
10	0.039	0.000	0.000	35	1.151	0.000	0.000	60	34.255	13.400	62.725	85	1019.515	0.000	100.000
11	0.044	0.000	0.000	36	1.318	0.000	0.000	61	39.234	10.957	73.682	86	1167.725	0.000	100.000
12	0.051	0.000	0.000	37	1.510	0.000	0.000	62	44.938	8.436	82.118	87	1337.481	0.000	100.000
13	0.058	0.000	0.000	38	1.729	0.000	0.000	63	51.471	6.199	88.316	88	1531.914	0.000	100.000
14	0.067	0.000	0.000	39	1.981	0.000	0.000	64	58.953	4.344	92.660	89	1754.613	0.000	100.000
15	0.076	0.000	0.000	40	2.269	0.000	0.000	65	67.523	2.904	95.564	90	2009.687	0.000	100.000
16	0.087	0.000	0.000	41	2.599	0.000	0.000	66	77.339	1.844	97.408	91	2301.841	0.000	100.000
17	0.100	0.000	0.000	42	2.976	0.000	0.000	67	88.583	1.102	98.510	92	2636.467	0.000	100.000
18	0.115	0.000	0.000	43	3.409	0.000	0.000	68	101.460	0.628	99.138	93	3000.000	0.000	100.000
19	0.131	0.000	0.000	44	3.905	0.000	0.000	69	116.210	0.361	99.499				
20	0.150	0.000	0.000	45	4.472	0.000	0.000	70	133.103	0.226	99.725				
21	0.172	0.000	0.000	46	5.122	0.000	0.000	71	152.453	0.157	99.883				
22	0.197	0.000	0.000	47	5.867	0.000	0.000	72	174.616	0.117	100.000				
23	0.226	0.000	0.000	48	6.720	0.000	0.000	73	200.000	0.000	100.000				
24	0.259	0.000	0.000	49	7.697	0.000	0.000	74	229.075	0.000	100.000				
25	0.296	0.000	0.000	50	8.816	0.000	0.000	75	262.376	0.000	100.000				

HORIBA Laser Scattering Particle Size Distribution Analyzer LA-950

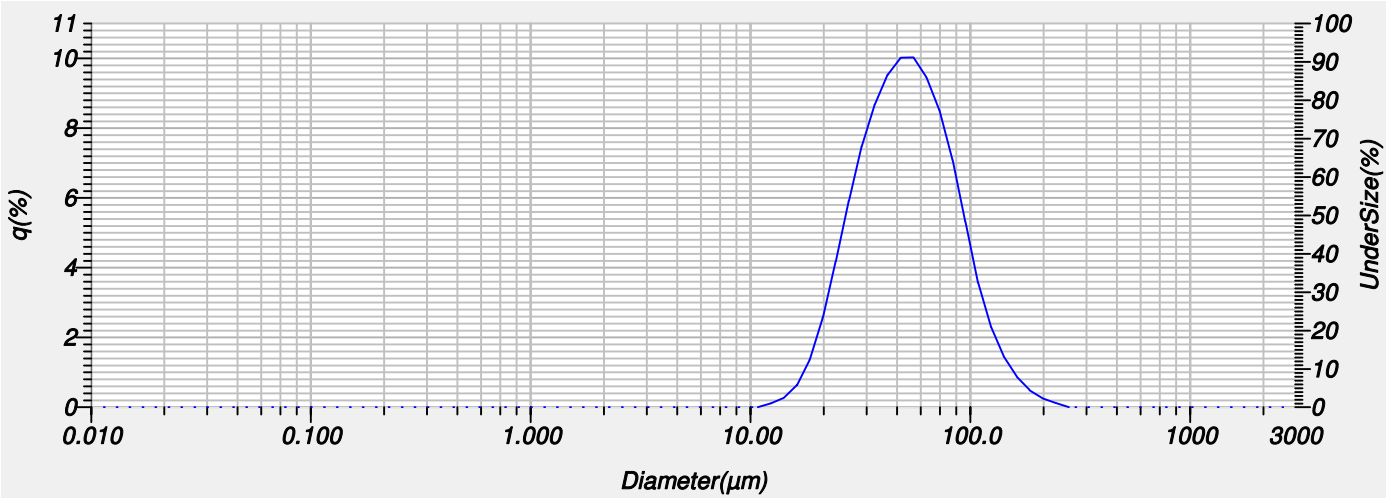
Sample Name	: Sample B	Median Size	: 39.79392(µm)	: (	
ID#	: 201002011510495	Mean Size	: 45.64269(µm)		
Data Name	: 201002011510495	Std.Dev.	: 25.0658(µm)		
Transmittance(R)	: 64.1(%)	Geo.Mean Size	: 40.1739(µm)		
Transmittance(B)	: 75.2(%)	Geo.Std.Dev.	: 1.6491(µm)		
Circulation Speed	: 3	Mode Size	: 36.7942(µm)		
Agitation Speed	: 1	Span	: 1.3917		
Ultra Sonic	: OFF	Diameter on Cumulative %	: (1)5.000 (%)- 17.9979(µm)		
Form of Distribution	: Manual		: (2)10.00 (%)- 21.2136(µm)		
Distribution Base	: Volume		: (3)20.00 (%)- 26.1485(µm)		
Refractive Index (R)	: [Fumed SiO2(1.459 - 0.000i),DI water[		: (4)30.00 (%)- 30.4693(µm)		
Refractive Index (B)	: 0.000i),DI water(1.330)]		: (5)40.00 (%)- 34.9322(µm)		
Material	: SiO2		: (6)60.00 (%)- 45.3604(µm)		
Source	: 0 Min Sonic		: (7)70.00 (%)- 52.1634(µm)		
Lot Number	: 101901120S		: (8)80.00 (%)- 61.4677(µm)		
Test or Assay. Number	: Rep 1		: (9)90.00 (%)- 76.5935(µm)		



No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)
1	0.011	0.000	0.000	24	0.259	0.000	0.000	47	5.867	0.000	0.000	70	133.103	0.827	98.905	93	3000.000	0.000
2	0.013	0.000	0.000	25	0.296	0.000	0.000	48	6.720	0.000	0.000	71	152.453	0.496	99.401			
3	0.015	0.000	0.000	26	0.339	0.000	0.000	49	7.697	0.000	0.000	72	174.616	0.301	99.702			
4	0.017	0.000	0.000	27	0.389	0.000	0.000	50	8.816	0.000	0.000	73	200.000	0.185	99.887			
5	0.020	0.000	0.000	28	0.445	0.000	0.000	51	10.097	0.151	0.151	74	229.075	0.113	100.000			
6	0.022	0.000	0.000	29	0.510	0.000	0.000	52	11.565	0.288	0.439	75	262.376	0.000	100.000			
7	0.026	0.000	0.000	30	0.584	0.000	0.000	53	13.246	0.564	1.003	76	300.518	0.000	100.000			
8	0.029	0.000	0.000	31	0.669	0.000	0.000	54	15.172	1.093	2.096	77	344.206	0.000	100.000			
9	0.034	0.000	0.000	32	0.766	0.000	0.000	55	17.377	2.018	4.114	78	394.244	0.000	100.000			
10	0.039	0.000	0.000	33	0.877	0.000	0.000	56	19.904	3.428	7.542	79	451.556	0.000	100.000			
11	0.044	0.000	0.000	34	1.005	0.000	0.000	57	22.797	5.235	12.777	80	517.200	0.000	100.000			
12	0.051	0.000	0.000	35	1.151	0.000	0.000	58	26.111	7.131	19.908	81	592.387	0.000	100.000			
13	0.058	0.000	0.000	36	1.318	0.000	0.000	59	29.907	8.740	28.648	82	678.504	0.000	100.000			
14	0.067	0.000	0.000	37	1.510	0.000	0.000	60	34.255	9.848	38.497	83	777.141	0.000	100.000			
15	0.076	0.000	0.000	38	1.729	0.000	0.000	61	39.234	10.417	48.914	84	890.116	0.000	100.000			
16	0.087	0.000	0.000	39	1.981	0.000	0.000	62	44.938	10.409	59.323	85	1019.515	0.000	100.000			
17	0.100	0.000	0.000	40	2.269	0.000	0.000	63	51.471	9.823	69.146	86	1167.725	0.000	100.000			
18	0.115	0.000	0.000	41	2.599	0.000	0.000	64	58.953	8.671	77.817	87	1337.481	0.000	100.000			
19	0.131	0.000	0.000	42	2.976	0.000	0.000	65	67.523	7.094	84.911	88	1531.914	0.000	100.000			
20	0.150	0.000	0.000	43	3.409	0.000	0.000	66	77.339	5.480	90.391	89	1754.613	0.000	100.000			
21	0.172	0.000	0.000	44	3.905	0.000	0.000	67	88.583	3.854	94.245	90	2009.687	0.000	100.000			
22	0.197	0.000	0.000	45	4.472	0.000	0.000	68	101.460	2.424	96.670	91	2301.841	0.000	100.000			
23	0.226	0.000	0.000	46	5.122	0.000	0.000	69	116.210	1.409	98.079	92	2636.467	0.000	100.000			

HORIBA Laser Scattering Particle Size Distribution Analyzer LA-950

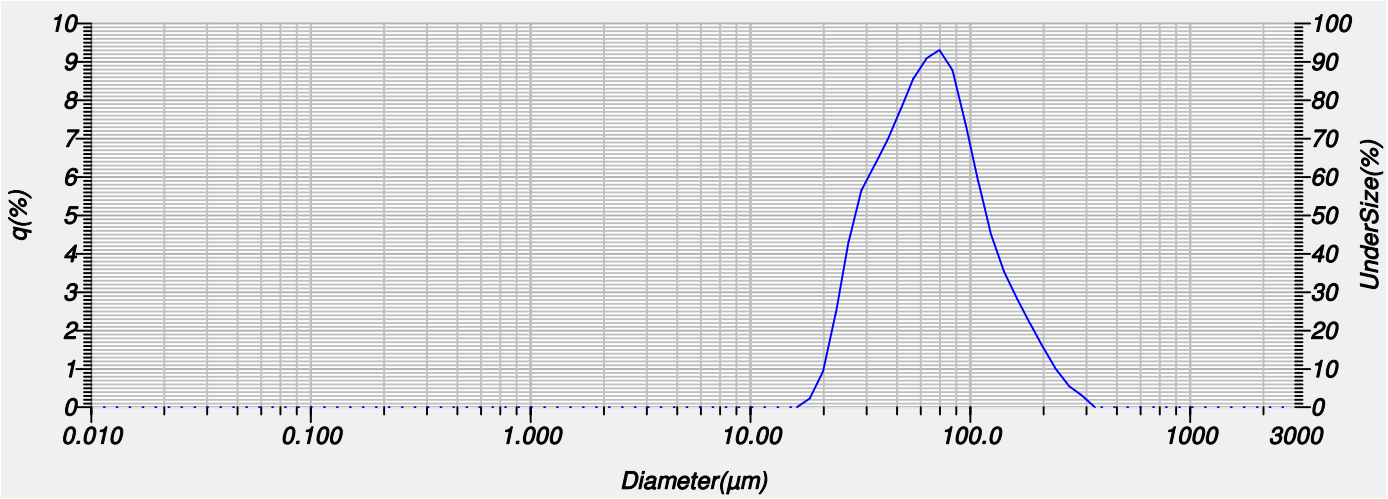
Sample Name	: Sample C	Median Size	: 51.04212(µm)	: (	
ID#	: 201109191403703	Mean Size	: 58.39515(µm)		
Data Name	: 201109191403703	Std.Dev.	: 31.6471(µm)		
Transmittance(R)	: 81.6(%)	Geo.Mean Size	: 51.3340(µm)		
Transmittance(B)	: 87.0(%)	Geo.Std.Dev.	: 1.6567(µm)		
Circulation Speed	: 3	Mode Size	: 54.8733(µm)		
Agitation Speed	: 1	Span	: 1.4145		
Ultra Sonic	: OFF	Diameter on Cumulative %	: (1)5.000 (%)- 22.8657(µm)		
Form of Distribution	: Auto		: (2)10.00 (%)- 26.6750(µm)		
Distribution Base	: Volume		: (3)20.00 (%)- 32.7782(µm)		
Refractive Index (R)	: [Clorox(1.460 - 0.000i),IPA(1.380)]		: (4)30.00 (%)- 38.5736(µm)		
Refractive Index (B)	: [Clorox(1.460 - 0.000i),IPA(1.380)] Sil		: (5)40.00 (%)- 44.5531(µm)		
Material	: 0 min sonication		: (6)60.00 (%)- 58.4443(µm)		
Source	: Lot #3150061535		: (7)70.00 (%)- 67.4409(µm)		
Lot Number	: Rep 1		: (8)80.00 (%)- 79.4494(µm)		
Test or Assay. Number	:		: (9)90.00 (%)- 98.8731(µm)		



No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)
1	0.011	0.000	0.000	24	0.259	0.000	0.000	47	5.867	0.000	0.000	70	133.103	2.291	96.872	93	3000.000	0.000
2	0.013	0.000	0.000	25	0.296	0.000	0.000	48	6.720	0.000	0.000	71	152.453	1.440	98.311			
3	0.015	0.000	0.000	26	0.339	0.000	0.000	49	7.697	0.000	0.000	72	174.616	0.856	99.167			
4	0.017	0.000	0.000	27	0.389	0.000	0.000	50	8.816	0.000	0.000	73	200.000	0.476	99.643			
5	0.020	0.000	0.000	28	0.445	0.000	0.000	51	10.097	0.000	0.000	74	229.075	0.243	99.887			
6	0.022	0.000	0.000	29	0.510	0.000	0.000	52	11.565	0.000	0.000	75	262.376	0.113	100.000			
7	0.026	0.000	0.000	30	0.584	0.000	0.000	53	13.246	0.104	0.104	76	300.518	0.000	100.000			
8	0.029	0.000	0.000	31	0.669	0.000	0.000	54	15.172	0.262	0.365	77	344.206	0.000	100.000			
9	0.034	0.000	0.000	32	0.766	0.000	0.000	55	17.377	0.626	0.992	78	394.244	0.000	100.000			
10	0.039	0.000	0.000	33	0.877	0.000	0.000	56	19.904	1.355	2.347	79	451.556	0.000	100.000			
11	0.044	0.000	0.000	34	1.005	0.000	0.000	57	22.797	2.561	4.908	80	517.200	0.000	100.000			
12	0.051	0.000	0.000	35	1.151	0.000	0.000	58	26.111	4.165	9.072	81	592.387	0.000	100.000			
13	0.058	0.000	0.000	36	1.318	0.000	0.000	59	29.907	5.894	14.966	82	678.504	0.000	100.000			
14	0.067	0.000	0.000	37	1.510	0.000	0.000	60	34.255	7.453	22.419	83	777.141	0.000	100.000			
15	0.076	0.000	0.000	38	1.729	0.000	0.000	61	39.234	8.665	31.084	84	890.116	0.000	100.000			
16	0.087	0.000	0.000	39	1.981	0.000	0.000	62	44.938	9.519	40.603	85	1019.515	0.000	100.000			
17	0.100	0.000	0.000	40	2.269	0.000	0.000	63	51.471	10.014	50.617	86	1167.725	0.000	100.000			
18	0.115	0.000	0.000	41	2.599	0.000	0.000	64	58.953	10.023	60.640	87	1337.481	0.000	100.000			
19	0.131	0.000	0.000	42	2.976	0.000	0.000	65	67.523	9.445	70.085	88	1531.914	0.000	100.000			
20	0.150	0.000	0.000	43	3.409	0.000	0.000	66	77.339	8.507	78.592	89	1754.613	0.000	100.000			
21	0.172	0.000	0.000	44	3.905	0.000	0.000	67	88.583	7.099	85.691	90	2009.687	0.000	100.000			
22	0.197	0.000	0.000	45	4.472	0.000	0.000	68	101.460	5.321	91.013	91	2301.841	0.000	100.000			
23	0.226	0.000	0.000	46	5.122	0.000	0.000	69	116.210	3.568	94.581	92	2636.467	0.000	100.000			

HORIBA Laser Scattering Particle Size Distribution Analyzer LA-950

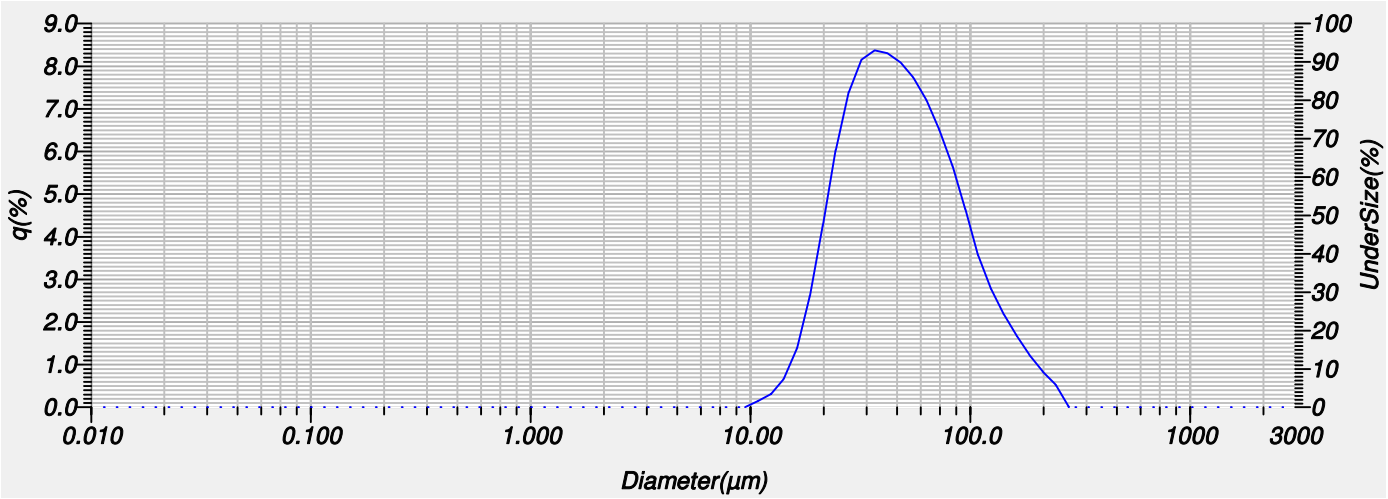
Sample Name	: Sample D				
ID#	: 201404171104960		Median Size	: 65.33407(µm)	:
Data Name	: 201404171104960		Mean Size	: 78.21938(µm)	
Transmittance(R)	: 64.9(%)		Std.Dev.	: 49.2444(µm)	
Transmittance(B)	: 81.4(%)		Geo.Mean Size	: 66.2810(µm)	
Circulation Speed	: 3		Geo.Std.Dev.	: 1.7614(µm)	
Agitation Speed	: 1		Mode Size	: 72.1028(µm)	
Ultra Sonic	: OFF		Span	: 1.7120	
Form of Distribution	: Manual		Diameter on Cumulative %	: (1)5.000 (%)- 27.3197(µm)	
Distribution Base	: Volume			: (2)10.00 (%)- 31.4657(µm)	
Refractive Index (R)	: Clorox1[Clorox(1.460 - 0.000i),IPA(1.3			: (3)20.00 (%)- 39.3478(µm)	
Refractive Index (B)	: Clorox1[Clorox(1.460 - 0.000i),IPA(1.3			: (4)30.00 (%)- 47.5185(µm)	
Material	: silica			: (5)40.00 (%)- 56.1050(µm)	
Source	: 0 min sonication			: (6)60.00 (%)- 75.6557(µm)	
Lot Number	: 154012638 PAL#21			: (7)70.00 (%)- 88.1938(µm)	
Test or Assay. Number	: REP 2			: (8)80.00 (%)- 106.9826(µm)	
Algorithm Option	: Ver.4.XX Compatible			: (9)90.00 (%)- 143.3164(µm)	



No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)
1	0.011	0.000	0.000	24	0.259	0.000	0.000	47	5.867	0.000	0.000	70	133.103	4.480	88.077	93	3000.000	0.000
2	0.013	0.000	0.000	25	0.296	0.000	0.000	48	6.720	0.000	0.000	71	152.453	3.530	91.607			
3	0.015	0.000	0.000	26	0.339	0.000	0.000	49	7.697	0.000	0.000	72	174.616	2.816	94.423			
4	0.017	0.000	0.000	27	0.389	0.000	0.000	50	8.816	0.000	0.000	73	200.000	2.177	96.600			
5	0.020	0.000	0.000	28	0.445	0.000	0.000	51	10.097	0.000	0.000	74	229.075	1.558	98.158			
6	0.022	0.000	0.000	29	0.510	0.000	0.000	52	11.565	0.000	0.000	75	262.376	0.988	99.146			
7	0.026	0.000	0.000	30	0.584	0.000	0.000	53	13.246	0.000	0.000	76	300.518	0.549	99.695			
8	0.029	0.000	0.000	31	0.669	0.000	0.000	54	15.172	0.000	0.000	77	344.206	0.305	100.000			
9	0.034	0.000	0.000	32	0.766	0.000	0.000	55	17.377	0.000	0.000	78	394.244	0.000	100.000			
10	0.039	0.000	0.000	33	0.877	0.000	0.000	56	19.904	0.219	0.219	79	451.556	0.000	100.000			
11	0.044	0.000	0.000	34	1.005	0.000	0.000	57	22.797	0.915	1.134	80	517.200	0.000	100.000			
12	0.051	0.000	0.000	35	1.151	0.000	0.000	58	26.111	2.425	3.559	81	592.387	0.000	100.000			
13	0.058	0.000	0.000	36	1.318	0.000	0.000	59	29.907	4.322	7.882	82	678.504	0.000	100.000			
14	0.067	0.000	0.000	37	1.510	0.000	0.000	60	34.255	5.660	13.541	83	777.141	0.000	100.000			
15	0.076	0.000	0.000	38	1.729	0.000	0.000	61	39.234	6.311	19.852	84	890.116	0.000	100.000			
16	0.087	0.000	0.000	39	1.981	0.000	0.000	62	44.938	6.958	26.810	85	1019.515	0.000	100.000			
17	0.100	0.000	0.000	40	2.269	0.000	0.000	63	51.471	7.754	34.564	86	1167.725	0.000	100.000			
18	0.115	0.000	0.000	41	2.599	0.000	0.000	64	58.953	8.558	43.122	87	1337.481	0.000	100.000			
19	0.131	0.000	0.000	42	2.976	0.000	0.000	65	67.523	9.084	52.206	88	1531.914	0.000	100.000			
20	0.150	0.000	0.000	43	3.409	0.000	0.000	66	77.339	9.303	61.509	89	1754.613	0.000	100.000			
21	0.172	0.000	0.000	44	3.905	0.000	0.000	67	88.583	8.776	70.284	90	2009.687	0.000	100.000			
22	0.197	0.000	0.000	45	4.472	0.000	0.000	68	101.460	7.411	77.695	91	2301.841	0.000	100.000			
23	0.226	0.000	0.000	46	5.122	0.000	0.000	69	116.210	5.903	83.598	92	2636.467	0.000	100.000			

HORIBA Laser Scattering Particle Size Distribution Analyzer LA-950

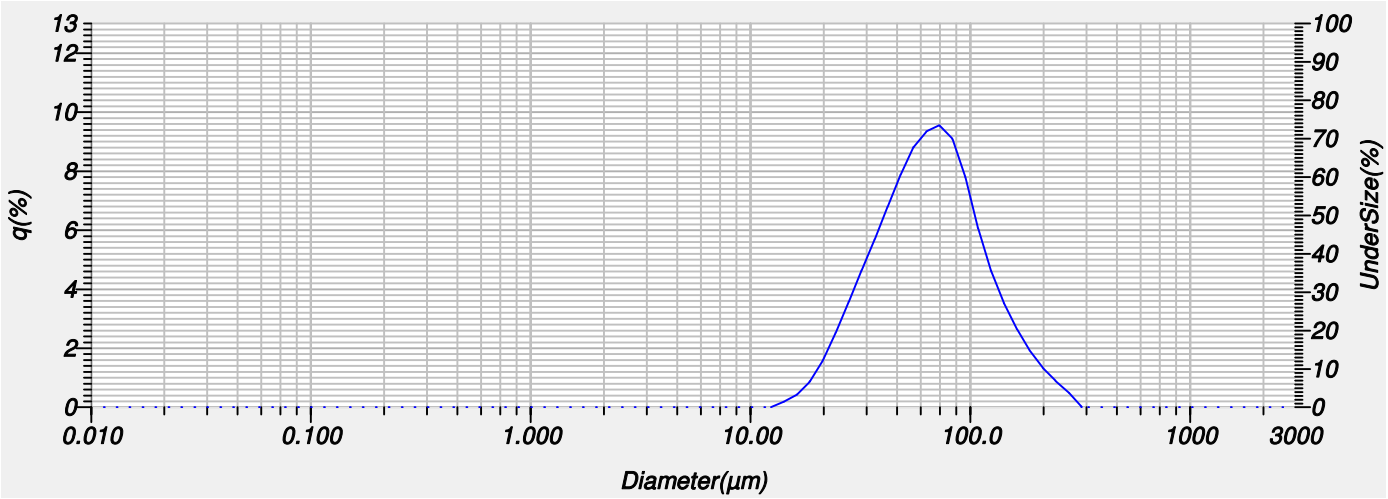
Sample Name	: Sample E		Median Size	: 46.83929(µm)	:
ID#	: 201107081501660		Mean Size	: 59.24709(µm)	
Data Name	: 201107081501660		Std.Dev.	: 40.5150(µm)	
Transmittance(R)	: 58.5(%)		Geo.Mean Size	: 48.9692(µm)	
Transmittance(B)	: 69.0(%)		Geo.Std.Dev.	: 1.8298(µm)	
Circulation Speed	: 3		Mode Size	: 36.7052(µm)	
Agitation Speed	: 1		Span	: 1.9045	
Ultra Sonic	: OFF		Diameter on Cumulative %	: (1)5.000 (%)- 19.8379(µm)	
Form of Distribution	: Auto			: (2)10.00 (%)- 23.1480(µm)	
Distribution Base	: Volume			: (3)20.00 (%)- 28.4490(µm)	
Refractive Index (R)	: Clorox1[Clorox(1.460 - 0.000i),IPA(1.3			: (4)30.00 (%)- 33.7638(µm)	
Refractive Index (B)	: Clorox1[Clorox(1.460 - 0.000i),IPA(1.3			: (5)40.00 (%)- 39.7295(µm)	
Material	: Silica			: (6)60.00 (%)- 55.5983(µm)	
Source	: 0 Min sonication			: (7)70.00 (%)- 66.8537(µm)	
Lot Number	: UB755401			: (8)80.00 (%)- 83.0589(µm)	
Test or Assay. Number	: Rep 1			: (9)90.00 (%)- 112.3531(µm)	



No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)
1	0.011	0.000	0.000	24	0.259	0.000	0.000	47	5.867	0.000	0.000	70	133.103	2.756	93.641	93	3000.000	0.000
2	0.013	0.000	0.000	25	0.296	0.000	0.000	48	6.720	0.000	0.000	71	152.453	2.167	95.808			
3	0.015	0.000	0.000	26	0.339	0.000	0.000	49	7.697	0.000	0.000	72	174.616	1.655	97.463			
4	0.017	0.000	0.000	27	0.389	0.000	0.000	50	8.816	0.000	0.000	73	200.000	1.205	98.668			
5	0.020	0.000	0.000	28	0.445	0.000	0.000	51	10.097	0.000	0.000	74	229.075	0.821	99.489			
6	0.022	0.000	0.000	29	0.510	0.000	0.000	52	11.565	0.140	0.140	75	262.376	0.511	100.000			
7	0.026	0.000	0.000	30	0.584	0.000	0.000	53	13.246	0.305	0.445	76	300.518	0.000	100.000			
8	0.029	0.000	0.000	31	0.669	0.000	0.000	54	15.172	0.662	1.107	77	344.206	0.000	100.000			
9	0.034	0.000	0.000	32	0.766	0.000	0.000	55	17.377	1.370	2.477	78	394.244	0.000	100.000			
10	0.039	0.000	0.000	33	0.877	0.000	0.000	56	19.904	2.586	5.063	79	451.556	0.000	100.000			
11	0.044	0.000	0.000	34	1.005	0.000	0.000	57	22.797	4.260	9.323	80	517.200	0.000	100.000			
12	0.051	0.000	0.000	35	1.151	0.000	0.000	58	26.111	6.013	15.336	81	592.387	0.000	100.000			
13	0.058	0.000	0.000	36	1.318	0.000	0.000	59	29.907	7.382	22.718	82	678.504	0.000	100.000			
14	0.067	0.000	0.000	37	1.510	0.000	0.000	60	34.255	8.148	30.866	83	777.141	0.000	100.000			
15	0.076	0.000	0.000	38	1.729	0.000	0.000	61	39.234	8.367	39.233	84	890.116	0.000	100.000			
16	0.087	0.000	0.000	39	1.981	0.000	0.000	62	44.938	8.300	47.533	85	1019.515	0.000	100.000			
17	0.100	0.000	0.000	40	2.269	0.000	0.000	63	51.471	8.080	55.613	86	1167.725	0.000	100.000			
18	0.115	0.000	0.000	41	2.599	0.000	0.000	64	58.953	7.719	63.332	87	1337.481	0.000	100.000			
19	0.131	0.000	0.000	42	2.976	0.000	0.000	65	67.523	7.196	70.528	88	1531.914	0.000	100.000			
20	0.150	0.000	0.000	43	3.409	0.000	0.000	66	77.339	6.499	77.028	89	1754.613	0.000	100.000			
21	0.172	0.000	0.000	44	3.905	0.000	0.000	67	88.583	5.654	82.682	90	2009.687	0.000	100.000			
22	0.197	0.000	0.000	45	4.472	0.000	0.000	68	101.460	4.643	87.325	91	2301.841	0.000	100.000			
23	0.226	0.000	0.000	46	5.122	0.000	0.000	69	116.210	3.560	90.885	92	2636.467	0.000	100.000			

HORIBA Laser Scattering Particle Size Distribution Analyzer LA-950

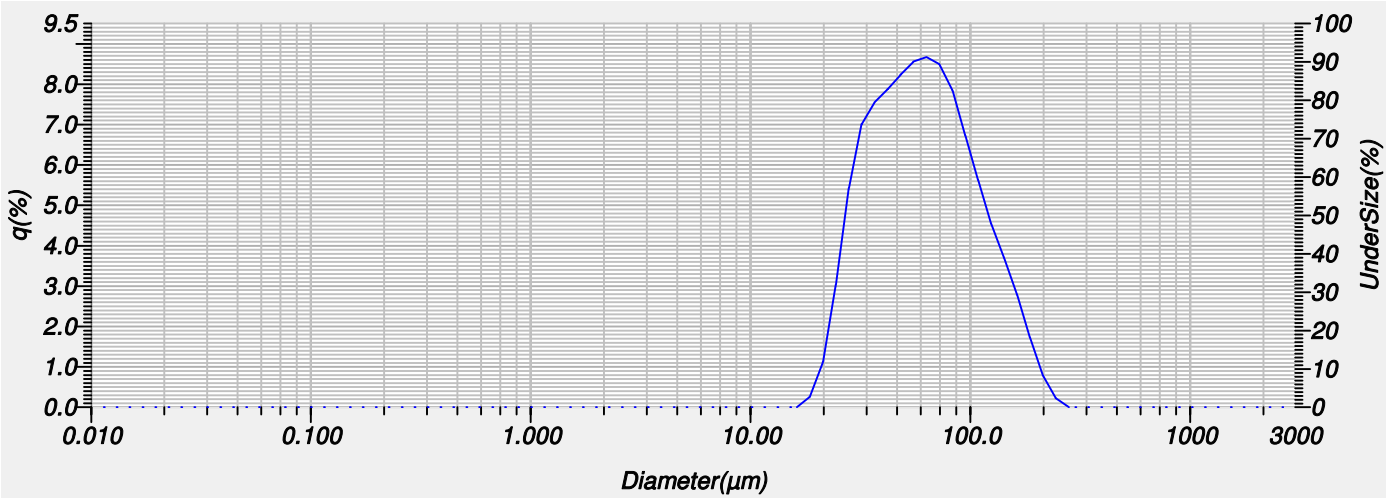
Sample Name	: Sample F		Median Size	: 65.41489(µm)	:
ID#	: 201004021336532		Mean Size	: 76.41821(µm)	
Data Name	: 201004021336532		Std.Dev.	: 45.9917(µm)	
Transmittance(R)	: 71.2(%)		Geo.Mean Size	: 65.0845(µm)	
Transmittance(B)	: 75.8(%)		Geo.Std.Dev.	: 1.7632(µm)	
Circulation Speed	: 3		Mode Size	: 72.1294(µm)	
Agitation Speed	: 1		Span	: 1.6233	
Ultra Sonic	: OFF		Diameter on Cumulative %	: (1)5.000 (%)- 25.3526(µm)	
Form of Distribution	: Manual			: (2)10.00 (%)- 30.7020(µm)	
Distribution Base	: Volume			: (3)20.00 (%)- 39.7051(µm)	
Refractive Index (R)	: Clorox1[Clorox(1.460 - 0.000i),IPA(1.3			: (4)30.00 (%)- 48.0030(µm)	
Refractive Index (B)	: Clorox1[Clorox(1.460 - 0.000i),IPA(1.3			: (5)40.00 (%)- 56.4267(µm)	
Material	: Hydrophobic silica			: (6)60.00 (%)- 75.4608(µm)	
Source	: 0 MIN sonication			: (7)70.00 (%)- 87.5160(µm)	
Lot Number	: 1030011011			: (8)80.00 (%)- 104.6613(µm)	
Test or Assay. Number	: Rep 1			: (9)90.00 (%)- 136.8933(µm)	



No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)
1	0.011	0.000	0.000	24	0.259	0.000	0.000	47	5.867	0.000	0.000	70	133.103	4.603	89.271	93	3000.000	0.000
2	0.013	0.000	0.000	25	0.296	0.000	0.000	48	6.720	0.000	0.000	71	152.453	3.523	92.794			
3	0.015	0.000	0.000	26	0.339	0.000	0.000	49	7.697	0.000	0.000	72	174.616	2.629	95.423			
4	0.017	0.000	0.000	27	0.389	0.000	0.000	50	8.816	0.000	0.000	73	200.000	1.902	97.324			
5	0.020	0.000	0.000	28	0.445	0.000	0.000	51	10.097	0.000	0.000	74	229.075	1.320	98.645			
6	0.022	0.000	0.000	29	0.510	0.000	0.000	52	11.565	0.000	0.000	75	262.376	0.871	99.516			
7	0.026	0.000	0.000	30	0.584	0.000	0.000	53	13.246	0.000	0.000	76	300.518	0.484	100.000			
8	0.029	0.000	0.000	31	0.669	0.000	0.000	54	15.172	0.183	0.183	77	344.206	0.000	100.000			
9	0.034	0.000	0.000	32	0.766	0.000	0.000	55	17.377	0.417	0.600	78	394.244	0.000	100.000			
10	0.039	0.000	0.000	33	0.877	0.000	0.000	56	19.904	0.862	1.462	79	451.556	0.000	100.000			
11	0.044	0.000	0.000	34	1.005	0.000	0.000	57	22.797	1.573	3.035	80	517.200	0.000	100.000			
12	0.051	0.000	0.000	35	1.151	0.000	0.000	58	26.111	2.510	5.545	81	592.387	0.000	100.000			
13	0.058	0.000	0.000	36	1.318	0.000	0.000	59	29.907	3.561	9.106	82	678.504	0.000	100.000			
14	0.067	0.000	0.000	37	1.510	0.000	0.000	60	34.255	4.624	13.730	83	777.141	0.000	100.000			
15	0.076	0.000	0.000	38	1.729	0.000	0.000	61	39.234	5.675	19.405	84	890.116	0.000	100.000			
16	0.087	0.000	0.000	39	1.981	0.000	0.000	62	44.938	6.772	26.177	85	1019.515	0.000	100.000			
17	0.100	0.000	0.000	40	2.269	0.000	0.000	63	51.471	7.865	34.042	86	1167.725	0.000	100.000			
18	0.115	0.000	0.000	41	2.599	0.000	0.000	64	58.953	8.797	42.839	87	1337.481	0.000	100.000			
19	0.131	0.000	0.000	42	2.976	0.000	0.000	65	67.523	9.345	52.184	88	1531.914	0.000	100.000			
20	0.150	0.000	0.000	43	3.409	0.000	0.000	66	77.339	9.545	61.729	89	1754.613	0.000	100.000			
21	0.172	0.000	0.000	44	3.905	0.000	0.000	67	88.583	9.081	70.810	90	2009.687	0.000	100.000			
22	0.197	0.000	0.000	45	4.472	0.000	0.000	68	101.460	7.804	78.615	91	2301.841	0.000	100.000			
23	0.226	0.000	0.000	46	5.122	0.000	0.000	69	116.210	6.053	84.668	92	2636.467	0.000	100.000			

HORIBA Laser Scattering Particle Size Distribution Analyzer LA-950

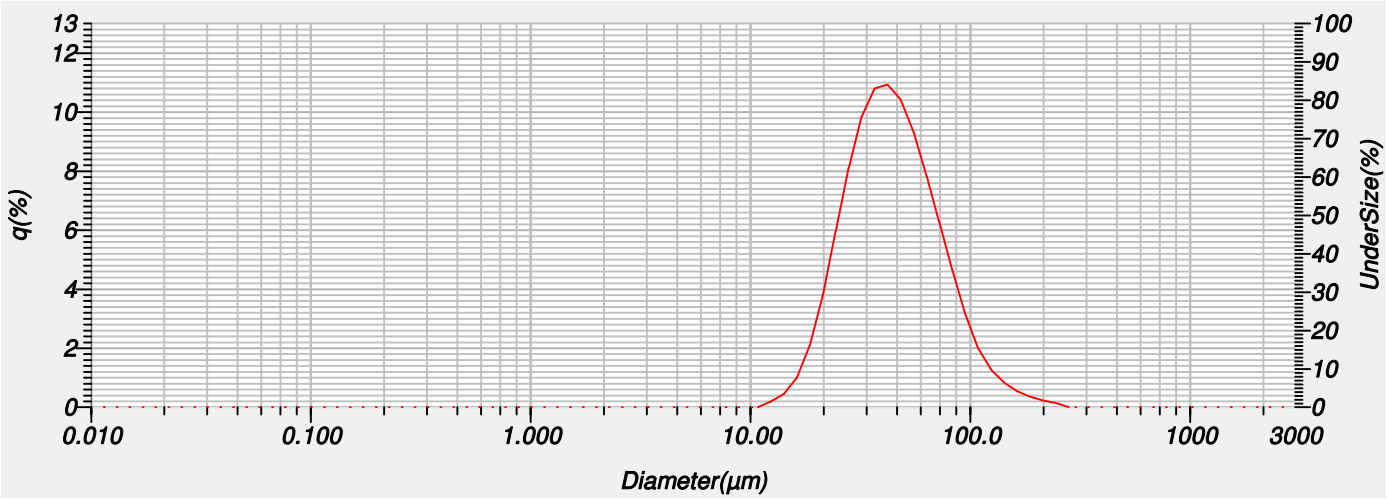
Sample Name	: Sample G	Median Size	: 59.94545(µm)	:	
ID#	: 201307221306595	Mean Size	: 70.91200(µm)		
Data Name	: 201307221306595	Std.Dev.	: 40.8425(µm)		
Transmittance(R)	: 80.6(%)	Geo.Mean Size	: 61.0590(µm)		
Transmittance(B)	: 87.5(%)	Geo.Std.Dev.	: 1.7213(µm)		
Circulation Speed	: 3	Mode Size	: 63.0625(µm)		
Agitation Speed	: 1	Span	: 1.6653		
Ultra Sonic	: OFF	Diameter on Cumulative %	: (1)5.000 (%)- 26.5495(µm)		
Form of Distribution	: Manual		: (2)10.00 (%)- 30.0591(µm)		
Distribution Base	: Volume		: (3)20.00 (%)- 36.3226(µm)		
Refractive Index (R)	: Clorox1[Clorox(1.460 - 0.000i),IPA(1.3		: (4)30.00 (%)- 43.3000(µm)		
Refractive Index (B)	: Clorox1[Clorox(1.460 - 0.000i),IPA(1.3		: (5)40.00 (%)- 51.1495(µm)		
Material	:		: (6)60.00 (%)- 70.1618(µm)		
Source	: 0 min sonication		: (7)70.00 (%)- 82.7502(µm)		
Lot Number	: 153030522		: (8)80.00 (%)- 100.1213(µm)		
Test or Assay. Number	: Rep 1		: (9)90.00 (%)- 129.8884(µm)		
Algorithm Option	: Ver.4.XX Compatible				



No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)
1	0.011	0.000	0.000	24	0.259	0.000	0.000	47	5.867	0.000	0.000	70	133.103	4.540	90.818	93	3000.000	0.000
2	0.013	0.000	0.000	25	0.296	0.000	0.000	48	6.720	0.000	0.000	71	152.453	3.692	94.510			
3	0.015	0.000	0.000	26	0.339	0.000	0.000	49	7.697	0.000	0.000	72	174.616	2.781	97.291			
4	0.017	0.000	0.000	27	0.389	0.000	0.000	50	8.816	0.000	0.000	73	200.000	1.722	99.013			
5	0.020	0.000	0.000	28	0.445	0.000	0.000	51	10.097	0.000	0.000	74	229.075	0.769	99.782			
6	0.022	0.000	0.000	29	0.510	0.000	0.000	52	11.565	0.000	0.000	75	262.376	0.218	100.000			
7	0.026	0.000	0.000	30	0.584	0.000	0.000	53	13.246	0.000	0.000	76	300.518	0.000	100.000			
8	0.029	0.000	0.000	31	0.669	0.000	0.000	54	15.172	0.000	0.000	77	344.206	0.000	100.000			
9	0.034	0.000	0.000	32	0.766	0.000	0.000	55	17.377	0.000	0.000	78	394.244	0.000	100.000			
10	0.039	0.000	0.000	33	0.877	0.000	0.000	56	19.904	0.250	0.250	79	451.556	0.000	100.000			
11	0.044	0.000	0.000	34	1.005	0.000	0.000	57	22.797	1.094	1.344	80	517.200	0.000	100.000			
12	0.051	0.000	0.000	35	1.151	0.000	0.000	58	26.111	2.994	4.337	81	592.387	0.000	100.000			
13	0.058	0.000	0.000	36	1.318	0.000	0.000	59	29.907	5.401	9.738	82	678.504	0.000	100.000			
14	0.067	0.000	0.000	37	1.510	0.000	0.000	60	34.255	7.003	16.741	83	777.141	0.000	100.000			
15	0.076	0.000	0.000	38	1.729	0.000	0.000	61	39.234	7.546	24.287	84	890.116	0.000	100.000			
16	0.087	0.000	0.000	39	1.981	0.000	0.000	62	44.938	7.864	32.151	85	1019.515	0.000	100.000			
17	0.100	0.000	0.000	40	2.269	0.000	0.000	63	51.471	8.228	40.380	86	1167.725	0.000	100.000			
18	0.115	0.000	0.000	41	2.599	0.000	0.000	64	58.953	8.555	48.934	87	1337.481	0.000	100.000			
19	0.131	0.000	0.000	42	2.976	0.000	0.000	65	67.523	8.667	57.602	88	1531.914	0.000	100.000			
20	0.150	0.000	0.000	43	3.409	0.000	0.000	66	77.339	8.493	66.094	89	1754.613	0.000	100.000			
21	0.172	0.000	0.000	44	3.905	0.000	0.000	67	88.583	7.839	73.934	90	2009.687	0.000	100.000			
22	0.197	0.000	0.000	45	4.472	0.000	0.000	68	101.460	6.724	80.658	91	2301.841	0.000	100.000			
23	0.226	0.000	0.000	46	5.122	0.000	0.000	69	116.210	5.620	86.278	92	2636.467	0.000	100.000			

HORIBA Laser Scattering Particle Size Distribution Analyzer LA-950

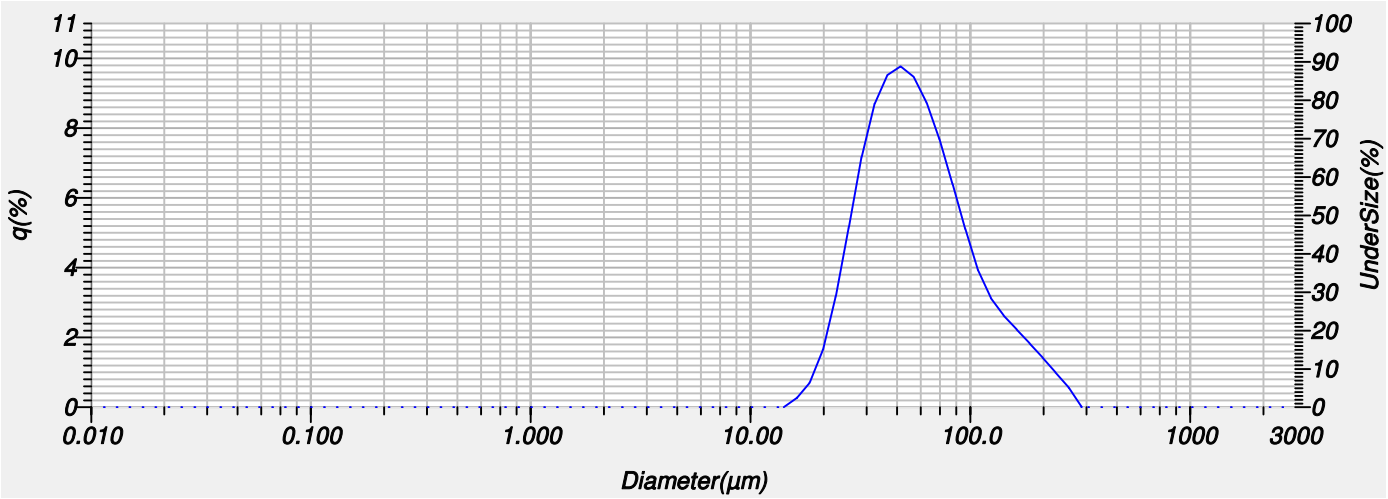
Sample Name	: Sample H	Median Size	: 43.24837(µm)	: (	
ID#	: 200709041139822	Mean Size	: 50.50944(µm)		
Data Name	: 200709041139822	Std.Dev.	: 28.6774(µm)		
Transmittance(R)	: 82.0(%)	Geo.Mean Size	: 44.4886(µm)		
Transmittance(B)	: 86.7(%)	Geo.Std.Dev.	: 1.6329(µm)		
Circulation Speed	: 3	Mode Size	: 41.8895(µm)		
Agitation Speed	: 1	Span	: 1.4000		
Ultra Sonic	: OFF	Diameter on Cumulative %	: (1)5.000 (%)- 20.8541(µm)		
Form of Distribution	: Auto		: (2)10.00 (%)- 24.1462(µm)		
Distribution Base	: Volume		: (3)20.00 (%)- 29.1484(µm)		
Refractive Index (R)	: Clorox1[Clorox(1.460 - 0.000i),IPA(1.3		: (4)30.00 (%)- 33.6146(µm)		
Refractive Index (B)	: Clorox1[Clorox(1.460 - 0.000i),IPA(1.3		: (5)40.00 (%)- 38.1833(µm)		
Material	: Hydrophobic silica Disp		: (6)60.00 (%)- 49.1782(µm)		
Source	: 0 sec sonication		: (7)70.00 (%)- 56.5830(µm)		
Lot Number	: 3156062337		: (8)80.00 (%)- 66.7650(µm)		
Test or Assay. Number	: Rep 1		: (9)90.00 (%)- 84.6944(µm)		



No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)
1	0.011	0.000	0.000	24	0.259	0.000	0.000	47	5.867	0.000	0.000	70	133.103	1.260	97.925	93	3000.000	0.000
2	0.013	0.000	0.000	25	0.296	0.000	0.000	48	6.720	0.000	0.000	71	152.453	0.825	98.750			
3	0.015	0.000	0.000	26	0.339	0.000	0.000	49	7.697	0.000	0.000	72	174.616	0.541	99.291			
4	0.017	0.000	0.000	27	0.389	0.000	0.000	50	8.816	0.000	0.000	73	200.000	0.351	99.642			
5	0.020	0.000	0.000	28	0.445	0.000	0.000	51	10.097	0.000	0.000	74	229.075	0.222	99.865			
6	0.022	0.000	0.000	29	0.510	0.000	0.000	52	11.565	0.000	0.000	75	262.376	0.135	100.000			
7	0.026	0.000	0.000	30	0.584	0.000	0.000	53	13.246	0.186	0.186	76	300.518	0.000	100.000			
8	0.029	0.000	0.000	31	0.669	0.000	0.000	54	15.172	0.441	0.626	77	344.206	0.000	100.000			
9	0.034	0.000	0.000	32	0.766	0.000	0.000	55	17.377	0.999	1.626	78	394.244	0.000	100.000			
10	0.039	0.000	0.000	33	0.877	0.000	0.000	56	19.904	2.074	3.700	79	451.556	0.000	100.000			
11	0.044	0.000	0.000	34	1.005	0.000	0.000	57	22.797	3.782	7.482	80	517.200	0.000	100.000			
12	0.051	0.000	0.000	35	1.151	0.000	0.000	58	26.111	5.943	13.425	81	592.387	0.000	100.000			
13	0.058	0.000	0.000	36	1.318	0.000	0.000	59	29.907	8.110	21.535	82	678.504	0.000	100.000			
14	0.067	0.000	0.000	37	1.510	0.000	0.000	60	34.255	9.831	31.366	83	777.141	0.000	100.000			
15	0.076	0.000	0.000	38	1.729	0.000	0.000	61	39.234	10.793	42.159	84	890.116	0.000	100.000			
16	0.087	0.000	0.000	39	1.981	0.000	0.000	62	44.938	10.926	53.085	85	1019.515	0.000	100.000			
17	0.100	0.000	0.000	40	2.269	0.000	0.000	63	51.471	10.410	63.494	86	1167.725	0.000	100.000			
18	0.115	0.000	0.000	41	2.599	0.000	0.000	64	58.953	9.325	72.819	87	1337.481	0.000	100.000			
19	0.131	0.000	0.000	42	2.976	0.000	0.000	65	67.523	7.833	80.652	88	1531.914	0.000	100.000			
20	0.150	0.000	0.000	43	3.409	0.000	0.000	66	77.339	6.250	86.902	89	1754.613	0.000	100.000			
21	0.172	0.000	0.000	44	3.905	0.000	0.000	67	88.583	4.629	91.531	90	2009.687	0.000	100.000			
22	0.197	0.000	0.000	45	4.472	0.000	0.000	68	101.460	3.146	94.677	91	2301.841	0.000	100.000			
23	0.226	0.000	0.000	46	5.122	0.000	0.000	69	116.210	1.987	96.665	92	2636.467	0.000	100.000			

HORIBA Laser Scattering Particle Size Distribution Analyzer LA-950

Sample Name	: Sample I	Median Size	: 54.48487(µm)
ID#	: 201009241056618	Mean Size	: 69.05283(µm)
Data Name	: 201009241056618	Std.Dev.	: 46.5359(µm)
Transmittance(R)	: 77.2(%)	Geo.Mean Size	: 57.9947(µm)
Transmittance(B)	: 87.3(%)	Geo.Std.Dev.	: 1.7656(µm)
Circulation Speed	: 3	Mode Size	: 48.0794(µm)
Agitation Speed	: 1	Span	: 1.8580
Ultra Sonic	: OFF	Diameter on Cumulative %	: (1)5.000 (%)- 25.2968(µm)
Form of Distribution	: Manual		: (2)10.00 (%)- 29.2186(µm)
Distribution Base	: Volume		: (3)20.00 (%)- 35.3152(µm)
Refractive Index (R)	: Hydrophobic Silica[silica(1.459 - 0.00(		: (4)30.00 (%)- 41.1002(µm)
Refractive Index (B)	: Hydrophobic Silica[silica(1.459 - 0.00(		: (5)40.00 (%)- 47.3356(µm)
Material	: SiO2		: (6)60.00 (%)- 63.2228(µm)
Source	: 0 Min Sonic		: (7)70.00 (%)- 74.7645(µm)
Lot Number	: 3158031235		: (8)80.00 (%)- 92.6265(µm)
Test or Assay. Number	: Rep 1		: (9)90.00 (%)- 130.4505(µm)



No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)	UnderSize(%)	No.	Diameter(µm)	q(%)
1	0.011	0.000	0.000	24	0.259	0.000	0.000	47	5.867	0.000	0.000	70	133.103	3.107	90.461	93	3000.000	0.000
2	0.013	0.000	0.000	25	0.296	0.000	0.000	48	6.720	0.000	0.000	71	152.453	2.611	93.072			
3	0.015	0.000	0.000	26	0.339	0.000	0.000	49	7.697	0.000	0.000	72	174.616	2.203	95.275			
4	0.017	0.000	0.000	27	0.389	0.000	0.000	50	8.816	0.000	0.000	73	200.000	1.809	97.084			
5	0.020	0.000	0.000	28	0.445	0.000	0.000	51	10.097	0.000	0.000	74	229.075	1.397	98.481			
6	0.022	0.000	0.000	29	0.510	0.000	0.000	52	11.565	0.000	0.000	75	262.376	0.977	99.457			
7	0.026	0.000	0.000	30	0.584	0.000	0.000	53	13.246	0.000	0.000	76	300.518	0.543	100.000			
8	0.029	0.000	0.000	31	0.669	0.000	0.000	54	15.172	0.000	0.000	77	344.206	0.000	100.000			
9	0.034	0.000	0.000	32	0.766	0.000	0.000	55	17.377	0.257	0.257	78	394.244	0.000	100.000			
10	0.039	0.000	0.000	33	0.877	0.000	0.000	56	19.904	0.701	0.959	79	451.556	0.000	100.000			
11	0.044	0.000	0.000	34	1.005	0.000	0.000	57	22.797	1.624	2.583	80	517.200	0.000	100.000			
12	0.051	0.000	0.000	35	1.151	0.000	0.000	58	26.111	3.154	5.736	81	592.387	0.000	100.000			
13	0.058	0.000	0.000	36	1.318	0.000	0.000	59	29.907	5.147	10.883	82	678.504	0.000	100.000			
14	0.067	0.000	0.000	37	1.510	0.000	0.000	60	34.255	7.164	18.047	83	777.141	0.000	100.000			
15	0.076	0.000	0.000	38	1.729	0.000	0.000	61	39.234	8.696	26.742	84	890.116	0.000	100.000			
16	0.087	0.000	0.000	39	1.981	0.000	0.000	62	44.938	9.517	36.259	85	1019.515	0.000	100.000			
17	0.100	0.000	0.000	40	2.269	0.000	0.000	63	51.471	9.768	46.028	86	1167.725	0.000	100.000			
18	0.115	0.000	0.000	41	2.599	0.000	0.000	64	58.953	9.474	55.502	87	1337.481	0.000	100.000			
19	0.131	0.000	0.000	42	2.976	0.000	0.000	65	67.523	8.732	64.233	88	1531.914	0.000	100.000			
20	0.150	0.000	0.000	43	3.409	0.000	0.000	66	77.339	7.683	71.917	89	1754.613	0.000	100.000			
21	0.172	0.000	0.000	44	3.905	0.000	0.000	67	88.583	6.403	78.320	90	2009.687	0.000	100.000			
22	0.197	0.000	0.000	45	4.472	0.000	0.000	68	101.460	5.108	83.428	91	2301.841	0.000	100.000			
23	0.226	0.000	0.000	46	5.122	0.000	0.000	69	116.210	3.926	87.354	92	2636.467	0.000	100.000			

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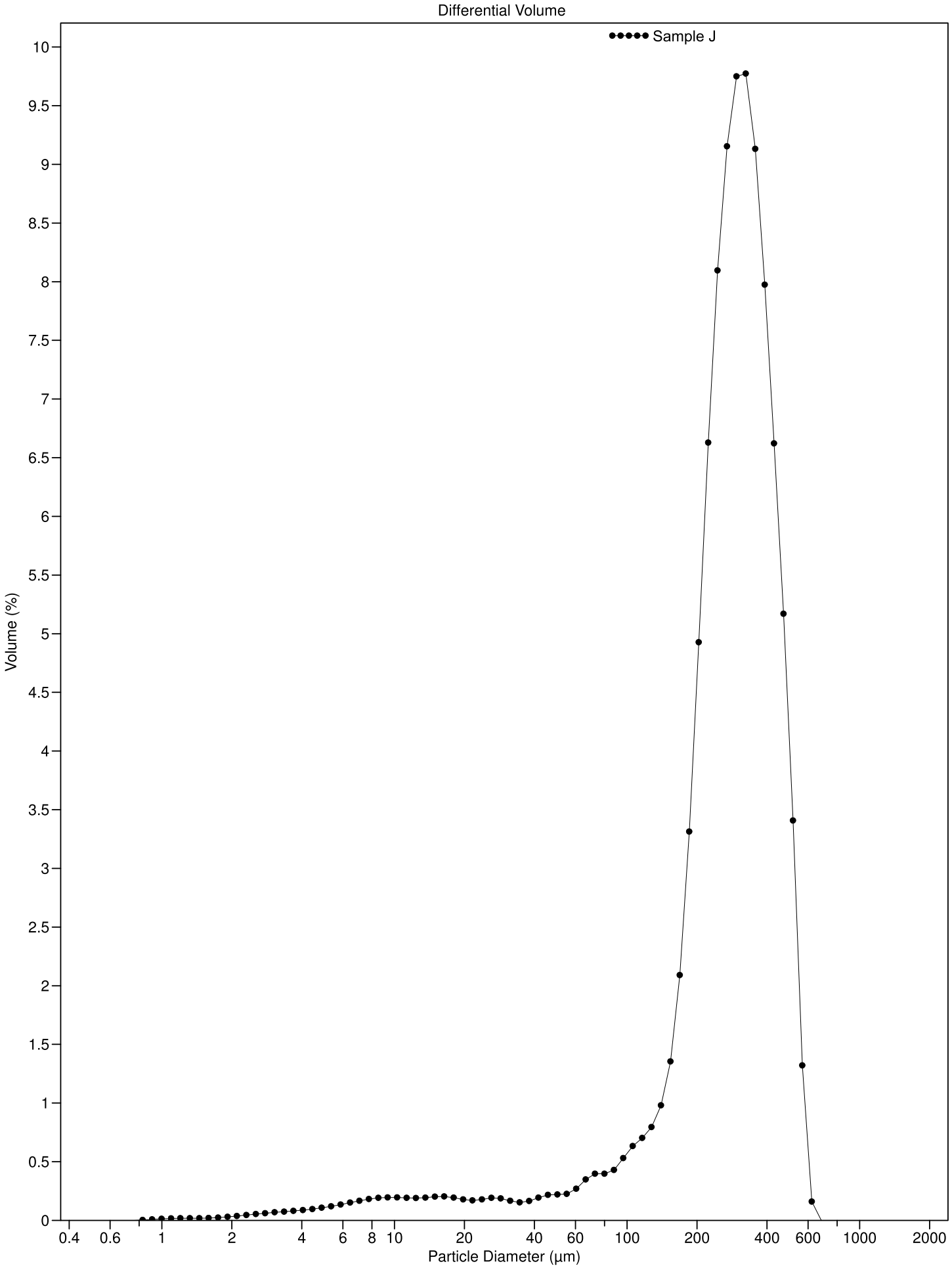
Operator:	1		
Bar code:	1 min Sonication		
Run number:	Fraunhofer.rfd		
Comment 2:	0.31%		
Optical model:	Small Volume Module		
Residual:	11:16 12 Jun 2015	Run length:	90 seconds
LS 230	10%		
Start time:	Water		
Obscuration:	2.2 g/mL		
Fluid:	3.39	Firmware:	4.00
Sample Density:			
Software:			


Differential Volume
Sample J
Volume (%)
Particle Diameter (µm)
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
5.5
6
6.5
7
7.5
8
8.5
9
9.5
10
0.4
0.6
1
2
4
6
8
10
20
40
60
100
200
400
600
1000
2000

Volume Statistics (Arithmetic) Sample J

Calculations from 0.375 µm to 2000 µm

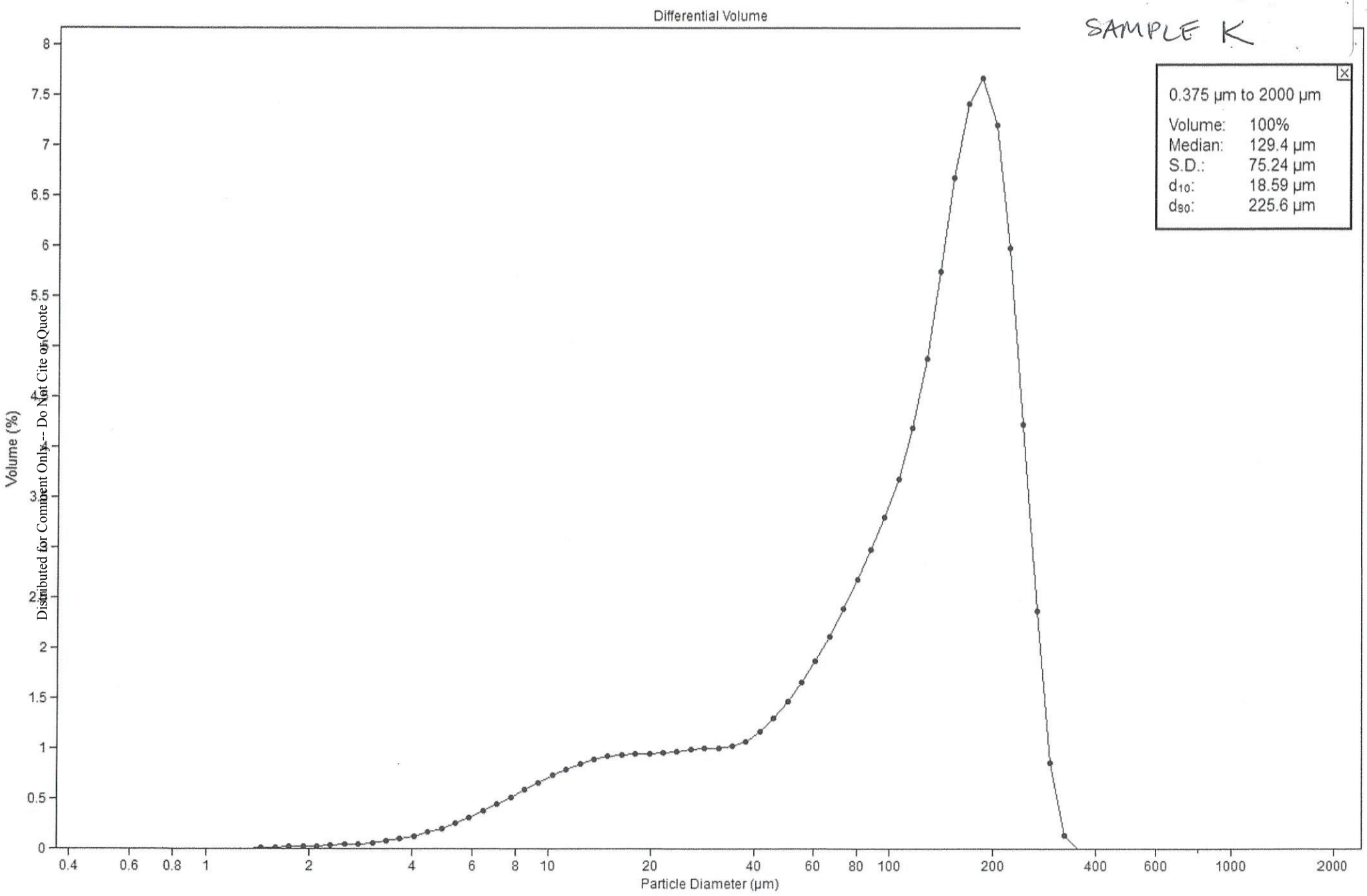
Volume:	100%		
Mean:	291.0 µm	S.D.:	122.9 µm
Median:	291.4 µm	Variance:	15101 μm^2
D(3,2):	96.90 µm	Skewness:	-0.200 Left skewed
Mode:	324.4 µm	Kurtosis:	-0.027 Platykurtic

d_{10}: 131.4 µm d_{50}: 291.4 µm d_{90}: 450.1 µm

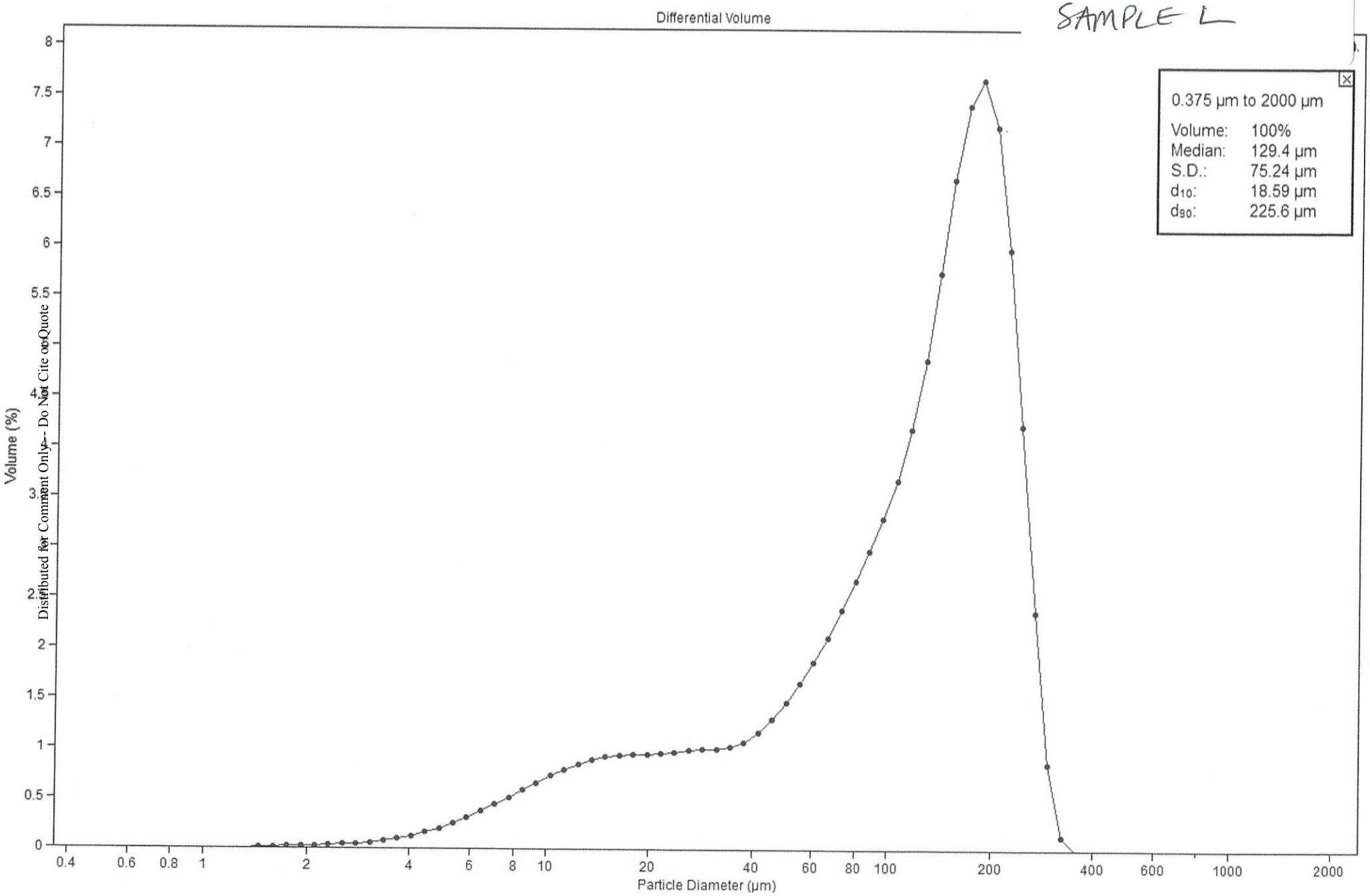
<1 µm	<10 µm	<100 µm	<1000 µm
0.019%	2.07%	7.96%	100%

Sample J

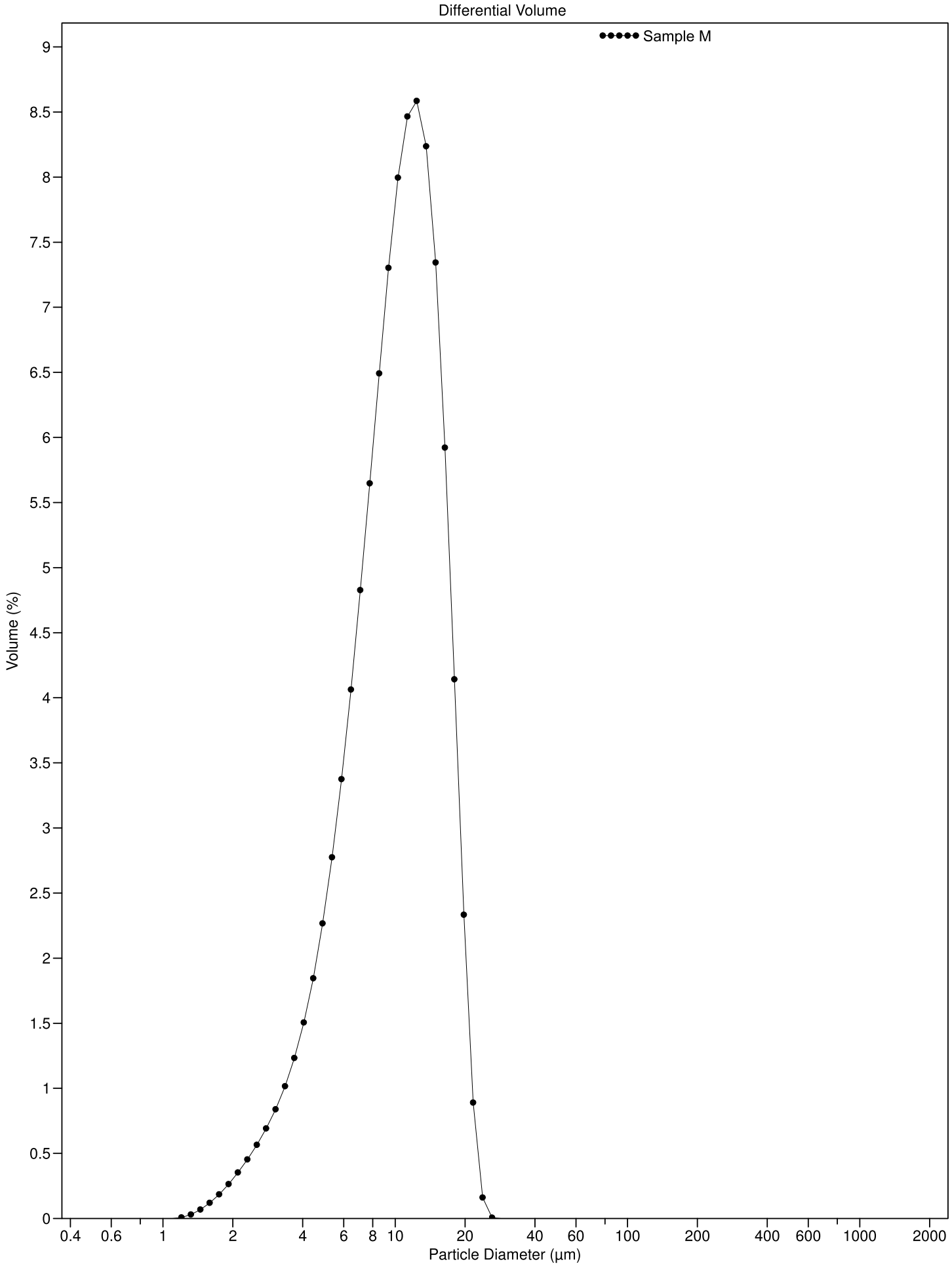
Channel Number	Channel Diameter (Lower) µm	Diff. Volume %	Channel Number	Channel Diameter (Lower) µm	Diff. Volume %
1	0.375	0	48	30.07	0.17
2	0.412	0	49	33.01	0.15
3	0.452	0	50	36.24	0.16
4	0.496	0	51	39.78	0.19
5	0.545	0	52	43.67	0.22
6	0.598	0	53	47.94	0.22
7	0.656	0	54	52.62	0.23
8	0.721	0	55	57.77	0.27
9	0.791	0.0032	56	63.41	0.35
10	0.868	0.0091	57	69.61	0.40
11	0.953	0.014	58	76.42	0.40
12	1.047	0.017	59	83.89	0.43
13	1.149	0.018	60	92.09	0.53
14	1.261	0.018	61	101.1	0.63
15	1.385	0.019	62	111.0	0.70
16	1.520	0.021	63	121.8	0.80
17	1.668	0.024	64	133.7	0.98
18	1.832	0.030	65	146.8	1.35
19	2.011	0.037	66	161.2	2.09
20	2.207	0.045	67	176.9	3.31
21	2.423	0.054	68	194.2	4.93
22	2.660	0.061	69	213.2	6.63
23	2.920	0.068	70	234.1	8.10
24	3.205	0.075	71	256.9	9.15
25	3.519	0.081	72	282.1	9.75
26	3.863	0.088	73	309.6	9.77
27	4.240	0.096	74	339.9	9.13
28	4.655	0.11	75	373.1	7.97
29	5.110	0.12	76	409.6	6.62
30	5.610	0.14	77	449.7	5.17
31	6.158	0.15	78	493.6	3.41
32	6.760	0.17	79	541.9	1.32
33	7.421	0.18	80	594.9	0.16
34	8.147	0.19	81	653.0	0
35	8.943	0.20	82	716.8	0
36	9.817	0.20	83	786.9	0
37	10.78	0.19	84	863.9	0
38	11.83	0.19	85	948.3	0
39	12.99	0.19	86	1041	0
40	14.26	0.20	87	1143	0
41	15.65	0.20	88	1255	0
42	17.18	0.19	89	1377	0
43	18.86	0.18	90	1512	0
44	20.70	0.17	91	1660	0
45	22.73	0.18	92	1822	0
46	24.95	0.19		2000	
47	27.39	0.19			



SAMPLE L



File name:	L:\IM-Analytical\Coulter LS230 Data Files\		
File ID:	150417		
Sample ID:	Sample M		
Operator:	dpb		
Bar code:	314031741		
Run number:	1		
Comment 2:	0 min Sonication		
Optical model:	Fraunhofer.rfd		
Residual:	0.13%		
LS 230	Small Volume Module		
Start time:	11:25 17 Apr 2015	Run length:	90 seconds
Obscuration:	10%		
Fluid:	Water		
Sample Density:	2.2 g/mL		
Software:	3.39	Firmware:	4.00


Differential Volume
Sample M
Volume (%)
Particle Diameter (µm)
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
5.5
6
6.5
7
7.5
8
8.5
9
0.4
0.6
1
2
4
6
8
10
20
40
60
100
200
400
600
1000
2000

Volume Statistics (Arithmetic) Sample M

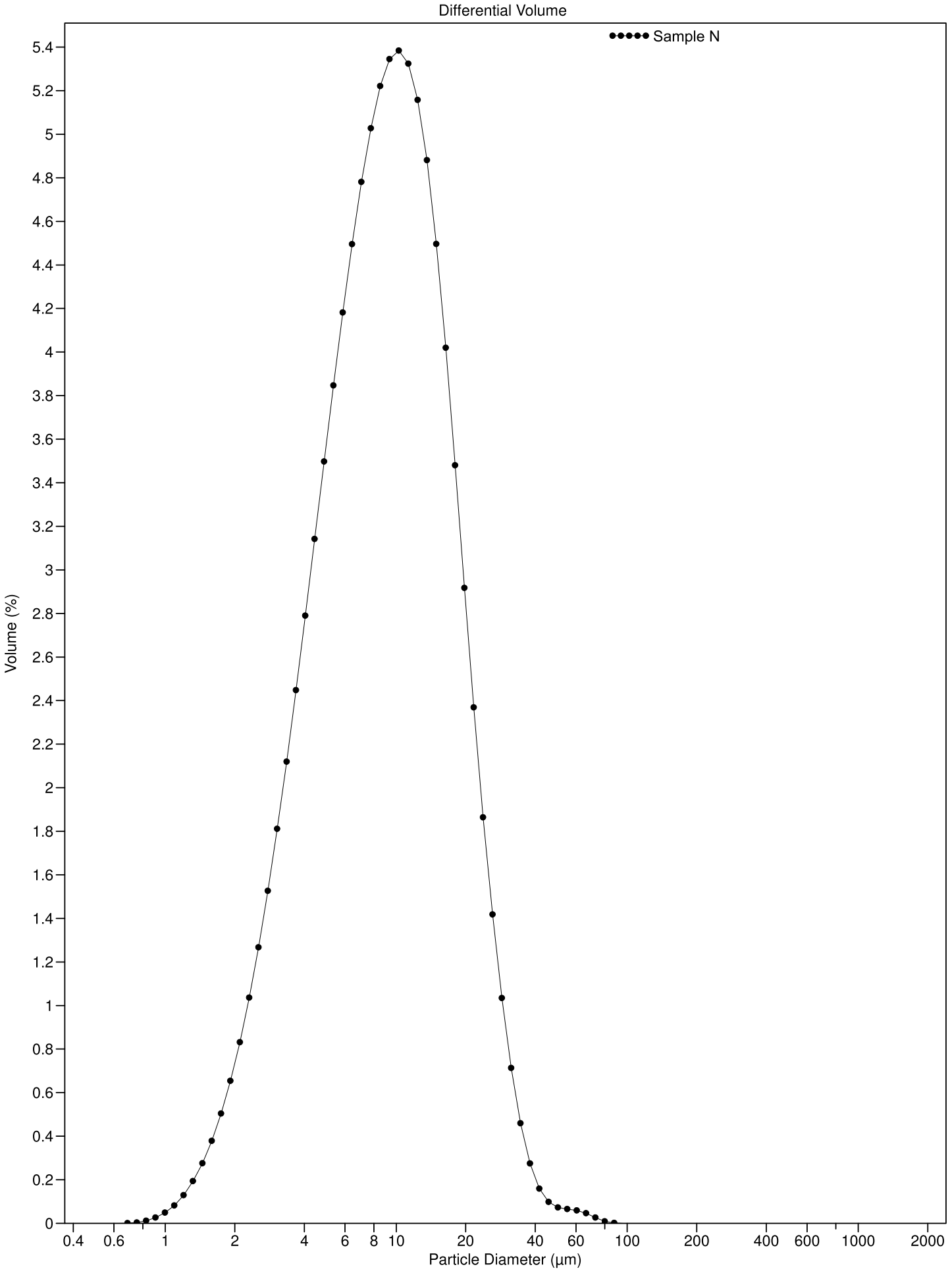
Calculations from 0.375 µm to 2000 µm

Volume:	100%		
Mean:	10.52 µm	S.D.:	4.391 µm
Median:	10.31 µm	Variance:	19.28 μm^2
D(3,2):	8.240 µm	Skewness:	0.250 Right skewed
Mode:	12.40 µm	Kurtosis:	-0.476 Platykurtic

d_{10}: 4.820 µm d_{50}: 10.31 µm d_{90}: 16.54 µm

<1 µm	<10 µm	<100 µm	<1000 µm
0%	47.4%	100%	100%

File name:	L:\IM-Analytical\Coulter LS230 Data Files\		
File ID:	15071		
Sample ID:	Sample N		
Operator:	CA		
Bar code:	lot#314111711		
Comment 2:	min Sonication		
Optical model:	Fraunhofer.rfd		
Residual:	0.32%		
LS 230	Small Volume Module		
Start time:	8:27 15 Jul 2015	Run length:	90 seconds
Obscuration:	9%		
Fluid:	Water		
Sample Density:	2.2 g/mL		
Software:	3.39	Firmware:	4.00


Differential Volume
Sample N
Volume (%)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
2.2
2.4
2.6
2.8
3
3.2
3.4
3.6
3.8
4
4.2
4.4
4.6
4.8
5
5.2
5.4
0.4
0.6
1
2
4
6
8
10
20
40
60
100
200
400
600
1000
2000
Particle Diameter (µm)

Volume Statistics (Arithmetic) Sample N

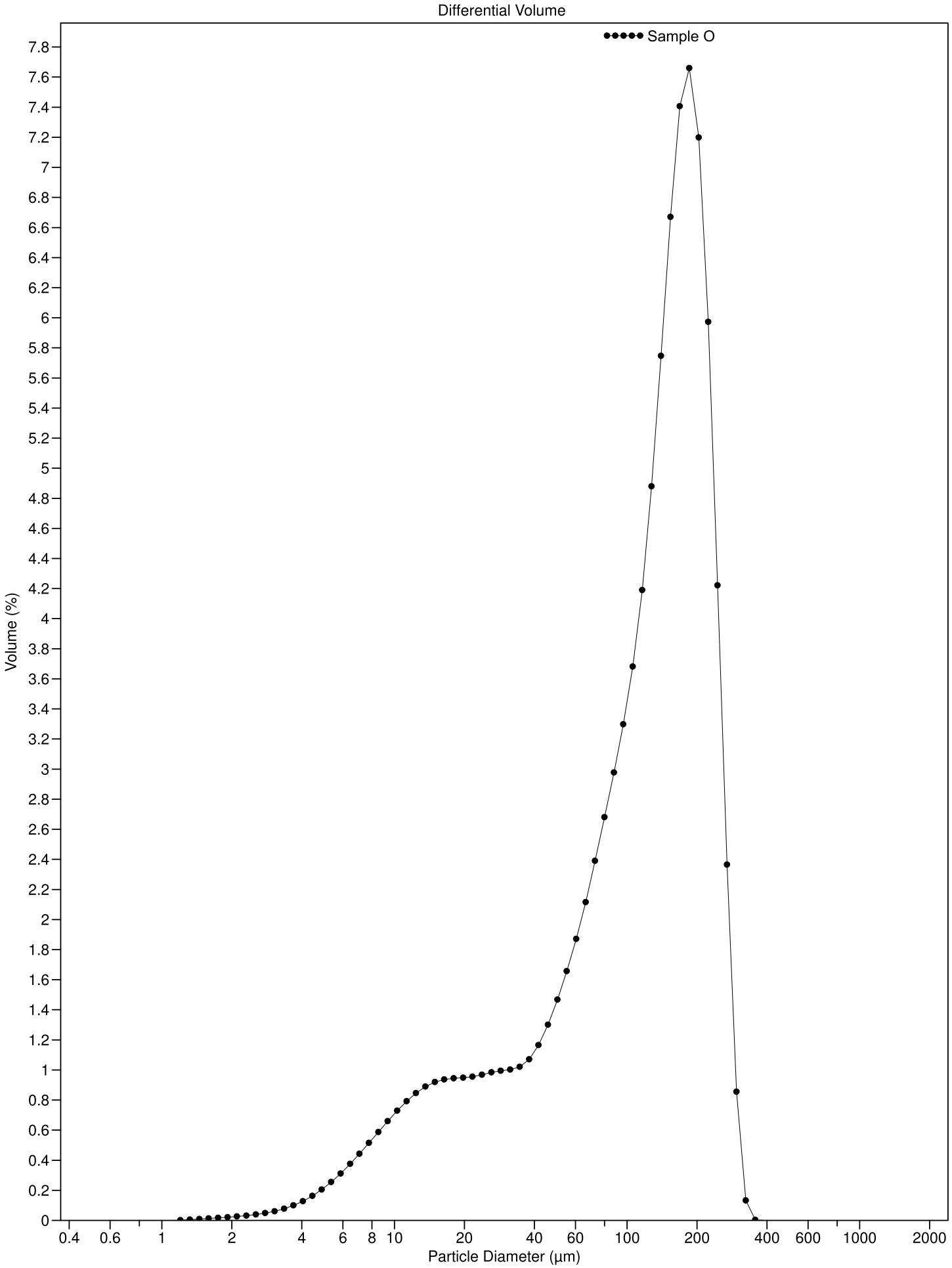
Calculations from 0.375 µm to 2000 µm

Volume:	100%		
Mean:	10.59 µm	S.D.:	7.315 µm
Median:	8.893 µm	Variance:	53.52 μm^2
D(3,2):	6.670 µm	Skewness:	1.971 Right skewed
Mode:	10.29 µm	Kurtosis:	7.720 Leptokurtic

d_{10}: 3.386 µm d_{50}: 8.893 µm d_{90}: 19.86 µm

<1 µm	<10 µm	<100 µm	<1000 µm
0.068%	56.7%	100%	100%

File name:	L:\IM-Analytical\Coulter LS230 Data Files\		
File ID:	02272013		
Sample ID:	Sample O		
Bar code:	lot#1578223		
Run number:	1		
Comment 2:	0 min Sonication		
Optical model:	Silica.rfd		
Fluid R.I.:	1.33	Sample R.I.:	1.46 i0.1
Residual:	0.24%		
LS 230	Small Volume Module		
Start time:	9:56 27 Feb 2013	Run length:	60 seconds
Obscuration:	9%		
Fluid:	Water		
Sample Density:	2.2 g/mL		
Software:	3.39 3.19	Firmware:	2.02


Differential Volume
Sample O
Volume (%)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
2.2
2.4
2.6
2.8
3
3.2
3.4
3.6
3.8
4
4.2
4.4
4.6
4.8
5
5.2
5.4
5.6
5.8
6
6.2
6.4
6.6
6.8
7
7.2
7.4
7.6
7.8
0.4
0.6
1
2
4
6
8
10
20
40
60
100
200
400
600
1000
2000
Particle Diameter (µm)

Volume Statistics (Arithmetic) Sample O

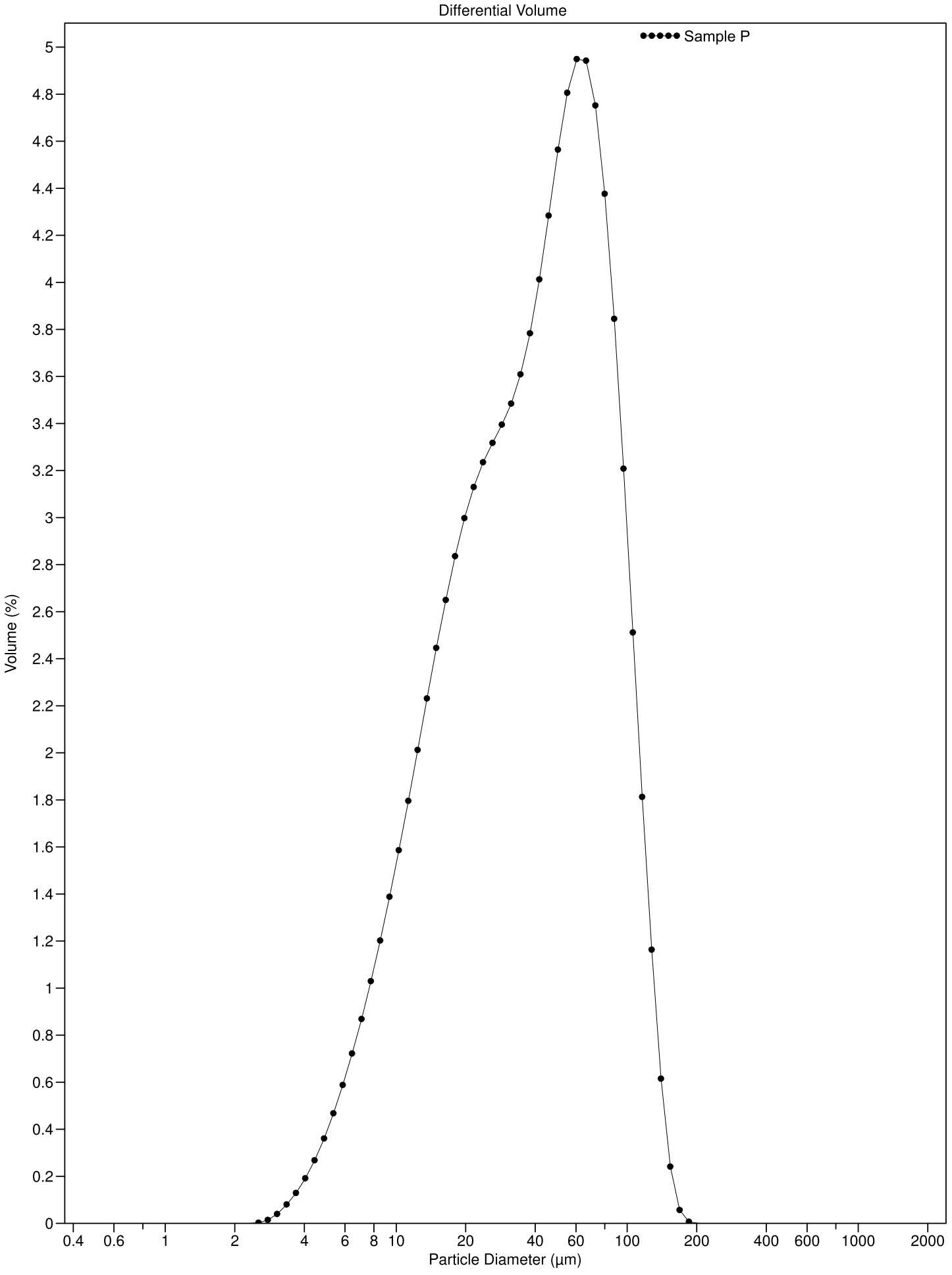
Calculations from 0.375 µm to 2000 µm

Volume:	100%		
Mean:	126.0 µm	S.D.:	75.24 µm
Median:	129.4 µm	Variance:	5662 μm^2
D(3,2):	46.94 µm	Skewness:	0.072 Right skewed
Mode:	185.4 µm	Kurtosis:	-0.965 Platykurtic

d_{10}: 18.59 µm d_{50}: 129.4 µm d_{90}: 225.6 µm

<1 µm	<10 µm	<100 µm	<1000 µm
0%	4.23%	38.6%	100%

File name:	L:\IM-Analytical\Coulter LS230 Data Files\		
File ID:	120626		
Sample ID:	Sample P		
Operator:	CA		
Bar code:	1214143		
Run number:	1		
Comment 2:	No Sonication		
Optical model:	Silica.rfd		
Fluid R.I.:	1.33	Sample R.I.:	1.46 i0.1
Residual:	0.34%		
LS 230	Small Volume Module		
Start time:	14:09 26 Jun 2012	Run length:	60 seconds
Obscuration:	10%		
Fluid:	Water		
Sample Density:	2.2 g/mL		
Software:	3.39 3.19	Firmware:	2.02


Differential Volume
Sample P
Volume (%)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
2.2
2.4
2.6
2.8
3
3.2
3.4
3.6
3.8
4
4.2
4.4
4.6
4.8
5
0.4
0.6
1
2
4
6
8
10
20
40
60
100
200
400
600
1000
2000
Particle Diameter (µm)

Volume Statistics (Arithmetic) Sample P

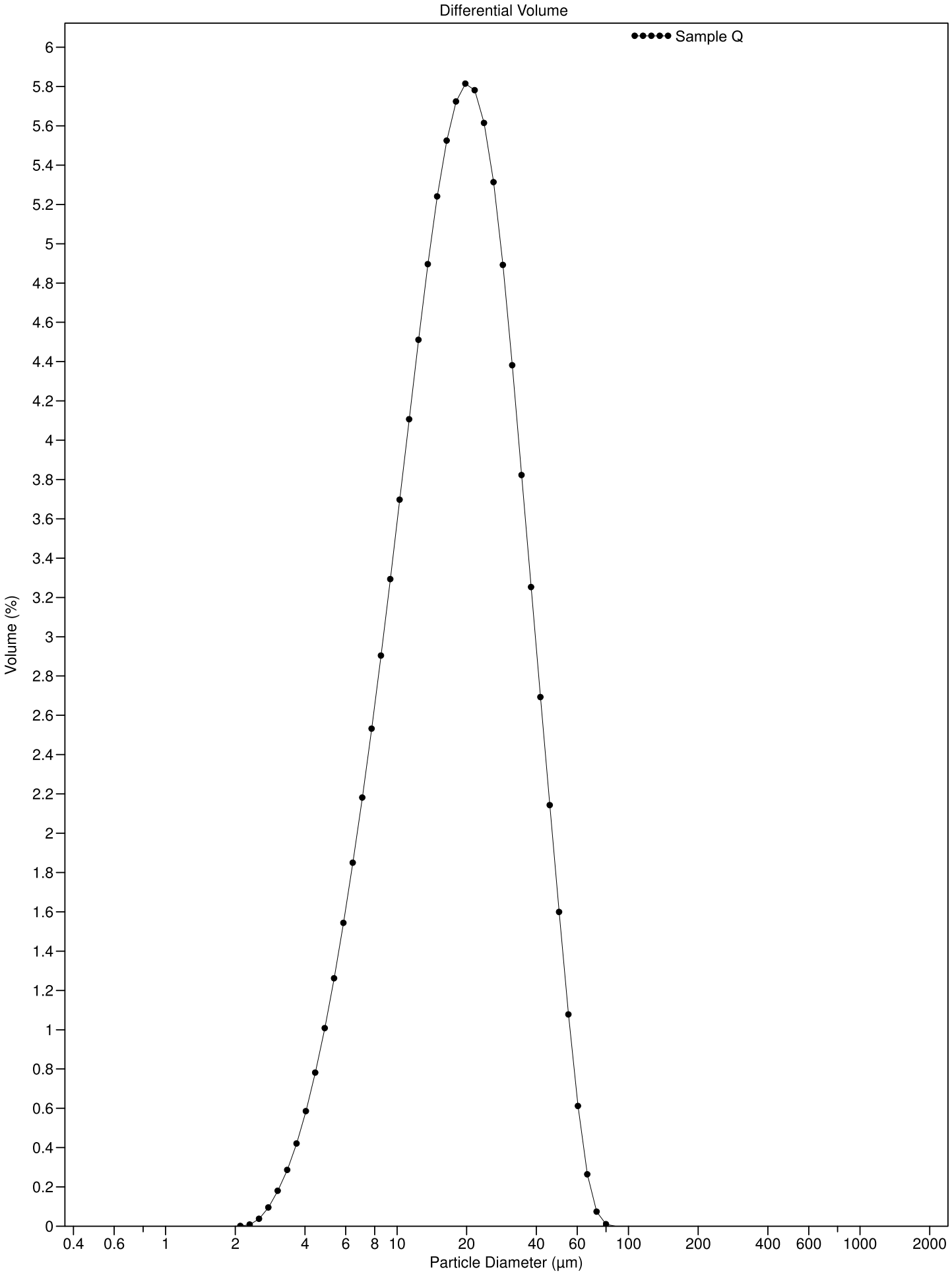
Calculations from 0.375 µm to 2000 µm

Volume:	100%		
Mean:	46.31 µm	S.D.:	31.33 µm
Median:	39.92 µm	Variance:	981.6 μm^2
D(3,2):	25.05 µm	Skewness:	0.826 Right skewed
Mode:	60.52 µm	Kurtosis:	0.125 Leptokurtic

d_{10}: 11.40 µm d_{50}: 39.92 µm d_{90}: 91.27 µm

<1 µm	<10 µm	<100 µm	<1000 µm
0%	7.65%	93.2%	100%

File name:	L:\IM-Analytical\Coulter LS230 Data Files\		
File ID:	120626		
Sample ID:	Sample Q		
Operator:	CA		
Bar code:	1265071		
Run number:	1		
Comment 2:	No Sonication		
Optical model:	Silica.rfd		
Fluid R.I.:	1.33	Sample R.I.:	1.46 i0.1
Residual:	0.39%		
LS 230	Small Volume Module		
Start time:	14:16 26 Jun 2012	Run length:	60 seconds
Obscuration:	8%		
Fluid:	Water		
Sample Density:	2.2 g/mL		
Software:	3.39 3.19	Firmware:	2.02


Differential Volume
Sample Q
Volume (%)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
2.2
2.4
2.6
2.8
3
3.2
3.4
3.6
3.8
4
4.2
4.4
4.6
4.8
5
5.2
5.4
5.6
5.8
6
0.4
0.6
1
2
4
6
8
10
20
40
60
100
200
400
600
1000
2000
Particle Diameter (µm)

Volume Statistics (Arithmetic) Sample Q

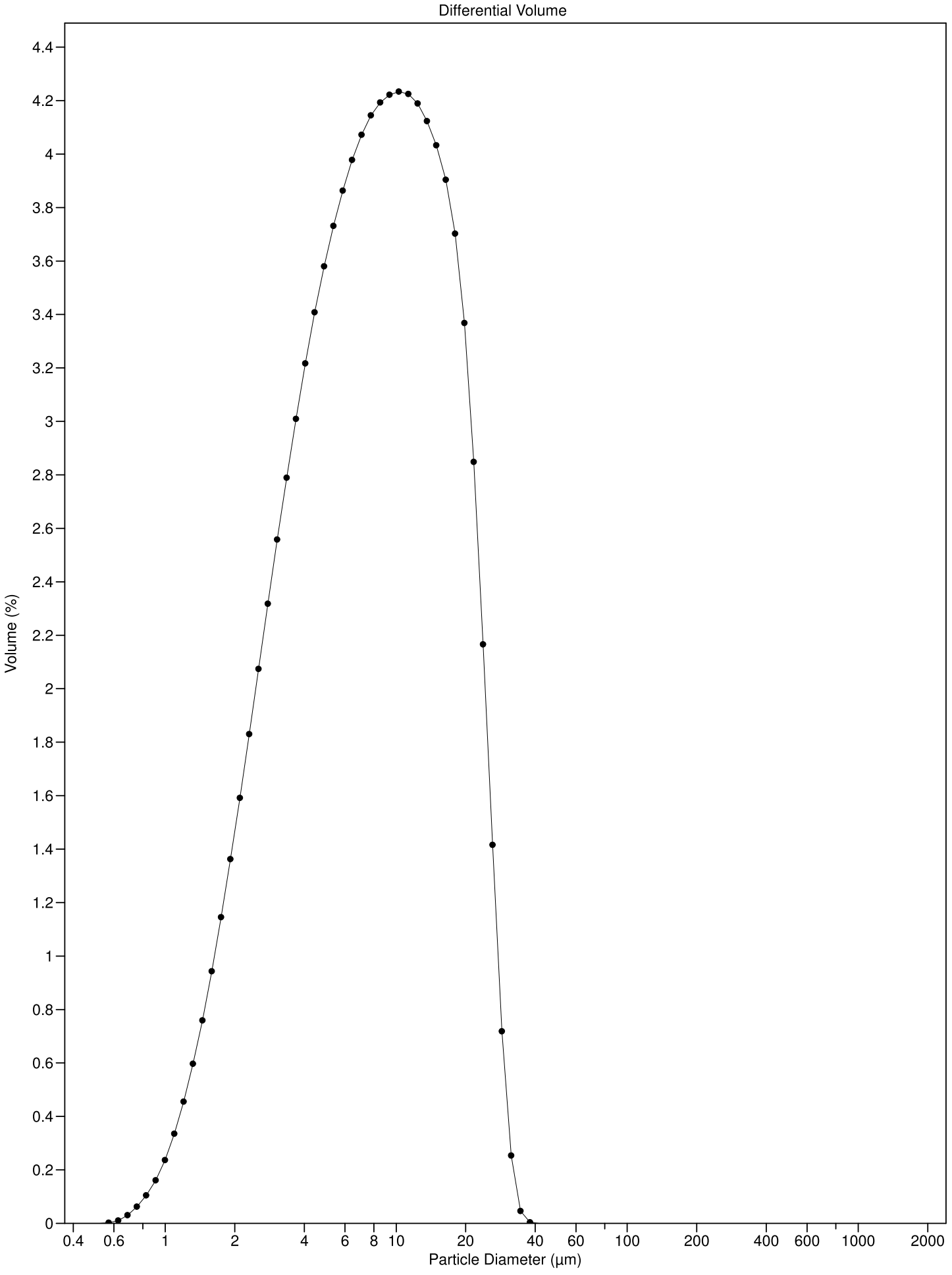
Calculations from 0.375 µm to 2000 µm

Volume:	100%		
Mean:	20.69 µm	S.D.:	12.24 µm
Median:	18.08 µm	Variance:	149.8 μm^2
D(3,2):	14.12 µm	Skewness:	1.047 Right skewed
Mode:	19.76 µm	Kurtosis:	0.949 Leptokurtic

d_{10}: 7.350 µm d_{50}: 18.08 µm d_{90}: 38.11 µm

<1 µm	<10 µm	<100 µm	<1000 µm
0%	19.7%	100%	100%

File name:	L:\IM-Analytical\Coulter LS230 Data Files\ 012 Projects\120701_ ot#531_01.$ls 120701_ _lot#531_01.$ls		
File ID:	120701		
Sample ID:	Sample R		
Operator:	CA &DPB		
Bar code:	lot#531		
Run number:	1		
Comment 2:	no Sonication		
Optical model:	Silica.rfd		
Fluid R.I.:	1.33	Sample R.I.:	1.46 i0.1
Residual:	0.20%		
LS 230	Small Volume Module		
Start time:	9:59 2 Jul 2012	Run length:	60 seconds
Obscuration:	9%		
Fluid:	Water		
Sample Density:	2.2 g/mL		
Software:	3.39 3.19	Firmware:	2.02


Differential Volume
Volume (%)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
2.2
2.4
2.6
2.8
3
3.2
3.4
3.6
3.8
4
4.2
4.4
0.4
0.6
1
2
4
6
8
10
20
40
60
100
200
400
600
1000
2000
Particle Diameter (µm)

Volume Statistics (Arithmetic) Sample R

Calculations from 0.375 µm to 2000 µm

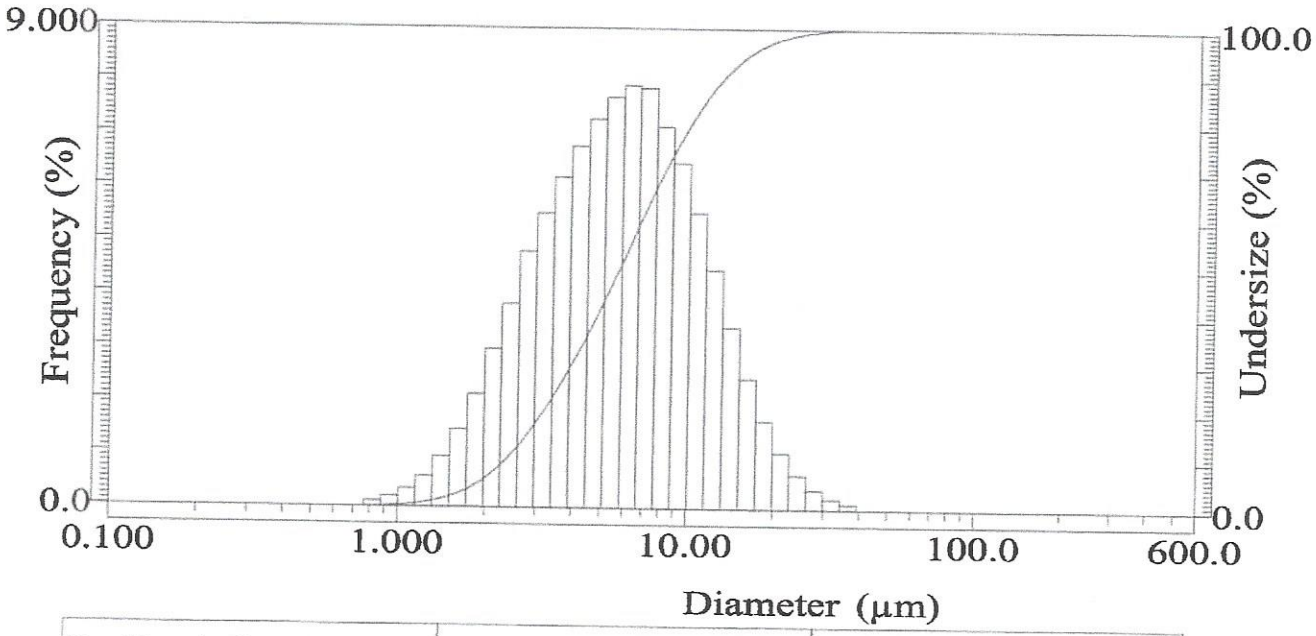
Volume:	100%		
Mean:	9.448 µm	S.D.:	6.536 µm
Median:	7.733 µm	Variance:	42.71 μm^2
D(3,2):	5.286 µm	Skewness:	0.923 Right skewed
Mode:	10.29 µm	Kurtosis:	0.184 Leptokurtic

d_{10}: 2.466 µm d_{50}: 7.733 µm d_{90}: 19.31 µm

<1 µm	<10 µm	<100 µm	<1000 µm
0.49%	61.6%	100%	100%

Filename	:
ID#	:201806101538812 SAMPLE S
Circulation Speed	:6
Ultra sonic	:01:00
Laser T%	: 75.7(%)
Distribution Base	:Volume
R.R.Index	:1.18-0.10i
Axis Selection	:LogX-LinY
Sample Name	:ZFR 600 CH-1034-186-14
Material	:N/A
Lot Number	:N/A
Sample Preparation	:
Dispersion Medium	:
Dispersion Steps	:

Median	:	5.787(μm)
Diameter on %	:	(1)5.000 (%)- 1.892(μm)
		(2)10.00 (%)- 2.377(μm)
		(3)20.00 (%)- 3.181(μm)
		(4)30.00 (%)- 3.984(μm)
		(5)40.00 (%)- 4.838(μm)
		(6)60.00 (%)- 6.873(μm)
		(7)70.00 (%)- 8.215(μm)
		(8)80.00 (%)- 10.058(μm)
		(9)90.00 (%)- 13.171(μm)
		(10)95.00 (%)- 16.414(μm)
% on Diameter		
Mean	:	7.008(μm)
S.D.	:	4.801(μm)
Mode	:	6.288(μm)
Span	:	2.509



No.	Diameter	Freq. %	Under %	No.	Diameter	Freq. %	Under %	No.	Diameter	Freq. %	Under %
1	0.115	0.000	0.000	25	2.976	4.797	17.300	49	77.339	0.000	100.000
2	0.131	0.000	0.000	26	3.409	5.518	22.818	50	88.583	0.000	100.000
3	0.150	0.000	0.000	27	3.905	6.182	28.999	51	101.460	0.000	100.000
4	0.172	0.000	0.000	28	4.472	6.777	35.776	52	116.210	0.000	100.000
5	0.197	0.000	0.000	29	5.122	7.297	43.073	53	133.103	0.000	100.000
6	0.226	0.000	0.000	30	5.867	7.701	50.774	54	152.453	0.000	100.000
7	0.259	0.000	0.000	31	6.720	7.918	58.692	55	174.616	0.000	100.000
8	0.296	0.000	0.000	32	7.697	7.868	66.561	56	200.000	0.000	100.000
9	0.339	0.000	0.000	33	8.816	7.157	73.718	57	229.075	0.000	100.000
10	0.389	0.000	0.000	34	10.097	6.468	80.186	58	262.376	0.000	100.000
11	0.445	0.000	0.000	35	11.565	5.532	85.718	59	300.518	0.000	100.000
12	0.510	0.000	0.000	36	13.246	4.469	90.187	60	344.206	0.000	100.000
13	0.584	0.000	0.000	37	15.172	3.400	93.588	61	394.244	0.000	100.000
14	0.669	0.000	0.000	38	17.377	2.436	96.023	62	451.556	0.000	100.000
15	0.766	0.000	0.000	39	19.904	1.643	97.666	63	517.200	0.000	100.000
16	0.877	0.110	0.110	40	22.797	1.045	98.711	64	592.387	0.000	100.000
17	1.005	0.193	0.303	41	26.111	0.629	99.340				
18	1.151	0.336	0.638	42	29.907	0.360	99.700				
19	1.318	0.572	1.211	43	34.255	0.197	99.897				
20	1.510	0.934	2.145	44	39.234	0.103	100.000				
21	1.729	1.451	3.596	45	44.938	0.000	100.000				
22	1.981	2.122	5.719	46	51.471	0.000	100.000				
23	2.269	2.966	8.685	47	58.953	0.000	100.000				
24	2.599	3.818	12.503	48	67.523	0.000	100.000				

Sympatec GmbH
System-Partikel-Technik

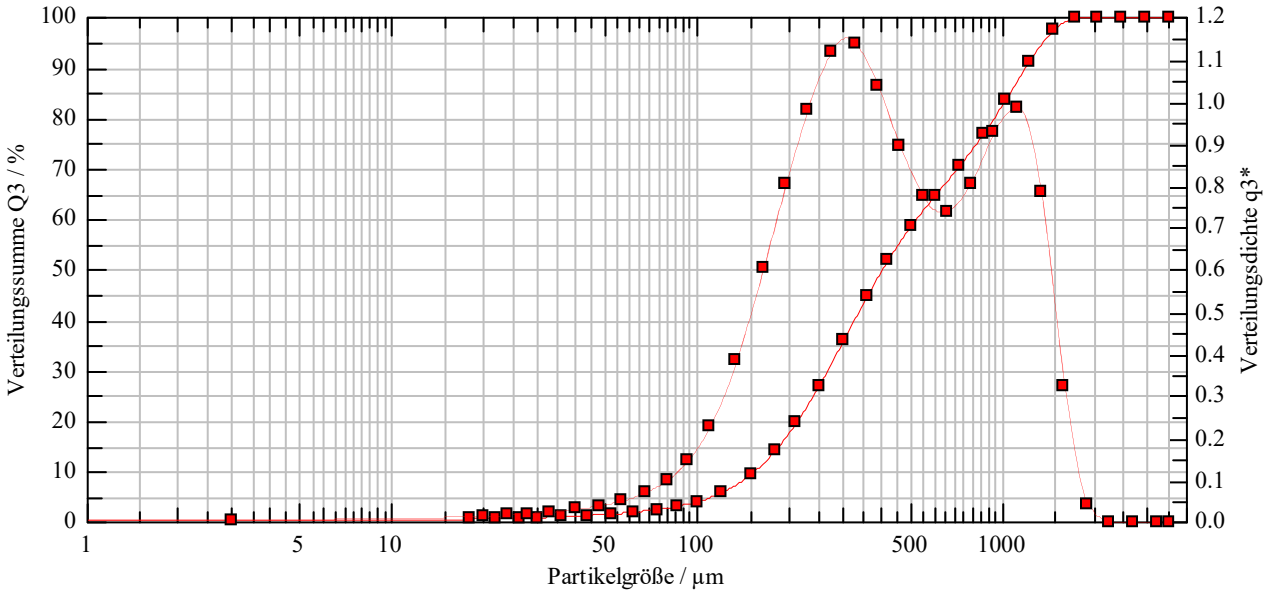
HELOS-Partikelgrößenanalyse
WINDOX 5

HELOS (H0089) & GRADIS, R7: 0.5/18.0...3500µm

Sample T **2012-06-15, 11:31:55**,543

WARNUNG: Vermutlich Meßbereichsüberschreitung durch grobe Partikel.

x_{10} = 153,75 µm	**x_{50} = 405,36 µm**	**x_{90} = 1190,32 µm**	**SMD = 263,23 µm**	**VMD = 555,06 µm**	
x_{16} = 190,26 µm	x_{84} = 1033,53 µm	x_{99} = 1660,59 µm	S_V = 0,02 m²/cm³	S_m = 227,94 cm²/g	



KFS-Magic 1060

Verteilungssumme

x_0/µm	Q_3/%	x_0/µm	Q_3/%	x_0/µm	Q_3/%	x_0/µm	Q_3/%
18,00	0,41	74,00	2,34	300,00	35,76	1220,00	91,14
22,00	0,51	86,00	2,98	360,00	44,75	1460,00	97,24
26,00	0,62	100,00	3,92	420,00	51,70	1740,00	99,69
30,00	0,74	120,00	5,70	500,00	58,47	2060,00	100,00
36,00	0,91	150,00	9,40	600,00	64,59	2460,00	100,00
44,00	1,16	180,00	14,17	720,00	70,42	2940,00	100,00
52,00	1,43	210,00	19,53	860,00	76,63	3500,00	100,00
62,00	1,81	250,00	26,93	1020,00	83,48		

Verteilungsdichte (log.)

x_m/µm	$q_3$lg	x_m/µm	$q_3$lg	x_m/µm	$q_3$lg	x_m/µm	$q_3$lg
3,00	0,00	67,73	0,07	273,86	1,11	1115,53	0,98
19,90	0,01	79,77	0,10	328,63	1,14	1334,62	0,78
23,92	0,02	92,74	0,14	388,84	1,04	1593,86	0,32
27,93	0,02	109,54	0,22	458,26	0,90	1893,25	0,04
32,86	0,02	134,16	0,38	547,72	0,77	2251,13	0,00
39,80	0,03	164,32	0,60	657,27	0,74	2689,31	0,00
47,83	0,04	194,42	0,80	786,89	0,80	3207,80	0,00
56,78	0,05	229,13	0,98	936,59	0,92		

Auswertung: WINDOX 5.7.1.0, *HRLD*

Revalidierung:
Referenzmessung: 06-15 11:30:45
Kontamination: 0,00 %

:Sample T

Dichte: 1,0000 g/cm³, Formfaktor: 1,000
Disp. Meth.: Gradis
C_{opt}= 5,06 %

Triggerbedingung: KMA Trocken

Start: c.opt >= 1%
Gültigkeit: immer
Stopp: 5s c.opt <= 1% oder 0s Echtzeit

Benutzerparameter:

Bediener: Höfellner
Bezeichnung:

Nanoscale Materials Stewardship Program (NMSP) Voluntary Submittal Package

for

Synthetic Amorphous Silica (CAS No. 7631-86-9)

Prepared for:

U.S. Environmental Protection Agency
Nanoscale Materials Stewardship Program
Office of Pollution Prevention and Toxics
1200 Pennsylvania Ave., NW
Washington, DC 20460-0001

Prepared by:

The Synthetic Amorphous Silica and Silicates Industry Association
815 Connecticut Ave., N.W., Suite 220
Washington, DC 20006

July 25, 2008

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Executive Summary

The Synthetic Amorphous Silica and Silicates Industry Association (SASSI) [1] is pleased to provide to the United States Environmental Protection Agency (US EPA) this data submission package for synthetic amorphous silica (SAS, CAS No. 7631-86-9) under the voluntary basic program of the Nanoscale Materials Stewardship Program (NMSP). SASSI recognizes the importance of the NMSP program and its aims to "gather existing data and information from manufacturers, importers, processors, and users of existing chemical nanoscale materials," to "identify and encourage use of risk management practices in developing and commercializing nanoscale materials," to "encourage the development of additional test data," and to "encourage responsible development of nanoscale materials." (US EPA, 2008). This submission package was prepared with the assistance of Gradient Corporation.

SASSI's data submission focuses on synthetic amorphous silica (SAS), a form of silicon dioxide (SiO_2) that is intentionally manufactured, and hence differs from other classes of amorphous silica (*i.e.*, naturally occurring amorphous silica such as diatomaceous earth, which contains some crystalline silica). There are essentially two main polymorphs of SAS that are described according to their manufacturing process: wet process silica (CAS # 112926-00-8, precipitated silica or silica gel) and thermal process silica (CAS # 112945-52-5, pyrogenic silica). Inhalation exposure to SAS in occupational settings is associated with only transient and reversible pulmonary effects in humans and animals. SAS is distinct from and contrasts with crystalline silica, for which elevated exposures have been associated with increased risk for pulmonary diseases such as silicosis, tuberculosis, chronic obstructive pulmonary disease (COPD), and lung cancer. For SAS, available epidemiological studies do not support adverse health impacts from SAS exposure in occupational settings (ECETOC, 2006).

SAS is a component of a diverse range of products, *e.g.*, fillers in rubber and tires, free-flow or anti-caking agents in powder materials, and liquid carriers in the manufacture of animal feed and agrochemicals. Many consumer products such as toothpaste, cosmetics, paints, and adhesives contain SAS. Worldwide production was estimated to be over 1.3 million metric tons in 2004 (Waddell, 2006).

[1] SASSI Member Companies: Rhodia, Inc., Cabot Corporation, PPG Industries, Inc., PQ Corporation, J.M. Huber Corporation, Evonik Industries, W. R. Grace & Co., and Wacker Chemical Corporation.

SAS has been in commerce for over sixty years , and it is SASSI's understanding, based on US EPA's Federal Register Notice (January 28, 2008) describing the NMSP, that the Agency seeks data on recently invented "engineered" nanoscale materials and also on other well-known substances that are nanostructured (US EPA, 2008). SAS is an existing substance already listed on the TSCA chemical inventory under the general CAS number for silicon dioxide (CAS No. 7631-86-9). In accordance with nanotechnology definitions currently in development by the International Organization for Standardization (ISO) Technical Committee (TC) 229 and the Organisation for Economic Co-operation and Development (OECD) Working Party on Nanotechnology (WPN), SAS would be considered a nanostructured material rather than a nanoparticle. [2] Thus, we present available information on exposure and health effects of SAS conforming to US EPA's basic NMSP.

This data submission was prepared to address the requirements of the basic NMSP program. Although SASSI appreciates the US EPA preference for submitters to use an optional data submission form, we have structured our own data submittal package, following US EPA's instructions that "participants may provide data in any format or on any form that they choose" (US EPA, 2008). Based on guidance provided in US EPA's "Concept Paper for the Nanoscale Materials Stewardship Program Under TSCA" and "Support Statement for an Information Collection Request (ICR)," we have organized information in this data submittal under four general categories: Material Characterization, Use and Potential Exposures, Hazard Assessment, and Risk Management (US EPA, 2007). In addition, in this submittal, SASSI has endeavored to address the suggestions and questions posed by EPA staff at a June 18, 2008 meeting at EPA offices in Washington, DC, with EPA and SASSI representatives.

Importantly, this submission primarily addresses manufactured SAS used in a number of well-established applications, rather than modified forms of SAS that may be found in some end-user products.

This submission presents available information from the peer-reviewed literature and official review documents to support three key conclusions regarding the properties and health effects of SAS:

[2] As discussed in greater detail in Section 1 of this data submittal, materials characterization data show that, as placed on the market, SAS products typically consist of particles that are larger-sized aggregates and agglomerates rather than individual nanoparticles. Although nano-sized upon their formation during manufacturing, primary SAS particles rapidly form stable aggregates and more transient agglomerates, with final SAS products typically consisting of large agglomerates that do not easily break down unless strong force is applied. Since these aggregates and agglomerates retain the surface structure of nano-sized primary SAS particles, manufactured SAS can be viewed as a nanostructured material.

(1) Solid powder forms of manufactured synthetic amorphous silica (SAS) are nanostructured materials rather than nano-objects[3] or nanoparticles.[4] A nanostructured material has features which are on the nanometer length scale but overall do not have dimensions at the nanoscale. This general point will be substantiated by describing SAS morphology and discussing what is known about the size and properties of manufactured SAS. Colloidal forms of SAS (or Silica Sol), or SAS suspensions in liquid (typically water), wherein SAS can exist as discrete nanoparticles, are not covered in this submission.

(2) The health effects of SAS have been reviewed in recent years, and all the available data on worker populations and animal studies support the fact that SAS is a non-toxic substance with characteristic health impacts that are similar to other low-toxicity, biologically inert dusts.

(3) Industrial hygiene practices regarding the control and handling of SAS are grounded in over 60 years of manufacture and use, and collected exposure data and worker experience do not indicate any adverse worker health impacts (ECETOC, 2006).

Overall, it is the conclusion of SASSI that SAS is a substance that does not pose any unique toxicity due to its nanostructure or other physical-chemical properties. Even in the populations with the potential for elevated SAS exposures, namely occupationally-exposed workers, evidence for adverse health effects is limited and relates primarily to general effects similar to those of other nontoxic, inorganic dusts. Based on available studies on health effects, SAS presents little (if any) health risk when handled properly.

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[3] ISO/TS 27687 (ISO, 2007) defines a nano-object to be a material with one, two, or three external dimensions at the nanoscale.

[4] ISO/TS 27687 (ISO, 2007) defines a nanoparticle as a particle with all three external dimensions at the nanoscale.

1 Material Characterization

Commercially available solid forms of synthetic amorphous silica (SAS) are nanostructured materials composed of micron-sized agglomerates rather than free nano-sized particles. In this section, we describe what is known about the chemical and physical properties of different forms of SAS during their manufacture and use. For the purposes of the NMSP submission, this section focuses on the size characterization of SAS. Specifically, we summarize studies that support the fact that commercial powder forms of SAS are large particles in the micron size range.

1.1 Sources, Manufacturing and Properties of Synthetic Amorphous Silica

Silica is the common name for silicon dioxide (SiO_2), which is composed of two of the most abundant elements on earth, oxygen and silicon. Indeed, silicon accounts for about 28% of the mass of the earth's crust (IARC, 1997). There are two general classes of silica, amorphous and crystalline silica, and both of these forms can be either naturally occurring or man-made. All forms of silicon dioxide fall under the generic CAS No. 7631-86-9, and they are all included in the US EPA TSCA inventory under this CAS number. However, to differentiate between these structural forms of silica, new CAS numbers have been generated in recent years for pyrogenic silica (112945-52-5) and for precipitated silica and silica gel (112926-00-8). [5]

Table 1-1 lists the general physical and chemical properties of silica and in Figure 1-1, the various classes of silica and associated CAS numbers are provided. Table 1-2 gives many of the commercial product trade names for the three major forms of solid SASs. The distinction between crystalline and amorphous forms of silica is an important one, because exposure to the crystalline form has been associated with a number of pulmonary health effects, including silicosis and possibly lung cancer, while studies of amorphous silica have not established evidence for adverse chronic health effects (ECETOC, 2006).

[5] As discussed in US EPA (1990), although new CAS numbers have been issued to differentiate the multiple physical forms of amorphous silica, these CAS numbers have not been added to the TSCA Inventory. As explained by US EPA (1990), this is because these CAS numbers were not issued in response to any TSCA review and/or registration activities. Furthermore, since the different physical forms of amorphous silica do not differ in their basic chemical composition, US EPA does not consider the different physical forms of amorphous silica to be separately reportable under TSCA.

Table 1-1 Summary of General SAS Identity and Physical and Chemical Properties (from OECD, 2004)

CAS Number:	7631-86-9 (Silica) 112945-52-5 (Silica, amorphous, pyrogenic) 112926-00-8 (Silica gel, precipitated)
Chemical Name:	Silicon dioxide
Molecular formula:	SiO_2
Molecular Weight:	60.08 g/mol
Substance type:	Inorganic
Physical state:	Solid, amorphous
Degree of Purity:	>95 %
Melting point (° C)	approx. 1700
Boiling point	Not applicable
Bulk density (g/L)	50-320
Vapor pressure	none
Water solubility (mg/L)	Approx. 15-68 at 20 °C
Partition coefficient n-octanol/water (log value)	Not applicable
Henry's law constant	Not applicable
Particle Size	Depends on form of Silica, See Table 1-3

Table 1-2 Registered Trade Names ® for Various Forms of SAS (ECETOC, 2006)

Silica Form	Trade names ®
Pyrogenic Silica	Aerosil, Cab-O-Sil, HDK, Cab-O-Sperse
Precipitated Silica	Acematt, Agrosil, Baysical, BS, Ciptane, Durosil, Elfadent, Gomasil, OK, HK, TS, TK, Flo-Gard, Hi-Sil, Huberderm, Huberpol, Hubersil, Hubersorb, Lo-Vel, Microsil, Neosyl, Neosil, Orasil, Perkasil, Eheosil, Rhodaxane, Rhoximat, RxCipients, San-sil, Sident, Silcasil, Silene, Siloa, Sipernat, Sorbosil, Sylowhite, Tixosil, Ultrasil, Vulkasil, Wessalon, Zeo, Seocal, Zeocopy, Zeodent, Zeofoam, Zeofree, Zeolex, Zeopharm, Zeopol, Zeosil, Zeosyl, Zeothix, ZS
Silica Gel	Chillgarde, EP, ES, Daraclar, Gasil, Lucilite Sorbsil, Silcron, Silica, Sil-Proof, Syloid, Sylodent, Sylojet, Syloblanc, Trisyl, Quantum, Britesorb

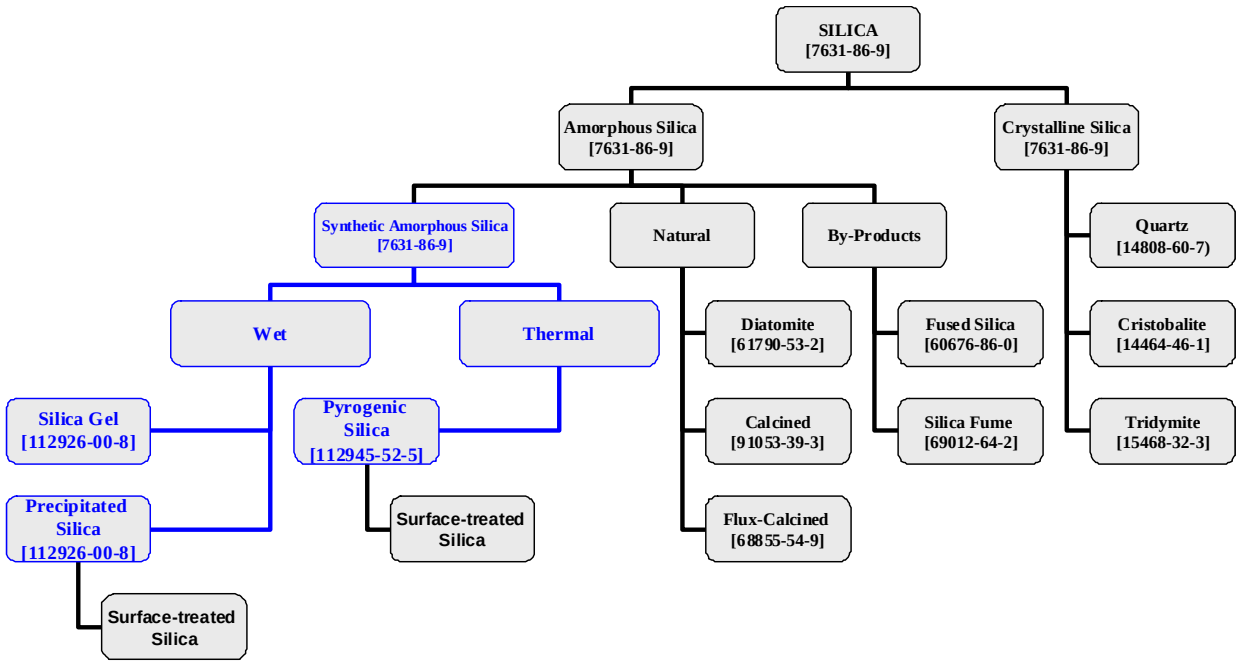


Figure 1-1 Polymorphs of Silica (adapted from ECETOC, 2006)

The building block of silica is the SiO_4 tetrahedron shown in Figure 1-2, which typically contains 4 oxygen atoms at the corners of a regular tetrahedron with silicon at the center. The siloxane (Si-O) bond length is only 0.162 nm, resulting in a bond with partial ionic character and high stability (Bergna and Roberts, 2006). The polymorphisms of silicas are based on different linkages of the tetrahedral $[SiO_4]^{4-}$ units. The crystalline silicas (quartz, tridymite, and cristobalite) form three-dimensional highly organized networks where the 4 oxygen atoms are shared with adjacent groups, with quartz being the most stable at room temperature. In contrast, the bulk structure of amorphous silica is determined by random packing of $[SiO_4]^{4-}$ units, resulting in a non-periodic structure as shown in Figure 1-3 (Bergna and Roberts, 2006).

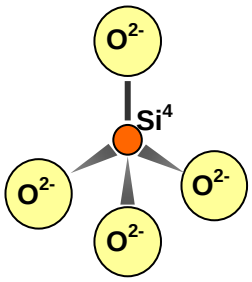
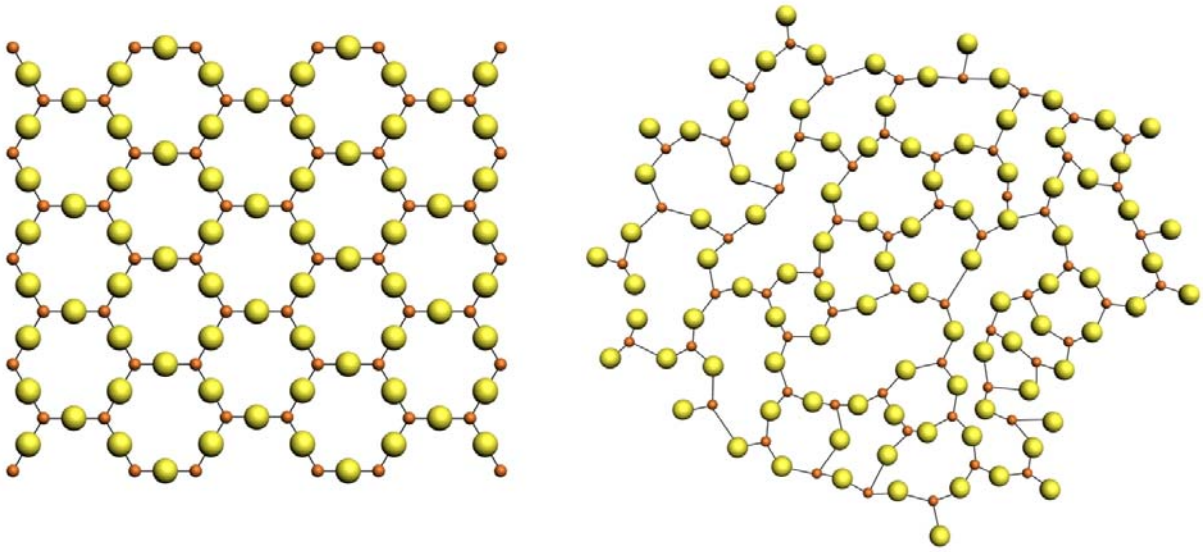


Figure 1-2 The Silica Tetrahedron



(a) **(b)**

Figure 1-3 Structural Differences Between Crystalline and Amorphous Silica (a) cross-sectional view of crystalline silica demonstrating the regular and periodic order and (b) cross-section of amorphous silica showing no regular order beyond the fundamental base of the tetrahedron

As shown in Figure 1-1 in blue, the two types of SAS that are covered in this submission are classified by their manufacturing process, *i.e.*, wet process silica (precipitated silica or silica gel) and thermal process silica (pyrogenic silica). There are other specific SAS varieties that are not covered in this submission. These include colloidal silica (silica sol), which encompasses stable dispersions of SAS in a liquid medium (typically water), and surface-modified SAS that is chemically treated to modify its surface characteristics (*e.g.*, to render the silica hydrophobic).

The two basic forms of SAS are characterized by their manufacturing process. Thermal or pyrogenic silica (also referred to as fumed silica, but distinct from fused silica or silica fume) is manufactured *via* a combustion process that involves volatile chlorosilanes and/or methylchlorosilanes being fed into a burner together with a mixture of hydrogen and air (Figure 1-4). The structural properties of pyrogenic silica are largely determined during manufacturing by adjusting the feed rates of hydrogen, air, and silanes into the burner (Bergna and Roberts, 2006). The specific surface area and particle size are primarily determined by the flame temperature (Bergna and Roberts, 2006). This

manufacturing process has been studied and described extensively in the literature (for *e.g.* see Roth, 2007; Tsantilis and Pratsinis, 2004; Ulrich, 1984; Wooldridge, 1998).

The mixture of volatile chlorosilanes and/or methylchlorosilanes, hydrogen, and air is combusted in a reaction chamber with temperatures that range from 1200 to 1600 °C. This flame produces silicon dioxide molecules which immediately nucleate and begin colliding to form SiO_2 nuclei. At this point in the process, coagulation rates are very rapid. Thus nuclei collide and rapidly sinter and coalesce into spherical primary particles. After some time, heat losses from the reactor cause a decrease in the temperature such that sintering and coagulation rates are approximately equal. At this point, the surface area (usually $<400 m^2/g$) and primary particles (typically ~5-50 nm) have reached their ultimate value. However, it should be noted that these primary particles do not exist outside of the reaction chamber due to rapid coagulation (Barthel *et al*., 1999). This is further demonstrated by Figure 1-5 which shows that coagulation results in the depletion of individual nanoparticles on the order of milliseconds (Ulrich, 1984). Moreover, because the decrease in reactor temperature is relatively slow, particles either completely coalesce or are sintered into much larger particles. Thus, coagulation continues and the sintering rate is sufficient that primary particles fuse upon collision to form stable silicon dioxide aggregates (~0.1 - 0.5 μm).

This process continues until reactor temperatures are decreased to the point where the sintering rate is effectively zero. Even though the collision rate has decreased significantly at this point, these aggregate clusters continue to collide, resulting in particles that are bound by Van der Waals forces and hydrogen bonding. These particles, known as agglomerates, typically range from ~0.5μm to >250 μm depending on how and at what point in the process they are measured (EC, 2007; IARC, 1997; IUCLID 7631-86-9; ECETOC, 2006). In the remaining steps of the process, silica agglomerates are filtered from the byproduct hydrochloric acid gas typically *via* baghouse filtration. The product is then heated to remove any residual hydrochloric acid. The resulting product is a fluffy white powder composed of stable micron-sized particles. Figure 1-6 shows a diagram of the thermal manufacturing process and Table 1-3 lists some of the properties of pyrogenic silica.

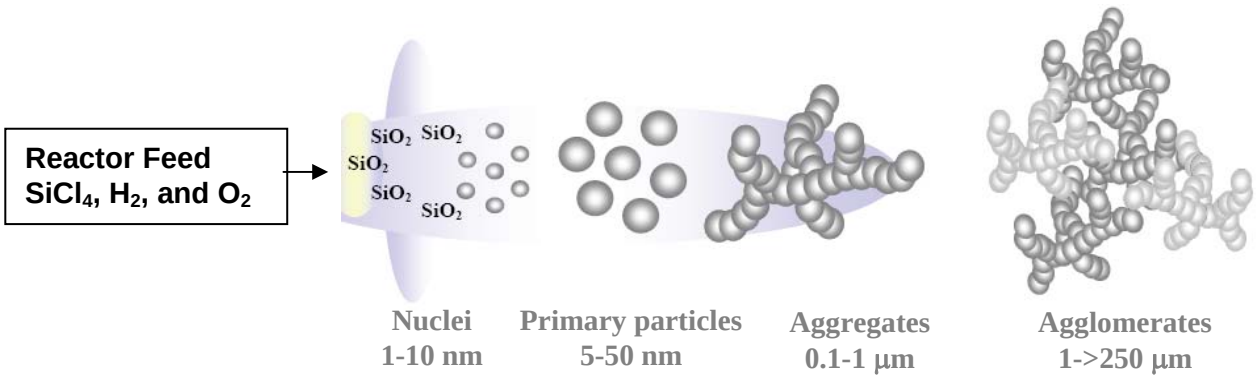


Figure 1-4 General Structure Development Sequence During SAS Manufacturing (from ECETOC, 2006)

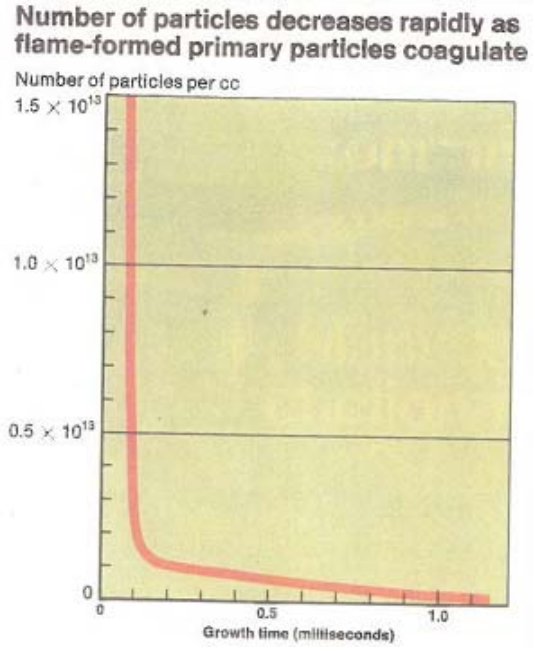


Figure 1-5 Depletion of the Small Particles Over Milliseconds

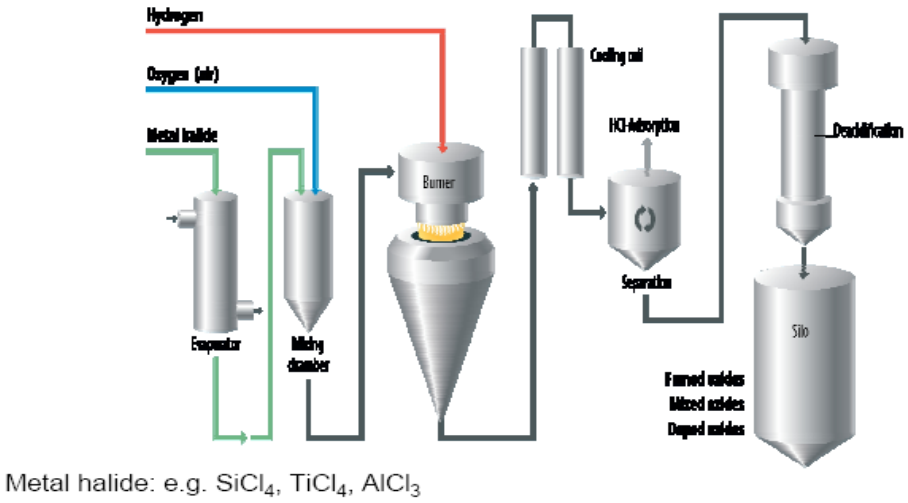


Figure 1-6 Typical Process Diagram for the Manufacture of Pyrogenic SAS (from Maier, 2008)

Synthetic amorphous precipitated silica and silica gels are manufactured *via* a wet process that involves an alkali metal silicate solution (or water glass) and acids, typically sulfuric acid. The process steps, as shown in Figures 1-7 and 1-8 for precipitated and silica gel, respectively, involve precipitation, filtration, washing, drying, milling, and granulation, followed by packing and shipping of the product. The size of the primary particles and the amount of aggregation and agglomeration are determined by the reaction conditions such as the pH, temperature, concentration, and amount of stirring. Silica gels are generally manufactured under acidic conditions with primary particles in the range of 1-10 nm that quickly adhere to form aggregates ranging from 1-20 μm upon drying. On the other hand, precipitated silica products are manufactured under neutral/alkaline conditions with primary particles in the range of 5-100 nm, aggregates ranging from 0.1-1 μm, and agglomerates ranging from 1-250 μm.

After precipitation, the various silica products are filtered *via* different methods (*e.g.* filter press, membrane filter press, or belt/drum filter) depending on the product being manufactured. At this stage, the product is also washed to remove any salts. The product is then dried either by plate, belt, or rotary drum. Alternatively, spray dryers can be used. Lastly, the milling stage establishes the final particle size distribution (ECETOC, 2006). Typical physical and chemical properties of precipitated silica and silica gel are given in Table 1-3. An overview of the manufacturing processes for various forms of silica is shown in Figure 1-9.

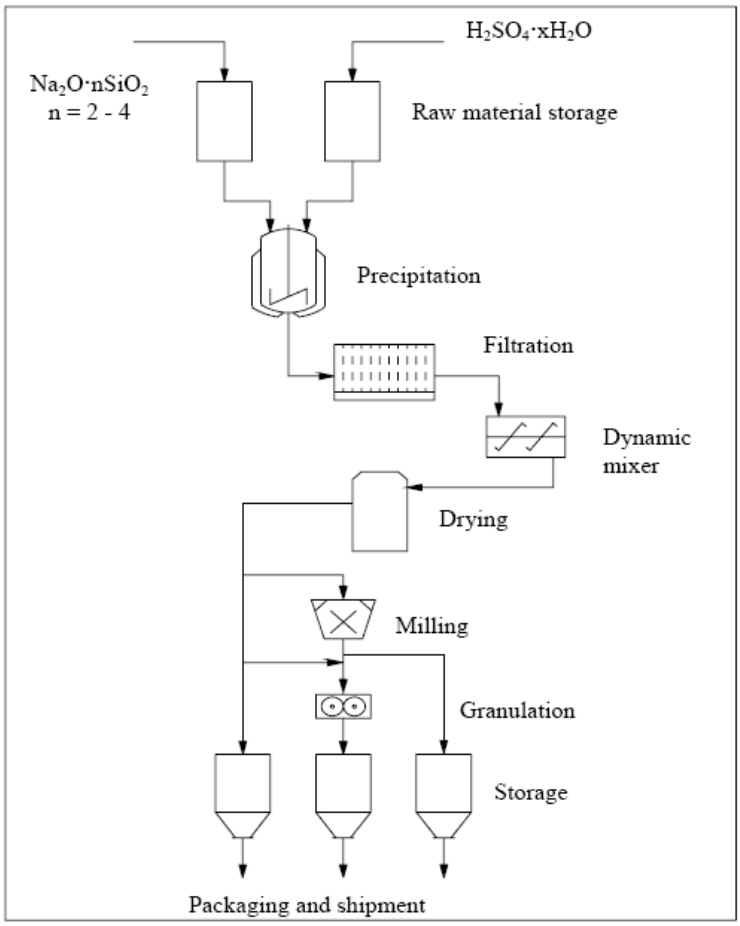


Figure 1-7 Manufacturing of Precipitated SAS (from ECETOC, 2006)

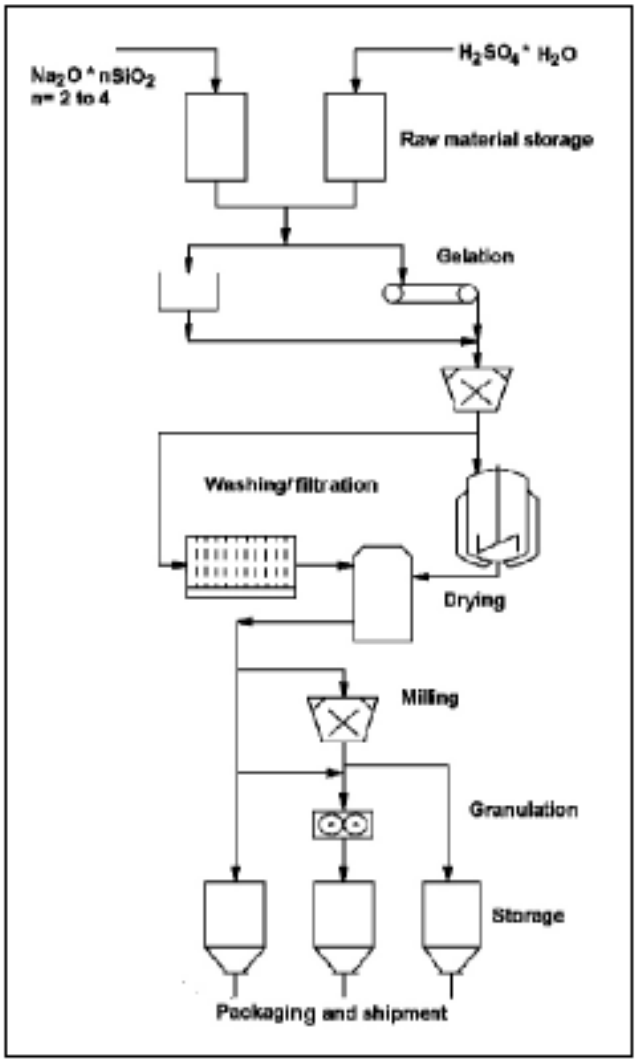


Figure 1-8 Manufacturing of Silica Gel (from EC, 2007)

Table 1-3 Typical Physical and Chemical Properties of Specific SAS Forms (from ECETOC, 2006)

Property (units)	Pyrogenic	Precipitated	Gel
Purity, % SiO_2 (by weight)	>99.8	>95	>95 (dry)
Color	white	white	white
Specific surface area (BET, m^2/g)	50-400	30-500	250-1,000
Loss on drying (% by weight)	<2.5	5-7	2-6
pH	3.6-4.5	5-9	3-8
Tapped (bulk) density (g/L)	30-250	30-500	500-1,000
Ignition loss (% by weight)	<2	3-14	2-15
Particle size			
Primary particle (nm)	5-50	5-100	1-10
Aggregate (μm)	0.1-1	0.1-1	1-20
Agglomerate (μm)	1-250*	1-250*	NA
Porosity			
Mean pore size (μm)	None	>0.03	0.0001-1
Pore size distribution	None	very wide	narrow
Specific gravity (g/cm^3)	2.2	1.9-2.2	1.8-2.2
Structure, DBP absorption (ml/100g)	250-350	80-320	80-350

* Agglomerate particle size is typically 100 μm

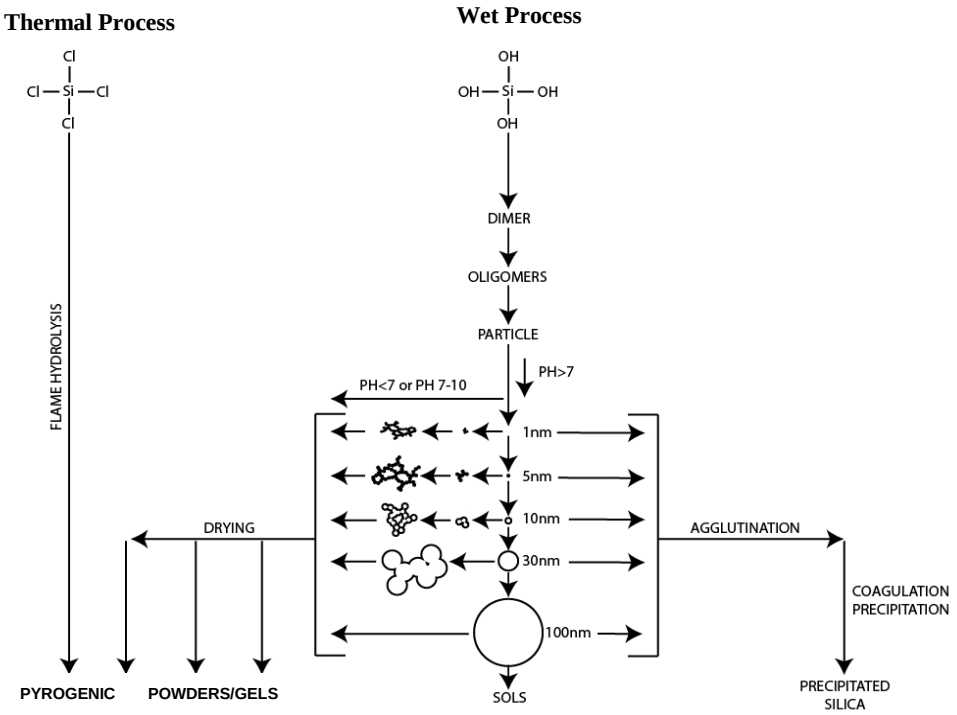


Figure 1-9 Overview of Silica Product Manufacturing Processes (from Bergna and Roberts, 2006)

The manufacturing process, feedstock, and reaction conditions (*e.g.*, flow rates, temperature, and pH) determine the different forms of SAS and their uses in a number of different products. SAS has gained usage as a reinforcing agent in silicone rubber products such as elastomers, as a thickening agent and for inhibiting separation of pastes and ointments (toothpaste), as a carrier of fragrances and flavors, as a functional pigment and flattening agent in paints and paper products, as an anti-caking agent in food products, as an excipient in pharmaceuticals, and as a semiconductor polishing agent in chemical mechanical planarization (Bergna and Roberts, 2006; ECETOC, 2006). Some of the applications of specific forms of SAS and related critical properties are listed in Table 1-4.

Table 1-4 Some Applications of Synthetic Amorphous Silica Forms

Form of SAS	Application	Important Properties
Gels	Desiccant, adsorbent	Porosity
	Paints: matting	Aggregate size
	Toothpaste: cleaning, rheology control	Aggregate/agglomerate size
Precipitated	Rubber reinforcement	Particle size, surface area
	Free-flow, anti-caking agent	Aggregate size, porosity
	Toothpaste: cleaning, rheology control	Aggregate/agglomerate size
	Paints: matting	Aggregate size
Pyrogenic	Rubber reinforcement	Surface area, purity, structure
	Heat insulation	Aggregate size, purity
	Rheology control (liquid systems)	Surface chemistry, aggregate/agglomerate size
	Chemical Mechanical Planarization	Aggregate size/agglomerates size, purity
	Anti-caking	Particle size, surface area

Solid forms of SAS, including pyrogenic and precipitated silicas and silica gels, are white, fluffy, or powdery amorphous forms of silicon dioxide (SiO_2). Furthermore, these industrial solid forms of SAS are characterized as high purity substances consisting of 95-99.8% SiO_2 with only trace amounts of other metal oxides, sulfates, and/or chlorides present. Pyrogenic silica is the purest form of SAS (>99.8% SiO_2) (ECETOC, 2006).

Given that SAS consists of a relatively unreactive hydrophobic siloxane unit (Si-O-Si) and hydrophilic silanol groups (Si-OH), the solubility of SAS depends on the number of silanol groups per unit surface area (per nm^2). For wet process silica gels, the concentration of silanol groups range from 5 to 8 SiOH/nm^2 and for pyrogenic silica, the number is much lower due to the thermal process, ranging from 1.25 to 2.5 SiOH/nm^2. In general, synthetic amorphous silica is much more soluble than crystalline silica. The saturation concentration in water averages about 120 mg/L compared to 5 mg/L for crystalline silica (ECETOC, 2006). Furthermore, the saturation concentration increases with increasing specific surface area of the SAS (or decreasing particle size). The solubility of SAS has implications for its toxicity, as more soluble forms of silica will be removed from the lungs at a much faster rate. Studies simulating the dissolution behavior of SAS in the lungs under physiological conditions show that total dissolution occurs within one day and that dissolved SAS is likely to be rapidly removed from the lungs (ECETOC, 2006). Also of note, dissolved silica is rapidly excreted from the body via urine. Details from these studies can be found in section 2.3.2 of the ECETOC report (2006).

Other key properties of specific forms of SAS are listed above in Table 1-3. Depending on the manufacturing process, SAS forms differ across several physical and chemical properties, including size and surface area. In addition, the loss on drying, a measure of the amount of physically bonded water, differs for pyrogenic SAS, which has the lowest water content (2.5% or less), and wet process SAS (2-15%). The tapped density describes the weight of the bulk product in powder form. Typical values range from 50 g/L for milled SAS products to 600 g/L for granulated or very dense products. Lastly, porosity is an important characteristic of many SASs. The International Union of Pure and Applied Chemistry (IUPAC) distinguishes between micropores (diameters d = 2 nm), mesopores (d = 2–50 nm), and macropores (d > 50 nm). Pyrogenic SAS is characterized as having no or very small pores (microporous), whereas precipitated and silica gel can be either mesoporous, macroporous, or microporous.

1.2 Particle Size Characteristics of SAS

As discussed below, based on a considerable body of research on the manufacturing process of SAS and materials characterization data, solid forms of manufactured SAS are known to consist predominantly of particle aggregates and agglomerates that generally have sizes exceeding 100 nanometers and ranging up to hundreds of microns. Indeed, solid forms of SAS (precipitated, pyrogenic, and silica gel) belong to the family of industrial aciniform aggregates (IAA), aciniform meaning "clusters of grapes". These IAAs are of significant commercial importance, as some 15 million metric tons are produced worldwide each year (Gray and Muranko, 2006). IAAs have in common the fact that aggregates are formed from primary particles that collide and are chemically bonded, resulting in stable entities. As described in the previous section, these aggregates can further adhere to each other forming larger, but more weakly attached agglomerates that are held together by hydrogen bonding and Van der Waals forces. Figure 1-10 illustrates the differences between a primary particle, an aggregate, and an agglomerate for aciniform compounds. Due to nucleation and condensation, particle growth occurs during the manufacturing of all solid forms of SAS (pyrogenic, precipitated, and silica gel) and thus the aggregates are the smallest and most stable entity for these forms of SAS. The aggregate size for most solid SAS ranges from about 0.1 to 1 μm. Although primary particles exist for solution-based SAS (silica sol) these particles quickly agglomerate upon drying. Thus, solid powder forms of commercial SAS do not exist as easily dispersible nanoparticles (*i.e.*, particles with a diameter of <100 nm). Surface-modification of SAS, which typically renders the product hydrophobic, tends to enhance agglomeration resulting in larger clusters of particles.

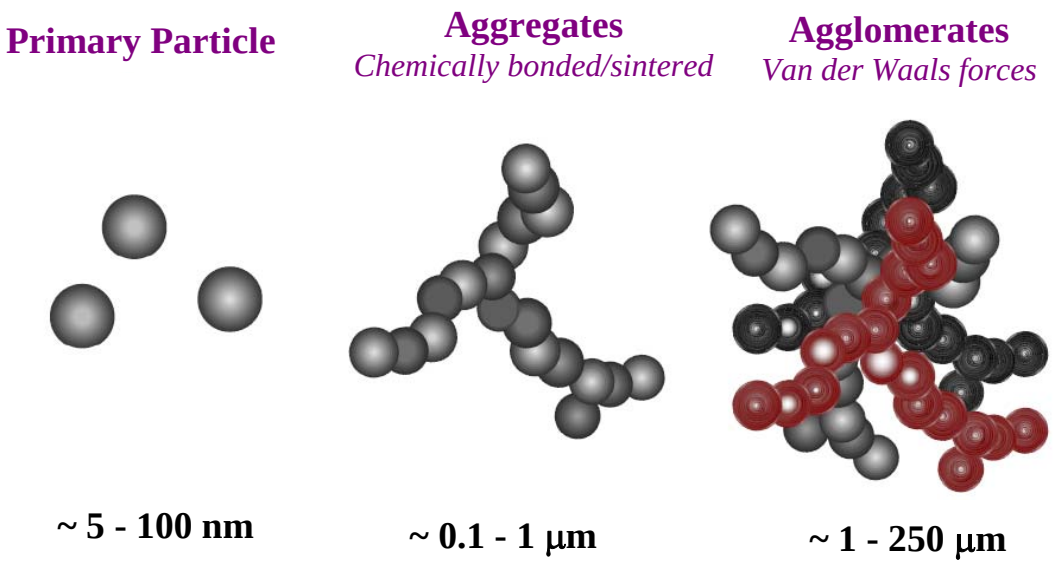


Figure 1-10 Agglomerate of Industrial Aciniform Aggregates (IAA) Showing the Primary Particle, Aggregate, and Agglomerate Structures (adapted from Maier, 2008)

As described in the ECETOC report (2006), particle size distributions have been characterized under typical SAS handling conditions (filling, shipping, and storage of SAS products). These conditions involve handling dry powder SAS at high concentrations. The sizing methods used to assess distributions of particle dimensions were non-destructive (*i.e.*, low shearing) methods, such as dry sieving and Fraunhofer laser light diffraction. By the dry-sieving method, no particles were found to pass through a mesh size of 90 μm and 35-83% of particles were found to pass through a mesh size of 125 μm. Using the Fraunhofer laser light diffraction method, pyrogenic SAS samples were estimated to have an average aerodynamic diameter of ~200 μm. Furthermore, the respirable fraction (portion of particles that can penetrate into the lungs, *i.e.*, below 10 μm aerodynamic diameter) for pyrogenic SAS comprised <1% by weight. These results support the fact that during manufacturing and handling of SAS products, worker are not exposed to particles in the nano-sized range.

These results are consistent with the findings of Gray and Muranko (2006) who reported that aggregates are the smallest separable entity for manufactured SAS, even for conditions of severe mechanical processing. In a series of experiments, which included mechanical processing *via* uniaxial compression, elastomer mixing, or ultrasonication, Gray and Muranko (2006) provided data that showed no release of primary SAS particles. Furthermore, the researchers observed that, although there can be

fracture of the largest and most complex aggregates under the high energy conditions of their experimental methods, this resulted in only modest reductions in the size of the largest aggregates.

In a similar study, Sauter *et al*. (2006) reported on dispersion of Aerosil 200V, a pyrogenic silica, in liquid using ultrasonic treatment or treatment *via* a rotor-stator system (*i.e., via* mechanical mixing). Due to the high tendency for these particles to agglomerate, the researchers found that very high energies were required (~10 GJ/m^3 = 10^{10} J/m^3) to obtain modest size reductions (from ~180 nm to ~120 nm). Interestingly, despite a similar amount of energy applied, the rotor-stator system was not able to achieve the same size-reductions that the ultrasonic treatment achieved. Importantly, and consistent with the findings by Gray and Muranko (2006), the authors found that the energy applied *via* either ultrasonic treatment or mechanical mixing (rotor-stator) was not strong enough to break apart agglomerates into primary particles. Additional studies of pyrogenic silica particle size distributions using various different particle sizing and dispersion techniques confirm that this product exists as a white fluffy solid composed of agglomerate sizes ranging from 10 to 90 μm without dispersion treatment (Barthel *et al*., 1999).

Similarly, in a recent study, Ma-Hock *et al*. (2007) provided additional findings confirming that SAS consists primarily as larger-sized (>100 nm) aggregates and agglomerates. For two types of hydrophobic pyrogenic SAS (e.g., surface-treated SAS) with differing surface areas (Aerosil R104, SA ~150 m^2/g and Aerosil R106, SA ~250 m^2/g) and an unspecified amorphous silicon dioxide "nanopowder," Ma-Hock *et al*. (2007) reported a range of primary particle sizes of 5 to 50 nm based on transmission electron microscopy (TEM) pictures, noting that the particles were suspended in ethanol for analysis. However, when the researchers attempted to obtain more quantitative primary particle size distributions using an ultrafine particle analyzer (UPA), they were unable to obtain primary particles because the primary particles are fused together forming aggregates. In addition, based on particle size distribution measurements made using both a Scanning Mobility Particle Sizer (SMPS) and an Optical Particle Counter (OPC) across the three SAS products as aerosolized at high energy using a dry powder brush feed aerosol generator or a nebulizer system, the researchers demonstrated a high degree of aggregation and agglomeration. Indeed, for the silicon dioxide sample, the researchers found substantial intersampling variability in the particle size distribution as measured by the SMPS because SiO_2 does not form a stable suspension. Ma-Hock *et al*. (2007) reported that median count distributions ranged from 0.20 μm to 0.45 μm, with a reported mass fraction of between 0.13 and 0.74% of the aerosolized SAS particles having diameters of less than 100 nm. These measurements thus confirmed that the main mass

fraction of aerosolized SAS particles consists of stable aggregates or agglomerates, even under the high dispersive energy typical of a brush dust feeder and nebulizer.

Scanning electron microscope (SEM) images as well as transmission electron microscope (TEM) images of various forms of SAS confirm the stable aggregated and agglomerate state of these products (Figures 1-11 to 1-16).

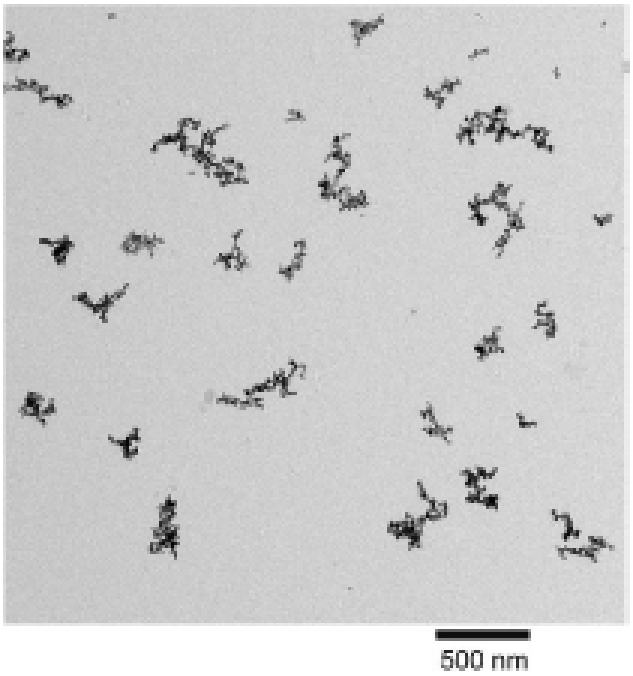


Figure 1-11 TEM of Precipitated Silica (Z1165) Showing Aggregate Structure (from Gray and Muranko, 2006)

Figure 1-12 TEM of Pyrogenic Silica (from Bogdan and Kulmala, 2006)

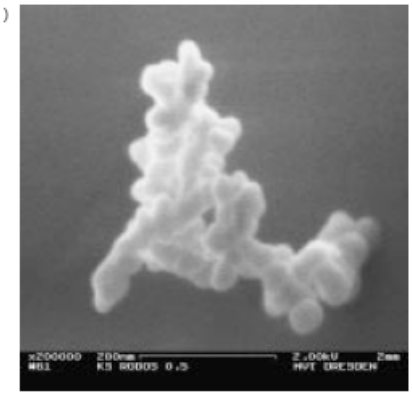


Figure 1-13 Electron Micrograph of a Pyrogenic Silica Aggregate (from Sheka *et al.*, 1999)

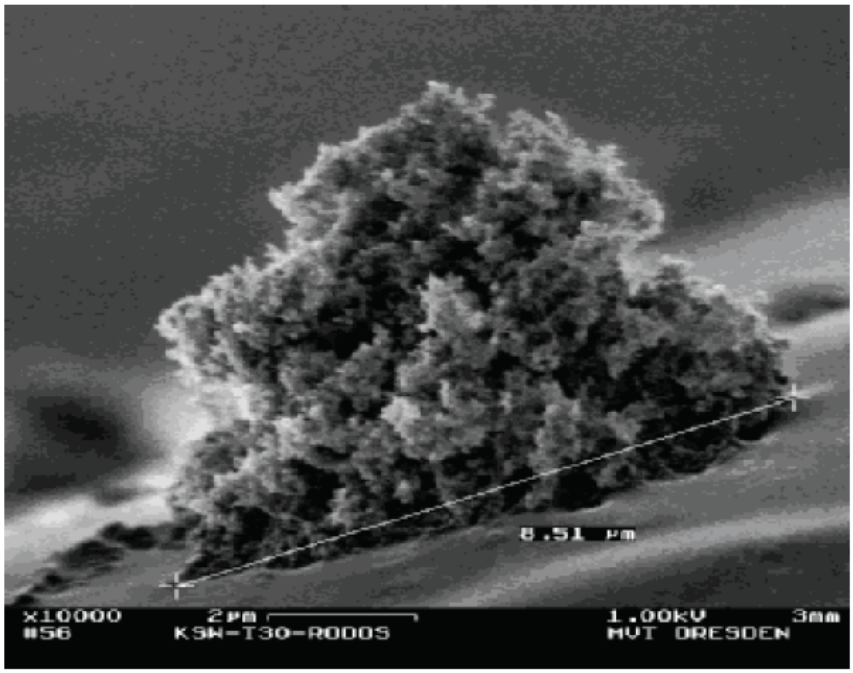


Figure 1-14 SEM of Pyrogenic Silica agglomerate (from ECETOC, 2006)

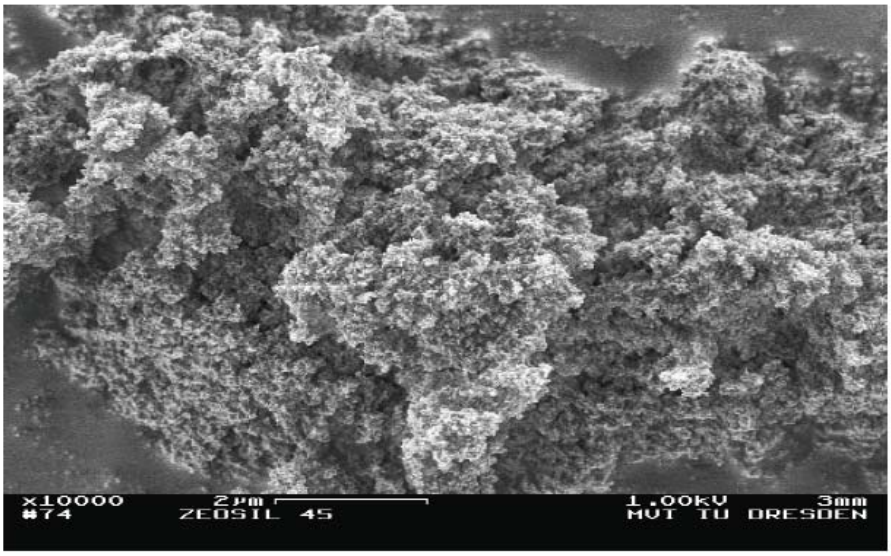


Figure 1-15 SEM of Agglomerated Precipitated Silica (from ECETOC, 2006)

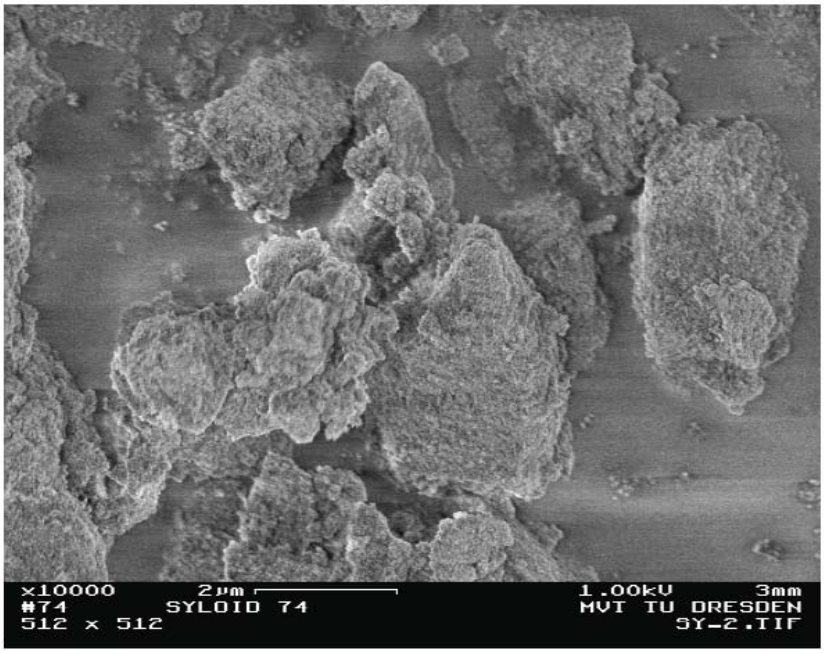


Figure 1-16 SEM of Silica Gel Aggregates (from ECETOC, 2006)

One of the concerns that has been raised for nanostructured materials is the possibility of disaggregation of the aggregates or agglomerates following deposition in the lungs and the subsequent release and potential translocation of any nano-sized units. Maier *et al*. (2006) tested whether disaggregation of samples of a commercial nanostructured titanium dioxide product (AEROXIDE TiO_2 P25, 20 nm primary particle size) occurred when mixed with dipalmitoyl phosphatidyl-choline (DPPC), the main surface-active component in lung surfactant. Like SAS, TiO_2 is a nanostructured industrial aciniform aggregate, which exists as highly aggregated and agglomerated particles. The authors calculated the energies needed to break apart aggregates and agglomerates of TiO_2, and assessed the particle size distribution of TiO_2 P25 in a pulmonary liquid model (PLM) that consisted of a DPPC dispersion.

Using computer-based molecular simulations, Maier *et al*. (2006) determined that 10 joules per square meter (J/m^2) of energy were required to break the oxide bonds between TiO_2 primary particles (*i.e.*, to break apart an aggregate) and 1 J/m^2 would be needed to break the weaker hydrogen bonds between aggregates (*i.e.*, to break apart an agglomerate), an order of magnitude difference. Importantly, the interaction energy between TiO_2 and the DPPC bilayer was calculated to be only 0.05 J/m^2, 200 times weaker than the energy needed to break apart the chemical bonds between primary particles in an

aggregate and 20 times weaker than interaggregate hydrogen bonds. Thus, based on their modeling simulations, the researchers concluded that DPPC does not promote the disaggregation of either TiO_2 agglomerates or aggregates.

To test their modeling calculations, Maier *et al*. (2006) also determined particle size distributions for TiO_2 P25 dispersions in DPPC using light-scattering methods (static laser scattering), finding TiO_2 particle sizes in the general range of about 0.8 to 100 μm no matter the TiO_2 concentration, the DPPC concentration, and the contact time. For these dispersions where TiO_2 P25 was added to the PLM with gentle shaking by hand, no particles in the ultrafine size range (*i.e.*, <100 nm) were observed. For some experiments where the TiO_2 P25 suspensions in PLM were treated with ultrasonication, a small signal corresponding to an additional particle fraction with aggregate sizes of about 100 nm was observed. As discussed by Maier *et al*. (2006), however, this particle fraction corresponded not to individual primary particles, but to smaller aggregates of 4 to 6 primary particles across. Lastly, a small Zeta potential (2.6 mV) was measured for TiO_2 in DPPC, much smaller than needed to disperse aggregates and so supporting an increased tendency towards agglomeration. Overall, these data thus support the conclusion that surfactants in the lungs or other biological fluids cannot break apart either aggregates or agglomerates which may become inhaled and deposit on lung surfaces.

Similar studies of disaggregation of SAS agglomerates in biologically-relevant fluids are not currently available. However, because SAS forms aggregates and agglomerates with similar bonding structures (*i.e.*, strong oxide bonds between primary particles, and weaker hydrogen bonds between aggregates), experiments using SAS would be expected to yield similar results. In addition, the results from Gray and Muranko (2006) and Sauter *et al*. (2006) support the fact that even under very high dispersion energy conditions (unlikely to be encountered in most exposure settings) there is only a very modest reduction in the size of SAS agglomerates.

1.3 Conclusion: Manufactured SAS Is Neither a Nanoparticle Nor a Nano-object

In this section we have presented information demonstrating that SAS is neither a nanoparticle nor a nano-object, consistent with nanotechnology terminology and definitions in development by the International Organization for Standardization (ISO) Technical Committee (TC) 229 and the Organisation for Economic Co-operation and Development (OECD) Working Party on Nanotechnology (WPN). Indeed, due to the nature of the manufacturing processes, SAS is typically found to be a highly

aggregated and agglomerated material whose external diameter is typically in the micron (μm) range not the nano-range. Moreover, the primary particles which give SAS its nanoscaled features are strongly bound to each other making it very unlikely that they will be found as independent entities in the final product. Thus, SAS falls under the category of a nanostructured material, consistent with the ISO and OECD definitions of nanostructured materials as having either an internal or surface structure on the nanoscale. Importantly, the human exposure potential, and SAS fate and behavior inside the body (*e.g.*, as to lung dosimetry, translocation potential, ability to pass through cell pores, *etc.*) will be dictated by either its aerodynamic diameter or its physical diameter rather than by its internal nanostructure. Because both SAS aggregates and agglomerates have diameters that lie outside the nano-region, they will behave similarly to respirable or inhalable-sized particles.

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2 Uses and Potential Exposures

Having been produced commercially for over sixty years, manufactured SAS has numerous applications in a variety of commercial and consumer products, including numerous food and pharmaceutical applications. In this section, we briefly summarize information related to the worldwide production and uses of manufactured SAS. In addition, we summarize what is known regarding potential exposures to SAS, focusing on occupational exposures where there is the greatest potential for human exposure. Importantly, due to the physical and chemical properties of powdered forms of SAS as described in the previous section, human exposure to SAS particles is expected to be largely in the form of micron-sized aggregates and agglomerates, thus concerns about nano-sized particle exposures do not apply to SAS.

2.1 Production and Uses

2.1.1 Production

Worldwide production of SAS was estimated to be almost 1000 kilotonnes (kt) in 1992 (ECETOC, 2006)and over 1300 kt (1.3 million tons)in 2004 (Waddell, 2006). The bulk of the production is for precipitated SAS products (800 kt). More recent production numbers for western Europe for 2000 also indicate a much greater production of precipitated SAS (286 kt), compared to pyrogenic SAS (72 kt) and silica gel (35 kt) (ECETOC, 2006). The current trend in annual sales (1997-2000) for Western Europe shows that sales for pyrogenic and precipitated SAS are increasing, whereas sales for silica gel have remained steady from 1997 to 2000 (ECETOC, 2006).

2.1.2 Uses

Forms of SAS have been in commerce since the 1950s and are used in a wide range of industrial applications and products. A summary of some of the major applications is provided below. For more details, refer to the ECETOC Report (2006).

As previously mentioned, precipitated silica is produced in much greater quantities than other forms of SAS. The primary use of precipitated silica is for the reinforcement of elastomer products like

tires, shoe soles, and mechanical rubber goods (seals, mats, belts, *etc.*). For tires, silica in tread compounds leads to significant improvements in rolling resistance and wet traction of tires without compromising tread wear (Bergna and Roberts, 2006). Precipitated silica is currently widely used in Europe and there is increasing demand in North America and Asia to cut fuel consumption and CO_2 emissions (Bergna and Roberts, 2006).

Pyrogenic silica (also known as fumed silica) is mainly used to improve mechanical strength, provide thermal stability, and reduce permeability of gases and liquids of silicone rubber. The higher surface area of pyrogenic silica yields higher transparency of the silicone rubber, which is important for certain applications such as medical tubing. Precipitated silica is also used in silicone products (Bergna and Roberts, 2006).

Both pyrogenic and precipitated silicas are widely used as carriers for liquids and semi-liquids or as free flow agents in powdered products (cosmetics, salts, and foods), particularly for hygroscopic and caking substances. For example, untreated pyrogenic silica has been cleared by the U.S. Food and Drug Administration (FDA) for use as a direct food additive in a number of different food products including grated cheese, dried eggs, dried egg yolks, and flavorings oils, and in materials that come into contact with foods during manufacturing, packaging, preparing, or transporting. In addition, SAS provides pastes and ointments with the desired consistency and prevents separation of the various ingredients, and thus has number of pharmaceutical and cosmetic applications. For these applications, the absorption capacity, kinetics of absorption, good flowability, and low dust content (good mechanical stability) are key characteristics (ECETOC, 2006). Figures 3-1 to 3-3 show use patterns in Western Europe in 1996 and, although somewhat dated, they provide a general sense of the wide range of products and applications for SAS and their commercial importance.

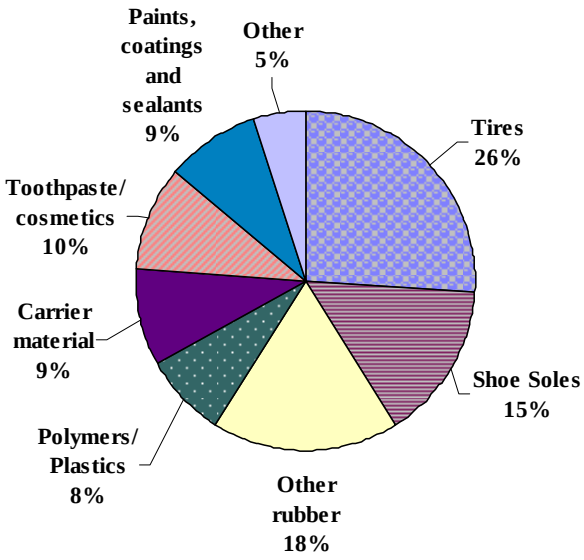

Figure 2-1 Uses of Precipitated Silica in Western Europe (1996, total production 231 kt, adapted from ECETOC, 2006)

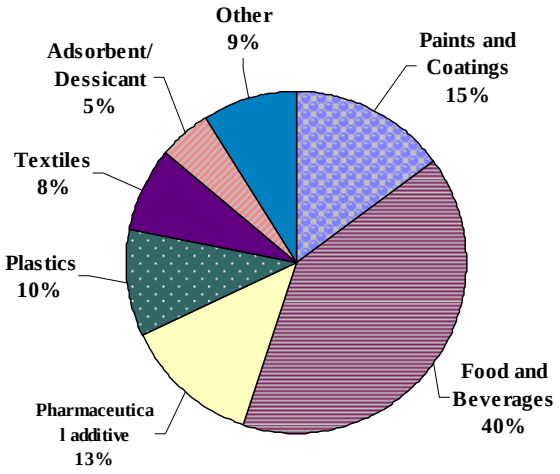

Figure 2-2 Uses of Silica Gel in Western Europe (1996, total production 20 kt, adapted from ECETOC, 2006)

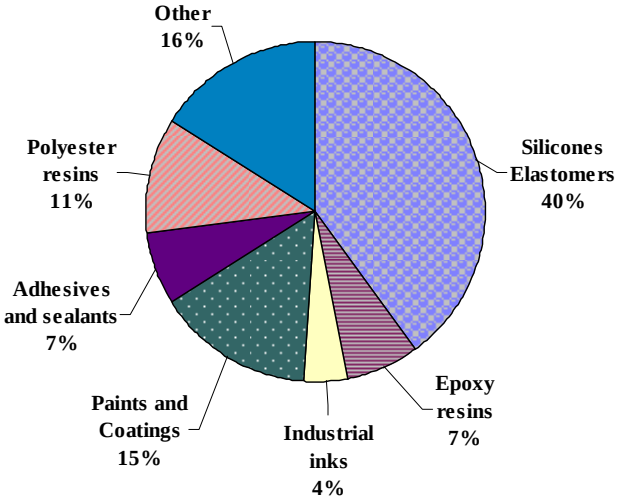

Figure 2-3 Uses of Pyrogenic Silica in Western Europe (1996, total production 46 kt, adapted from ECETOC, 2006)

2.2 Potential Exposures

2.2.1 Emissions, Distribution, and Environmental Fate

SAS can be released into the environment during the manufacturing process. Based on Western European production numbers, the amount of SAS released to air was estimated to be about 0.44 kt per year and the amount released to water was estimated to be 2.1 kt per year (ECETOC, 2006). Similarly, emissions of SAS into aquatic environments during use were estimated from Western European consumption data to be about 104 kt per year (ECETOC, 2006).

Based on the chemical properties of SAS, the relatively low water solubility (~114-151 mg/L) and low vapor pressure ($<10^{-3}$ Pa for Aerosil R972), released SAS will likely be distributed mostly to soil/sediment, less so to water, and negligibly to air (ECETOC, 2006).

Table 2-1 summarizes some of the environmental fate parameters for SAS. In general, SAS is an inert substance that is not expected to undergo any chemical transformations in soil, air, or water, except for dissolution in water. In fact, all forms of silica once dissolved in water are indistinguishable. The

dissolved silica is in the form of silicic acid, a bioavailable form of silica essential for aquatic organisms. Silica also accumulates in plants and plays a role in structural support to the cell walls. Silica has also been shown to be an essential nutrient in animal species, playing a role in bone development and associated with other structural components such as connective tissue, cartilage, and skin (ECETOC, 2006).

Silicic acid in the oceans comes from weathering of continental and oceanic crusts. Marine organisms such as diatoms take up the silicic acid to build their skeletons. When these organisms die, part of their skeleton dissolves and the remaining portions settle into the sediment. Similarly, dissolved silica in rivers results from weathering of rocks (ECETOC, 2006). The flux of naturally occurring dissolved silica in Western Europe has been estimated to be about 4,400 kt per year, thus the estimated release from manufacture and use of SAS is only about 2.4% of the naturally occurring silica present in European waterways (ECETOC, 2006).

Table 2-1 Environmental Fate (from OECD, 2004)

Photodegradation	stable in water and air
Stability in Water	stable: ion exchange processes possible
Stability in Soil	stable: silicates = soil components; ion exchange processes possible
Biodegradation	not applicable, inorganic substance
Bioaccumulation	not bioaccumulating due to inherent substance properties

2.2.2 Non-occupational Exposures

Most non-occupational exposures to silica are likely from ingestion of silica dissolved in water and from naturally-occurring silica or synthetic additives in food. In public water supplies, the median concentration of silica was 7.1 mg/L (based on the 100 largest US cities, ECETOC, 2006). Average daily intakes from food are estimated to range from 43 to 107 mg/day. Foods naturally high in silica include grains such as oats, barley, and rice (ECETOC, 2006). SASs are also widely used in a variety of food products such as beverage mixes, salad dressings, sauces, soups spices, and others (up to 2% by weight) as an anti-caking agent or thickener (see section 2.1.2). SAS is also commonly found in various pharmaceuticals contributing to overall oral exposures.

Although non-occupational exposure pathways are likely negligible, it is important to emphasize the scientific evidence indicating the excessive nature of the forces required to break apart SAS agglomerates and aggregates (see Section 1.2). It is thus highly unlikely that individual nano-sized SAS particles will be released during use of a consumer product, not only because SAS aggregates and agglomerates are typically contained within product matrices (*e.g.*, when used as a filler in rubber) but also because the nano-sized primary particles are tightly bound within larger-sized aggregates that are in turn held within robust agglomerates.

2.2.3 Occupational Exposures

Occupational exposures to SAS occur during production, packaging, and shipping of SAS products as well as during use. Only a few studies have measured occupational levels of SAS. These results are summarized in Tables 2-2 and 2-3. Total dust concentrations have been greatly reduced in recent years. For example, measured concentrations were as high as 199 mg/m^3 in 1959, but measurement data show substantial reductions down to ~40 mg/m^3 between 1974 and 1982. Between 1984 and 1986, measured levels were further reduced to between 2 and 4 mg/m^3 (IUCLID 7631-86-9). More contemporary concentrations measurements are even lower (see Table 2-3).

An on-going German monitoring and morbidity study of workers exposed to SAS has collected over 1,000 measurements of inhalable and respirable dust levels in SAS manufacturing plants (Table 2-3). Overall mean dust concentrations were 1.2 mg/m^3 (inhalable) and 0.3 mg/m^3 (respirable), values that are well below the German MAK standard of 4 mg/m^3 and US workplace standard of 6 mg/m^3 (ECETOC, 2006).

Table 2-2 1982-1996 Data on Occupational Exposures in SAS Manufacturing Plants (IARC, 1997)

SAS Form, region (job category)	Concentration (mg/m^3)	Comment
Precipitated SAS, France (production)	0-10.5 total 0-3.4 respirable	
Precipitated SAS, US (production)	<1.0-10 total	
Pyrogenic SAS, Europe- 9 plants (filling, packing, bagging, and mixing)	0.61-6.5 total 0.2-2.1 respirable	Personal samples, range of medians
Precipitated SAS and SAS gel, Europe- 9 plants (filling, packing, cleaning, blending)	1.0-8.8 total 0.5-2.1 respirable	Personal samples, range of medians

Table 2-3 Contemporary Levels of Inhalable and Respirable Dust in Five SAS Manufacturing Plants (from ECETOC, 2006)

Plant	Inhalable (mg/m^3)		Respirable (mg/m^3)	
	AM	GM	AM	GM
1	0.17-1.14	0.13-0.81	0.07-0.26	0.05-0.19
2	0.38/0.35	0.03/0.35	0.07/0.33	0.06/0.27
3	0.41-2.52	0.36-2.02	0.19-1.08	0.15-0.62
4	0.42-3.15	0.24-2.06	0.15-0.64	0.10-0.49
5	0.23-1.55	No data	0.10-0.34	No data

AM= arithmetic mean, GM= geometric mean

2.3 Conclusion: Information on SAS Uses and Potential Exposures Indicates a Low Exposure Potential to Nano-Sized SAS Particles

In this section we emphasized the long history of SAS use in numerous commercial and consumer products and thus its commercial importance. Consumers are likely to be exposed mainly *via* ingestion of natural and synthetic forms of silica and less likely to be exposed *via* inhalation or dermal contact. Occupational exposures, on the other hand, will include potential inhalation and dermal exposures. However, contemporary measurements in SAS manufacturing plants show that levels of inhalable and respirable SAS have decreased substantially and are well-below occupational health standards (see Section 4.1). Importantly, evidence of safe manufacture and use, coupled with data regarding the size distribution of solid forms of SAS (Section 1), have shown no indication of exposure to nano-sized SAS particles that would result in adverse health impacts.

3 Hazard Assessment

Available health effects data for manufactured SAS indicate very low, if any, toxicity in worker populations. In addition, over 60 years of use in commercial and consumer products provides compelling evidence of safety. In this section, we summarize the current state of knowledge on the health effects of SAS.

3.1 Epidemiological and Case Studies of SAS Health Effects

Because SAS have generally been considered to be of low toxicity, only a few quantitative epidemiological studies have been published examining the effects of occupational exposures. Occupational exposures to SAS occur during production, handling, and use in a variety of industries. Packing, weighing, reprocessing, and cleaning job categories are associated with the highest exposures, but engineering controls and use of personal protective equipment serve to reduce worker exposures (IARC, 1997).

Section 9 of the ECETOC report (2006) and Section 3 of the OECD SIDS (2004) provide detailed summaries of the available epidemiological studies of workers exposed to SAS. Also, a recent review of health hazards associated with inhalation of amorphous silica was conducted by Merget *et al*. (2001). In this review, Merget *et al*. (2001) concluded that "epidemiological studies do not support the hypothesis that amorphous silicas have any relevant potential to induce fibrosis in workers with high occupational exposure to these substances." However, Merget *et al*. (2001) did find that the data were too limited to rule out risk associated with chronic bronchitis, chronic obstructive pulmonary disease (COPD), or emphysema.

To address these data gaps, a large worker monitoring and morbidity study is currently underway to assess the health status of workers exposed to SAS compared to unexposed controls in five German manufacturing plants, three manufacturing pyrogenic SAS, and two manufacturing precipitated SAS. A total of 397 current workers with at least 1 month's exposure and with complete data are participants in the study (out of 510 eligible workers). In addition, 178 former workers with at least one month of exposure between 1980 and 1994 are included in the study, along with 210 unexposed control workers.

For each of the exposed and unexposed workers in the study, the following data were collected: 1) demographic and background information (*e.g.,* smoking and medical history) *via* questionnaire; 2) atopy (*via* skin prick test and IgE titers); 3) spirometric data and reversibility; 4) carbachol bronchial provocation data; and 5) chest radiographs (ECETOC, 2006).

As reported in the ECETOC report (2006), preliminary results indicate that chronic bronchitis prevalence was slightly higher in the exposed group, but still within a normal range. There were also differences in spirometric measurements between exposed and control subjects, but these differences may be explained by the more prevalent smoking habits among the exposed workers. Obstruction or restriction was no different across plants, and bronchial hyperresponsiveness was within normal ranges. Lastly, chest radiographs showed no evidence of increased risk of pneumoconiosis of exposed subjects compared to controls and no significant pleural thickening. A detailed report is in preparation, with additional statistical analyses and testing of differences between exposed and control workers while accounting for potential confounders. Overall, preliminary results do not show health risks from SAS exposures in these workplace settings (ECETOC, 2006).

The ECETOC report (2006) also summarizes results from a limited company study of 143 German workers in a pyrogenic SAS manufacturing plant in which medical records from 1959 to 1985 were evaluated. Pulmonary symptoms (cough, sputum, and shortness of breath) as well as abnormalities in lung pathology or function were found in 54 workers, but there was no evidence of silicosis. An additional study evaluated chest x-rays of 215 workers in a German pyrogenic manufacturing plant collected from 1947 to 1959. Concentrations in the bagging area were found to range from 2 to 7 mg/m^3 with much higher exposure concentrations taken near a filling nozzle (15 – 100 mg/m^3). No lung pathologies were observed in any of the x-rays.

In addition, summaries of studies of workers exposed to precipitated silica can be found in the ECETOC report (2006). In one US study, 165 workers in 2 manufacturing plants were evaluated. Cumulative indices were developed based on exposure concentrations and duration. The authors found that respiratory symptoms correlated with smoking but not with SAS exposure, and there was no evidence of pulmonary function and chest radiograph abnormalities associated with SAS exposure. In a separate study, company health records of 78 employees employed for between 1 and 16 years (average of 4.75 years) were examined. Exposures ranged from 0.3 to 204 mg/m^3. Annual x-ray evaluations found no evidence of silicosis or other pulmonary disease. However, symptoms of mechanical irritation

of the skin, eyes, nose and throat from dust exposures were reported. Lastly, a study in France of 150 workers exposed to precipitated silica for an average of 12.2 years evaluated effects on pulmonary function and chest x-rays. As in previous studies, x-rays did not show any signs of pneumoconiosis or fibrosis. A small, non-significant decrease in some of the pulmonary function measures (but not all) was observed in the exposed workers (ECETOC, 2006).

In conclusion, there is no evidence from occupational exposure studies of adverse pulmonary effects from SAS exposure. Specifically, there is no evidence of lung cancer or other chronic pulmonary diseases (*e.g.*, silicosis) in workers exposed during the manufacturing of SAS. For studies that assessed respiratory symptoms and pulmonary function, any effects were typically correlated with smoking and not SAS exposure (ECETOC, 2006). The long manufacturing history of SAS with no evidence of adverse health outcomes coupled with the current low measured levels of exposure to workers, support the low potential risk of adverse effects associated with manufactured SAS.

3.2 Experiments in Laboratory Animals

SAS toxicity has been studied *via* various different routes of administration (oral, dermal, inhalation, intravenous, and intratracheal) in different animal species (rats, mice, rabbits, dogs, and monkeys). A summary of the *in vivo* and *in vitro* toxicity results for acute (oral, inhalation, and dermal), repeated dose (oral and inhalation), genetic toxicity (*in vitro* and *in vivo*), carcinogenicity, and reproductive effects are give in Table 3-1. Results of key studies are briefly summarized below. Detailed summaries are provided in both the ECETOC report (2006) and OECD SIDS (2004).

Table 3-1 Summary of Toxicological Data (from OECD, 2004)

Test	Endpoint/Findings
Acute Oral Toxicity	LD_{50} >3300 mg/kg (limit test)
Acute Inhalation Toxicity	LC_0 >140 - >2,000 mg/m^3 (Maximum concentrations technically feasible)
Acute Dermal Toxicity	LD_{50} >5000 mg/kg (limit test)
Primary Irritation (skin, eye)	Not irritating
Sensitization	No data available*
Repeated Dose Toxicity (inhalation)	inflammatory reaction in the lung: NOEL(5 d) = 1.0 mg/m^3
Repeated Dose Toxicity (inhalation)	inflammatory reaction in the lung (rat) NOAEL(13 wks) = 1.3 mg/m^3
Repeated Dose Toxicity (oral)	no substance-related abnormalities in rat: NOAEL(6 months) = ~9000 mg/kgbw
Genetic Toxicity *in Vitro*	
A. Bacterial Test (Gene mutation)	not mutagenic
B. Non-Bacterial In-Vitro Test (Gene Mutation)	not mutagenic
C. Non-Bacterial In-Vitro Test (Chromosomal Aberration)	not mutagenic
Genetic Toxicity *in Vivo*	not mutagenic
Carcinogenicity (inhalation)	inconclusive
Carcinogenicity (oral)	not carcinogenic in rat and mouse
Reproductive Toxicity	no effects (limited study in rat)
Developmental / Teratogenicity	no adverse effects in rat, mouse, rabbit and hamster

*Sensitization has not been seen in worker populations

3.2.1 Acute Exposures

Acute effects of SAS exposure have been studied in rats (oral and inhalation studies) and rabbits (dermal studies and eye irritation studies). A large number of oral mortality studies have been conducted in rats using various forms of SAS (pyrogenic, precipitated, gel, and sol). Detailed results can be found in ECETOC (2006; Table 27). No differences were observed in LD_{50} values across different types of SAS. Overall, no deaths occurred and there were no signs of toxicity after oral administration of SAS of up to 5,000 mg SiO_2/kg bw. Only at extremely high doses of SAS (10,000 and 20,000 mg SiO_2/kg bw) were animal deaths observed (ECETOC, 2006).

Dermal studies of different SAS types in rabbits showed only slight erythema (redness of the skin) with intact or abraded skin and oedema (swelling) with abraded skin, which was completely reversible in 5 days. There was no indication of systemic adverse effects. In general, animal tests showed no toxicity *via* the dermal route (ECETOC, 2006).

Inhalation studies have been conducted for various forms of SAS (see Tables 29 and 30 in ECETOC, 2006 providing details for hydrophilic and hydrophobic SAS, respectively). Inhalation studies using hydrophilic forms of SAS have proven to be difficult to conduct due to the strong binding forces of the aggregates and the high tendency of the aggregates to form agglomerates. Thus, most inhalation tests have been conducted using lower test concentrations than the recommended concentration of 5,000 mg/m^3 for acute respirable dust inhalation testing (ECETOC, 2006).

The available acute inhalation testing data show differences in mortality and morbidity results for hydrophilic *vs*. hydrophobic forms of SAS. For studies conducted using hydrophilic SAS, no mortality was observed in all studies, except for one in which 1/10 animals died (exposures of 2,200 mg/m^3). These studies were generally conducted via nose-only exposure or whole-body exposure with concentrations ranging from 139 to 2,200 mg/m^3 over exposure durations of 1 to 4 hours. Respiratory irritation was observed only in a study of rats exposed to 2,200 mg/m^3 for 1 hour. Studies conducted at lower concentrations showed no clinical effects.

A higher respirable dust concentration can be achieved using hydrophobic SAS, which may be a possible explanation for the high mortality rates observed in some of the hydrophobic SAS studies compared to hydrophilic SAS studies. As shown in Table 30 of the ECETOC report (2006), mortality rates were high at concentrations of about 2,100 mg/m^3 or greater. At necropsy, the rat lungs of the deceased animals showed severe redness. In another study, pre-death symptoms included closed eyes, wetness and redness around the nose and mouth, and respiratory distress. As discussed in the ECETOC report (2006), Degussa and Cabot found that SAS exposures at high concentrations occluded smaller bronchioles and extravasation of blood was observed, which may be indicative of suffocation rather than a direct toxic effect of the substance.

Furthermore, ECETOC (2006) reports that most of the acute inhalation studies for which particle size data were available described test samples that were significantly different from commercially available SAS products in terms of the particle size distributions. This is largely attributed to the methods of dispersing the powdered forms of the product for effective delivery. Dispersal of SAS powders results in a reduction in the size fraction yielding particles with mass median aerodynamic diameters (MMAD) below 10 μm (*i.e.*, in the respirable range). Most commercial powder forms of SAS (>99%) have MMAD greater than 10 μm. Furthermore, particle size determinations have shown that 99% of the particle fraction of most SAS powders exceed a MMAD of 90 μm, a particle size likely to

only reach the upper airways, if inhaled at all (see section 1.2). Thus, the relevance of these acute inhalation studies to actual human exposures is questionable (ECETOC, 2006).

Skin and eye irritation has been tested in rabbits (ECETOC, 2006; Tables 31 and 32) and results have demonstrated that SAS is largely non-irritating to the skin and eyes. While some mild effects (*e.g.*, redness) were observed, these effects were readily reversible. However, case reports of occupational exposures have described dryness and eczema resulting from chronic dermal contact of SAS. These reactions may be avoided by using skin care products (ECETOC, 2006; OECD, 2004). For sensitization no experimental data are available. However, based on its structure and physico-chemical properties, SAS is not expected to cause skin sensitization. In addition, there is long record of medical surveillance in worker populations that shows no evidence of skin sensitization (OECD, 2004)

3.2.2 Subchronic and Chronic Exposures

To assess effects from repeated exposures to SAS *via* oral, dermal, and inhalation routes of exposures, toxicity studies have been conducted for rats, rabbits, guinea pigs, mice and monkeys. Oral studies in rats confirm the absence of any toxic effects from ingestion. For example, chronic administration of SAS at a concentration of up to 5% in the diet to mice and rats caused no microscopic changes or neoplasms (ECETOC, 2006 Table 33). One dermal study was available in which the researchers found no effects from dermal exposure for intact and abraded skin of rabbits using concentrations of up to 10,000 mg/kg bw (ECETOC, 2006 Table 34). Numerous inhalation studies have been conducted in rats, guinea pigs, rabbits, and monkeys and across a variety of SAS forms (pyrogenic, precipitated, and silica gel). Exposure concentrations have ranged from 0.5 to 150 mg/m^3. These studies suggest that SAS causes transient increases in markers of inflammation and cell injury. In addition, in some studies, there was evidence of an inflammatory response, focal fibrosis, and granulomatous nodule formation, but the studies with a recovery period found that these pulmonary effects were not persistent. Importantly, in contrast to crystalline silica exposure, SAS exposure did not induce irreversible or progressive lung injury, and there was no evidence of lung tumors (ECETOC, 2006).

The repeated dose inhalation studies are summarized in the ECETOC report (2006, Tables 35 and 36 for hydrophilic and hydrophobic SAS, respectively). NOAELs have been determined based on these inhalation studies and range from 0.5 to 10 mg/m^3 depending on the SAS product used in the study. However, it is important to emphasize, as discussed in the ECETOC report (2006), that many of the

"adverse" effects that these NOAELs are based on reversible effects in the post-exposure recovery period.

3.2.3 Genetic and Reproductive Toxicity

SAS has been found to be non-mutagenic using several *in vitro* test systems (*e.g., Salmonella typhimurium* and *Escherichia coli*). In addition, in mammalian cells, neither point mutations nor chromosomal aberrations have been detected, and no genotoxicity was observed in *in vivo* studies (ECETOC, 2006).

Studies carried out in rats, mice, hamsters and rabbits have demonstrated no toxic effects on male and female fertility and no teratogenic effects or developmental abnormalities in progeny. The NOEL for maternal and fetal toxicity was >1600 mg/kg for silica gel and >500 mg/kg for pyrogenic silica (ECETOC, 2006).

3.3 IARC's 1996 Evaluation of Silica

The International Agency for Research on Cancer (IARC) offers a well-established paradigm for ranking potential cancer risk. For IARC, *sufficient* human evidence consists of epidemiology data that show: "A positive relation between exposure and cancer observed, with chance, bias, and confounding ruled out with reasonable confidence" (IARC, 1997). If chance, bias, and confounding cannot be ruled out with reasonable confidence, then IARC judges the human evidence to be less than sufficient, *i.e.*, *limited or inadequate*. If some positive associations have been reported, but such associations are neither consistent nor of sufficient quality, then IARC turns to animal evidence to assess the potential for carcinogenicity. Similarly in animals, *inadequate* evidence for IARC consists of evidence from studies that "cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available" (IARC, 1997). Based on its evaluation of the human and animal data, IARC assigns agents to the following carcinogenic classifications:

Group 1: The agent is carcinogenic to humans.

Group 2A: The agent is probably carcinogenic to humans.

Group 2B: The agent is possibly carcinogenic to humans.

Group 3: The agent is not classifiable as to its carcinogenicity to humans.

Group 4: The agent is probably not carcinogenic to humans.

It should be appreciated that within the context of the IARC rankings, the dose (or exposure level) is still crucial to assessing possible hazard. That is, even Group 1 carcinogens, which include relatively common substances such as alcoholic beverages, aflatoxins (natural contaminants of peanuts and other crops), asbestos, smokeless tobacco products, benzene, birth-control pills, formaldehyde, sand, soot, sunlight, and wood dust (IARC, 2008) would not normally be considered a serious hazard in the absence of sufficient, prolonged exposure.

In its 1996 evaluation of silica, IARC classified *amorphous* silica as a Group 3 carcinogen based on *inadequate* evidence in humans and *inadequate* evidence of increased tumors in animals.

3.4 Conclusion: Animal and Human Health Effects Data Show Little Evidence of Toxic Effects from Exposure to SAS

The health effects database that includes both animal and human studies indicates that adverse health impacts from SAS exposure are minimal, if any. Such a conclusion is supported by the recommendation in the recent OECD SIDS Initial Assessment Report (OECD, 2004) that SAS is "currently of low priority for further work" based on the low exposure potential to humans. As was described in detail in Sections 1 and 2, the physical characteristics as well as the available worker exposure data support the conclusion that exposure to respirable SAS is low and that there is no evidence of health hazards from current manufacture and use of these SAS products.

3.5 Environmental Effects

The effects of SAS on various micro-organisms, as well as aquatic and terrestrial organisms, have been investigated. In addition, the effects of SAS on ecosystems have been examined. Details can be found in the ECETOC report (2006). In general, there is no evidence of acute toxicity of SAS to organisms in the environment, except for the desiccant effects on insects exposed *via* direct contact with SAS. In fact, silica plays a critical role in many biological systems. For example, it forms the skeleton or shells of diatoms, radiolarians, and sponges, provides structural strength to plant stems, and is used by

plants to form needles that are used for protection. Silicon is essential for growth and development of diatoms and thus dissolved silica influences the phytoplankton populations in fresh and marine waters along with a number of other controlling factors (other nutrients such as phosphorus and nitrogen, light, temperature, *etc.*) (ECETOC, 2006). Importantly, the quantities of silica released into the environment are negligible compared to the natural flux of silica, particularly in aquatic environments (ECETOC, 2006).

As described in greater detail in the ECETOC report, ecotoxicity testing has been conducted for SAS using a variety of aquatic and terrestrial species and microorganisms. Aquatic toxicity tests conducted in accordance with OECD guidelines using good laboratory practices (GLP) have reported LC_{50} and EC_{50} values in fish and crustaceans were greater than 10,000 mg/L and 1,000 mg/L, respectively (ECETOC, 2006; Table 25). In many of the tests, the concentrations exceeded the limit of solubility of the product being tested, thus true concentrations were often not available. Tests for various micro-organisms including *Escherichia coli, Proteus sp., Pseudomonas aeruginosa, and others* have observed the mortality of gram-negative bacteria such as *Escherichia coli* in 6 hours to 3 days when in contact with SAS, whereas gram-positive bacteria were more resistant. Lastly, tests have been conducted in terrestrial organisms in relation to the use of silica as a biocide. Mortality of insects was observed at low humidity and when water was not available, probably due to the dehydration effects of the silica *via* contact. Ingestion routes were not toxic to the insects tested. Details are provided in the ECETOC report (2006; Table 26).

In conclusion, the amount of SAS released into the natural environment is negligible compared to the natural flux of silica in the environment (see Section 2.2.1). In laboratory experiments, SAS was not toxic to most organisms, although desiccant properties of SAS are likely responsible for observed mortality in tested insects. In general, SAS poses little to no risk of adverse ecological effects.

4 Risk Management

Industrial hygiene practices regarding the control and handling of SAS during manufacture and use are grounded in a considerable history. In this section, we summarize the current risk management practices that ensure the safety of SAS manufacturing and use.

4.1 Occupational Standards

Regulations and occupational guidelines for various forms of silica vary somewhat across different countries. In general, separate exposure limits have been adopted to distinguish between the different forms of silica and, in particular, to distinguish between amorphous and crystalline forms. Table 4-1 provides a list of selected occupational exposure limits for amorphous forms of silica (including SAS) that have been established for protection of workers.

These workplace exposure limits and standards are generally based on total dust determinations, but some countries have established separate limits for the respirable fraction [6] and consider amorphous silica to have similar toxicity to other low solubility, low toxicity dusts. For example, the National Institute for Occupational Safety and Health (NIOSH), consistent with its recognition of amorphous silica as a low-toxicity nuisance dust, recommends an allowable 8-hour time weighted average (TWA) of 6 mg/m^3. The current OSHA Permissible Exposure Limits (8-hour TWA) are 20 mppcf and 80 $mg/m^3/\%SiO_2$. [7] In 1980, OSHA changed the PEL for SAS to 6 mg/m^3, however this PEL was vacated on June 30, 1993. In 1991, the American Conference of Governmental Industrial Hygienists (ACGIH) established TLV-TWA for various forms of amorphous silica, recommending a TLV-TWA of 10 mg/m^3 for precipitated silica based on the default TLV for "particulates not otherwise specified" (Haber and Maier, 2002). However, due to insufficient data, in 2006 ACGIH withdrew all of the TLVs established for the various forms of amorphous silica (however, the values remain in the ACGIH records for a period of 10 years after withdrawal). In Germany, the MAK value for synthetic amorphous silicas, including

[6] The respirable fraction constitutes the inhaled particles that penetrate to the alveolar region of the lung and is defined by the measured mass fraction of total aerosol that has a 50 % cutoff of 4 μm (the aerodynamic diameter).

[7] mppcf = millions of particles per cubic foot of air; Based on available information, the expression "80 $mg/m^3/\%SiO_2$" means 80 mg/m^3 divided by the numerical percentage of crystalline silica ($\%SiO_2$). Note: 20 mppcf is considered to be equivalent to $6mg/m^3$. See http://www.cdc.gov/niosh/npg/pdfs/2005-149.pdf .

pyrogenic, precipitated, and silica gel, was set at 4 mg/m^3, based on a LOAEL in rats of 6 mg/m^3 (Haber and Maier, 2002).

Table 4-1 Occupational Exposure Limits for SAS and Amorphous Silicas (adapted from ECETOC, 2006)

Type of silica / Country	TWA (mg/m^3)		Reference
	Inhalable fraction	Respirable fraction	
Precipitated SAS, SAS gel			
Belgium	10	-	Moniteur Belge, 2002
Canada, Alberta	10	-	Province of Alberta, 2003
Chile	8	-	Ministerio de Salud, 1999
Spain	10	-	INSHT, 2001
Silica, amorphous			
Canada. Alberta	10	3	Province of Alberta, 2003
Finland	5	-	HTP-arvot, 2005
Germany	4	-	Bundesministerium für Arbeit und Sozialordnung, 2000
Ireland	6	2.4	NAOSH, 2002
Mexico	10	3	Norma Oficial Mexicana, 2000
Norway	-	1.5	Arbeidstyilsynet, 2003
Thailand	0.8	-	Ministry of Interior, 2001
UK	6	2.4	HSE, 2005
US	6		NIOSH, 2005 [8]

[8] http://www.cdc.gov/Niosh/npg/npgd0552.html

4.2 Safe Handling Practices and Procedures

As with all nuisance dust exposures, SAS occupational control measures mainly involve assuring proper ventilation to maintain dust levels below occupational standards as listed in Section 4.1. As discussed in Section 3.2.3, levels of silica dust have decreased substantially over the years due to process changes and more stringent control. When exhaust ventilation is not possible, the use of appropriate respirators may be warranted depending on the exposure concentrations. In addition, suitable gloves, as well as use of barrier lotions, are recommended when handling SAS to prevent excessive drying of the skin. Protective clothing and eye protection may also be warranted for workers with repeated or prolonged exposures (ECETOC, 2006).

If adverse effects occur upon exposure to SAS, standard first aid measures are recommended. In the event of skin or eye contact with SAS, flushing with plenty of water is warranted. SAS may cause dryness and cracking of the skin that may result in redness, swelling, and itching. Medical treatment may be required if this occurs. Use of a protective skin cream barrier and avoiding direct skin contact with SAS are recommended safety measures (ECETOC, 2006).

In areas where SAS dust is generated, appropriate ventilation should be used. If workers experience trouble breathing, subjects should be moved to areas with fresh air and medical treatment should be sought if symptoms persist. SAS is not expected to cause any adverse effects from ingestion. Precautionary measures for SAS ingestion involve drinking plenty of water and seeking medical attention for any symptoms that develop (ECETOC, 2006).

Proper storage of SAS includes tightly closed containers and a dry, cool, and well-ventilated storage area. SAS does not pose a hazard as a result of fire or spillage. Lastly, SAS is not considered a hazardous waste and can be disposed in a landfill or *via* incineration. However, disposal of SAS to soils, waterways, sewers, and drains should be avoided.

Although most manufacturers of SAS do not have medical surveillance programs specifically to address any health impacts from exposures to fugitive SAS dusts, several companies have annual checkups which incorporate pulmonary function and chest x-rays as part of their general health surveillance program for workers.

4.3 Conclusion: Current SAS Exposure Standards and Work Practices are Protective of Health

Occupational standards have been established to protect workers from exposures to potentially high concentrations of particles. The limits set for SAS dusts are similar to those for other non-toxic nuisance dusts. Under conditions that restrict dust exposures to levels below occupational standards, SAS is not expected to be a hazard to worker populations, because the long track record of workers' exposures has demonstrated no adverse health hazards from workplace exposures to SAS. Moreover, the accumulated data on SAS suggest that the internal nanostructure of SAS does not give rise to unanticipated health hazards.

5 Summary Conclusions

In this submission SASSI has presented information to support three key points regarding the safe manufacture and use of SAS substances and products containing SAS. These key points include:

(1) Solid powder forms of manufactured synthetic amorphous silica (SAS) are not nano-objects or nanoparticles, but rather nanostructured with features which are on the nanometer length scale, but overall do not have dimensions at the nanoscale. This conclusion was supported by presenting a large body of studies that have characterized SAS particle size during the manufacturing process. These studies demonstrate the strong bonding of SAS particles into stable aggregates and agglomerates with dimensions in the micron range.

(2) Consumer exposure is mainly *via* ingestion of naturally-occurring and synthetic additives to foods and dissolved silica in water. Workers, on the other hand, will be exposed to SAS *via* inhalation and dermal contact. Current worker exposure data show that levels in manufacturing plants have decreased substantially in recent years and are well-below regulatory standards. Given that exposure are low, and supported by studies in worker population and in animals, SAS can be considered a non-toxic substance having characteristic health impacts that are similar to other low-toxicity, biologically inert dusts. In addition, there is no evidence that SAS is harmful to ecological systems.

(3) Safe industrial hygiene practices of SAS control and handling are in place to ensure that SAS exposure levels meet regulatory and occupational standards. A long worker exposure history has shown no evidence of adverse health impacts and collected exposure data indicate levels of exposure that are well-below health-protective regulatory standards.

Overall, SAS is a substance that does not pose any unique toxicity due to its nanostructure or other physical-chemical properties. Over 60 years of manufacture and use of SAS has shown that SAS presents little (if any) health risk when handled properly.

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SASSI Particle Size Data Publications: JACC 51, Sept. 2006; NMSP, July 2008

From JACC 51, Table 1, page 12

Particle size	Pyrogenic	PPT	Gel	Sol	Unit
Primary particle size	0.005 - 0.05 g	0.005 - 0.1 g	0.001 - 0.01	0.005 - 0.02	µm
Aggregate size	0.1 - 1	0.1 - 1	1 - 20	NA	µm
Agglomerate size	1 - 250	1 - 250	NA	NA	µm

From JACC 51, page:

"By adjusting certain process parameters, the mean particle size, particle size distribution and degree of aggregation and/or agglomeration can be varied over relatively broad ranges. However, the smallest particles in precipitated and pyrogenic SAS remain the corresponding aggregates, not the primary particles (Hurd and Flower, 1988).

Given their size range, commercial SAS do not fall into the class of nanoparticles, which are defined as particles of less than 100 nm in diameter (BSI, 2005).

Microphotographs of actual SAS particles in commercial products are shown in Figures 8, 9 and 10 (courtesy of Stintz M, Technical University of Dresden and Heinemann M, Wacker Chemie, Burghausen, Germany)."

From NMSP Report, Page 17:

As described in the ECETOC report (2006), particle size distributions have been characterized under typical SAS handling conditions (filling, shipping, and storage of SAS products). These conditions involve handling dry powder SAS at high concentrations. The sizing methods used to assess distributions of particle dimensions were non-destructive (i.e., low shearing) methods, such as dry sieving and Fraunhofer laser light diffraction. By the dry-sieving method, no particles were found to pass through a mesh size of 90 □m and 83% of particles were found to pass through a mesh size of 125 □m. Using the Fraunhofer laser light diffraction method, pyrogenic SAS samples were estimated to have an average aerodynamic diameter of ~200 □m. Furthermore penetrate into the lungs, i.e., below 10 µm aerodynamic diameter) for pyrogenic SAS comprised <1% by weight. These results support the fact that during manufacturing and handling of SAS products, worker are not exposed to particles in the nano-sized range.

These results are consistent with the findings of Gray and Muranko (2006) who reported that aggregates are the smallest separable entity for manufactured SAS, even for conditions of severe mechanical processing. In a series of experiments, which included mechanical processing via uniaxial compression, elastomer mixing, or ultrasonication, Gray and Muranko (2006) provided data that showed no release of primary SAS particles. Furthermore, the researchers observed that, although there can be fracture of the largest and most complex aggregates under the high energy conditions of their experimental methods, this resulted in only modest reductions in the size of the largest aggregates.

In a similar study, Sauter et al. (2006) reported on dispersion of Aerosil 200V, a pyrogenic silica, in liquid using ultrasonic treatment or treatment via a rotor-stator system (i.e., via mechanical mixing). Due to the high tendency for these particles to agglomerate, the researchers found that very high energies were required (~10 GJ/m3 = 10 10 J/m3) to obtain modest size reductions (from ~180 nm to ~120 nm). Interestingly, despite a similar amount of energy applied, the rotor-stator system was not able to achieve the same size-reductions that the ultrasonic treatment achieved. Importantly, and consistent with the findings by Gray and Muranko (2006), the authors found that the energy applied via either ultrasonic treatment or mechanical mixing (rotor-stator) was not strong enough to break apart agglomerates into primary particles. Additional studies of pyrogenic silica particle size distributions using various different particle sizing and dispersion techniques confirm that this product exists as a white fluffy solid composed of agglomerate sizes ranging from 10 to 90 µm without dispersion treatment (Barthel et al., 1999).

Similarly, in a recent study, Ma-Hock et al. (2007) provided additional findings confirming that SAS consists primarily as larger-sized (>100 nm) aggregates and agglomerates. For two types of hydrophobic pyrogenic SAS (e.g., surface-treated SAS) with differing surface areas (Aerosil R104, SA ~150 m2/g and Aerosil R106, SA ~250 m2/g) and an unspecified amorphous silicon dioxide "nanopowder," Ma-Hock et al. (2007) reported a range of primary particle sizes of 5 to 50 nm based on transmission electron microscopy (TEM) pictures, noting that the particles were suspended in ethanol for analysis. However, when the researchers attempted to obtain more quantitative primary particle size distributions using an ultrafine particle analyzer (UPA), they were unable to obtain primary particles because the primary particles are fused together forming aggregates. In addition, based on particle size distribution measurements made using both a Scanning Mobility Particle Sizer (SMPS) and an Optical Particle Counter (OPC) across the three SAS products as aerosolized at high energy using a dry powder brush feed aerosol generator or a nebulizer system, the researchers demonstrated a high degree of aggregation and agglomeration. Indeed, for the silicon dioxide sample, the researchers found substantial intersampling variability in the particle size distribution as measured by the SMPS because SiO2 does not form a stable suspension. Ma-Hock et al. (2007) reported that median count distributions ranged from 0.20 □m to 0.45 □m, with a aerosolized SAS particles having diameters of less than 100 nm. These measurements thus confirmed that the main mass fraction of aerosolized SAS particles consists of stable aggregates or agglomerates, even under the high dispersive energy typical of a brush dust feeder and nebulizer.

Scanning electron microscope (SEM) images as well as transmission electron microscope (TEM) images of various forms of SAS confirm the stable aggregated and agglomerate state of these products (Figures 1-11 to 1-16).