Peer Review Report

External Peer Review Comments

and FDA Responses

Interagency Working Group on Asbestos in Consumer Products (IWGACP)

White Paper: IWGACP Scientific Opinions on Testing Methods for Asbestos in Consumer Products Containing Talc

Office of Cosmetics and Colors (OCAC)
U.S. Food and Drug Administration
U.S. Department of Health and Human Services

December 2024

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I. INTRODUCTION

Versar, Inc. (Versar), an independent Food and Drug Administration (FDA) contractor, coordinated an external letter peer review of the Interagency Working Group on Asbestos in Consumer Products (IWGACP) document titled "*White Paper: IWGACP Scientific Opinions on Testing Methods for Asbestos in Cosmetic Products Containing Talc*." The peer review was conducted for FDA's Office of Cosmetics and Colors (OCAC).

The FDA is responsible for providing regulatory oversight of the safety and proper labeling of cosmetics, including protecting consumers from health hazards associated with contaminants that may be present in cosmetic products. Talc is a mineral-derived ingredient found in various cosmetic products, most notably body powders, baby powder and makeup products which are loose or compressed powders (e.g., blush and eyeshadow). Concern about the purity of talc used in cosmetics increased in the 1960s and 1970s when numerous cosmetic products tested positive for asbestos. At that time, there were no published test methods applicable to trace levels of asbestos in talc. In 1976, the Cosmetic, Toiletry, and Fragrance Association (CTFA) implemented a voluntary method for asbestos-testing (J4-1 method) that recommends using X-ray diffraction (XRD) and then polarized light microscopy (PLM) only if XRD is positive. Talc suppliers to the pharmaceutical industry use a similar two-step method to certify that talc meets the United States Pharmacopeia's (USP's) requirement for "Absence of Asbestos." The CTFA J4-1 and USP methods remain recognized methods to test for asbestos in talc used in cosmetics and pharmaceuticals, respectively, despite long-identified shortcomings in specificity and sensitivity compared with electron microscopy-based methods.

FDA has periodically performed testing of talc-containing cosmetics for asbestos using optical and electron microscopy methods which have, on occasion, provided positive findings. Although the use of both types of microscopy has been widely accepted among experts in geology, analytical microscopy and the health sciences, some degree of controversy surrounding the identity of the mineral particles detected by these methods remains evident. Other federal agencies have encountered similar controversy involving detection and identification of asbestos in consumer products or bulk building materials containing substances derived from minerals that might be contaminated with asbestos. In response, FDA sought input from federal scientists in different agencies having vast experience in asbestos analysis and full understanding of all technical issues prevailing within the realm of asbestos test methodology and applying the resulting test data to making regulatory decisions. In 2018, FDA formed the IWGACP to obtain expert opinions regarding the most appropriate testing approach to detect and identify asbestos in talc-containing cosmetic products.[1] The outcome of the IWGACP deliberations is a White Paper with 12 Technical Appendices.

Versar identified five experts to serve as peer reviewers. For the purpose of this review, three peer reviewers with expertise in the following fields/disciplines: 1) Geology of silicates, 2) Analytical microscopy of minerals, and/or 3) Chemistry and morphology of asbestos/asbestiform minerals, were selected to answer 20 charge questions. Another two peer reviewers, with expertise in the following fields/disciplines: 1) Toxicology, 2) Epidemiology, and/or 3) Public

[1] Although the original scope of the IWGACP was consumer products that contain talc, in early 2020 the scope was narrowed to talc intended for use in cosmetics and talc-containing cosmetic products.

health, answered four health-related charge questions. All reviewers were asked to provide edits and suggestions to improve the White Paper and Technical Appendices.

Peer Reviewers:

Elena Belluso, Ph.D.
University of Torino, Italy

Dr. Elena Belluso is a full professor at the University of Torino, Italy in Environmental Mineralogy at the Department of Earth Sciences. Dr. Belluso is also Director of the "Giovanni Scansetti" Interdepartmental Centre for Studies on Asbestos and Other Toxic Particulates and is the University of Torino expert for asbestos and other harmful particulates. She holds a PhD in Mineralogy and Crystallography from the Modena, Pavia, Torino University consortium and an M.A. in Geological Sciences from the University of Torino. Dr. Belluso has experience in characterization and quantification by Transmission and Scanning Electron Microscopy with annexed Energy Dispersive Spectrometry (TEM-EDS, SEM-EDS) of minerals and inorganic particles present in air, rocks, human and animal biological tissues and human fluids for medical diagnosis and environmental pollution evaluation. She is also experienced in crystal chemical and structural characterization by modern analytical methods (X-ray powder Diffractometry XRPD, TEM-EDS, SEM-EDS, micro-Raman etc.) of natural and synthetic silicates, fibrous minerals, both pristine and differently treated (Fe-doped, Ni-doped, in vitro cell culture) samples of regulated and non-regulated mineral fibers (such as asbestiform fluoredenite, asbestiform sepiolite etc.). She has been a reviewer for several journals in the fields of environmental mineralogy, materials science, crystal growth, physical-chemistry, environmental and inorganic chemistry and has authored or co-authored about 280 papers, book chapters and communications.

Arthur L. Frank, Ph.D.
Drexel University

Arthur L. Frank received his M.D. degree from the Mount Sinai School of Medicine and his Ph.D. in biomedical sciences from the City University of New York. He was trained in both internal medicine and occupational medicine and holds board certification in both fields. As a commissioned officer in the Public Health Service, he conducted research at the National Cancer Institute. His major research activities have included the study of occupational lung diseases such as asbestosis, silicosis, and occupational cancers (especially those related to asbestos exposure), and Dr. Frank has worked in the area of agricultural safety and health.

Myron Getman, B.S.
New York State Department of Health Asbestos Laboratory

Mr. Myron Getman has been a Research Scientist and Technical Director at the New York State Department of Health Wadsworth Center for over 20 years. He has worked in asbestos research and analysis pertaining to the physical properties of asbestiform minerals, fibrous amphiboles, fibrous particulates, and unknown "white powders" by Polarized Light Microscopy (PLM); Phase Contrast Microscopy (PCM); Transmission Electron Microscopy (TEM); Scanning Electron Microscopy (SEM); and Fourier-Transform Infrared Spectroscopy (FTIR). Mr. Getman

also developed a New York-approved method (ELAP Item 198.8) for analysis of surfacing materials containing vermiculite for asbestos in conjunction with the Division Director's Office, Environmental Laboratory Approval Program (ELAP), Division of Laboratory Quality Certification (DLQC), and private laboratories/interests. He has published and assisted in research for both applied and basic research related to asbestos and its analysis.

Martin Harper, Ph.D.
University of Florida

Dr. Martin Harper was born in the United Kingdom and received a degree in Geology from Oxford University; a Post-Graduate Diploma in Environmental Pollution Controls; a Master of Science in Earth Sciences and the Environment; and obtained his Ph.D. in occupational health research from the London School of Hygiene and Tropical Medicine. Dr. Harper served as Chief of the Exposure Assessment Branch in the Health Effects Laboratory Division of the US National Institute for Occupational Safety and Health (NIOSH), in Morgantown, WV and as Director of Scientific Research for Zefon International, Inc. He is a Chartered Chemist and Fellow of the Royal Society of Chemistry and is a Certified Industrial Hygienist and Fellow of the American Industrial Hygiene Association. Dr. Harper has published more than 140 peer-reviewed journal papers, book chapters, encyclopedia articles and standards. He has received three awards from the American Industrial Hygiene Association, four from the American Society for Testing and Materials, two from NIOSH, and has been nominated twice for CDC awards. He served as Chair of the ISO Technical Committee 146, sub-Committee 2 (Air Quality: Workplace Atmospheres) for six years. He served for four years as an Editorial Board member for Journal of Environmental Monitoring, and for six years as Editor of the Analytical Performance Issues column for Journal of Occupational and Environmental Hygiene. Dr. Harper's research interests include sampling and analysis of aerosols, mineral fibers (asbestos), silica and nanoparticles; quality assurance of measurements; exposure assessment strategies and models; and risk assessment.

James E. Lockey, M.D. M.S.
University of Cincinnati

Dr. James Lockey is Professor-Emeritus at the University of Cincinnati College of Medicine, Department of Environmental Health, and the Department of Internal Medicine, Pulmonary Division. Dr. Lockey's research focus over the last thirty years has been on adverse pulmonary effects from various types of occupational and environmental exposures. Dr. Lockey's research includes an ongoing study of the health impact from exposure to asbestiform mineral fibers found in Libby vermiculite ore; a twenty-five-year longitudinal study of workers exposed to refractory ceramic fibers; and development of an environmental sensor for real-time personal exposure assessment of ultrafine particulates in collaboration with the Mechanical, Industrial and Nuclear Engineering at the University of Cincinnati. Dr. Lockey received United States Presidential appointments to the National Advisory Board on Radiation and Worker Health, to the Armed Forces Epidemiology Board, and subsequently to the Department of Defense Health Board. Dr. Lockey also evaluates patients with various occupational pulmonary related disorders including workers with isocyanate-induced asthma and workers with a history of vermiculite exposure.

II. CHARGE TO REVIEWERS

Following this section of the peer review report, the charge questions will be represented by their Charge Question number only. Please refer back to this section II. CHARGE TO REVIEWERS for individual questions.

In January 2022 the FDA released a White Paper developed by the IWGACP that contains scientific opinions for the testing of talc intended for use in cosmetics, and talc-containing cosmetic products,[2] to improve detection and identification of asbestos fibers, as well as other potentially harmful amphibole particles that can affect cosmetic product safety. As part of the FDA's commitment to protecting U.S. consumers from unsafe cosmetic products, the Agency is considering how it might apply any of the opinions outlined in the White Paper in the agency's ongoing sampling and testing efforts related to asbestos in talc-containing cosmetics, and talc intended for use in cosmetic products.

The IWGACP was headed by the FDA and originally consisted of 38 subject matter experts from eight U.S. federal agencies. The IWGACP was asked by FDA to develop a consensus document that would support the development of standardized testing methods for talc and talc-containing cosmetics. In February 2020, the FDA hosted a public meeting to solicit information on asbestos testing methods. The IWGACP considered the comments and information received at the public meeting and in the docket in the development of its scientific opinions. These opinions are intended to improve test method reliability and provide procedures for laboratories to comprehensively report asbestos and other potentially harmful mineral particles in talc-containing cosmetics.

The FDA requested peer review of the White Paper as a next step toward standardized testing methods for asbestos and other mineral particles that could potentially affect talc-containing cosmetic product safety.

FDA provided peer reviewers with the following documents and website links:

1. White Paper: Interagency Working Group on Asbestos in Consumer Products (IWGACP) Scientific Opinions on Testing Methods for Asbestos in Cosmetic Products Containing Talc (including talc intended for use in cosmetics) December 2021
2. Technical Appendices to the White Paper. December 2021
3. Public Comments in the FDA Docket FDA-2020-N-0025: Testing Methods for Asbestos in Talc and Cosmetic Products Containing Talc; Public Meeting; Request for Comments (Docket) see https://www.regulations.gov/docket/FDA-2020-N-0025
4. Public Meeting on Testing Methods for Asbestos in Talc and Cosmetic Products Containing Talc

The peer reviewers examined the provided materials in order to respond to the charge questions provided below. **In their response to each of the charge questions, the peer reviewers were asked to elaborate on the basis for their response. If the peer reviewers disagreed, they**

[2] Hereafter referred to as talc-containing cosmetics; for convenience, in this document we also use the terms "cosmetics" or "cosmetic products" to refer to cosmetic products formulated with talc.

were asked to explain their rationale, and to suggest a preferred alternative to address the issue or matter captured in the challenge question.

I. What Test Methods Should be Used by Laboratories?

IWGACP White Paper Scientific Opinion #3: The IWGACP advised that testing laboratories use a combination of polarized light microscopy (PLM) with dispersion staining and transmission electron microscopy (TEM) with energy dispersive spectroscopy (EDS) and selected area electron diffraction analysis (SAED) to achieve the sensitivity and specificity to detect and identify mineral particles as described in IWGACP White Paper Scientific Opinions #1 and #2 in Section II below.

Rationale:

Since the objective of analytical methods is to determine whether asbestos and/or amphibole particles are present in talc or a talc-containing cosmetic, this approach of using PLM and TEM will maximize the likelihood of detecting pertinent particles in different size ranges and interlaboratory agreement on identity of the mineral types. The IWGACP advises using TEM even if the findings of PLM are negative. Scanning electron microscopy (SEM) could be useful as a complementary method but has shortcomings due to its inability to obtain diagnostic electron diffraction patterns or observe the inner hollow structure of chrysotile.

The IWGACP concluded that PLM can serve as a microscopic technique for analyzing cosmetics for asbestos, although PLM is never to be considered conclusive of the absence of asbestos in a cosmetic. PLM has substantial limitations in its ability to resolve particles of asbestos and other amphibole minerals (< 5 μm in length with a length to width aspect ratio (AR) $\geq 3:1$) that are too small to be detected and identified using visible light. TEM, on the other hand, can detect and identify these particles. Thus, TEM has a limit of detection for asbestos and other amphibole minerals that is several orders of magnitude lower than PLM (on a weight percent). In recent testing of cosmetic products commissioned by FDA, many of the samples which tested positive for asbestos by TEM were negative for asbestos by PLM, thus, corroborating the need to use TEM when PLM does not detect asbestos.

The IWGACP concludes that sensitivity and specificity of the current voluntary cosmetic talc analytical methodology [Cosmetic, Toiletry, and Fragrance Association (CTFA) J4-1 method] are inadequate. This is because the J4-1 method has a stated nominal limit of detection of 0.5% by weight for amphiboles and calls for testing using PLM to determine if asbestiform amphibole is present only if the screening test using X-ray diffraction (XRD) is positive (i.e., PLM is not required). The J4-1 method has no requirement to report chrysotile asbestos.

Question 1: The IWGACP concluded that the absence of a standardized testing method for the analysis of asbestos in talc-containing cosmetic products (including specifications of the methods of sample preparation, microscopic technique, and criteria and terminology for reporting the detected particles) has led many analytical laboratories to combine and/or adapt published test methods developed for the analysis of asbestos in air or building materials. Do you agree that this could, at least in part, account for discrepancies in laboratory findings?

Question 2: Do you agree that the CTFA J4-1 method is inadequate for testing for asbestos in talc intended for use in cosmetics, where asbestos may be present at trace levels?

Question 3: Do you agree that a negative finding for amphibole and chrysotile by PLM should not be considered conclusive as a negative finding for asbestos in a cosmetic product?

Question 4: Do you agree with the IWGACP that in order to state that a sample does not contain detectable asbestos, TEM must be used because amphibole and chrysotile particles <5 μm (and >0.5 μm) with an AR >3:1 may be below the resolution of PLM to detect and identify?

Question 5: Do you agree that TEM, which can identify minerals via elemental analysis (i.e., EDS) and determine crystal structure (i.e., SAED), exceeds the current capability of SEM to identify minerals, and that TEM should be required in the testing of talc-containing cosmetics to identify asbestos that could be present at trace levels (i.e., orders of magnitude <1%)?

II. How Should Samples Be Prepared?

IWGACP White Paper Scientific Opinion #6. Samples should be prepared to mitigate interference from the sample matrix using techniques similar to those used for the testing of bulk materials for asbestos.

In Appendix J, the IWGACP described gravimetric methods and other sample preparation methods which were published either in the scientific literature or asbestos testing standards. For instance, IWGACP identified a method that involves "heavy liquid separation" (HLS) of talc and amphibole based on differences in mineral densities; however, HLS does not appear to be effective for the separation of chrysotile from talc. Importantly, IWGACP did not find any published methods with evidence of HLS having been formally validated for separation of asbestos from talc-containing cosmetics.

The IWGACP is advising development and publication of a method to prepare samples of cosmetics for analysis to reduce interference from the matrix. Application of gravimetric reduction methods described in standards for analysis of bulk materials appears to be the most common approach laboratories currently use to concentrate chrysotile and amphiboles, if present, in cosmetics.

Question 6: Based on the issue addressed in **Question 1** regarding the lack of a standardized testing method contributing to discrepancies in laboratory findings, do you agree that written protocols for sample preparation methods should be developed, validated, and published for preparation of samples of talc and talc-containing cosmetics for chrysotile and amphibole determination by microscopy, and followed by laboratories?

Question 7: Do you generally agree that gravimetric reduction methods involving ignition and acid digestion should be used to analyze cosmetic products for chrysotile and amphibole particles? Do you also generally agree that such methods should also be used to analyze talc used to manufacture cosmetic products for chrysotile and amphibole particles, given that talc ores and powder made from such ores often contain accessory minerals that might interfere with the analysis? If you generally agree, are there any exceptions in which this approach might be problematic to the detection of amphibole or chrysotile?

Question 8: In your opinion, is there a particular method (e.g., HLS) that shows promise and should be further developed, validated, and published as a preferred method for isolating amphibole and chrysotile particles from talc and talc-containing cosmetics?

III. What Should Laboratories Report?

IWGACP White Paper Scientific Opinion #1: The IWGACP advised that laboratories use both PLM and TEM methods to identify/report at minimum, the presence of the following types of particles:

a. amphibole minerals defined as asbestos in federal regulations
b. other amphibole minerals
c. chrysotile
d. particles that contain talc and an amphibole
e. talc particles exhibiting non-platy morphology (e.g., particles appearing as curved plates, or ribbons)

IWGACP White Paper Scientific Opinion #2: The IWGACP advised that, in the interest of comprehensive reporting, laboratories tabulate, at minimum, all amphibole and chrysotile particles (see 1a, 1b, 1c, and 1d) having a length ≥ 0.5 μm (500 nm) and an AR ≥ 3:1 by indicating respective length, width, and mineral type in talc and talc-containing cosmetic products, and avoid categorizing such particles as non-asbestiform when there is ambiguity as to habit of growth (e.g., whether the particle is asbestos or the result of attrition of a non-asbestiform amphibole).

Rationale:

The IWGACP is concerned about cosmetic product safety. The IWGACP opinions for inclusive reporting will enhance transparency and help to provide a cumulative record of mineral particles, thereby facilitating more well-conceived health-based decisions about cosmetic product safety. The approach ensures reporting of mineral particles that can be inhaled into the lungs and potentially be harmful from use of a cosmetic product, regardless of how they formed (i.e., in the earth or during cosmetic raw material milling). The health effects, although discussed generally to support the particle characteristics that laboratories report, were not the primary focus of this work group's activities.

The AR ≥ 3:1 is consistent with the NIOSH Bulletin 62 (2011) and the current regulations for counting asbestos by light microscopy by OSHA Method ID-191. Reporting of particles ≥ 0.5 μm in length is consistent with the rules for identification and counting established by the global standard for TEM sampling and analysis, ISO 10312:2019, and by the 1987 Federal AHERA standards for asbestos in school buildings. The IWGACP concluded that many studies indicate that asbestos and other mineral particles < 5 μm in length (and greater than 0.5 μm) could pose a health concern. This approach ensures the size range of mineral particles suspected of contributing to pleural disease and cancer are reported consistently and objectively.

The IWGACP acknowledges that differential counting for the purpose of classifying amphibole mineral particles into asbestiform and non-asbestiform types using TEM images is often difficult (and is inconsistently applied). To account for and describe the morphology of amphibole particles detected, IWGACP advises applying the definitions for the types of particle structures

in standards for TEM: ISO 10312:2019 and ISO 13794:2019, rather than attempting classification based on dimensions or shape.

Question 9: Do you agree that classifying amphibole mineral particles into asbestiform and non-asbestiform types using TEM images is often difficult (and the classification is inconsistently applied)?

Question 10: Do you agree that laboratories should avoid using the term 'fiber' to describe amphibole particles and talc unless it is certain that such particles are asbestiform?

Question 11: Do you agree that Annexes titled "Structure Counting Criteria" in ISO 10312:2019 and ISO 13794:2019 are useful to report morphology of particles of chrysotile and amphibole, including for identifying amphibole particles when it is indeterminate as to whether such particles grew in the asbestiform habit?

Question 12: Do you have any other thoughts on how the dilemma of uncertainty as to habit of growth (i.e., asbestiform versus non-asbestiform) might be resolved?

Health-Related Questions:

Question 13: Do you agree with the IWGACP Scientific Opinion #1 to have laboratories identify/report (document) all detected particles meeting criteria 1a, 1b, 1c, 1d, and 1e in IWGACP Scientific Opinion #2 because they could be potentially harmful if inhaled during cosmetic product use?

Question 14: Since scientific studies have shown that asbestos is harmful, do you have an opinion about whether chrysotile and asbestiform amphibole particles >0.5 µm in length and aspect ratio >3:1 (i.e., short asbestos fibers) should be reported by laboratories testing talc-containing cosmetic products since they could pose a health concern?

Question 15: Do you agree with the IWGACP Scientific Opinion #2 that chrysotile and all amphibole particles with dimensions >0.5 µm (500 nm) and with an aspect ratio (AR) >3:1 should be reported by laboratories testing talc-containing cosmetics because they could pose a health concern?

Question 16: Do you have an opinion about whether amphibole particles formed during processing and milling of talc intended for cosmetics that are not "asbestiform" in habit of growth, could pose a health concern and should be reported?

IV. How Should Laboratories Report Findings to Facilitate Quantitation or Estimation of Amounts Detected?

IWGACP White Paper Scientific Opinion #4: The IWGACP advised that TEM results should be reported by tabulating each particle by size and mineral type [3] to facilitate an estimate of the

[3] Particles of the types specified in IWGACP Scientific Opinion #1 meeting the dimensions specified in IWGACP Scientific Opinion #2.

number of particles per unit mass of sample analyzed (i.e., particles/gram of talc, particles/gram cosmetic product), rather than as weight percent.

Rationale:

The IWGACP concludes that reporting as weight percent can be misleading, especially for TEM analysis of talc-containing cosmetics where widths of particles can vary by well over an order of magnitude. Also, weight percent does not necessarily correlate with the number of particles, because one large particle could dominate the weight percent value.

Question 17: Do you agree that the tabulation of chrysotile and amphibole detected by TEM should include each particle on the TEM grid that meets the criteria for identification, and that length and width should be reported for each such particle?

Question 18: Do you have an opinion or suggestion pertaining to quantification of asbestos and amphibole particles in talc and talc-containing cosmetics?

V. How Should Laboratories Report their Results?

IWGACP White Paper Scientific Opinion #5. The IWGACP advised that an adequate number of TEM images that show the morphology of representative particles in each category (as described in Scientific Opinion #1), an adequate number of EDS spectra and SAED patterns to support mineral identification, and descriptions of each particle using the terminology included, for example, EPA's regulations promulgated under AHERA and Annex C of ISO 10312:2019, should be provided (see Appendix F).

Question 19: In consideration of potential for variation in particle chemistry and morphology, what is a minimum number of particles for which images, spectra and SAED patterns should be provided in the laboratory report to be representative of the sample? Please provide further commentary related to this topic.

IWGACP White Paper Scientific Opinion #7. The IWGACP advised that the content and format of analytical reports should facilitate consistent and comprehensive reporting of particles (as described in IWGACP Scientific Opinions #1 and #2), in conjunction with adequate documentation of findings (see Appendix K).

Question 20. Do you agree with this scientific opinion, and do you have any additional thoughts?

VI. How Can Reference Standards Be Applied?

The IWGACP concluded that qualified reference standards (e.g., NIST Standard Reference Materials (SRM)) containing asbestos are, in general, lacking and that qualified reference standards would be helpful for identifying asbestos in talc (and potentially, cosmetics that contain talc). IWGACP experts recognize that laboratories need reference materials for training and to confirm analyst proficiency. In addition, reference materials would help improve detection limits when chrysotile or amphibole particles are not homogenously distributed in the sample. However, the IWGACP also recognized that a standard for the identification of asbestos in talc or talc-containing cosmetics would be difficult to develop, qualify, and maintain.

Question 21: Given these difficulties, do you have any thoughts that could be helpful toward future development of reference standards for microscopy analysis of talc and cosmetics?

Question 22: Do you have any comments or thoughts on how to apply reference standards towards ensuring laboratory proficiency given concerns that amphibole and/or chrysotile particles are not homogenously distributed in a sample of talc or a cosmetic product?

VII. How Can Suitable Limits of Detection Be Established?

In deliberations on methods of sample preparation, the IWGACP concluded that limits of detection of chrysotile and amphiboles should be as low as practical to rule out possibility of contamination of cosmetics with hazardous particles, while also recognizing that sample sizes will probably be significantly smaller as microscopy methods with lower limit of detection are employed.

Question 23: When using gravimetric reduction to prepare samples, do you have any suggestions on how to address the matter of sample size that could improve the likelihood of detecting non-homogeneous chrysotile and amphibole particles, if present in talc or cosmetics?

VIII. Laboratory Quality Management System Questions

IWGACP White Paper Scientific Opinion #8. The IWGACP advised that policies and procedures covering rigorous training, quality assurance, and quality control accompany the implementation of these methods to maintain intra- and inter-laboratory consistency and to ensure laboratories are qualified and their qualifications are reviewed regularly (timeframe depends on organization) (see Appendix H).

Question 24. Do you any thoughts on the implementation of a quality management system pertaining to the testing of cosmetics as advocated by the IWGACP?

III. SUMMARY OF PEER REVIEWER COMMENTS

Three reviewers (Reviewers 3, 4 and 5) were invited to provide their independent scientific peer review concerning asbestos test methods proposed in the IWGACP White Paper "IWGACP Scientific Opinions on Testing Methods for Asbestos in Cosmetic Products Containing Talc". Two additional reviewers (Reviewers 1 and 2) were invited to provide their independent scientific peer review concerning asbestos health effects addressed in the White Paper. These two sets of review comments are summarized below, within each set organized by charge question. These summaries exclude many additional details, specific observations and/or corrections provided in corresponding individual review comments presented later in this document.

I. GENERAL IMPRESSIONS

Reviewer 1 indicates the White Paper is balanced, informative, and scientifically supported, with comprehensive recommendations to protect the general public from known and potential health hazards, including generally accurate medical comments and references. The conclusions were found to be sound and justified by the science presented.

Reviewer 2 concludes that the White Paper reflects a concise review and that establishment of a standard analytic approach for identification of elongate mineral particles (EMP) will better inform health-based decisions regarding consumer use of these cosmetic products. In their focused review of the Health Based Characteristics (Appendix E), the reviewer states that tabulations including fiber size distribution and morphology characterization that includes all fibers >0.5 µm in length and aspect ratios >3:1 will help address significant exposure data gaps. The potential contribution of fibers <5 µm in length to disease in animal and human data is clearly documented. However, risk associated specifically with fibers <5 µm in length is difficult to determine due to high correlation across fiber size distributions and cumulative exposure levels that most likely are not applicable to routine consumer use of cosmetic talc. Reviewer 2 suggests that the White Paper summarize the review by Boulanger et al. 2014 including limitations of applicable studies, data gaps, and why the pathogenicity of short fibers remains a concern. This reviewer also suggests that: 1) the White Paper include a focus on more contemporary human data linking very low cumulative fiber exposure (CFE) to Libby amphibole asbestos (LAA) (0.15 - <0.45 fiber-years/cm3) and to localized pleural thickening (Rohs et al. 2008; Lockey et al. 2015) and also include citation/discussion of O'Brien et al. (2020) within Section V, where ovarian cancer is included as an adverse outcome associated with asbestos exposure and, 2) that a uniquely fiber susceptible mesothelial cell line could be used to obtain objective estimates of relative risk posed by fibers of different length, including short (<5 µm) and long fibers and various mineral morphological configurations.

Reviewer 3 indicates the White Paper represents a major step forward in dealing with the subject matter issue, agrees with the evidence that PLM alone is not likely to be sufficient to assess asbestos contamination and that TEM can, and should, be used to support PLM, and points out where the White Paper appears inadequate to support positions taken. A key such deficiency noted by Reviewer 3 is that test method selection "*should be driven by the target level and, without that, it is not technically possible to assume that any analytical procedure is appropriate*." Thus, the White Paper asserts that "*Data interpretation, as it pertains to health or risk assessment, is beyond [its] scope of this White Paper*," but also recognizes that "*Data interpretation involving quantitative estimates of asbestos and other amphiboles in talc and talc-containing cosmetics depends on sampling and testing methodology*." Reviewer 3 interprets

these positions to be contradictory, because they contend that the risk assessment must precede the establishment of methodology to support it. From a discussion of existing U.K. proficiency testing schemes, Reviewer 3 concludes that "*no laboratory using any method, including TEM, can confidently assume, without participation in these, or similar proficiency schemes, that it is always correctly identifying the presence or nature of asbestos or is reporting levels accurately between 0.025% and 0.1% by weight*" and that "*the only way to ensure analytical capability is through a properly designed proficiency test program, which involves the addition of asbestos to talc in amounts relevant to the target level of identification and quantitation, followed by milling to a common grain size, in order to properly mimic real samples*."

Reviewer 3 also provides comments on the content of the Health Based Characteristics (Appendix E), including the summary of Stayner et al. (2008), but FDA notes this reviewer is not a health expert. The reviewer disputes a White Paper statement concerning the origin of dimension criteria used historically for occupational asbestos measures and recommends consideration of Walton et al. (1982).

Reviewer 4 indicates the White Paper is clearly written, succinct with supporting evidence well presented, and the resulting conclusions are sound, which when followed will provide an effective method for analysis of cosmetic talc for asbestos. The Appendices are especially useful in that they provide further detail about the reasoning presented within the White Paper. This reviewer appreciates that the IWGACP recommends well-established technologies and preparation techniques, and anticipates any method developed using the opinions to be readily adopted and utilized. However, the reviewer objects to the use of visual estimation in PLM analysis.

No general impressions were provided by Reviewer 5.

II. RESPONSE TO CHARGE QUESTIONS

I. What Test Methods Should be Used by Laboratories?

***Charge Question 1*:** The IWGACP concluded that the absence of a standardized testing method for the analysis of asbestos in talc-containing cosmetic products (including specifications of the methods of sample preparation, microscopic technique, and criteria and terminology for reporting the detected particles) has led many analytical laboratories to combine and/or adapt published test methods developed for the analysis of asbestos in air or building materials. Do you agree that this could, at least in part, account for discrepancies in laboratory findings?

Summary of Responses:

Yes, the three reviewers agree that the IWGACP provided adequate information, data, and justification that laboratories utilizing various methodologies developed for other materials in combination with varying degrees of analytical expertise would provide a broad range of results that could lead to discrepancies in laboratory findings. Reviewer 3 notes that TEM can be applied in different laboratories with many differences in details that may or may not lead to substantial discrepancies, thus performance of standardized methods, including allowed variations, must be established quantitatively in view of observed data on test-specific variability and false-positive rates.

Charge Question 2: Do you agree that the CTFA J4-1 method is inadequate for testing for asbestos in talc intended for use in cosmetics, where asbestos may be present at trace levels?

Summary of Responses:

Yes, the three reviewers agree that the CTFA J4-1 method (i.e., using XRD, and then PLM if XRD is positive) is inadequate for testing for asbestos in talc intended for use in cosmetics, where asbestos may be present at trace levels (<0.1%).

Reviewer 4 indicates the White Paper appropriately described XRD limitations and demonstrates that CTFA J4-1 is unsuitable to determine lower concentrations of asbestos in cosmetic talc because of those limitations, as well as ineffective utilization of PLM. Reviewer 3 stated the IWGACP made a good case that TEM should be preferable if the target level (trace level) is set below <0.1% asbestos, but indicated that the White Paper does not define "trace levels" and that 0.1% asbestos would be detectable by PLM. Thus, they have no objection in theory to using PLM per the CTFA J4-1 method if asbestos is greater than 0.1%.

Charge Question 3: Do you agree that a negative finding for amphibole and chrysotile by PLM should not be considered conclusive as a negative finding for asbestos in a cosmetic product?

Summary of Responses:

The three reviewers generally agree. Reviewer 3 agrees the White Paper provided information on performance characteristics of PLM that strongly suggest false negatives may occur using PLM, but that evidence would be better supported had samples from the products analyzed at AMA been shared with additional laboratories for confirmation. Reviewer 4 concurs that the White Paper provides adequate information to support its opinion that a negative finding by PLM should not be considered conclusive. The reviewer stated that the IWGACP's opinion is consistent with best practices and methodological requirements for materials with low asbestos content, smaller asbestos structures, or problematic matrices.

Reviewer 5 responds "Not completely" and that an example of the testing the same sample by PLM and by TEM would be conclusive, but also that PLM is "not useful" in this context.

Charge Question 4: Did the IWGACP provide adequate information and/or data to support its opinion that in order to state that a sample does not contain detectable asbestos, TEM must be used because amphibole and chrysotile particles <5 μm (and >0.5 μm) with an AR >3:1 may be below the resolution of PLM to detect and identify?

Summary of Responses:

All three reviewers concurred that adequate information was provided. Reviewer 3 concurs that PLM alone is insufficient to determine whether individual fibrous particles of nanometer widths are present in a sample due to inadequate visibility, in addition to (although not noted in the White Paper) limited diffraction color and extinction angle discrimination in very thin fibers, and aspect-ratio determination of particles less than a few micrometers in length. Reviewer 4 concurs

with the White Paper concerning PLM's limited ability to properly identify observed structures below a certain size.

Charge Question 5: Did the IWGACP provide adequate information and/or data to support its opinion that TEM, which can identify minerals via elemental analysis (i.e., EDS) and determine crystal structure (i.e., SAED), exceeds the current capability of SEM to identify minerals, and that TEM should be used in the testing of talc-containing cosmetics to identify asbestos that could be present at trace levels (i.e., orders of magnitude <1%)?

Summary of Responses:

Generally, the reviewers agree with the recommendation that PLM alone is not adequate and that TEM is the preferred complementary method to compensate for limitations that were adequately documented in the White Paper. A suggestion was made that SEM has certain merits and is worth considering, while noting that current SEM technology cannot match TEM for analysis of crystal structures of particles, especially since electron diffraction patterns are conclusive for identifying chrysotile and important for identifying amphibole.

Reviewer 3 states that SEM should not be discounted, especially if, in the future, electron back-scatter analysis becomes more common, and that to facilitate innovation it is generally better to define performance than prescriptive analytical procedures. The reviewer notes some drawbacks of TEM—including its inability to examine large numbers of fibers (which are more easily scanned under SEM) and inability to see three-dimensional structures that can more easily identify asbestos.

Reviewer 4 indicates the White Paper adequately explains the superiority of analysis for asbestos by TEM when compared to that of SEM. TEM currently has better resolution and well-established analytical criteria with significant supporting data and observations. Additionally, routine use of TEM by asbestos testing laboratories facilitates adoption of this White Paper recommendation. They agree that SEM could be used as a complementary technique.

Reviewer 5 responds "yes, surely," but advises the White Paper should specify that a TEM instrument must have a double-tilt stage holder so that dual zone axis SAED patterns can be obtained.

II. How Should Samples Be Prepared?

Charge Question 6: Based on the issue addressed in **Question 1** regarding the lack of a standardized testing method contributing to discrepancies in laboratory findings, do you agree that written protocols for sample preparation methods should be developed, validated, and published for preparation of samples of talc and talc-containing cosmetics for chrysotile and amphibole determination by microscopy, and followed by laboratories?

Summary of Responses:

Overall, the three reviewers agree with the IWGACP opinion that written protocols should be developed, validated and published, and that the White Paper adequately explains the need for standardized methods. Reviewer 3 agrees that uncertainty is added when laboratories are free to

determine sample preparation procedures and recommends that sample preparation procedures can and should be subject to performance-based evaluation in the development of a consensus standard.

Reviewer 4 states that a standardized cosmetic talc methodology would help ensure compatible and comparable results which, due to the commonality of the method would be repeatable between laboratories.

Charge Question 7: Did the IWGACP provide adequate information and/or data to support its opinion that gravimetric reduction methods involving ignition and acid digestion should be used to analyze cosmetic products for chrysotile and amphibole particles? Did the IWGACP provide adequate information and/or data to support its opinion that such methods should also be used to analyze talc used to manufacture cosmetic products for chrysotile and amphibole particles, taking into account the information from the IWGACP that talc ores and powder made from such ores often contain accessory minerals that might interfere with the analysis? If you generally agree, are there any exceptions in which this approach might be problematic to the detection of amphibole or chrysotile?

Summary of Responses:

Overall, the three reviewers agree with the IWGACP opinion, and that adequate information and data were provided in the White Paper. Reviewer 3 notes there is value in the removal of organic matter that might obscure fibers and affect EDS or SAED determinations. Acid reduction, which can remove acid-soluble materials, for example calcite and brucite in talc ores, is also used in the analysis of asbestos in vinyl floor tiles. However, other potentially interfering minerals (e.g., serpentine, wollastonite) are insoluble in dilute acid. In general, sample preparation steps should be added only, if necessary, insofar as the usefulness outweighs the increased uncertainty, and may be more helpful for PLM than TEM.

Reviewer 4 regularly utilizes gravimetric reduction of all bulk building material samples and agrees with the IWGACP's recommendation and explanation about why gravimetric reduction is a critical step in the preparation of a sample. The reviewer notes there are likely few instances when gravimetric reduction may hinder testing cosmetic talc or related products, for example, the presence of resistant particulates such as titanium dioxide, which could interfere with PLM if not mitigated by proper slide preparation. The reviewer also notes that the close proximity of talc and chrysotile densities will pose challenges.

Reviewer 5 agrees ignition is useful for talc-containing cosmetics where talc is mixed with many other substances, some of which are organics, but not for talc-containing source materials (i.e., raw material) used to manufacture cosmetics. The problem may come from the presence of other mineral phases mixed/intergrown with talc such as chlorite, and the possible presence of the asbestiform antigorite and/or asbestiform polygonal serpentine. Antigorite and serpentine, which may be abundant in some cases, have been recognized for a few years but are not classified as asbestos. They are confused with chrysotile if the sample is not examined by TEM-EDS+SAED. It is important to underline that antigorite may be present in talc containing rocks.

Charge Question 8: In your opinion, is there a particular method (e.g., HLS) that shows promise and should be further developed, validated, and published as a preferred method for isolating amphibole and chrysotile particles from talc and talc-containing cosmetics?

Summary of Responses:

Overall, the reviewers point out certain separation methods and identify certain challenges, which were covered in the White Paper and Appendix J.

Reviewer 3 has used Fluidized Bed Asbestos Segregator (FBAS) but is not aware if FBAS can successfully separate asbestos and talc. The reviewer is aware of various sedimentation, elutriation and heavy liquid separation techniques, but has not used them in analysis of talc.

Reviewer 4 agrees with the IWGACP that chrysotile presents a challenge by HLS. The reviewer indicates limitations to HLS that may be overcome with additional sample preparation steps, such as gravimetric reduction.

Reviewer 5 recommends that the FBAS preparation method should be further investigated for isolating amphibole and chrysotile particles from talc and talc-containing cosmetic products. The reviewer notes that talc presents some unique problems that are not present in soils.

III. What Should Laboratories Report?

Charge Question 9: Do you agree that classifying amphibole mineral particles into asbestiform and non-asbestiform types using TEM images is often difficult (and the classification is inconsistently applied)?

Summary of Responses:

Overall, the reviewers do not dispute that differential counting is difficult using TEM, nor do they dispute that amphibole populations are diverse and may contain asbestiform and non-asbestiform particles. However, the peer reviewers identified some issues for consideration.

Reviewer 3 views that any amphibole particle thinner than 0.5 μm with an aspect ratio >10:1 is likely to be asbestiform, that most particles can be classified as either asbestos or non-asbestiform with little difficulty, especially as more particles are observed, and that a minimum limit on the number of observed particles is necessary to obtain an accurate count and define a quantitative determination of content. Reviewer 3 indicates that issues only arise with a small sub-set of particles that are arguable, and the problem becomes less significant the more particles are observed. Reviewer 3 also notes that TEM images are very useful to discriminate between "asbestiform" and "not asbestiform" only if the definition of both terms is adequate.

Reviewer 4 concurs that the White Paper recommendation is appropriate and supported. Based on this reviewer's experience, the examples provided support the IWGACP conclusion and illustrate the potential for subjective interpretation of morphology using TEM images without a good definition.

Reviewer 5 disputes this White Paper opinion, questions that it is supported by the information and data provided and maintains that TEM images can discriminate between "asbestiform" and "not asbestiform" if clear and appropriate definitions of these terms are provided.

Charge Question 10: Do you agree that laboratories should avoid using the term 'fiber' to describe amphibole particles and talc unless it is certain that such particles are asbestiform?

Summary of Responses:

Overall, the reviewers agree that the term "fiber" should only be used in the proper context. Reviewer 3 views the term fiber to have a purely qualitative and geometric definition (one axis being longer than the other two). As noted by Reviewer 5 asbestiform fibers are merely a subset of mineral fibers and not all fibers are asbestiform. Qualitative terms, including fiber, are best not used to avoid confusion of definition.

Reviewer 4 concurs that the term "fiber" should be avoided and finds this position supported and appropriate, but notes that this will be challenging because the term is "thoroughly embedded within the environmental testing community," and that adoption and requirement of "EMP" and related criteria should help facilitate a move away from the term "fiber."

Reviewer 5 indicates the opinion of the IWGACP is clear, but that the White Paper does not provide adequate information and/or data on this issue, and does not explain why it did not consider and/or select the WHO (1997) definition of a fiber (i.e., length $\geq$ 5 µm, diameter $\leq$ 3 µm, AR $\geq$ 3:1) as a proposed alternative definition of relevant fibers. The reviewer suggests that it would be very useful for the IWGACP to clearly define any terms with the correlated characteristics and dimensions and also introduce a sketch map showing the different terms.

Charge Question 11: Do you agree that Annexes titled "Structure Counting Criteria" in ISO 10312:2019 and ISO 13794:2019 are useful to report morphology of particles of chrysotile and amphibole, including for identifying amphibole particles when it is indeterminate as to whether such particles grew in the asbestiform habit?

Summary of Responses:

Overall, the reviewers agree with the IWGACP opinion and seem to be unanimous that ISO criteria in the Annexes are useful for reporting morphology of detected particles. Reviewers 3 and 5 expressed some skepticism about strict adoption of the counting criteria espoused in the ISO standards.

Charge Question 12: Do you have any other thoughts on how the dilemma of uncertainty as to habit of growth (i.e., asbestiform versus non-asbestiform) might be resolved?

Summary of Responses:

Overall, there are mixed opinions on how this matter might be resolved. Reviewer 3 suggests that if a population of particles is considered, and many particles are available for viewing, the matter of characterizing any individual particle might be moot. Reviewer 4 suggests that the analyst not be forced into a position of having to judge the habit of growth beyond being given "limited criteria" (dimensions) with instruction to merely report particles. Reviewer 5 had no additional thoughts on this matter.

Reviewer 3 implies that such uncertainty can be ignored provided the number of other particles whose structure is clear is sufficiently large. The reviewer states there is no need to expend substantial effort on a single particle of uncertain origin amongst a population of other particles whose habit of growth is obvious.

Reviewer 4 states they have observed conflicts over what, morphologically, constitutes asbestos, and that the morphological boundaries proposed in the White Paper can simplify bench-level analysis (i.e., recording structures with a >0.5 µm length and >3:1 aspect ratio). The reviewer states the analyst should not have to consider anything beyond certain, limited criteria and should not be put into the position of having to make questionable interpretations of what they observe or record. Every effort must be taken to avoid primary, bench-level bias, and a method which utilizes the proposed morphological requirements achieves this goal.

Reviewer 5 states they answered this question above.

Health-Related Questions:

Charge Question 13: Do you agree with the IWGACP Scientific Opinion #1 to have laboratories identify/report (document) all detected particles meeting criteria 1a, 1b, 1c, 1d, and 1e in IWGACP Scientific Opinion #2 because they could be potentially harmful if inhaled during cosmetic product use?

Summary of Responses:

Both peer reviewers concur with the IWGACP Scientific Opinion #1. Reviewer 1 concurs that all types of asbestos-containing materials, as well as winchite and richterite (i.e., materials 1a–1c) can cause disease. The reviewer concurs that commercial cosmetic talc products pose such risk because they can be contaminated with both chrysotile and amphibole, and that materials 1d–1e can at least potentially cause disease, although in the case of 1e only non-malignant talcosis at sufficiently large exposures. This reviewer states that tabulation of at least materials 1a–1d is warranted, and, coupled with Scientific Opinion #2, is well justified and tracks well with strong public health principles of protection.

Reviewer 2 concurs that data presented in the White Paper provides information that indicates particles meeting criteria 1a–e could potentially represent a health risk and that (per Boulanger, et al. 2014) "the toxicity of SAF (short asbestos fibers) cannot be dismissed".

Charge Question 14: Since scientific studies have shown that asbestos is harmful, do you have an opinion about whether chrysotile and asbestiform amphibole particles >0.5 µm in length and aspect ratio >3:1 (i.e., short asbestos fibers) should be reported by laboratories testing talc-containing cosmetic products since they could pose a health concern?

Summary of Responses:

Both peer reviewers concur that short asbestos fibers should be reported by laboratories. Reviewer 1 states the bulk of the scientific evidence that small asbestos fibers <5 µm can cause disease and justify the opinion, including studies that report predominately short chrysotile fibers <5 µm found in the majority of pleural tissue samples obtained from mesothelioma cases examined. These studies support the conclusion that "shorter fibers should definitely be counted and reported given that they represent a significant potential health risk."

Reviewer 2 indicates that "*…reporting the presence of regulated asbestos fibers >0.5 µm in length and aspect ratios >3:1 … will provide data to better determine the propensity for short fibers to cause and/or contribute to adverse health effects*" and that the "*potential toxicity of short fibers including regulated asbestos especially at lower exposure levels and without co-exposure to longer fibers cannot be definitely defined based on limited available data*"**.**

Charge Question 15: Do you agree with the IWGACP Scientific Opinion #2 that chrysotile and all amphibole particles with dimensions >0.5 µm (500 nm) and with an aspect ratio (AR) >3:1 should be reported by laboratories testing talc-containing cosmetics because they could pose a health concern?

Summary of Responses:

Both peer reviewers concur with IWGACP Scientific Opinion #2. Reviewer 1 notes that: 1) while there is excellent documentation for short chrysotile being a causative agent of disease (see response to Question 14), there is less scientific evidence to support all amphiboles beyond the five regulated amphiboles, except for winchite and richterite; and 2) although Libby amphibole exposures clearly can contribute to disease and Death Valley talc appears to contain these two fibers, they are not aware of either winchite or richterite being detected in cosmetic talc samples. The reviewer believes it would be reasonable to put in place a requirement to report non-regulated amphiboles, until sufficient appropriate sampling and analysis provide reasonable assurance that these fibers do not occur in cosmetic talc.

Reviewer 2 concurs with the IWGACP Scientific Opinion #2 because various physical and chemical characteristics correlated with toxicity for the six regulated asbestos fibers are not unique to those fibers alone. The reviewer states similar toxicities both in animal and/or human studies have been associated with, for example, "*…erionite, man-made silicon carbide fibers and whiskers including extremely short fibers with high aspect ratios as well as winchite and richterite fibers associated with Libby vermiculite...*". The reviewer adds that including these studies, and in particular the association between very low cumulative exposures of LAA fibers and pleural toxicity, would strengthen the White Paper position at exposure levels similar to those associated with use of cosmetic talc with amphibole contamination.

Charge Question 16: Do you have an opinion about whether amphibole particles formed during processing and milling of talc intended for cosmetics that are not "asbestiform" in habit of growth, could pose a health concern and should be reported?

Summary of Responses:

Reviewer 1 states the overall point about the hazards of asbestos in talc is made, although the reviewer has a concern about the scientific veracity of some references. The reviewer suggests that the White Paper should include more discussion about asbestos-contaminated talc provided in the IARC report, which clearly makes the point that that if there is asbestos found in talc, then the material should be treated as if it were asbestos.

Reviewer 2 responds affirmatively that the report supports the observation that particles formed during processing and milling can result in the formation of an increased number of EMPs, particularly under 5 µm in length, which therefore pose a potential health risk. Reviewer 2 provides additional references for inclusion in the White Paper to support this position.

IV. How Should Laboratories Report Findings to Facilitate Quantitation or Estimation of Amounts Detected?

Charge Question 17: Do you agree that the tabulation of chrysotile and amphibole detected by TEM should include each particle on the TEM grid that meets the criteria for identification, and that length and width should be reported for each such particle?

Summary of Responses:

Overall, the three peer reviewers agree with the White Paper conclusion.

Reviewer 4 points out that while the question refers to "an entire grid," counting and reporting/tabulating every structure on every grid is a standard, required practice in the analysis of air and water samples by TEM. The reviewer supports and agrees with the conclusion that structures should be tabulated and reported by size and type. The reviewer notes that this could prove untenable at magnifications appropriate to detect structures ≈0.5 µm in length, implying (as outlined in the White Paper) that appropriate stopping rules for grid openings or number of structures counted need to be developed.

Reviewer 5 agrees with the IWGACP conclusions, and the information provided is adequate, but qualifies they do not agree with all the criteria indicated for identification.

Charge Question 18: Do you have an opinion or suggestion pertaining to quantification of asbestos and amphibole particles in talc and talc-containing cosmetics?

Summary of Responses:

Generally, the reviewers agree that weight percent might not give an appropriate measure when doing exposure/risk analysis and seem to suggest that a significant number of particles need to be detected and sized using electron microscopy in order to perform an exposure/risk analysis.

Reviewer 3 recommends that the method should require a target number of particles to be examined (much greater than 100), and the limit of detection and uncertainty should be based on that target number. Particles <5 µm can be included in calculations of asbestos percentage, but not used to estimate risk quantitatively. A second result, with particles >5 um should be provided for a quantitative risk profile, unless inclusion of particles <5 µm can be established and defended.

Reviewer 4 indicates that for asbestos and talc materials, weight percent "is not truly indicative of a potential health risk" and that "the number of structures of concern per mass of a material would be a superior measurement". Reviewer 4 opines that materials like talc should be quantified by number of asbestos structures per mass, not by percent mass.

Reviewer 5 suggests complementary use of SEM-EDS and TEM-EDS+SAED (comment 3 in Section III of individual response).

V. How Should Laboratories Report their Results?

Charge Question 19: In consideration of potential for variation in particle chemistry and morphology, what is a minimum number of particles for which images, spectra and SAED patterns should be provided in the laboratory report to be representative of the sample? Please provide further commentary related to this topic.

Summary of Responses:

Overall, the reviewers agree that a statistically representative number of particles should be examined, with various suggestions made as to how one may be able to arrive at that number.

Reviewer 3 recommends that all images, and all data on every particle examined by spectra and SAED, should be accessible. Reporting only selected data can lead to biased conclusions. The number of particles that meet the criteria for concern should be given as a percentage of the total number of particles in the fields examined. This total number of particles should be predicated on a target concentration level.

Reviewer 4 states this is a challenging question to answer because there could, hypothetically, be some variability in the minerals present in an ore body and, as a result, present in cosmetic talc. The reviewer recommends that: 1) all structures be sketched and a minimum of 30 micrographs be taken with SAED and EDS of the first 10 structures of each mineral type; 2) every tenth structure after the first 10 of each type should also be identified by SAED and EDS. SAED and EDS could always be performed as needed by the analyst to confirm a mineral type; and 3) all micrographs should be made available to clients upon request but that a minimum of at least one representative micrograph for each mineral type present be incorporated in a final report.

Reviewer 5 stated that 100 particles should not be the maximum number but the correct number to examine to have good statistical support. In several papers (although on other topics) the number of analyzed particles is higher than 100: as an example, Dong et al. (2019) examined 400 particles.

Charge Question 20: Do you agree with this scientific opinion, and do you have any additional thoughts? Related to:

IWGACP White Paper Scientific Opinion #7. The IWGACP advised that the content and format of analytical reports should facilitate consistent and comprehensive reporting of particles (as described in IWGACP Scientific Opinions #1 and #2), in conjunction with adequate documentation of findings (see Appendix K).

Summary of Responses:

Overall, the reviewers support the opinion that consistent reporting is important and there appears to be a suggestion that a standardized blank table be provided for testing talc and cosmetics.

Reviewers 3 and 4 agree with this White Paper recommendation. Reviewer 4 further suggests that a stock/example bench sheet and report should be provided that laboratories could adapt their laboratory information management system (LIMS) and reporting systems. Reviewer 5 differs in part with White Paper recommendations concerning the criteria for comprehensive reporting (i.e., including the number of particles to investigate, and criteria indicated for identification presented in Scientific Opinion #1 and #2) (see individual comments).

VI. How Can Reference Standards Be Applied?

Charge Question 21: Given these difficulties, do you have any thoughts that could be helpful toward future development of reference standards for microscopy analysis of talc and cosmetics?

Summary of Responses:

Overall, the reviewers offer some suggestions and generally indicate reference standards should be created since they are useful, if not necessary, to establish and verify analyst proficiency when following a talc or cosmetic testing protocol.

Reviewer 3 states that reference asbestos materials are available for the production of proficiency test samples. The reviewer recommends that, at least, and until properly appropriate proficiency test materials are available, laboratories should participate in Asbestos in Materials Scheme (AIMS) and the Low Asbestos Content Scheme (LACS) schemes that rely on existing reference samples reviewed in individual Reviewer 3 comments.

Reviewer 4 indicates that standard reference materials (SRMs) are critically important, that if/when available they be adequately typified for known asbestos content/contamination, and that synthetic (spiked) materials be produced with known/controlled numbers of asbestos structures per unit talc volume. The situation related to the lack of NIST SRMs is well known in the asbestos testing industry and their related assessing bodies. The absence is one of the most common complaints/frustrations received by the reviewer's program.

Reviewer 5 indicates such reference standards could be obtained by mixing, in suitable quantity, a pure talc (i.e. without natural fibrous contaminants, obtained by synthesis) with fully characterized asbestos types that naturally contaminate talc. The talc synthesis is now fine-tuned: see for example the review by Claverie et al. (2017). The suitable asbestos may be characterized by TEM-EDS+SAED and SEM-EDS investigation.

Charge Question 22: Do you have any comments or thoughts on how to apply reference standards towards ensuring laboratory proficiency given concerns that amphibole and/or chrysotile particles are not homogenously distributed in a sample of talc or a cosmetic product?

Summary of Responses:

Overall, the reviewers concur that homogeneity is important, and their comments serve to point out complexities in developing, maintaining, and applying homogeneous reference standards. The reviewers provide some suggestions for how to achieve homogeneity.

Reviewer 3 recommends that SRMs used to establish laboratory proficiency must, of necessity, be homogenous in order to ensure that proficiency is properly and consistently determined, implying that inhomogeneous samples must be homogenized before analysis using the least destructive techniques available in order not to reduce particle size and crystallinity of particles. It has been demonstrated that some milling techniques carry inhomogeneities through to the final product to the extent that sedimentation concentration techniques do not homogenize samples before analysis.

Reviewer 4 does not believe simple possession of a reference sample, even with experienced laboratories, would be adequate to demonstrate or develop proficiency. When a sample arrives at a laboratory, one of their initial concerns is the homogenization of the sample if it is not already homogenous. A proficiency test sample must, likewise, be homogenized from an adequately large volume of source material before it is typified for accessory mineral content. They indicate that regularly produced proficiency testing materials/samples need to be sent to participating laboratories for analysis and scoring, using adequately large volumes of spiked samples or ore-based, thoroughly homogenized materials that participant laboratories must cone, quarter or the like.

Reviewer 5 indicates that homogenization can be achieved by "quartering" (see Panarese and Vannocci 2006), preferably by >2 different laboratories accredited by national agencies with results compared and averaged. Thus, they think that the non-homogenous distribution of asbestos in the samples can be overcome by homogenization of the sample during preparation and by examining more than one sample for each product. Furthermore, the characterization of the reference standards should be carried out by different laboratories (at least 3) accredited by national agencies and the results should be compared and averaged.

VII. How Can Suitable Limits of Detection Be Established?

Charge Question 23: When using gravimetric reduction to prepare samples, do you have any suggestions on how to address the matter of sample size that could improve the likelihood of detecting non-homogeneous chrysotile and amphibole particles, if present in talc or cosmetics?

Summary of Responses:

One reviewer suggests that enough sample be provided to obtain "accurate results" and as a contingency for a retest or testing by another laboratory. Reviewer 5 suggested that homogenizing the sample before it is tested can ensure a more accurate determination.

Reviewer 3 has no experience in gravimetric reduction and offers no related suggestions.

Reviewer 4 recommends that material used should be sufficient to yield accurate results with enough remaining after preparation for analysis to allow potential retesting or archiving, and expects analytical sensitivities to be like those of EPA water methods 100.1 or 100.2 with sensitivity measured in EMPs per mass of sample (mg or gr) specified in relation to the number of TEM grid openings analyzed. This reviewer assumes that cosmetics are homogeneous, an assumption that has never been verified by FDA or by anyone else, as far as we are aware.

Reviewer 5 refers to their response in Question 22, and recommends gravimetric reduction as described by Oberta et al. (2018) to avoid the problem of a non-homogenized sample.

VIII. Laboratory Quality Management System Questions

Charge Question 24: Do you any thoughts on the implementation of a quality management system pertaining to the testing of cosmetics as advocated by the IWGACP?

Summary of Responses:

Reviewer 3 had a variety of thoughts germane to technical challenges that have not been addressed in test methods, lack of requirements for reporting uncertainties in measurements, and the need for an established formal program for training of analysts. Reviewer 3 indicates all three of these issues to be a problem across the spectrum of asbestos testing laboratories and types of samples. Training and proficiency testing are of the utmost importance according to reviewer 4, who recommended a tailored approach that meets FDA's needs. Reviewer 5 points out skills in mineral identification using SAED are of utmost importance, reiterating how important it is for the laboratory to have the capability to obtain SAED patterns parallel and perpendicular to the incident e-beam to avoid mischaracterization of minerals.

IV. INDIVIDUAL REVIEWER COMMENTS

1. **Reviewer #1**

Comments on FDA's *IWGACP Scientific Opinions on Testing Methods for Asbestos in Cosmetic Products Containing Talc – Health Analysis*

Reviewer #1

I. GENERAL IMPRESSIONS

Overall, the document sent for review regarding the assessments of asbestos in cosmetic talc is comprehensive.

Given that increasingly the scientific literature supports significant concern about asbestos contamination of cosmetic talc materials, together with the well-recognized risk of industrial talc in other settings (i.e., tire manufacturing, paint making, wallboard) that has caused disease, concern for the general public is most appropriate.

The document correctly notes that the mechanism of asbestos-related disease is not yet well understood, but in no way should this preclude protection of the general public from known and potential health hazards.

As for the medically related comments, by and large these were generally accurate and many of the references one would wish to see were present. Some statements (noted in sections below) were made with a bit too much certainty, and some serious disease issues not properly commented upon.

Overall, the thrust of the documents sent for review were informative with mostly reasonable sources of information, given in a balanced manner, and the presentation was clear for the most part. The conclusions reached were found to be sound and justified by the science presented.

II. RESPONSE TO CHARGE QUESTIONS

Health-Related Questions

Charge Question 13

From a health perspective it has been well documented and reflected in the present documents that all types of asbestos-containing materials, and also exposure to winchite and richterite, can cause disease. All fiber types are implicated and data documents that commercial cosmetic talc products can be contaminated with both chrysotile and amphibole. This applies to (a – c).

Less clear is any role for mixed particles (d), and there is no known evidence for non-platy morphology (e) causing serious disease. However, given as seen elsewhere in the materials supplied for review, this should be recognized as having the potential to cause disease, since breakdown in the body, at least for (d) might yield individual asbestos fibers that could be free in tissue as if they had arrived initially as free fibers. There is less justification for (e) materials. One should consider, however, that those particles could potentially, in large enough quantities, cause non-malignant talcosis, though this has not ever been reported from home talc use. If (e) should not be reported, then overall reporting requirements from laboratories would be made a bit easier.

With regard to Opinion #2, my comments above fit nicely in agreement with Opinion #2 to tabulate all 1a – 1d materials. This is well justified and tracks well with strong public health principles of protection.

Charge Question 14
Absolutely, short fibers of the six regulated asbestos fibers should be reported. The bulk of scientific evidence about fiber size and the ability of even smaller fibers being able to cause disease well justifies this. This comes from the early work on fiber size by Stanton and colleagues in animals where he documents even fibers less than 5 microns in his system cause disease, as well as the human data that followed. The work of Dodson and Suzuki in the United States, Bignon in France, and Kohyama in Japan all clearly document the finding of predominately short chrysotile fibers, less than 5 microns, in the majority of cases of mesotheliomas are found in the pleura. Shorter fibers should definitely be counted and reported given that they represent a significant potential health risk.

Charge Question 15
In general, this is a correct conclusion. However, while there is excellent documentation for short chrysotile being a causative agent of disease (see response to Question 14), there is less scientific evidence to support all amphiboles beyond the five regulated amphiboles, except for winchite and richterite. There is no question the Libby amphiboles contribute to disease, and there appears to be documentation that Death Valley talc contains these two fibers. However, to date there appears to be no scientific documentation that winchite or richterite have been found in cosmetic talc samples.

It could therefore be suggested that since no requirement has been in place to ever report non-regulated amphiboles, it would be reasonable to now put in place such a requirement. If after some reasonable period of time, or after some significant numbers of samples have had such a reporting requirement, none of these fibers are ever found in cosmetic talc, consideration could be given to reduce this reporting requirement. This is predicated upon sufficient widespread testing with good tests.

Charge Question 16
Although some of the references seem to be questionable about the scientific veracity given their origin, the overall point about the hazards of asbestos in talc is made. However, one significant citation seems to be missing, the IARC discussion of asbestos-contaminated talc. This should be cited, and clearly makes the point that if there is asbestos found in talc, then material should be treated as if it were asbestos, with all other IARC references about asbestos then being applicable.

III. Specific Observations

White Paper: IWGACP Scientific Opinions on Testing Methods for Asbestos in Cosmetic Products Containing Talc

Page	Paragraph/Line	Comment
5	3/point 5	TEM use should also, throughout the document, specify more details of testing, such as using smallest pore size opening of any filters used to minimize fiber loss, especially of smaller fibers.
8	2nd paragraph	Not clear why the term elongated mineral particles is so extensively used, current regulations make clear as to what is asbestos (six regulated fibers), and individual fibers such as winchite and richterite could be specifically added.
9	2/8	Technically, the larynx as the opening of the lungs is a "primary" site of exposure. In addition to the GI tract and ovaries, the kidneys could be added.
12	2/12	Not sure the use of "EMP" solves this issue and may only further add to confusion. The use of "regulated" asbestos would be clearer and already in use. Individual other fibers could be added. (See 1.a., top p. 18).

Appendices to White Paper: IWGACP Scientific Opinions on Testing Methods for Asbestos in Cosmetic Products Containing Talc

Page	Paragraph/Line	Comment
43	1st full/1-3	There is really no equality, as implied by how written, of the different parameters mentioned. Some are truly implicated in disease; some are more questionable.
43	2nd full/1-2	These factors do not truly affect "exposure", in reality, they affect "outcome".
44	1st full/2-3	Could add that not only found on but also found in examined tissues.
44	3rd full/1	While there is solid evidence for inhalation and ingestion, less so for possible perineal exposure. Ovarian asbestos may arrive via blood stream. Should be more cautious and use term may or maybe referring to perineal exposure.
45	1/4	The phrase "it is generally accepted" might more accurately state "from some animal studies it is generally thought…"
45	1/8-9	The idea that fiber load in the lung is important is a truly false concept and should not be so stated. It is well known chrysotile has much shorter ½ life in the lungs than amphibole, and after long latency little may be found in the lung, but may well have transferred to the pleura, giving rise to mesotheliomas. False to consider only longer lasting amphibole in the lung.
48	1st/5	Correct use of term "may" occur, should be reflected in earlier comment [44/3rd full/1].
56	Table F.1	Why no mention of chrysotile to be measured?

2. Reviewer #2

Reviewer #2

I. GENERAL IMPRESSIONS

Appendices to White Paper

This review focuses on Appendix E, Health Based Characteristics.
The role that fibers <5 μm in length potentially contribute to disease in animal and human data are clearly documented based on the limited number of studies that reported complete particle size exposure distributions. This issue is well illustrated in Figures E-2 through E-4. However, the specific risk that can be assigned to fiber <5 μm in length alone is difficult to determine because of the high correlation across fiber size distributions both in animal and human studies and cumulative exposure levels that most likely are not applicable to routine consumer use of cosmetic talc. A very comprehensive review of short and long fiber size toxicity studies was published by Boulanger, et al, in 2014. This reviewer suggests summarizing this review of animal and human studies, the limitations of applicable studies, where data gaps exist, and why the pathogenicity of short fibers remains a concern.

Because of the long latency from initial asbestos exposure and disease onset and the lack of individual consumer personal airborne asbestos exposure data, correlating adverse outcomes to low cumulative fiber exposure (CFE) levels similar to that most likely associated with cosmetic talc use will remain problematic. *A priori* fiber size distribution and morphology characterization that includes all fibers >0.5 μm in length and aspect ratios >3:1 will help address significant exposure data gaps. The importance of this is well documented in this section.

Within the White Paper (section V, page 9), one of the adverse health outcomes listed is pleural disease. With this in mind, various participants of the IWGACP were investigators on the health impact associated with exposure to Libby amphibole asbestos (LAA). As reported in Appendix D, there are fiber size distributions and fiber morphologic similarities between Libby Amphibole Asbestos **(**LAA) fibers contaminating Libby vermiculite and amphibole fibers contaminating some talc mineral sources. (Figures D-3 and D-4). The review of airborne particle size distribution from Libby, Montana utilizing TEM identified a significant cumulative distribution function for particles less than 5 um in length and corresponding high aspect ratios (EPA, July 14, 2010).

This reviewer suggests the panel focus on more contemporary human data that links very low CFE to LAA (0.15 - <0.45 fiber-years/cm^3) and localized pleural thickening. (Rohs, et al, 2008; Lockey, et al, 2015). These low cumulative exposure levels are likely more comparable to potential lifetime CFE levels experienced with routine consumer use of cosmetic talc with amphibole contamination than are historical epidemiology studies on workers exposed to much higher airborne levels of asbestos. The occurrence of pleural thickening is indicative that the mesothelial cell line is being adversely impacted by amphibole fibers at very low CFE levels. The same cell line is uniquely sensitive to amphibole fiber exposure and induction of malignant mesothelioma. Left unanswered, at this low-level exposure, is the question of how to apportion health risk across fiber distributions that includes both short (<5 μm) and long fibers and various

mineral morphological configurations. Bottom line, use of cosmetic talc should not be associated with any measurable adverse health impact including the uniquely fiber susceptible mesothelial cell line. Cumulative exposure levels associated with adverse pleural outcomes are well established and can be objectively used as a benchmark for comparison purposes.

The EPA in 2014 did a comprehensive toxicological review of LAA in support of summary information on the Integrated Risk Information System (IRIS) (EPA/635/R-11/002F. www.epa.gov/iris). As part of this review, the EPA assigned an inhalation reference concentration (RfC) for LAA based on review of the exposure and available health outcome data from the above noted studies on workers exposed to Libby vermiculite at an expander plant in Marysville, Ohio. "An RfC is defined as an estimate of an environmental exposure that is likely to be without an appreciable risk of adverse health effects over a lifetime". The health endpoint was localized pleural thickening and the calculated RfC airborne fiber level was 9×10^{-5} fiber/cc. Laboratory simulation of typical consumer use of cosmetic talc and calculation of potential lifetime CFE could be compared to the LAA RfC.

Reference:

Rohs AM, Lockey JE, Dunning KK, et al. Low-level fiber-induced radiographic changes caused by Libby vermiculite. *Am J Respir Crit Care Med. Vol 177, pp 630-637, 2008*.

Lockey JE, Dunning KK, Hilbert TJ, et al. HRCT/CT and associated spirometric effects of low Libby amphibole asbestos exposure. *JOEM Vol 57(1) Jan. 2015*.

WHITE PAPER

The White Paper reflects a concise review of current and recommended analytical methodology and rational for increasing the sensitivity and specificity for qualitative and quantitative identification of potential amphibole contamination of cosmetic talc. Establishment of a standard analytic approach for identification of EMP will better inform health-based decisions regarding consumer use of these cosmetic products.

This reviewer suggests in Section V the authors focus on more contemporary data that indicates very low cumulative exposure to amphibole fibers at levels more likely equivalent to use of cosmetic talc have been associated with pleural toxicity. (See review of appendices to White Paper)

Also, within Section V, ovarian cancer is included as an adverse outcome associated with asbestos exposure. The article by O'Brien, et al. published in 2020 in *JAMA* is included for information purposes.

Reference:

O'Brien KM, Tworoger SS, Harris HR, et al. Association of powder use in the genital area with risk of ovarian cancer. *JAMA* 2020; 323(1): 49-59.

II. RESPONSE TO CHARGE QUESTIONS

Health-Related Questions

Charge Question13
The data selected for presentation does provide information that indicates particles meeting criteria 1a, 1b, 1c, 1d, and 1e could potentially represent a health risk. There is scientific consensus that long fibers definitely contribute to asbestos-related disease. Within epidemiologic studies, exposure to short asbestos fibers especially in 1) high exposure situations and also at 2) lower exposure levels and when associated with a component of long fibers (≥ 5 μm) have been associated with lung cancer. As concluded by Boulanger, et al. 2014, in this very comprehensive review, "the toxicity of SAF (short asbestos fibers) cannot be dismissed".

Charge Question 14
The potential toxicity of short fibers including regulated asbestos especially at lower exposure levels and without co-exposure to longer fibers cannot be definitely defined based on limited available data. Thus, **reporting** the presence of regulated asbestos fibers >0.5 μm in length and aspect ratios >3:1 both from a qualitative and quantitative perspective will provide data to better determine the propensity for short fibers to cause and/or contribute to adverse health effects.

Charge Question 15
The various physical and chemical characteristics that are correlated with toxicity for the six regulated asbestos fibers are not unique to these fibers alone. Similar toxicities both in animal and/or human studies have been associated, for example with erionite, man-made silicon carbide fibers and whiskers including extremely short fibers with high aspect ratios as well as winchite and richterite fibers associated with Libby vermiculite. Inclusion of these studies and in particular the association between very low cumulative fiber exposure levels of LAA and pleural toxicity would strengthen the IWGACP positions at exposure levels more equivalent to those associated with use of cosmetic talc with amphibole contamination.

Charge Question 16
The report does support the observation that particles formed during processing and milling can result in the formation of increased number of EMP, particularly under 5 μm in length and therefore pose a potential health risk.

References:
Lapin CA, Craig DK, Valerio MG, et al. A subchronic inhalation toxicity study in rats exposed to silicon carbide whiskers. *Fundam Appl Toxicol* 16:128-146, 1991.

Johnson NF, Hoover MD, Thomassen DG, et al. In vitro activity of silicon carbide whiskers in comparison to other industrial fibers using four cell culture systems. *Am J Ind Med* 21: 807-823, 1992.

Scansetti G, Piolatto G, Botta GC. Airborne fibrous and nonfibrous particles in a silicon carbide manufacturing plant. *Ann Occup Hyg*, 35: 145-153, 1992.

Dufresne A, Perrault G, Sebastien P, et al. Morphology and surface characteristics of particulates from silicon carbide industries. *Am Ind Hyg Assoc J*, 48: 718-729, 1987.

Baris YI, Simonato L, Artvinli M, et al. Epidemiological and environmental evidence of the health effects of exposure to erionite fibres: a four-year study in the Cappadocian region of Turkey. *Int J Cancer*, 39: 10-17, 1987.

Rohs AM, Lockey JE, Dunning KK, et al. Low-level fiber-induced radiographic changes caused by Libby vermiculite. *Am J Respir Crit Care Med. Vol 177, pp 630-637, 2008*.

Lockey JE, Dunning KK, Hilbert TJ, et al. HRCT/CT and associated spirometric effects of low Libby amphibole asbestos exposure. *JOEM Vol 57(1) Jan. 2015*.

III. Specific Observations

None provided.

3. Reviewer #3

Comments on FDA's *IWGACP Scientific Opinions on Testing Methods for Asbestos in Cosmetic Products Containing Talc- Testing Methods*

Reviewer #3

I. GENERAL IMPRESSIONS

The White Paper represents a major step forward in dealing with the subject matter issue. I agree with the evidence that PLM alone is not likely to provide the required level of analysis and TEM can and should be used to support PLM. I also commend the IWGACP for their recognition of the "next steps and future research" that will be necessary to ensure full confidence in future analytical results. However, I find the White Paper is not wholly adequate to support all positions. Unfortunately, there is no really suitable question or questions in which to provide the bulk of my comments below, and so they must appear in this rather lengthy commentary.

The greatest discordance arises from a failure to propose a target concentration for qualitative or quantitative analysis. The target level of analytical capability in turn should be driven by a risk assessment. "Absence" is not a target that can be achieved quantitatively without the impractical analysis of every particle. "Trace" is not meaningful without quantifiable definition. Since no risk assessment is presented, no target levels of analysis can be proposed (and thus have not been). The selection of proper analytical procedure should be driven by the target level, and, without that, it is not technically possible to assume that any analytical procedure is appropriate. The IWGACP attempts to dodge the question of risk assessment: "Data interpretation, as it pertains to health or risk assessment, is beyond the scope of this White Paper." However, it also recognizes that: "Data interpretation involving quantitative estimates of asbestos and other amphiboles in talc and talc-containing cosmetics depends on sampling and testing methodology." The sampling and analytical methodology only has value when the data is interpreted in a risk assessment. The risk assessment must precede the establishment of methodology to support it.

Nevertheless, the assumption is made that the "absence" of asbestos is a target "trace" level, and most likely below 0.1%. The White Paper stated that AMA reports their ability to detect 10,000,000 asbestos fibers/gm of talc (based on finding one fiber 0.5 μm long and 0.04 μm wide). Assuming the talc is milled to 4 μm diameter, this represents 1 asbestos particle per 1,500 talc particles. However, the White Paper also states that "[M]any laboratories, including AMA, routinely … count up to 100 mineral particles (maximum) as a stopping point for TEM analysis." Thus, there is a strong (>93%) probability that the one fiber on which this supposed limit of detection is predicated will not be found. As an example of the true limits of detection possible, Dr. Eric Chatfield reported at an ASTM Johnson conference that amphibole asbestos had not been detected previously in UICC chrysotile (from Rhodesia) despite the analysis of 20,000 fibers. However, Dr. Chatfield using more extensive research reported the presence of 0.003% by weight Amosite. This may have been overlooked in the prior analysis as it represents less than 1 fiber in 20,000. He also reported the presence of 0.045% by weight tremolite asbestos which should have been 9 fibers in 20,000 (assuming similar size and density). The fact that this was not noticed in the prior analysis of 20,000 particles is troubling, but similar sizes of particles may have reduced the possibility of notice.

In the quality assurance of asbestos analysis at low levels in bulk materials, there are relevant existing proficiency testing schemes. In the United Kingdom, the government Health and Safety

Executive operates two proficiency test schemes of relevance, the Asbestos In Materials Scheme (AIMS) and the Low Asbestos Content Scheme (LACS). The AIMS scheme often includes samples with around 0.1% added asbestos, while the LACS scheme often includes samples containing 0.05% and lower. Participant laboratories use their preferred analytical procedures, which include the procedures of most concern in the White Paper, PLM, SEM and TEM, to identify and quantify asbestos and other mineral particles. The added asbestos minerals are reference materials so there is no question regarding identity or asbestiform habit. The samples are thoroughly tested for homogeneity. These are not wholly challenging samples; they are not finely milled, as are cosmetics, and so there are no dimensional issues (i.e., asbestos fibers are typically > 5 μm in length). In addition, most samples of close relevance consisted of marble (calcite), which is not platy or fibrous and which is not a silicate mineral and thus does not interfere with crystallographic or elemental analysis.

The AIMS program had the following experiences:
Round 62 included a sample with 0.1% chrysotile and 0.1% Amosite, which were not detected by several laboratories, and a crushed marble containing wollastonite where many saw it as asbestos: 23 laboratories by PLM-only; 6 with electron microscopy (SEM or TEM). “Fibrous” wollastonite consists of crystals which are acicular, and can therefore have appropriate dimensions to be counted, and these fine crystals can exhibit optical properties closely related to asbestos, accounting for misidentification under PLM. However, the different chemistry and electron diffraction patterns should have enabled proper identification with electron microscopy.
Round 67 included a sample of marble containing 0.3% anthophyllite asbestos, which was not identified by 15 laboratories and miss-classified as Amosite by 8 others.
Round 72 included a sample of marble containing 0.1% chrysotile and 0.1% Amosite. A number of laboratories using PLM, SEM or TEM either failed to detect one or the other asbestos type, or misidentified the asbestos as actinolite, anthophyllite or crocidolite.

The LACS program had the following experiences:
Round 3 was marble containing Amosite (UICC), which 96 laboratories correctly reported (but 4 laboratories had errors). 42 of the laboratories reported quantitatively with a median of 0.09%. 74% of the laboratories were given a score of “Satisfactory”.
Round 10 was marble containing 0.025% Amosite and 0.025% anthophyllite asbestos. 40 laboratories missed the anthophyllite asbestos, while one identified actinolite asbestos; 2 laboratories missed Amosite, while one laboratory incorrectly identified the presence of crocidolite and one incorrectly identified chrysotile. Only 52% of the laboratories using TEM-EDX-ED quantification were considered “Satisfactory”, while 86% of the laboratories using SEM-EDX were considered “Satisfactory”.
Round 11 was diatomaceous earth containing 0.05% crocidolite. While 124 laboratories correctly reported crocidolite, 3 laboratories incorrectly reported crocidolite together with Amosite, one incorrectly reported Amosite alone, and 4 reported no asbestos at all. Quantification was considered < 50% “Satisfactory” by all methods used, including TEM-EDX-ED.

These results make it abundantly clear that no laboratory using any method, including TEM, can confidently assume, without participation in these, or similar proficiency schemes, that it is always correctly identifying the presence or nature of asbestos or is reporting levels accurately between 0.025% and 0.1% by weight. This is the case even for simple geological samples containing highly fibrous minerals in a non-fibrous and non-silicate matrix. It should be noted

that fine milling of asbestos, as would happen in talc milling, destroys the ability to recognize asbestos by morphology and crystallography, e.g.: "*milling procedures not only change the size distribution, but also the particle shape and crystal structure of asbestos fibers"* (Spurny, et al., 2010), and *"After [dry] grinding for 30 s to 10 min, tremolite asbestos and anthophyllite asbestos showed a … decrease in crystallinity. Moreover, after grinding up to 10 min, tremolite and anthophyllite fibres were all below the limits defining a countable fibre …"* (Bloise et al., 2018). Therefore, the likelihood of identifying and quantifying asbestos that has been milled to < 5 µm in length at levels below 0.1% in a silicate talc matrix which includes on-edge talc plates and possibly talc fibers is even less than with these proficiency test samples. In conclusion, the only way to ensure analytical capability is through a properly designed proficiency test program, which involves the addition of asbestos to talc in amounts relevant to the target level of identification and quantitation, followed by milling to a common grain size, in order to properly mimic real samples. As it is always appropriate to attempt to match real world samples, other ingredients, including titanium dioxide and iron oxides and/or organic binders could also be added.

Finally, the decision to include all particles greater than 0.5 µm in length (AR 3:1) is highly questionable. While a particle that is clearly asbestiform yet shorter than 5 µm is indicative of the presence of asbestos in a sample, no convincing argument for including such particles for a health-based risk assessment has been put forward (in fact there is no basis given for any health risk assessment in the IWGACP opinions for any particle size, as noted above). There has been a confusion regarding the appropriate length metric as a basis of the health concerns regarding asbestos particles. It is true that approximately one-half of the particles in asbestos dust clouds are shorter than 5 µm as reported many authors. However, it is not true, as some have suggested that the metric of > 5 µm used in occupational regulations is based on some aspect relating to the ability to measure particles in the past. In particular, the statement in the IWGACP Technical Appendix that "Decisions to limit elongate particle size definition to specific size fractions (e.g., length > 5 µm; width > 0.2 µm, and aspect ratio > 3:1) were established for the convenience of using light microscopy to estimate exposures in occupational environments (Rooker, Vaughan et al. 1982)" is wholly untrue; this manuscript says nothing regarding how particle size definitions came to be established. Important insights into this matter have been reported but seem to have been overlooked in recent discussions. In particular, I would like to draw attention to:
Walton, W.H. (1982) The nature, hazards and assessment of occupational exposure to airborne asbestos dust: a review. Part 2: Measurement parameters for asbestos: the biological evidence *Annals of Occupational Hygiene*, 25(2), 155–186.

In Section 2.1 Origin of the ARC criteria for asbestos fibres, Walton reports:
"… Holmes (1973) says that the lower length limit of 5 µm 'was chosen somewhat arbitrarily in the early days of the development of the method'; but in recent conversation with the present writer he emphasized that it was intended to allow a margin of safety below the limits of 10-20 µm suggested by Vorwald *et al.* [1951] and Beattie and Knox [Knox and Beattie, 1954; Beattie and Knox, 1961; Beattie, 1961].

The writer is grateful to the ARC for access to the Committee's early papers. These indicate that the radical decision to concentrate on fibres *longer* than 5 µm was taken primarily on medical/scientific advice rather than from the more pragmatic considerations mentioned by Addingley [1953] and Holmes [1973], although no doubt these were a welcome bonus."

There are also further pertinent early studies that are reported by Walton, for example in Section 2.4 Dimensions of fibres found in human lung tissue:
"Timbrell (1980) studied Finnish anthophyllite workers and reported the maximum retention occurred at fibre lengths from 7 to 13 μm."

In Section 2.5 Relationship between fibre dimensions and biological activity:
"Short asbestos fibres, < ca. 5 μm, contained within phagosomes are not toxic to the macrophages and are mostly cleared in the manner of an inert dust (Miller et al., 1978; Heppleston, 1981). Long fibres, >ca. 10-20 μm, cannot be taken up by macrophages and removed in this way; attempted phagocytosis leaves them protruding through the cell membrane and, it is thought, may promote the release of enzymes. Hence the greater hazard of long asbestos fibres."

And in Section 2.7 Discussion of parameters:
"Numerous animal studies have demonstrated the fibrogenicity and carcinogenicity of long fibres but have shown only small or zero effects from short fibres, the dividing line being variously given in the range 20-5 μm."
In support of this proposition, Walton cites Stanton and Wrench (1972); Stanton and Layard (1978), Pott (1977), Beck, *et al.* (1971), Wright and Kuschner (1977). He reports that in the animal experiments of Wright and Kushner: "In each case the long samples produced marked interstitial fibrosis and the short fibres only a macrophage reaction, despite having been administered in rather larger mass quantities than the long fibres."

It is quite likely that "under chronic exposure conditions, short fibers inhibit the lung's natural clearance mechanisms and provide greater potential for interaction at the biological interface, increased generation of reactive oxygen species (ROS), and activation of cellular inflammatory responses leading to fibrosis" as reported in IWGACP Appendix 3, section 2 *The importance of fiber reactivity and morphology*, and this was known at the time of Walton. However, the exposures need to cause this inhibition are extreme and IWGACP has provided no evidence that such chronic high exposures would occur through the use of talc-containing products.

The IWGACP relies heavily (original italics and underline) on the work of Stayner et al (2008), citing "*all fibre size indices, including fibres <5 um in length, were highly statistically significant predictors of lung cancer or asbestosis mortality.*" However, the article also states: "Cumulative exposures were highly correlated across all fibre size categories in this cohort (0.28–0.99, p values < 0.001), which complicates the interpretation of the study findings."

A recent study comparing optical and electron microscopy measurements from a factory manufacturing chrysotile products reported: "We found that a policy that ignores very short fibers yields a very similar estimate of cumulative lung cancer mortality to a policy that does not, at least for the textile industry studied" (Richardson, 2018).

IWGACP also notes that Libby Amphibole fibers often found to be shorter than the 5 μm length criterion. However, it is telling that EPA has decided that "[F]or Libby Amphibole asbestos, the RfC is expressed as a Lifetime Daily Exposure in fibers/cc (*in units of the fibers as measured by PCM*), and the IUR is expressed as cancer risk per fibers/cc (*in units of the fibers as measured by PCM*)." In other words, the risk assessment uses PCMe and ignores fibers shorter than 5 μm.

Finally, a reference of great importance to this discussion is the "*Report on the Expert Panel on Health Effects of Asbestos and Synthetic Vitreous Fibers: The Influence of Fiber Length*", prepared for the Agency for Toxic Substances and Disease Registry, Division of Health Assessment and Consultation, by the Eastern Research Group, Inc. (March 17, 2003). A specific finding of this report regarding Cancer effects of short fibers is that "Given findings from epidemiologic studies, laboratory animal studies, and in vitro genotoxicity studies, combined with the lung's ability to clear short fibers, the panelists agreed that there is a strong weight of evidence that asbestos and SVFs shorter than 5 μm are unlikely to cause cancer in humans." With respect to non-cancer endpoints, the panel concluded "In laboratory animals, for example, short asbestos and SVFs at sufficiently high doses have been shown to cause inflammation, pulmonary interstitial fibrosis, and pleural reactions; however, the doses needed to cause these effects in humans may not be relevant to environmental exposures."

II. RESPONSE TO CHARGE QUESTIONS

I. What Test Methods Should be Used by Laboratories?

Charge Question 1

The IWGACP provided information on the performance characteristics of testing methods that strongly suggest substantial discrepancies could occur between laboratories using different analytical finishes. However, IWGACP did not back that suggestion up with specific data from comparative testing exercises between laboratories using different procedures, other than from a single laboratory (AMA). A "standardized" testing method implies a particular level of detail, which should be rooted in performance. In particular, even a specific analytical technique, e.g., "TEM" can be applied in different laboratories with many differences in details, which could also lead to substantial discrepancies, or not. The performance of standardized methods and allowed variations needs to be established quantitatively. In the proficiency test examples provided above PLM was able to detect asbestos in several of the samples in multiple laboratories, while, conversely, false positives were observed in laboratories using TEM.

Charge Question 2

Not precisely, because IWGACP did not define "trace levels". 0.1% could be considered a trace level, and is detectable by PLM, according to the text of the Appendix. IWGACP has to establish a target level, which should be derived from a formal risk assessment. If this target level is 0.1% or higher, there should be no objection in theory to using PLM. The IWGACP has made a good case that TEM should be preferable if the target level is set much lower.

Charge Question 3

The IWGACP provided information on the performance characteristics of PLM that strongly suggest that false negatives may occur. However, in quantitative support of this information IWGACP reports on 52 analyses of cosmetic products where 9 samples included identification of chrysotile and/or tremolite asbestos by TEM, but where PLM did not identify the presence of asbestos, and these analyses were performed at one laboratory (AMA). The experience of the AIMS and LACS programs clearly shows the possibility of false positive determinations by TEM (in addition to the possibility that there may have been additional samples with false negatives by TEM). It would have been better if samples from the products analyzed at AMA had been shared with additional laboratories for confirmation of these results.

Charge Question 4
IWGACP provided adequate information and data to support its opinion that PLM alone is insufficient to determine whether individual fibrous particles of nanometer widths are present in a sample, due to inadequate visibility. Further, it is difficult to determine diffraction colors and extinction angles in fibers that are very thin, although this is not also noted. Using PLM, it is also difficult to determine the aspect ratios of particles shorter than a few micrometers in length, and this too is not noted. Of greatest relevance to this discussion is Round 2 of LACS, which was talc containing wollastonite (i.e., no asbestos), where 17 (18%) of laboratories incorrectly reported the presence of asbestos. One laboratory reported crocidolite and chrysotile, two laboratories reported chrysotile, and one laboratory reported tremolite asbestos. Twelve laboratories reported the presence of anthophyllite asbestos. Unfortunately, at this time in the scheme, analytical finish was not requested or reported. However, the report states "elongate wollastonite "fibres" may have similar refractive indices to tremolite/anthophyllite and may be miss identified if polarised light microscopy is used" suggesting some of the errors were a result of laboratories using PLM. However, it is also possible, according to the report, that fibrous talc particles were miss-identified as anthophyllite asbestos, especially if electron diffraction was not used with TEM. A canvas of the laboratories which reported errors, and which are still in the scheme found that they all use TEM or SEM today, but it is not known what they used at the time.

Charge Question 5
A considerable drawback of TEM is the inability to examine large numbers of fibers, which are more easily scanned under SEM. A further drawback of TEM is the general inability to see three-dimensional structures that can more easily identify the asbestiform habit. Thus, SEM should not be discounted, especially if, in the future, electron back-scatter analysis becomes more common. It is better to define performance than to be prescriptive of analytical procedures, in order to not stifle innovation.

II. How Should Samples Be Prepared?

Charge Question 6
There is no doubt that a degree of uncertainty is added to analyses when laboratories are free to determine sample preparation procedures. This is especially true when samples are a) inhomogeneous, and/or b) contain extraneous potentially interfering substances (subject of the following question). The comminution and homogenization inherent in cosmetic talc product manufacture greatly reduces the concern over sample inhomogeneity. Thus, it may be possible to be more relaxed than stringent in prescribing sample preparation procedures (although it is understood that this would not apply to raw talc ores). Sample preparation procedures can be and should be subject to a performance-based evaluation in the development of a consensus standard.

Charge Question 7
Ignition is used to remove organic material and was originally used in airborne asbestos fiber measurements to remove smoke particles. However, this practice was discontinued quite early on. Where talc products contain large quantities of organic matter that might obscure fibers and affect EDS or SAED determinations, there is value to be had in removal. Ignition does not affect the determination as it is commonly used in the determination of asbestos in vinyl floor tiles. Acid reduction can remove acid-soluble materials, for example calcite and brucite in talc ores,

and is also used in the analysis of asbestos in vinyl floor tiles. However, other potentially interfering minerals in the analysis of talc, for example serpentine and wollastonite are insoluble in dilute acid. Removal of any material then no longer allows the determination of concentration by particle count. In general, the addition of preparations steps to any analysis is discouraged unless necessary as it can lead to a greater uncertainty in the result, which may outweigh their usefulness. It seems that these techniques would be more helpful for PLM than TEM, but as I have not used them, I cannot give an opinion as to their value in either analytical finish.

Charge Question 8

I am aware of various sedimentation, elutriation and heavy liquid separation techniques, but I have not used them in analysis of talc. The IWGACP White Paper provides evidence that they generally are not optimal for this particular separation as documented. The one technique I have personal experience of is the Fluidized Bed Asbestos Segregator (FBAS), which was designed to release and collect respirable asbestos particles from soil. However, as noted, soil is very different from milled talc in that the particles are generally larger and less regular. I am not aware that it has been used for the purpose of separating asbestos talc and would not know if it could be successful. However, if it were successful, it could provide information regarding inhalation risk. Unfortunately, it is only commercially available in one laboratory at this time. Otherwise, I support the position that further research on techniques for concentration would be valuable, assuming that it is necessary to reach target concentration levels.

III. What Should Laboratories Report?

Charge Question 9

Any amphibole particle that is thinner than 0.5 μm with an aspect ratio > 10:1 is more than likely asbestiform. The difficulties arise when particles with this aspect ratio are thicker than 0.5 μm, as they could be cleavage fragments or asbestiform bundles, and when the aspect ratio is < 10:1. The best way to determine whether the growth habit of a bundle which does not exhibit curvature or split ends is to observe nano-fibrillar bundling (individual fibrils < 100 nm diameter), best seen under SEM or high-resolution TEM. However, most particles can be classified as either asbestos or non-asbestiform with little difficulty. Issues only arise with a small sub-set of particles that are arguable, and the problem becomes less significant the more particles are observed. Setting a minimum limit on the number of particles that must be observed, which is necessary in order to have an accurate count to define a quantitative determination of content, will minimize the issue substantially.

However, the intention to count all particles > 0.5 μm long is only logical if variation in length of a particle is considered to play no part in the health outcome. That implies that the disease-causing qualities are chemical, and a result of the chemistry of elements at the boundary of the particle. Cleavage fragments show much the same faces as whole crystals, including asbestiform crystals, since cleavage is along the same planes within the crystal as those that characterize the growth faces. Therefore, if chemistry results in an adverse outcome, there is likely to be the same risk from either particle. In any case, any asbestos particle which has been reduced in length by any comminution process has likely broken across the preferred basal cleavage plane, and thus practically all asbestos fibers are in some respect “cleavage fragments”.

Charge Question 10
The term fiber has a purely geometric definition; one axis being longer than the other two. As a descriptor without quantitative parameters, it is purely qualitative and can be ascribed to any particle having a primary elongate axis, in the same way as "acicular" or "prismatic". While asbestiform is a fibrous habit, asbestiform particles are not the only fibers. Qualitative terms, including fiber, are best not used to avoid confusion of definition.

Charge Question 11
I agree but see my response to Question 9. If a particle length of 0.5 μm is the criterion for counting, then it is illogical to exclude non-asbestiform particles from the count.

Charge Question 12
As noted in my response to question 9, there is no need to expend substantial effort on a single particle of uncertain origin amongst a population of other particles whose structure is clear.

IV. How Should Laboratories Report Findings to Facilitate Quantitation or Estimation of Amounts Detected?

Charge Question 17
Agreed. I have been able to view reports from contract laboratories that also include a rough drawing of the particle and notes regarding the analyst opinion of the nature.

Charge Question 18
The method should require a target number of particles to be examined (which should be much greater than 100) and the limit of detection and uncertainty should be based on this target number. Particles shorter than 5 μm can be included in the calculation of asbestos percentage provided this calculation is not to be used in a quantitative estimation of risk. A second result, without such particles, should be provided for risk estimates, unless a risk profile for particles shorter than 5 μm can be established quantifiably and defended.

V. How Should Laboratories Report their Results?

Charge Question 19
All images, and all data on every particle examined by spectra and SAED, should be accessible. Reporting only selected data leads to likely biased conclusions. The number of particles that meet the criteria for concern should be given as a percentage of the total number of particles in the fields examined. This total number of particles should be predicated on a target concentration level.

Charge Question 20
It is unlikely that anyone would want to contradict this opinion. I have no additional thoughts.

VI. How Can Reference Standards Be Applied?

Charge Question 21
Reference asbestos materials are available for the production of proficiency test samples. NIOSH collected several materials, which are available in a homogenized standard format from Research Triangle Institute (RTI). This includes tremolite asbestos from Lone Pine, CA and

Cemetery Ridge, AZ; anthophyllite asbestos from Palm Desert, CA, and actinolite asbestos from Juneau, AK (this last may not be available as yet, but NIOSH has the raw material). "Libby Amphibole" is available from USGS. UICC chrysotile can be made available from NIOH in South Africa. The LACS and AIMS samples likely use the reference materials of the Health and Safety Laboratory of the UK Health & Safety Executive. The HSE/HSL operates the programs and distributes the samples, although the preparation of the samples may be under contract with the Laboratory of the Government Chemist. Both the HSE/HSL and LGC (who has an office in the USA) have commercial capabilities and could be approached regarding the preparation of reference standards or proficiency testing samples for the analysis of talc and talc-containing products. RTI manufactures proficiency test samples and has a reference repository of asbestos materials; they also could be approached. At least, and until properly appropriate proficiency test materials are available, laboratories should participate in the AIMS and LACS schemes.

Charge Question 22
Reference standards for use in laboratory proficiency must, of necessity, be homogenous in order to ensure that proficiency is properly and consistently determined. Inhomogeneous samples must also be homogenized before analysis. This should use the least destructive techniques available in order not to reduce the size and crystallinity of particles. It has been demonstrated that some milling techniques simply carry inhomogeneities through to the final product. Sedimentation concentration techniques will act towards homogenizing the sample before analysis.

VII. How Can Suitable Limits of Detection Be Established?

Charge Question 23
I have no experience in gravimetric reduction and can offer no suggestions in this regard.

VIII. Laboratory Quality Management System Questions

Charge Question 24
There are various issues with the establishment and implementation of quality management systems. One issue is the parameters of operation of the transmission electron microscope. Electron beam damage under electron microscopy results in a conflict between the high current and beam dose preferred to produce bright images and the lower beam doses necessary to produce good diffraction patterns (Steel and Small, 1985). For example, electron beam damage has been shown to cause broadening and weakening of diffraction spots in chrysotile (Zusmann and Brindley, 1957) and damage even in more robust amphibole structures (Martin et al., 2016).

A fundamental tenet of ISO 17025 General requirements for the competence of testing and calibration laboratories is that laboratories appreciate, assign and report an uncertainty to their analyses. Generally, I do not see this with asbestos analysis. The example analytical report from AMA referenced in the IWGACP White Paper includes neither an uncertainty in the identification (which would be based in the calibration and uncertainty of the EDS) nor in the calculation of quantitative content. I cannot emphasize enough how poor this situation is. It must be addressed for any method to be considered "valid".

Finally, it is IWGACP's opinion that "The analysts should have received formal training in mineral identification and determination of asbestos, as well as in the instrumentation and methods required for the analysis." While I am in full agreement with the sentiment, it is

nothing more than wishful thinking until such 'formal training" is established and approved. NIOSH established the "582" course for PCM. Perhaps they could be approached to provide similar for TEM. Otherwise, established training providers, such as McCrone, could provide details of their offerings for certification. The American Industrial Hygiene Association has established a registry program for PCM analysts and perhaps this could be extended to other analytical techniques.

Additional References cited in this review but not given in the text

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Spurny, K.R., Stöber, W., Opiela, H. and Weiss, G. (1980) On the problem of milling and ultrasonic treatment of asbestos and glass fibers in biological and analytical applications. American Industrial Hygiene Association Journal, 41(3): 198-203.
Steel, E.B., and Small, J.A. (1985) Accuracy of transmission electron microscopy for the analysis of asbestos in ambient environments. Analytical Chemistry, 57: 209–213.
Zusmann, J., and Brindley, G.W. (1957) Electron diffraction studies of serpentine minerals. American Mineralogist, 42: 133–153.

III. Specific Observations

None provided.

4. Reviewer #4

Comments on FDA's *IWGACP Scientific Opinions on Testing Methods for Asbestos in Cosmetic Products Containing Talc – Testing Methods*

Reviewer #4

I. GENERAL IMPRESSIONS

The analysis of cosmetic talc for potential asbestos contamination is an area which needs improvement. Standardization is needed so that results from different laboratories can be compared to one another and so that results are comparable and readily understandable. The IWGACP, in my opinion, has provided an effective guidance document which, when followed, will provide a method I believe will be effective in the analysis of cosmetic talc for asbestos.

While the White Paper is clearly written and explanatory in its own right, the Appendices are especially useful in that they provide further detail in the reasoning presented within the White Paper. With the exception of a few minor corrections or differences in language, I found the information to be clearly presented, supporting evidence well presented, and the resulting conclusions sound. Additionally, the writing is succinct and easily accessible.

As someone who studies asbestos, has developed methods for the quantification of asbestos content, analyzes materials for asbestos content, and produces synthetic asbestos-containing proficiency samples, I appreciate that the IWGACP recommends well-established technologies and preparation techniques. As those techniques and technologies are regularly utilized by the existing asbestos testing community, I would anticipate any method developed using the opinions presented in the White Paper to be readily adopted and utilized. However, I can't support the use of visual estimation in PLM analysis.

II. RESPONSE TO CHARGE QUESTIONS

Charge Question 1
In my opinion and based upon my experience with the methods described, the IWGACP did provide adequate information, data, and justification for its opinion. Laboratories utilizing various methodologies developed for other materials in combination with varying degrees of analytical expertise would provide a broad range of results. My experience with proficiency testing has shown me that, even with a single mandated methodology, a range of results can be expected. Additionally, the choice of one analytical technique or another could potentially bias the reported results in ways which may not be readily apparent.

Charge Question 2
The limitations of X-ray Diffraction are well understood within the asbestos testing community. The IWGACP appropriately described these limitations and, in my opinion, demonstrated CTFA J4-1 not suitable to determine lower concentrations of asbestos in cosmetic talc because of XRD's limitations but also because of an ineffective utilization of PLM.

Charge Question 3
I believe the IWGACP did provide adequate information to support its opinion that a negative finding by PLM should not be considered conclusive. PLM's limitations are known, and the Working Group's opinion is consistent with best practices and methodological requirements for

materials with low asbestos content, smaller asbestos structures, or problematic matrices such as window glazing or caulking, suspended ceiling tiles, and non-friable organically bound building materials.

Charge Question 4
The IWGACP provided adequate information explaining PLM's physical limitations towards detecting smaller (ex "TEM") structures. Additionally, and as pointed out, there is a difference in observing a structure and being able to properly identify a structure by PLM by its various optical properties. References to Abbe's calculations are particularly useful in demonstrating the limit of detection under ideal circumstances.

Charge Question 5
The superiority of analysis for asbestos by TEM when compared to that of SEM was adequately explained. SEM analytical capabilities will, undoubtedly, continue to be expanded upon but TEM currently has better resolution and well-established analytical criteria with significant supporting data and observations. Additionally, TEM is routinely used in asbestos testing laboratories – making adoption of any method resulting from the Working Group's White Paper more likely. As the Working Group indicated, SEM could be used as a complimentary technique but its inability image electron diffraction patterns present a significant analytical weakness.

II. How Should Samples Be Prepared?

Charge Question 6
Yes. The need for a standardized methodology was adequately explained. As was illustrated by the White Paper and Appendices, different technologies have different sensitivities and limitations. As is continuously demonstrated in methodologies for testing soils for asbestos content, results could cover a wide spectrum of results. Without an accepted, standardized methodology, results could potentially be susceptible to bias. Similarly, comparisons between laboratory-developed, non-standardized methods could result in additional ambiguity. Only a validated and publicly available method can resolve this problem. Following the lead of the environment testing framework, a standardized cosmetic talc methodology would help ensure compatible and comparable results which, due to the commonality of the method would be repeatable between laboratories.

Charge Question 7
As someone who regularly utilizes gravimetric reduction of all bulk building material samples, I understand and agree with the IWGACP's recommendation. I also find they explained why gravimetric reduction is a critical step in the preparation of a sample. Being a Geologist and having familiarity with the formation of talc and associated minerals, as well as being involved in the testing for asbestos, I fully appreciate the potential for incorrect identification of a mineral. To that end, the inclusion of heavy liquid separation is beneficial addition. Having mostly worked with bulk building materials or surrogates, I would suggest there are few instances in which I would anticipate gravimetric being a hindrance to testing cosmetic talc or related products. Instances which come to mind are those in which concentration of resistant interfering particulates such as titanium dioxide. Assuming the testing is being performed on a raw (milled, etc. before having been incorporated into a final product) material. I don't foresee this situation being of as much concern. Mineral misidentification could be a problem absent adequate training but then, I believe, the usage of the EMP morphological criteria would ensure

incorrectly identified amphiboles were still counted. However, it would be reasonable to expect any resulting method to be adapted, whether intended or not, by the asbestos testing industry for the analysis of finished, consumer products other than cosmetics which contain talc. In this case, there may be instances of interference concentration which may interfere with PLM analysis. Proper slide preparation should mitigate these problems. Finally, the close proximity of the densities of talc and chrysotile will prove to be a challenge.

Charge Question 8
In my experience, the combination of gravimetric reduction and PLM analysis followed by TEM analysis is the best for the determination of asbestos content in building materials. I believe this methodology would be equally effective in the analysis of cosmetic talc. Chrysotile, however, does present a challenge because its density prevents easy (but not impossible with careful calibration) separation from talc with heavy liquids. Accurate calibration of a heavy liquid like lithium metatungstate should make this separation possible but doing so may be impracticable. Preparation may require a 2-step process post ashing and acid treatment. Perhaps, there may be an initial heavy liquid, sedimentation (like that used by Dr. Webber and referenced by the Working Group), or elutriation step to concentrate the chrysotile content and then a second heavy liquid separation to concentrate the amphibole component.

III. What Should Laboratories Report?

Charge Question 9
My experience in testing for asbestos is consistent with the Working Group's observation regarding morphology being inconsistently applied to either validate or invalidate the asbestiform growth habit of a mineral particle. Having read a significant number of samples, many of which I prepared from known asbestos sources, I have observed structure which may or may not be considered asbestos depending upon the morphological criteria used. The IWGACP did adequately support their position and support the reporting of EMP structures. The examples provided did support their conclusion and illustrate the potential for subjective morphological interpretation of structure images.

Charge Question 10
The Group's explanation why the use of the term "fiber" should be avoided was supported and appropriate. However, the use of the term is thoroughly embedded within the environmental testing community – supported, in part, through the cross-pollination between light microscopy and electron microscopy terminologies. Overcoming the use of "fiber" will be challenging as it will almost certainly continue to be used colloquially and existing laboratories interested in engaging in any future potential talc testing will probably adapt their current benchsheets, reports, and LIMS programs. I believe it is likely the term would incorrectly be reported in future cosmetic talc results. Adoption and requirement of "EMP" and the related criteria should help facilitate a move away from the term "fiber."

Charge Question 11
I agree with the IWGACP's opinion on the usage of the ISO criteria to report morphology. The use of these structural terms can communicate a lot about the minerals and matrices and the potential for exposure. Having done this type of analysis on Libby, MT vermiculite-related samples, I have found the analysis to be more time-consuming than a "typical" AHERA or bulk TEM analysis. While this may not be a problem within the academic or governmental setting, it

is important to the commercial testing industry and any quality assurance/control assessment program should anticipate bench-level "short cuts" to save time spent in analysis should these criteria be adopted.

Charge Question 12

I believe any future method needs to provide the most information possible to make decisions for public health with priority given to health over mineralogical definitions. I have observed conflicts over what, morphologically, constitutes asbestos. I believe the Working Group's proposed morphological boundaries can simplify bench-level analysis. The analyst should not have to consider anything beyond certain, limited criteria and should not be put into the position of having to make questionable interpretations of what they observe or record. By avoiding the potentially subjective determination of asbestiform versus non-asbestiform the analyst can more efficiently concern themselves with recording structures >0.5 μm and >3:1 aspect ratio. Whether or not these structures are more or less significant than other can be determined through later analysis or health research. In asbestos analysis, the analyst is the instrument. Every effort must be taken to avoid primary, bench-level bias and a method which utilizes the proposed morphological requirements achieves this goal. Any opportunity where a potentially harmful structure is not counted must be avoided.

IV. How Should Laboratories Report Findings to Facilitate Quantitation or Estimation of Amounts Detected?

Charge Question 17

Yes, the IWGACP did provide enough information and data. Counting all structures on a grid opening is a standard, required practice in the analysis of air and water samples by TEM. The question, however, refers to an entire grid. Counting and reporting/tabulating every structure on every grid could prove untenable at the magnifications appropriate to detect structures ≈0.5 μm in length. As outlined in the White Paper, appropriate stopping rules for grid openings counted or number of structures counted would need to be developed. I support and agree with the conclusion structures should be tabulated and reported by size and type.

Charge Question 18

I agree with the observation that the weight percent of asbestos is not be truly indicative of a potential health risk. The number of structures of concern per mass of a material would be a superior measurement. As Dr. Chatfield and others have adequately demonstrated, the majority of mass is in the larger structures – which may not have as negative health impact should someone become exposed because they can't easily be inhaled or ingested. My early work with Libby vermiculite bears out this observation. The majority of the mass in exfoliated vermiculite ore was in a distinctly non-respirable fraction which was easily picked out with tweezers and a dissection microscope. After having been suspended in water and having an aliquot withdrawn after the vermiculite ore had settle or floated, the amount of respirable fibers observed by TEM was significant. The mass of these respirable structures was negligible relative to the total mass of the original sample. It is my opinion materials like talc should be quantified by number of asbestos structures per mass, not by percent mass.

V. How Should Laboratories Report their Results?

Charge Question 19
This is a challenging question to answer because there could, hypothetically, be some variability in the minerals present in an ore body and, as a result, present in cosmetic talc. My predominate experience is with building materials and air samples. In those analytes, homogeneity is easily determined. Additionally, they aren't cosmetics and were never intended to be applied to a person's body. It is my expectation cosmetic talc would be held to a higher standard of homogeneity for that reason and the likelihood of ingestion or inhalation is significantly increased. As such, I would suggest all structures be sketched and a minimum of 30 micrographs with SAED and EDS of the first 10 structures of each mineral type. Additionally, I would recommend every tenth structure after the first 10 of each type to also be identified by SAED and EDS. SAED and EDS could always be performed as needed by the analyst to confirm a mineral type. Finally, I believe all micrographs should be made available to clients upon request but that a minimum of at least one representative micrograph for each mineral type present be incorporated in a final report.

Charge Question 20
The Working Group supported Opinion #7. I would also like to suggest that any potential method provide a stock, example benchsheet and report which laboratories could adapt to their LIMS and reporting systems. Having been involved with laboratory assessment, I appreciate the variety of final reports produced by laboratories. Providing example documents would benefit laboratories and facilitate adoption of reporting standards.

VI. How Can Reference Standards Be Applied?

Charge Question 21
The difficulty of doing something does not imply it ought not be done. The situation related to the lack of NIST SRMs is well known in the asbestos testing industry and their related assessing bodies. The absence is one of the most common complaints/frustrations received by my program and the current draft TNI standard for asbestos analysis has been edited to accommodate, as best possible, standards other than SRMs. Having these materials is critically important but, based upon the current situation, I fear NIST is unable to improve the situation by providing the required SRMs. Assuming the production of SRMs were to become a reality, I would suggest that either ore bodies be adequately typified for their known asbestos content/contamination or synthetic (spiked) materials be produced with a means where the number of asbestos structures per volume of talc can be controlled.

Charge Question 22
I do not believe simple possession of a reference sample, even with experienced laboratories, would be adequate to demonstrate or develop proficiency. Proficiency testing materials would need to be regularly produced and sent to participating laboratories for analysis and scoring. Settling or uneven distributions within individual samples can be mitigated by utilizing spiked samples or ore-based materials which have been thoroughly homogenized and requiring participant laboratories to cone and quarter or similar. When a sample arrives at a laboratory, one of their initial concerns is the homogenization of the sample if it is not already homogenous. A proficiency test sample must, likewise, be homogenized from an adequately large volume of

source material before it is typified for accessory mineral content. Spikes could then be utilized and contaminate minerals taken into consideration prior to distribution.

VII. How Can Suitable Limits of Detection Be Established?

Charge Question 23

From what I understand of cosmetics, they are fairly homogenous when compared to building materials. Additionally, the talc would be highly processed. As such, I would suspect the sample size may be less than what is needed to test building materials – especially considering the size of the particles of interest – but I expect similar sample masses should ideally be required. What needs to be ensured is there is enough material to produce accurate results and enough remaining after preparation for analysis for potential retesting or archiving. A hypothetical limit of detection should be in EMP/mass (i.e., EMPs/gr) if the IWGACP's opinions are followed. In that case, I expect analytical sensitivities to be more like EPA water methods 100.1 or 100.2 with a sensitivity in EMPs per mass of sample (mg or gr), dependent upon the number of TEM grid openings analyzed.

VIII. Laboratory Quality Management System Questions

Charge Question 24

Skilled training and proficiency are of utmost importance. I share the opinion that basic analytical expertise is not dependent upon a specific educational background but that thorough in-depth training and technical competence are must-haves. Assuming laboratories are regularly provided with sufficiently challenging proficiency testing samples, a robust quality assurance and control program is in place and training is comprehensive and completely documented, I believe a laboratory will adequately perform analysis of cosmetic talc. I also believe an accreditation requirement like that seen in the environmental testing industry would be required but one which is better suited to the needs of the FDA.

III. Specific Observations

White Paper: IWGACP Scientific Opinions on Testing Methods for Asbestos in Cosmetic Products Containing Talc

Page	Paragraph/Line	Comment
11	Paragraph 3, line 6	I would suggest removing "trace mineral" and replace it with "contaminate" or "impurity" as indicated in footnote 14 on page 8.
19	Paragraph 1, line 3	I wouldn't use the word "avoid" as it is soft language which can imply permissibility under undefined circumstances.

Appendices to White Paper: IWGACP Scientific Opinions on Testing Methods for Asbestos in Cosmetic Products Containing Talc

Page	Paragraph/Line	Comment
9	Paragraph 4, line1	"...used to detect asbestos…." should be changed to read "...used to detect fibers…." or "...used to detect fibrous particles…." because PCM cannot identify asbestos.
30	Paragraph 4, line 4	I have never heard of structures being reported as "splintery."

Page	Paragraph/Line	Comment
34, others	General	Why are all the micrographs from SEM when TEM is the recommended method? Are there no suitable TEM micrographs?
48	Paragraph 3, line 2	I like the term "censored EMPs," but some might take exception to its usage.
112	Paragraph 1, line 3	New York Item 198.8 utilizes lithium metatungstate or sodium polytungstate – not just sodium polytungstate.
119	Paragraph 2, Section C,i,1	I can't support the Working Group accepting "visual estimation." Point counting is a better technique for repeatable results and it removes the likelihood of visual biases or heuristics influencing the results. (Webber, et al. 1997. Analytical Trends in Asbestos Analysis: New York's Bulk Sample Proficiency-Testing Program. American Industrial Hygiene Association Journal. 58, 809-813.)
119	Footnote 60	I would recommend stronger language than "discouraged" if the IWGACP does not want growth habit being used to determine whether an otherwise countable structure is or is not asbestos.

5. Reviewer #5

Comments on FDA's *IWGACP Scientific Opinions on Testing Methods for Asbestos in Cosmetic Products Containing Talc – Testing Methods*

Reviewer #5

I. GENERAL IMPRESSIONS

None provided.

II. RESPONSE TO CHARGE QUESTIONS

I. What Test Methods Should be Used by Laboratories?

Charge Question 1
Yes, the IWGACP provide adequate information and data.

Charge Question 2
Yes, surely yes.

Charge Question 3
Not completely: an example of the testing the same sample by PLM and by TEM would be conclusive.

Anyway, as detailed later, in my opinion PLM is not a useful method for the target.

Charge Question 4
Yes, surely yes.

Charge Question 5
Yes, surely yes.

However, the IWGACP does not indicate that TEM instrument must have a double-tilt stage holder. This holder allows to obtain the dual zone axis SAED patterns.

II. How Should Samples Be Prepared?

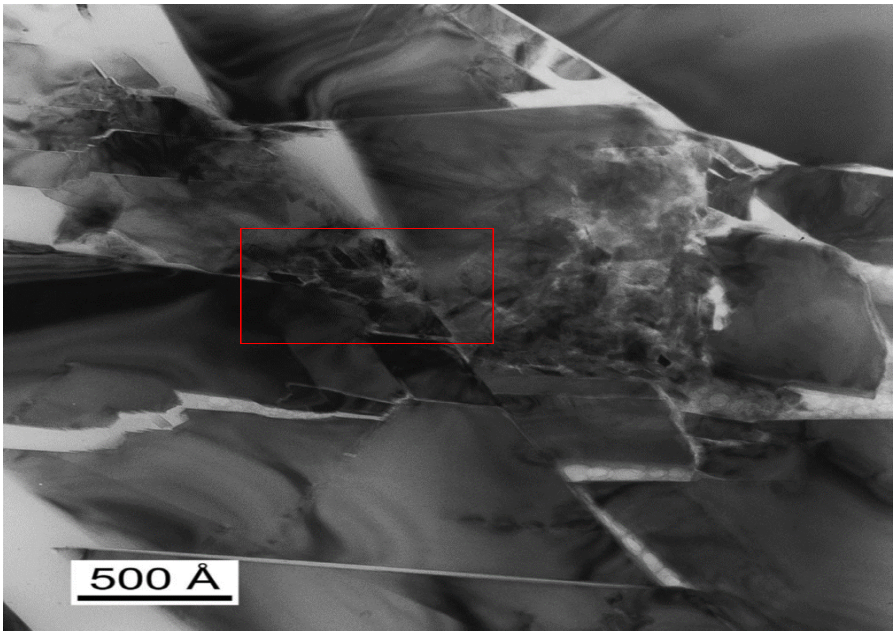
Charge Question 6
Yes, the IWGACP provide adequate information and data.

Charge Question 7
Yes, the IWGACP provide adequate information and data regarding samples of cosmetics.

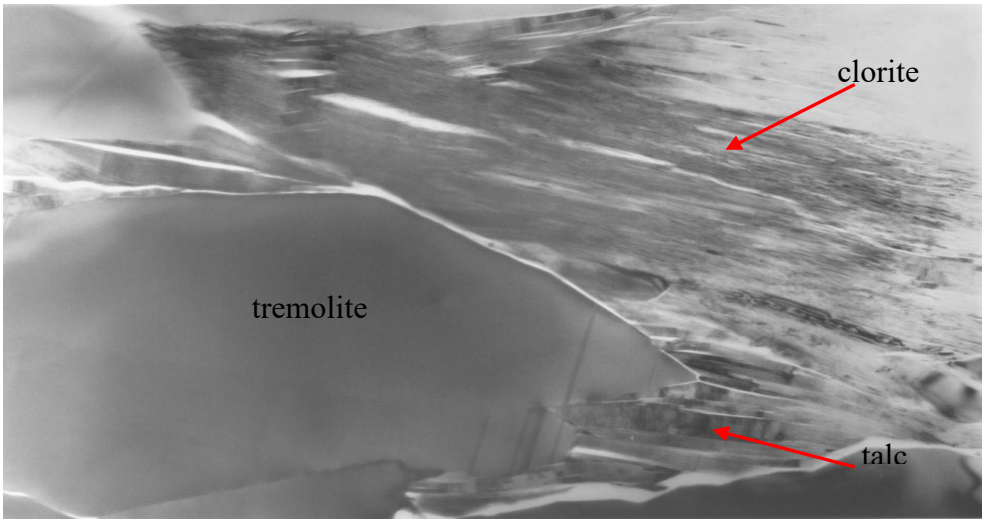
I agree only in part. Indeed, the first part of the sample preparation should be different if the sample is a cosmetic product or talc not yet used to manufacture cosmetic products (i.e., raw material). In the first case in fact the talc is mixed with many other substances some of them are organics and the ignition is useful.

Therefore, the IWGACP provide adequate information and data for the cosmetic samples, but not enough for the talc not yet used for cosmetic preparation.

There is also the problem of some mineral that can be present in the same sample (as an example chlorite due to solid state transformation of tremolite asbestos: see both published (Gunter et al., 2007) and unpublished photo (Belluso, unpublished), the latter being a magnification of the first one)



TEM image of tremolite asbestos fibres as seen along the [001] fibre axes. The thin and long fibres are longitudinally aggregated in columnar prisms. (modified from Gunter et al., 2007)



Magnification of the inset of the above image, i.e., Figure 15

Yes, the problem may come from the presence of other mineral phases mixed/intergrown with talc. An example is chlorite, as detailed before, and another is the possible presence of the asbestiform antigorite and/or asbestiform polygonal serpentine. Both have been recognized for a few years (e.g.: Fitz Gerald et al., 2010; Belluso et al., 2017; Belluso et al., 2019); they are not asbestos classified, they may be abundant in some cases, and they are confused with chrysotile if they are not examined by TEM-EDS+SAED.
In the Figure, the main phases are asbestos tremolite, but other samples can contain mainly talc with amphibole asbestos and phyllosilicates as subordinate phases. Depending on the amount of these phases, the SAED technique may be not enough to detect them and it needs examine the sample by using the TEM high resolution images (i.e. HRTEM), as in the image above.
It is important to underline that antigorite may be present in talc containing rocks (e.g., Gunter et al., 2018; Rouméjon et al., 2019).

Charge Question 8
Yes, according to me there is another method for sample preparation that shows promise and should be further developed, validated, and published as a preferred method for isolating amphibole and chrysotile particles from talc and talc-containing cosmetics. It is the "fluidized

bed asbestos segregator preparation method" described by Januch et al. (2013) and used for example by Berry et al. (2919).

This kind of preparation is showed in the IWGACP-WhitePaperTechnicalAppendices-December2021 FINAL (p. 103 to 106). The conclusion IWGACP is the "there have been no published studies investigating the use of the FBAS method for determining the asbestos content in talc. Talc presents some unique problems that are not present in soils, such as, (a) the similarity of density (g/cm3) for talc and some asbestos amphibole minerals, and (b) the fine particle size of cosmetic talc."

Obviously, this method must be test for cosmetics and for talc (as a raw material) before proposing it as an official method, but it looks very promising. As for the claim that the density of talc and some asbestos amphibole minerals is similar, this is not exactly true and contradicted by the data shown in Table J-1 (p 110-111) and in Figure J-3 (p. 111).

III. What Should Laboratories Report?

Charge Question 9

I do not agree with this. According to me the information and data provided are not adequate. TEM images are very useful to discriminate between "asbestiform" and "not asbestiform" if the definition of both terms have been previously detailed.

First of all, the term "structure" used in the Fig. C.1 of the ISO 10312 (2019) and Fig. F-5 of the IWGACP-WhitePaperTechnicalAppendices-December2021 is not adequate, in fact the pictures refer to morphology of fibrils, fibrils bundles, fibers in general, and aggregate (more or less compact) of fibrils, of fibers, and fibrils/fibers and particles.

The IWGACP "advises careful use of the term "fiber" because it is defined as a type of asbestos structure" (p. 19 of the IWGACP-WHITEPAPER-December2021 FINAL) but again the use of the term "structure" is not adequate: the term "fiber" must refer to the morphology/habit and not to structure.

Give that, another problem is that the IWGACP provides, as second opinion and advice, to "Tabulate, at minimum, all amphibole and chrysotile particles (see 1a, 1b, 1c, and 1d) having a length ≥ 0.5 μm (500 nm) and an AR ≥ 3:1 by indicating respective length, width, and mineral type" (p. 19 and others in IWGACP-WHITEPAPER-December2021 FINAL), but if analysts use only these two-dimensional criteria, then they consider also a particle with, as an example, a length of 40 μm and a width of 10 μm as AR is 4 and therefore respects AR ≥ 3: 1, but a particle with this size is too large to reach the pulmonary alveoli.

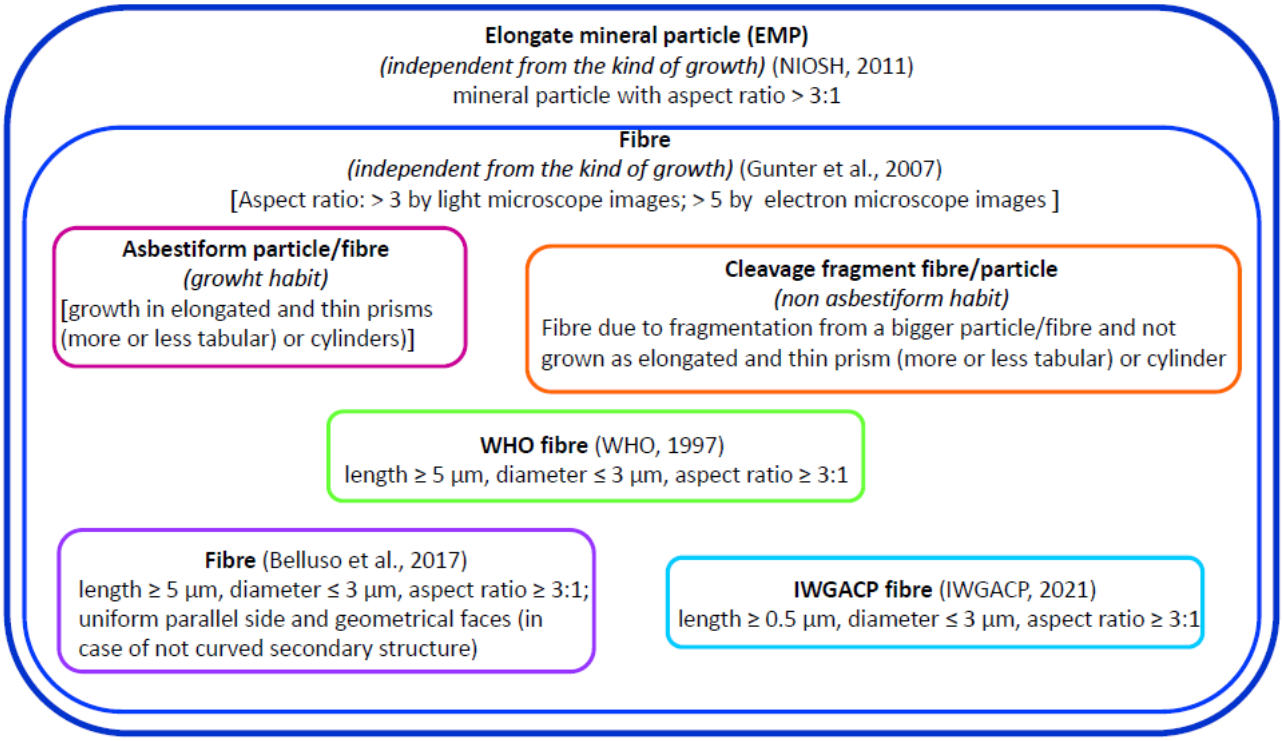
Charge Question 10

According to me, IWGACP does not provide adequate information and/or data on this issue. If the term "asbestiform" is considered related to growth (as stated in ANSES 2015 and instead not very clear in IWGACP-WHITEPAPER-December2021 FINAL, see p. 24 of the Glossary) and given that IWGACP indicates do not distinguish between cleavage fragments and native crystals, the use of term "fiber" is adequate.

Why does the IWGACP not plan to adopt the definition of WHO fibres (1997) i.e., length ≥ 5 µm, diameter ≤ 3 µm, aspect ratio ≥ 3:1 integrated by the recent evaluation (e.g. Stayner et al., 2008) that even fibres shorter than 5 µm may be harmful, lowering the lower limit to a length ≥ 0.5 µm? The opinion of IWGACP is clear, but the information and the comments are not sufficiently consistent and sometimes non clearly explained.

As an example, the report of ANSES (2015) clearly state definitions and meanings of fiber, elongated mineral fibers, asbestiform and non-asbestiform fibres, and provides indication for using each term.

According to me, given that it needs to include also the fibres shorter than 5 µm and at least 0.5 µm long, it is very useful that IWGACP clearly defines any terms with the correlated characteristics and dimensions and also introduce a sketch map showing the different terms, their definitions with their partial overlapping. An example of this sketch map is pasted below.



Charge Question 11
Yes, I agree, but only if the additions and the corrections, as I have detailed above (in the answers to questions 9 and 10) have been made.

Charge Question 12
I have answered this question above.

IV. How Should Laboratories Report Findings to Facilitate Quantitation or Estimation of Amounts Detected?

Charge Question 17

Yes, I agree with the IWGACP conclusions. The information is adequate. But, as stated above and below, I do not agree with all the criteria indicated for identification.

Charge Question 18
Yes, I suggested (see p. 16, third comment) the use of SEM-EDS and TEM-EDS+SAED in complementarity.

V. How Should Laboratories Report their Results?

Charge Question 19
As I detailed at page 18, second comment, 100 particles should not be the maximum number but the correct number to examine to have good statistics.
In several papers (although on other topics) the number of analyzed particle is bigger than 100: as an example, in the paper by Dong et al. (2019) 400 particles were analyzed.

Charge Question 20
As stated above and below, my opinion is in part different from that of IWGACP about the number of particles to investigate and about and about the criteria indicated for identification.

VI. How Can Reference Standards Be Applied?

Charge Question 21
Yes. I think it may be possible to obtain reference standards for this use by the mixing, in suitable quantity, a pure talc (i.e., without natural fibrous contaminants) obtained by synthesis with a fully characterize asbestos that can be natural contaminants of talc.

The talc synthesis is now fine-tuned: see for example the review by Claverie et al. (2017).
The suitable asbestos may be characterized by TEM-EDS+SAED and SEM-EDS investigation.

Charge Question 22
I think that the not homogenous distribution of asbestos in the samples can be overcome by homogenization of the sample during his preparation and by examine more than one sample for each product. The homogenization can be obtained by using a method usually used for rock samples and named “quartering”: for quartering, see for example the paper by Panarese and Vannocci (2006).

Furthermore, the characterization of the reference standards should be carried out by different laboratories (at least 3) accredited by national agencies and the results should be compared and averaged.

VII. How Can Suitable Limits of Detection Be Established?

Charge Question 23
To avoid the problem of the non-homogenized sample, I suggested here above the possible method.

A good approach to gravimetric reduction is in the paper by Oberta et al. (2018).

VIII. Laboratory Quality Management System Questions

Charge Question 24

As I indicated below, 2 implementations could be very useful.

1) The TEM operator must be a trained and experienced microscopist in TEM imaging of minerals, but also trained and experienced in SAED both in the acquisition of suitable diffraction patterns and in their measurement and processing of the obtained data (a crystallographic basis it is necessary).
2) Since the simple stage holder is not sufficient, all TEM laboratories must have double tilt stage holder. The double tilt stage holder must have both tilt axes in the plane perpendicular to the axis of the electronic beam.

III. Specific Observations

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Page	Paragraph/Line	Comment
10	VII. COMPARISON OF PLM AND TEM TESTING METHODS/ Line 5	This is not the only benefit of using TEM. In fact, using TEM images + chemical composition by EDS + SAED, the nature of the mineral fiber is unequivocally identified. See for example Belluso et al. (2019) and Germine and Puffer (2020).
12	X. DIMENSIONAL CRITERIA AND TERMINOLOGY FOR TABULATING ASBESTOS AND AMPHIBOLE PARTICLES/ Line 9	It is a correct approach to consider EMP without taking into account how they are formed. In fact, since at present the noxiousness of the respired cleavage fragments cannot be excluded, it is appropriate to consider EMP regardless their formation.
12	X. DIMENSIONAL CRITERIA AND TERMINOLOGY FOR TABULATING ASBESTOS AND AMPHIBOLE PARTICLES/ Line 10	I absolutely agree with the indicated approach: “The IWGACP believes the term “EMP” could help resolve discrepancies in the reporting of amphibole particles, and most importantly, that it would ensure more inclusive reporting by laboratories.”
13	X. DIMENSIONAL CRITERIA AND TERMINOLOGY FOR TABULATING ASBESTOS AND AMPHIBOLE PARTICLES/ Line 1	Another essential criterion, in addition to length, width, and ratio, is the parallelism of the long edges. This is both applicable for any kinds of EMP when observed in two dimensions (for example in TEM images). As an example, see Belluso et al. (2017).
13	XI. DETERMINING HABIT OF GROWTH OF AMPHIBOLE	The use of the term “structure” (that appears here and in other parts of the text) is not adequate because it must be referred to structural arrangement of chemical units as for example the atoms. Therefore, the

Page	Paragraph/Line	Comment
	MINERALS/ Lines 4 to 6	use of this term together with “asbestos” is not suitable given that IWGAP refers to the particular manner with fibrils (or singular particles) join. A possible alternative term may be “aggregation”. Besides, I do not agree the definition of the characteristics of the “asbestos aggregation”, i.e., a bundle. I give reasons below. The crystalline structure of the amphiboles determines both a growth and an oriented fracturing (cleavage) as elongated (or columnar) prisms. The secondary crystalline structure (i.e., the roll up of the layers constituted by octahedral + tetrahedral sheets + interlayer space) of chrysotile determines a growth in elongated tubular shapes (much more elongated than wide).
13	XI. DETERMINING HABIT OF GROWTH OF AMPHIBOLE MINERALS/ Lines 15 to 16	I agree with this sentence since the sample must be powdered for the TEM investigation and therefore the original habits will be (at least partially) mechanically modified. Owing to this the best investigation should include both a) SEM-EDS investigation and b) TEM-EDS+ SAED investigation. a) The investigation using SEM-EDS allows to: measure the original dimensions and define the original habit of the “particles”, without the mechanical fragmentation/alteration necessary for the TEM preparation of the sample. This investigation, after proper sample preparation, is also suitable for evaluating the quantity of a specific mineral species present together with others (as in the case of asbestos fibres in talc). b) The investigation by TEM-EDS+SAED allows to: distinguish among different types of silicate mineral and evaluating the related quantity of these last. By these data, it is possible to recalculate the quantities obtained by SEM-EDS investigation. As far as the cleavage fragments (formed for example following mechanical stress) that can be considered WHO fibers (i.e., on the base of the dimensions), at the present state of the knowledge is not possible evaluate them as harmless. Therefore, they should be considered and counted as fibers/EMPs.
14	XI. DETERMINING HABIT OF GROWTH OF AMPHIBOLE MINERALS/ Line 2	The term “acicular” used here and elsewhere in the text is not appropriate for the habit of asbestos and also for EMP. In fact, this term refers to the morphology of the needle and in particular to the its extremity. But a needle does not have the same width along its entire length and its edges are not parallel but converging at the end. 

Page	Paragraph/Line	Comment
		Terminal part of a needle
15	Table 1 – Summary of Useful Analytical Techniques and Corresponding Attributes and Measurements to Analyze Talc and/or Talc-containing Cosmetics Measurement and Utility-PLM / Line 2	The optical characteristics of such fine crystals (i.e., asbestos fibres and WHO fibres) are very difficult to identify by PLM!
15	Table 1 – Summary of Useful Analytical Techniques and Corresponding Attributes and Measurements to Analyze Talc and/or Talc-containing Cosmetics Measurement and Utility-TEM/SAED / Line 4 to 5	2 zone axes are sufficient because the distinction is between a limited number of mineral species so the search for identification is focused on a small number of mineral species.
15	XII. IDENTIFICATION AND REPORTING OF ASBESTOS AND AMPHIBOLES IN TALC-CONTAINING COSMETICS AND TALC INTENDED FOR USE IN COSMETICS/ Line 1 to 2	I disagree with this sentence because talc is a mineral and the "overall mineral composition" cannot be about talc but a rock containing talc.
16	XII. IDENTIFICATION AND REPORTING OF ASBESTOS AND AMPHIBOLES IN TALC-CONTAINING COSMETICS AND TALC INTENDED FOR USE IN	I completely agree with this statement! Both SEM-EDS and TEM-EDS+SAED should be used in complementarity. I declared this in the comments above.

Page	Paragraph/Line	Comment
	COSMETICS/ Line 20 to 21	
17	XIII. ISSUES RELATED TO SAMPLE QUANTITY AND ANALYTICAL SENSITIVITY/ Line 10 to 11	100 particles should not be the maximum number but the correct number to examine to have good statistics. In several papers (although on other topics) the number of analysed particles is bigger than 100: as an example, in the paper by Dong et al. (2019) 400 particles were analysed.
17	XIV. SCIENTIFIC OPINIONS ON TESTING APPROACH/ Line 1 to 2	As stated before, I disagree with this indication.
17	XIV. SCIENTIFIC OPINIONS ON TESTING APPROACH/ Line 4 to 5	I totally agree with the indications on sampling, sample preparation, and specification of the instruments, methods, and criteria used.
18	XIV. SCIENTIFIC OPINIONS ON TESTING APPROACH/ Line 1	As stated before, I disagree with this indication.
18	XIV. SCIENTIFIC OPINIONS ON TESTING APPROACH/ Line 6	As noted, before, there is a misunderstanding between the mineral talc and the talc containing rock. It should be better to write: “particles consisting of talc and an amphibole”.
19	XIV. SCIENTIFIC OPINIONS ON TESTING APPROACH/ Line 3	As noted here above.
19	XIV. SCIENTIFIC OPINIONS ON TESTING APPROACH/ Line 24	The term "fiber" must refer to the morphology/habit and not to structure
19	XIV. SCIENTIFIC OPINIONS ON TESTING APPROACH/ Line 26 to 27	The criterion for the width must consider that large particles do not arrive into lower respiratory system, and in particular into the alveoli.
20	XIV. SCIENTIFIC OPINIONS ON TESTING APPROACH/ Line 3 to 5	As noted above, I disagree with the combination of PLM (with dispersion staining) and TEM-EDS+SAED.
23	XV. NEXT STEPS AND FUTURE RESEARCH/ Line 22 to 24	I totally agree with this recommendation.
24	XVI. GLOSSARY OF TERMS/ Line 14	To avoid misunderstanding, a short note for A, X, and Z needs. The subscript 0-1 for A is missing.
24	XVI. GLOSSARY OF TERMS/ Line 23 to 26	I disagree with this statement. The fibrous habit of crystal growth (and also flexibility and other properties) has not been observed in “fibrous serpentine (chrysotile) and certain fibrous amphibole minerals”, but also in “asbestiform/fibrous” antigorite, sepiolite and others. See for

Page	Paragraph/Line	Comment
		example: Belluso et al. (2017, 2019); Giustetto et al. (2014); Keeling et al. (2006); Knidiri et al. (2014). The non-asbestiform term specification should be added in this glossary.
25	XVI. GLOSSARY OF TERMS/ Line 2 to 3	The term "asbestos" should be added to the names of cummingtonite-grunerite, anthophyllite, tremolite, and actinolite (e.g., tremolite asbestos).
27	XVI. GLOSSARY OF TERMS/ Line 1	I disagree with the written chemical composition. Fe should not be present in the chemical formula, in fact as an example garnierite, another mineral of the serpentine group, does not contain Fe, but Ni (https://www.mindat.org/min-2882.html)

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Page	Paragraph/Line	Comment
9	3. Light Microscopy/ Line 1 to 9 and Line	The method indicated (PLM) is used by many laboratories and recommended by institutions and / or authorities because both sample preparation and analysis are quick and economical. Furthermore, operator training is not time-consuming and inexpensive. However, this method (as stated in the Appendices to White Paper and also in several parts of the White Paper) has low resolution and therefore is not suitable if particles/EMP/fibres are very small/thin or if the bundle is constituted by more than one mineral species, both asbestos and not asbestos classified. For this last difficulty see many examples in Baronnet and Belluso (2002), Belluso et al. (2017), Gunter et al. (2007). Due to the reasons above detailed, the PLM (also by using liquids) is not a suitable method, and it should be substituted by SEM-EDS. The latter should be used in complementarity with TEM-EDS+SAED.
11	4. TEM/ Line 27	As stated, "only a relatively small amount of sample can be analyzed" through TEM. Therefore, as I have already illustrated above, the TEM-EDS+SAED investigation should be used in complementarity with the SEM-EDS investigation for the evaluation of both morphology and dimensions of particles/EMP/fibres of the sample not mechanically disturbed (since not prepared) and the quantity of the different species.
11	4. TEM/ Line 32 to 33	I totally agree! The TEM operator must be a trained and experienced microscopist in TEM imaging of minerals, but also trained and experienced in SAED both in the acquisition of suitable diffraction patterns and in their measurement and processing of the obtained data (a crystallographic basis it is necessary).
12	4. TEM/ Line 6	A simple stage holder is not sufficient. A double tilt stage holder is required, and this requirement must be indicated. The double tilt stage holder must have both tilt axes in the plane perpendicular to the axis of the electronic beam.
12	5. SEM/ Line 11 to 12	I totally agree with this statement. As I have stated several times, the best and most reliable results can be achieved (for the matter discussed) by using TEM-EDS + SAED in complement with SEM-EDS. PLM is not suitable for this type of investigation.
13	6. XRD/ Line 13 to 14	I totally agree: XRD techniques are not suitable for this type of investigation.

Page	Paragraph/Line	Comment
15	Measurement and Utility TEM/SAED/ Line 1 to 2	Also, the distribution and the shape of the diffraction sposts is very useful to distinguish some mineral species (e.g., chrysotile from asbestiform antigorite and asbestiform polygonal serpentine). See for example: Bloise et al. (2014); Wagner (2015).
15	Attribute to Report SEM/ Line1	"Attribute to report" must be also the dimensions and not only the morphology.
21	1. Chemical and Physical Properties of Talc and Applicable Terminology/ Line 9	Kaolin is a rock and kaolinite is a mineral.
22	1. Chemical and Physical Properties of Talc and Applicable Terminology/ Line 3 to 5	It would be better to define a size of this. In fact, it may be observed at the sub-micrometric scale or, as in Fig D, at the micrometric scale.
24	Table C-1. Mineral composition (wt%) of talc from various locations. Mineral/ Line 2 to 3	It is not clear if the data showed in Table C-1 are referred to tremolite asbestos and anthophyllite asbestos or unregulated tremolite and anthophyllite mineral species.
26	Caption of Figure C-3. SEM/ Line 2	The term "bundle" should be added in the Glossary compiled by IWGACP.
29	1. Nomenclature and General Chemical and Physical Properties of Asbestos/ Line 17 to 19	This sentence lists asbestiform winchite and richterite, two minerals of the asbestiform amphibole group, classified as carcinogenic substances, not directly used as a commercial product but contained (since naturally intergrown) in a specific clay rock mined and used as thermal insulation. Therefore, these two minerals had no commercial significance (like asbestos in talc). This different consideration must appear in this paragraph and two other asbestiform minerals must be added (i.e., asbestiform F-edenite and asbestiform erionite, both carcinogenic). These 2 minerals had no commercial significance but the rock that contained them was mined, marketed and used by the local building and road activities. See for example Belluso et al. (2017); Burragato et al. (2005); Carbone et al. (2007). (2010).
29	1. Nomenclature and General Chemical and Physical Properties of Asbestos/ Line 20 to 21	This sentence is true for amphibole asbestos, but not for chrysotile. Chrysotile has not a not fibrous counterpart either because the secondary crystal structure of antigorite and lizardite is different from that of the chrysotile, and because the habit of antigorite may be flattened prismatic, prismatic more or less elongated, and asbestiform. See for example Belluso et al. (2017); Keeling et al. (2008).

Page	Paragraph/Line	Comment
30	1. Nomenclature and General Chemical and Physical Properties of Asbestos/ Line 11	The comments on the use of term “acicular” have been presented above.
31	Figure D-1	Some of the shown figures do not show the non-fibrous habit (in the caption named “bulk form”)!
31	Table D-1 Non-Asbestos Mineral Analogues Serpentine group of minerals	As described above, lizardite and antgorite are not the “non-asbestos mineral analogues” of chrysotile.
32	Table D-1 Non-Asbestos Mineral Analogues Amphibole group of minerals	Grunerite is not the only one “non-asbestos mineral analogues” of amosite: so are cummingtonite and the minerals of the cummingtonite-grunerite isomorphous series.
33	2. Morphology of Asbestos and Amphibole Minerals/ Line 9	The term “fibril” is not specified in the IWGACP Glossary and should be added.
36	Figure D-4 (A)/ line 3 to 4	An asbestiform crystal (specifically a fibril) can also be prismatic, as illustrated in Figure F-2. According to this sentence, instead, a prismatic crystal cannot be asbestiform.
39	Figure D-4 (H). Caption	The non-asbestiform term specification needs. There is not in XVI. GLOSSARY OF TERM
42	1. Introduction/ Line 21 to 27	The indicated dimensions do not take into account the size of macrophages and their “ability” to phagocytize particles smaller than themselves. See Krombach et al. (1997).
69	3. Issues in the Identification and Classification of Mineral Particles/ Line 11 to 13	The "scrolled hollow" cannot be related to structure but to "secondary structure". Also, halloysite fibre has this secondary structure (visible through TEM images) but it contains Al instead of Mg.
71	Consideration A: Particle Dimensions/ Line 10 to 13	I'm not completely in agreement with this statement. As explained above, size, habits and different properties are together criteria for differentiating asbestiform and non-asbestiform particles.
74	Figure F-5. Capture	As detailed above, the term “structure” is not suitable in this context and can be misunderstood.
101	3. Ashing and Acid-Based Dissolution/ Line 1 to 2	In this paragraph, IWGACP talks about the preparation for analysis of both talcum powder samples for cosmetic production and cosmetic samples. But the talc samples NOT yet used for the manufacture of cosmetics do not contain substances other than minerals and therefore do NOT need to be ashed

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V. PEER REVIEWER COMMENT TABLE

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1. FDA Response to Charge Questions

CHARGE QUESTION 1. The IWGACP concluded that the absence of a standardized testing method for the analysis of asbestos in talc-containing cosmetic products (including specifications of the methods of sample preparation, microscopic technique, and criteria and terminology for reporting the detected particles) has led many analytical laboratories to combine and/or adapt published test methods developed for the analysis of asbestos in air or building materials. Do you agree that this could, at least in part, account for discrepancies in laboratory findings?

REVIEWER	COMMENT	RESPONSE
Reviewer #3	The IWGACP provided information on the performance characteristics of testing methods that strongly suggest substantial discrepancies could occur between laboratories using different analytical finishes. However, IWGACP did not back that suggestion up with specific data from comparative testing exercises between laboratories using different procedures, other than from a single laboratory (AMA). A "standardized" testing method implies a particular level of detail, which should be rooted in performance. In particular, even a specific analytical technique, e.g., "TEM" can be applied in different laboratories with many differences in details, which could also lead to substantial discrepancies, or not. The performance of standardized methods and allowed variations needs to be established quantitatively. In the proficiency test examples provided above [in general impressions], PLM was able to detect asbestos in several of the samples in multiple laboratories, while, conversely, false positives were observed in laboratories using TEM.	FDA agrees with Reviewer #3 and the IWGACP conclusion that (differences in) application of testing protocols not intended to test cosmetics for asbestos could in part contribute to discrepancies. With respect to whether adequate justification was provided by IWGACP, the reviewer suggests that supporting data from testing by multiple laboratories using different methods might have also helped support this IWGACP conclusion. Unfortunately, such an exercise was not part of the scope of the IWGACP. FDA agrees that if a standardized protocol were to be developed to test for asbestos in cosmetics, a demonstration of performance would be important.
Reviewer #4	In my opinion and based upon my experience with the methods described, the IWGACP did provide adequate information, data, and justification for its opinion. Laboratories utilizing various methodologies developed for other materials in combination with varying degrees of analytical expertise would provide a broad range of results. My experience with proficiency testing has shown me that, even with a single mandated methodology, a range of results can be	FDA agrees with Reviewer #4 and the IWGACP conclusion that (differences in) application of testing protocols not intended to test cosmetics for asbestos could in part contribute to discrepancies. The reviewer finds that the IWGACP provided adequate justification for its conclusion. The

CHARGE QUESTION 1. The IWGACP concluded that the absence of a standardized testing method for the analysis of asbestos in talc-containing cosmetic products (including specifications of the methods of sample preparation, microscopic technique, and criteria and terminology for reporting the detected particles) has led many analytical laboratories to combine and/or adapt published test methods developed for the analysis of asbestos in air or building materials. Do you agree that this could, at least in part, account for discrepancies in laboratory findings?		
REVIEWER	**COMMENT**	**RESPONSE**
	expected. Additionally, the choice of one analytical technique or another could potentially bias the reported results in ways which may not be readily apparent.	reviewer also suggests there might be other factors contributing to discrepancies.
Reviewer #5	Yes, the IWGACP provide adequate information and data.	FDA agrees with Reviewer #5 and the IWGACP conclusion that (differences in) application of testing protocols not intended to test cosmetics for asbestos could in part contribute to discrepancies. The reviewer finds that the IWGACP provided adequate justification for its conclusion.

CHARGE QUESTION 2. Do you agree that the CTFA J4-1 method is inadequate for testing for asbestos in talc intended for use in cosmetics, where asbestos may be present at trace levels?		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #3	Not precisely, because IWGACP did not define "trace levels". 0.1% could be considered a trace level, and is detectable by PLM, according to the text of the Appendix. IWGACP has to establish a target level, which should be derived from a formal risk assessment. If this target level is 0.1% or higher, there should be no objection in theory to using PLM. The IWGACP has made a good case that TEM should be preferable if the target level is set much lower.	FDA agrees with Reviewer #3 and the IWGACP that the CTFA J4-1 method that uses XRD (and PLM only if XRD is positive) may be inadequate for analysis of asbestos in cosmetic talc where levels are expected to be well below 0.1%. (On page 12 of the White Paper and page 67 of the Appendices, the IWGACP uses the term "trace levels" to refer to asbestos levels that are orders of magnitude below 1%). The reviewer believes that >0.1% asbestos would be detectable using PLM, whereas the CTFA J4-1 method reports a nominal limit of detection of 0.5% for amphibole asbestos. FDA disagrees that a formal risk assessment is required to establish recommendations on asbestos testing methods, or a target level.

CHARGE QUESTION 2. Do you agree that the CTFA J4-1 method is inadequate for testing for asbestos in talc intended for use in cosmetics, where asbestos may be present at trace levels?		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #4	The limitations of X-ray Diffraction are well understood within the asbestos testing community. The IWGACP appropriately described these limitations and, in my opinion, demonstrated CTFA J4-1 not suitable to determine lower concentrations of asbestos in cosmetic talc because of XRD's limitations but also because of an ineffective utilization of PLM.	FDA agrees with Reviewer #4 and the IWGACP that the CTFA J4-1 method is not suitable for analysis of trace levels of asbestos in cosmetic talc due to the recognized limitations associated with XRD and the ineffective utilization of PLM in the J4-1 protocol.
Reviewer #5	Yes, surely yes.	FDA agrees with Reviewer #5 and the IWGACP that the CTFA J4-1 method is inadequate for analysis of trace levels of asbestos in cosmetic talc.

CHARGE QUESTION 3. Do you agree that a negative finding for amphibole and chrysotile by PLM should not be considered conclusive as a negative finding for asbestos in a cosmetic product?		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #3	The IWGACP provided information on the performance characteristics of PLM that strongly suggest that false negatives may occur. However, in quantitative support of this information IWGACP reports on 52 analyses of cosmetic products where 9 samples included identification of chrysotile and/or tremolite asbestos by TEM, but where PLM did not identify the presence of asbestos, and these analyses were performed at one laboratory (AMA). The experience of the AIMS and LACS programs clearly shows the possibility of false positive determinations by TEM (in addition to the possibility that there may have been additional samples with false negatives by TEM). It would have been better if samples from the products analyzed at AMA had been shared with additional laboratories for confirmation of these results.	Reviewer #3 focuses on the potential for false positive results by TEM, which is appreciated, but does not address the IWGACP scientific opinion that when chrysotile or amphibole is not detected by PLM it cannot be concluded that a cosmetic product sample is negative. This reviewer suggests sharing of AMA samples of cosmetics which tested positive by TEM (and negative by PLM) to better support this IWGACP conclusion. The AMA testing was commissioned by the FDA, and such an exercise was not part of the scope of the IWGACP, the White Paper, or the peer review.
Reviewer #4	I believe the IWGACP did provide adequate information to support its opinion that a negative finding by PLM should not be considered conclusive. PLM's limitations are known and the Working Group's opinion is consistent with best practices and methodological requirements for materials with low asbestos content, smaller	FDA agrees with Reviewer #4 and the IWGACP scientific opinion that when chrysotile or amphibole are not detected by PLM it cannot be concluded that a cosmetic product sample is negative.

CHARGE QUESTION 3. Do you agree that a negative finding for amphibole and chrysotile by PLM should not be considered conclusive as a negative finding for asbestos in a cosmetic product?		
REVIEWER	**COMMENT**	**RESPONSE**
	asbestos structures, or problematic matrices such as window glazing or caulking, suspended ceiling tiles, and non-friable organically bound building materials.	
Reviewer #5	Not completely: an example of the testing the same sample by PLM and by TEM would be conclusive. Anyway, as detailed later, in my opinion PLM is not a useful method for the target.	Reviewer #5 agrees with the IWGACP scientific opinion that when chrysotile or amphibole are not detected by PLM it cannot be concluded that a cosmetic product sample is negative, suggesting that an example comparing testing of the same sample by PLM and TEM would be conclusive. FDA supports this opinion based on its findings from testing of cosmetics commissioned by FDA which in fact show multiple examples of positive TEM findings in samples for which negative findings were obtained by PLM. For more details, please see page 11 of the White Paper and https://www.fda.gov/media/135911/download.

CHARGE QUESTION 4. Did the IWGACP provide adequate information and/or data to support its opinion that in order to state that a sample does not contain detectable asbestos, TEM must be used because amphibole and chrysotile particles <5 µm (and >0.5 µm) with an AR >3:1 may be below the resolution of PLM to detect and identify?		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #3	IWGACP provided adequate information and data to support its opinion that PLM alone is insufficient to determine whether individual fibrous particles of nanometer widths are present in a sample, due to inadequate visibility. Further, it is difficult to determine diffraction colors and extinction angles in fibers that are very thin, although this is not also noted. Using PLM, it is also difficult to determine the aspect ratios of particles shorter than a few micrometers in length, and this too is not noted. Of greatest relevance to this discussion is Round 2 of LACS, which was talc containing wollastonite (i.e., no asbestos), where 17 (18%) of laboratories incorrectly reported the presence of	FDA agrees with Reviewer #3 and the IWGACP scientific opinion that PLM has limited resolution and thus, TEM must be used. FDA and this reviewer find that the IWGACP provided adequate support for this opinion in the White Paper. The reviewer provides additional insights from experiences conducting testing by several laboratories (i.e., round robin) using PLM, in which there was evidently mischaracterization of minerals. We are not

CHARGE QUESTION 4. Did the IWGACP provide adequate information and/or data to support its opinion that in order to state that a sample does not contain detectable asbestos, TEM must be used because amphibole and chrysotile particles <5 µm (and >0.5 µm) with an AR >3:1 may be below the resolution of PLM to detect and identify?		
REVIEWER	**COMMENT**	**RESPONSE**
	asbestos. One laboratory reported crocidolite and chrysotile, two laboratories reported chrysotile, and one laboratory reported tremolite asbestos. Twelve laboratories reported the presence of anthophyllite asbestos. Unfortunately, at this time in the scheme, analytical finish was not requested or reported. However, the report states "elongate wollastonite "fibres" may have similar refractive indices to tremolite/anthophyllite and may be miss identified if polarised light microscopy is used" suggesting some of the errors were a result of laboratories using PLM. However, it is also possible, according to the report, that fibrous talc particles were miss-identified as anthophyllite asbestos, especially if electron diffraction was not used with TEM. A canvas of the laboratories which reported errors, and which are still in the scheme found that they all use TEM or SEM today, but it is not known what they used at the time.	clear on the relevance of these insights. Perhaps these indicate the reviewer thinks mischaracterization is less likely using TEM. Also, please see response to charge question #3.
Reviewer #4	The IWGACP provided adequate information explaining PLM's physical limitations towards detecting smaller (ex "TEM") structures. Additionally, and as pointed out, there is a difference in observing a structure and being able to properly identify a structure by PLM by its various optical properties. References to Abbe's calculations are particularly useful in demonstrating the limit of detection under ideal circumstances.	FDA agrees with Reviewer #4 and the IWGACP scientific opinion that PLM has limited resolution and thus TEM must be used. FDA and this reviewer find that the IWGACP provided adequate support for this opinion in the White Paper. FDA appreciates the additional commentary from Reviewer #4 related to limits of detection of optical microscopy, a topic discussed in the White Paper.
Reviewer #5	Yes, surely yes.	FDA agrees with Reviewer #5 and the IWGACP scientific opinion that PLM has limited resolution and thus TEM must be used. FDA and this reviewer find that the IWGACP provided adequate support for this opinion in the White Paper.

CHARGE QUESTION 5. Did the IWGACP provide adequate information and/or data to support its opinion that TEM, which can identify minerals via elemental analysis (i.e., EDS) and determine crystal structure (i.e., SAED), exceeds the current capability of SEM to identify minerals, and that TEM should be used in the testing of talc-containing cosmetics to identify asbestos that could be present at trace levels (i.e., orders of magnitude <1%)?		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #3	A considerable drawback of TEM is the inability to examine large numbers of fibers, which are more easily scanned under SEM. A further drawback of TEM is the general inability to see three-dimensional structures that can more easily identify the asbestiform habit. Thus, SEM should not be discounted, especially if, in the future, electron back-scatter analysis becomes more common. It is better to define performance than to be prescriptive of analytical procedures, in order to not stifle innovation.	FDA agrees with Reviewer #3 and the IWGACP scientific opinion that in the realm of mineral identification by electron microscopy, TEM exceeds the current capability of SEM. However, the reviewer offers that SEM should be considered when improvements in obtaining electron diffraction patterns enable it to perform comparably with TEM for mineral identification.
Reviewer #4	The superiority of analysis for asbestos by TEM when compared to that of SEM was adequately explained. SEM analytical capabilities will, undoubtedly, continue to be expanded upon but TEM currently has better resolution and well established analytical criteria with significant supporting data and observations. Additionally, TEM is routinely used in asbestos testing laboratories – making adoption of any method resulting from the Working Group's White Paper more likely. As the Working Group indicated, SEM could be used as a complimentary technique but its inability image electron diffraction patterns present a significant analytical weakness.	FDA agrees with Reviewer #4 and the IWGACP scientific opinion that in the realm of mineral identification by electron microscopy TEM exceeds the current capability of SEM and that this opinion was adequately supported in the White Paper. Reviewer #4 notes that future commercial SEM instrumentation might achieve parity with its TEM counterparts at obtaining diffraction patterns to support mineral identification.
Reviewer #5	Yes, surely yes. However, the IWGACP does not indicate that TEM instrument must have a double-tilt stage holder. This holder allows to obtain the dual zone axis SAED patterns.	FDA agrees with Reviewer #5 and the IWGACP scientific opinion that in the realm of mineral identification by electron microscopy TEM exceeds the current capability of SEM and that this opinion was adequately supported in the White Paper. FDA agrees with this reviewer that the ability to obtain dual zone axis SAED patterns provides added assurance against mischaracterization when certain minerals with similar diffraction patterns are both present. The

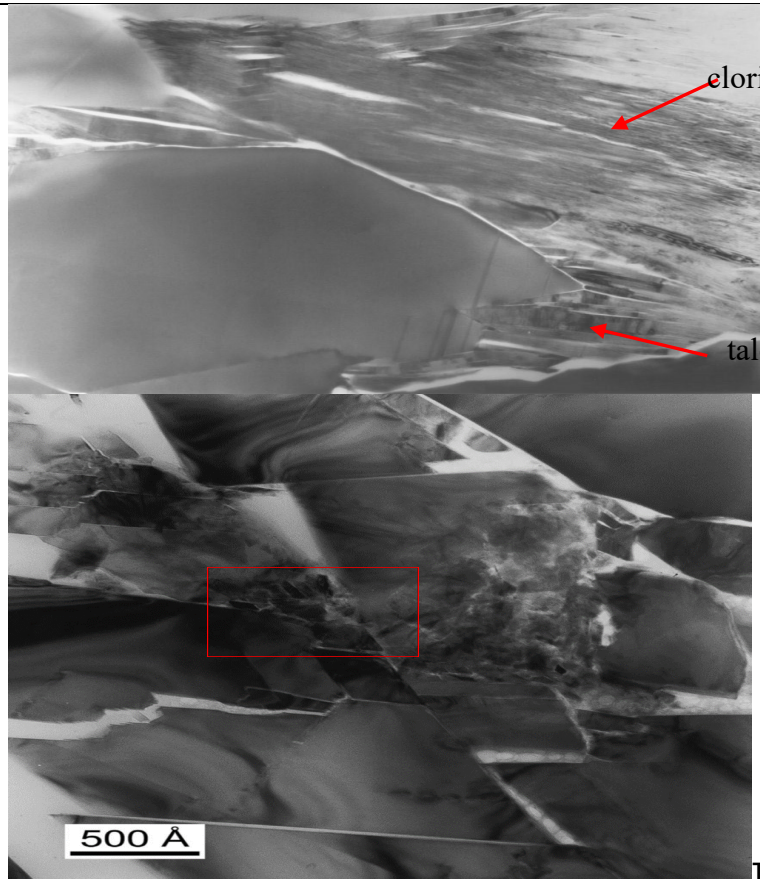
CHARGE QUESTION 5. Did the IWGACP provide adequate information and/or data to support its opinion that TEM, which can identify minerals via elemental analysis (i.e., EDS) and determine crystal structure (i.e., SAED), exceeds the current capability of SEM to identify minerals, and that TEM should be used in the testing of talc-containing cosmetics to identify asbestos that could be present at trace levels (i.e., orders of magnitude <1%)?		
REVIEWER	**COMMENT**	**RESPONSE**
		IWGACP noted this on Table 1 of the White Paper.

CHARGE QUESTION 6. Based on the issue addressed in **Question 1** regarding the lack of a standardized testing method contributing to discrepancies in laboratory findings, do you agree that written protocols for sample preparation methods should be developed, validated, and published for preparation of samples of talc and talc-containing cosmetics for chrysotile and amphibole determination by microscopy, and followed by laboratories?		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #3	There is no doubt that a degree of uncertainty is added to analyses when laboratories are free to determine sample preparation procedures. This is especially true when samples are: a) inhomogeneous, and/or b) contain extraneous potentially interfering substances (subject of the following question). The comminution and homogenization inherent in cosmetic talc product manufacture greatly reduces the concern over sample inhomogeneity. Thus, it may be possible to be more relaxed than stringent in prescribing sample preparation procedures (although it is understood that this would not apply to raw talc ores). Sample preparation procedures can be and should be subject to a performance-based evaluation in the development of a consensus standard.	Reviewer #3 agrees with the IWGACP opinion in that lack of direction on how to prepare talc and cosmetic samples could be a factor in discrepancies in test results. For this reason, this reviewer and FDA agree with the suggestion in the charge question that written procedures for sample preparation should be subjected to a formal performance-based interlaboratory evaluation before being published. FDA appreciates the reviewer comment pointing out sample inhomogeneity might not be as much of a concern due to how commercial talc raw materials and cosmetics are processed. However, certificates of analysis received by FDA representing testing of talc-containing cosmetic products show variable weight loss from gravimetric reduction of multiple aliquots of the same sample. Thus, gravimetric reduction data do not support the supposition that inhomogeneity is not a concern.
Reviewer #4	Yes. The need for a standardized methodology was adequately explained. As was illustrated by the White Paper and Appendices, different technologies have different sensitivities and limitations.	Reviewer #4 agrees that given lack of standardization, there is a need to develop and arrive at consensus on written protocols to prepare and test

CHARGE QUESTION 6. Based on the issue addressed in **Question 1** regarding the lack of a standardized testing method contributing to discrepancies in laboratory findings, do you agree that written protocols for sample preparation methods should be developed, validated, and published for preparation of samples of talc and talc-containing cosmetics for chrysotile and amphibole determination by microscopy, and followed by laboratories?		
REVIEWER	**COMMENT**	**RESPONSE**
	As is continuously demonstrated in methodologies for testing soils for asbestos content, results could cover a wide spectrum of results. Without an accepted, standardized methodology, results could potentially be susceptible to bias. Similarly, comparisons between laboratory-developed, non-standardized methods could result in additional ambiguity. Only a validated and publicly available method can resolve this problem. Following the lead of the environment testing framework, a standardized cosmetic talc methodology would help ensure compatible and comparable results which, due to the commonality of the method would be repeatable between laboratories.	samples of talc and cosmetics, and that this premise was well-supported in the White Paper. The reviewer provides a perspective that indicates asbestos test results for various types of solid samples are subject to differences in methodology, supporting a conclusion that a standardized methodology should help reduce interlaboratory variability. FDA agrees that such an approach would be beneficial going forward.
Reviewer #5	Yes, the IWGACP provide adequate information and data.	Reviewer #5 agrees that given lack of standardization, there is a need to develop and arrive at consensus on written protocols to prepare and test samples of talc and cosmetics, and that this premise was well-supported in the White Paper. FDA agrees that such an approach would be beneficial going forward.

CHARGE QUESTION 7. Did the IWGACP provide adequate information and/or data to support its opinion that gravimetric reduction methods involving ignition and acid digestion should be used to analyze cosmetic products for chrysotile and amphibole particles? Did the IWGACP provide adequate information and/or data to support its opinion that such methods should also be used to analyze talc used to manufacture cosmetic products for chrysotile and amphibole particles, taking into account the information from the IWGACP that talc ores and powder made from such ores often contain accessory minerals that might interfere with the analysis? If you generally agree, are there any exceptions in which this approach might be problematic to the detection of amphibole or chrysotile?		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #3	Ignition is used to remove organic material and was originally used in airborne asbestos fiber measurements to remove smoke particles. However, this practice was discontinued quite early on. Where talc products contain large quantities of organic matter that might obscure fibers and affect EDS or SAED determinations, there is value to be had in removal. Ignition does not affect the determination as it is commonly used in the determination of asbestos in vinyl floor tiles. Acid reduction can remove acid-soluble materials, for example calcite and brucite in talc ores, and is also used in the analysis of asbestos in vinyl floor tiles. However, other potentially interfering minerals in the analysis of talc, for example serpentine and wollastonite are insoluble in dilute acid. Removal of any material then no longer allows the determination of concentration by particle count. In general, the addition of preparations steps to any analysis is discouraged unless necessary as it can lead to a greater uncertainty in the result, which may outweigh their usefulness. It seems that these techniques would be more helpful for PLM than TEM, but as I have not used them I cannot give an opinion as to their value in either analytical finish.	FDA agrees with Reviewer #3 and the IWGACP scientific opinion that materials which may interfere with analysis should be removed using ignition and acid digestion. An exception provided by the reviewer involving calculation of content of chrysotile/amphibole based on total number of mineral particles in the sample seems irrelevant if quantitation can be expressed on the basis of total mass of sample, as was recommended in the IWGACP White Paper.
Reviewer #4	As someone who regularly utilizes gravimetric reduction of all bulk building material samples, I understand and agree with the IWGACP's recommendation. I also find they explained why gravimetric reduction is a critical step in the preparation of a sample. Being a Geologist and having familiarity with the formation of talc and associated minerals, as well as being involved in the testing for asbestos, I fully appreciate the potential for incorrect identification of a mineral. To that end, the inclusion of heavy liquid separation is beneficial addition. Having mostly worked with bulk building materials or surrogates, I would suggest there are few instances in which I would anticipate gravimetric being a hindrance to testing cosmetic talc or related products. Instances which come to mind are those in which concentration of resistant interfering particulates such as titanium dioxide. Assuming the testing is being performed on a raw (milled, etc. before having been incorporated into a final product) material. I don't foresee this situation being of as	FDA agrees with Reviewer #4 and the IWGACP scientific opinion that minerals and organic matter that may interfere with analysis or contribute to causing mineral misidentification should and can be removed using ignition and acid digestion. The reviewer indicates exceptions might be rare (e.g., titanium dioxide). Additional comments provided by this reviewer align with other IWGACP

CHARGE QUESTION 7. Did the IWGACP provide adequate information and/or data to support its opinion that gravimetric reduction methods involving ignition and acid digestion should be used to analyze cosmetic products for chrysotile and amphibole particles? Did the IWGACP provide adequate information and/or data to support its opinion that such methods should also be used to analyze talc used to manufacture cosmetic products for chrysotile and amphibole particles, taking into account the information from the IWGACP that talc ores and powder made from such ores often contain accessory minerals that might interfere with the analysis? If you generally agree, are there any exceptions in which this approach might be problematic to the detection of amphibole or chrysotile?		
REVIEWER	**COMMENT**	**RESPONSE**
	much concern. Mineral misidentification could be a problem absent adequate training but then, I believe, the usage of the EMP morphological criteria would ensure incorrectly identified amphiboles were still counted. However, it would be reasonable to expect any resulting method to be adapted, whether intended or not, by the asbestos testing industry for the analysis of finished, consumer products other than cosmetics which contain talc. In this case, there may be instances of interference concentration which may interfere with PLM analysis. Proper slide preparation should mitigate these problems. Finally, the close proximity of the densities of talc and chrysotile will prove to be a challenge.	scientific opinions stated in the White Paper.
Reviewer #5	Yes, the IWGACP provide adequate information and data regarding samples of cosmetics. I agree only in part. Indeed, the first part of the sample preparation should be different if the sample is a cosmetic product or talc not yet used to manufacture cosmetic products (i.e., raw material). In the first case in fact the talc is mixed with many other substances some of them are organics and the ignition is useful. Therefore, the IWGACP provide adequate information and data for the cosmetic samples, but not enough for the talc not yet used for cosmetic preparation. There is also the problem of some mineral that can be present in the same sample (as an example chlorite due to solid state transformation of tremolite asbestos: see both published (Gunter et al., 2007) and unpublished photo (Belluso, unpublished), the latter being a magnification of the first one)	FDA agrees with Reviewer #5 that the IWGACP provided adequate information to support gravimetric reduction for cosmetic samples. FDA agrees with the observation by the reviewer that raw material talc should not contain appreciable organic impurities that would interfere with analysis. Thus, FDA does not consider ignition to be beneficial when preparing a sample of raw material talc for microscopy analysis. This reviewer provides additional insight into amphibole and serpentine minerals that have been observed in certain talc ores for which mineral identification may benefit from use of high resolution (HR) TEM.

CHARGE QUESTION 7. Did the IWGACP provide adequate information and/or data to support its opinion that gravimetric reduction methods involving ignition and acid digestion should be used to analyze cosmetic products for chrysotile and amphibole particles? Did the IWGACP provide adequate information and/or data to support its opinion that such methods should also be used to analyze talc used to manufacture cosmetic products for chrysotile and amphibole particles, taking into account the information from the IWGACP that talc ores and powder made from such ores often contain accessory minerals that might interfere with the analysis? If you generally agree, are there any exceptions in which this approach might be problematic to the detection of amphibole or chrysotile?		
REVIEWER	**COMMENT**	**RESPONSE**
	 **TEM image of tremolite asbestos fibres as seen along the [001] fibre axes. The thin and long fibres are longitudinally aggregated in columnar prisms. (modified from Gunter et al., 2007)**	

CHARGE QUESTION 7. Did the IWGACP provide adequate information and/or data to support its opinion that gravimetric reduction methods involving ignition and acid digestion should be used to analyze cosmetic products for chrysotile and amphibole particles? Did the IWGACP provide adequate information and/or data to support its opinion that such methods should also be used to analyze talc used to manufacture cosmetic products for chrysotile and amphibole particles, taking into account the information from the IWGACP that talc ores and powder made from such ores often contain accessory minerals that might interfere with the analysis? If you generally agree, are there any exceptions in which this approach might be problematic to the detection of amphibole or chrysotile?		
REVIEWER	**COMMENT**	**RESPONSE**
	Magnification of the inset of the above image, i.e. Figure 15 Yes, the problem may come from the presence of other mineral phases mixed/intergrown with talc. An example is chlorite, as detailed before, and another is the possible presence of the asbestiform antigorite and/or asbestiform polygonal serpentine. Both have been recognized for a few years (e.g.: Fitz Gerald et al., 2010; Belluso et al., 2017; Belluso et al., 2019); they are not asbestos classified,	

CHARGE QUESTION 7. Did the IWGACP provide adequate information and/or data to support its opinion that gravimetric reduction methods involving ignition and acid digestion should be used to analyze cosmetic products for chrysotile and amphibole particles? Did the IWGACP provide adequate information and/or data to support its opinion that such methods should also be used to analyze talc used to manufacture cosmetic products for chrysotile and amphibole particles, taking into account the information from the IWGACP that talc ores and powder made from such ores often contain accessory minerals that might interfere with the analysis? If you generally agree, are there any exceptions in which this approach might be problematic to the detection of amphibole or chrysotile?		
REVIEWER	**COMMENT**	**RESPONSE**
	they may be abundant in some cases, and they are confused with chrysotile if they are not examined by TEM-EDS+SAED. In the Figure, the main phases is asbestos tremolite, but other samples can contain mainly talc with amphibole asbestos and phyllosilicates as subordinate phases. Depending of the amount of these phases, the SAED technique may be not enough to detect them and it needs examine the sample by using the TEM high resolution images (i.e. HRTEM), as in the image above. It is important to underline that antigorite may be present in talc containing rocks (e.g. Gunter et al., 2018; Rouméjon et al., 2019).	

CHARGE QUESTION 8. In your opinion, is there a particular method (e.g., HLS) that shows promise and should be further developed, validated, and published as a preferred method for isolating amphibole and chrysotile particles from talc and talc-containing cosmetics?		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #3	I am aware of various sedimentation, elutriation and heavy liquid separation techniques, but I have not used them in analysis of talc. The IWGACP White Paper provides evidence that they generally are not optimal for this particular separation as documented. The one technique I have personal experience of is the Fluidized Bed Asbestos Segregator (FBAS), which was designed to release and collect respirable asbestos particles from soil. However, as noted, soil is very different from milled talc in that the particles are generally larger and less regular. I am not aware that it has been used for the purpose of separating asbestos talc and would not know if it could be successful. However, if it were successful, it could provide information regarding inhalation risk. Unfortunately, it is only commercially available in one laboratory at this time. Otherwise, I support the position that further research on techniques for concentration would be valuable, assuming that it is necessary to reach target concentration levels.	FDA appreciates the comment from Reviewer #3 pertaining to further research on methods of separation of asbestos from talc. FDA agrees that FBAS could be useful to separate asbestos from talc. However, the efficacy of this approach for sample preparation for the detection and measurement of the amount of asbestos in talc has yet to be demonstrated.

CHARGE QUESTION 8. In your opinion, is there a particular method (e.g., HLS) that shows promise and should be further developed, validated, and published as a preferred method for isolating amphibole and chrysotile particles from talc and talc-containing cosmetics?		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #4	In my experience, the combination of gravimetric reduction and PLM analysis followed by TEM analysis is the best for the determination of asbestos content in building materials. I believe this methodology would be equally effective in the analysis of cosmetic talc. Chrysotile, however, does present a challenge because its density prevents easy (but not impossible with careful calibration) separation from talc with heavy liquids. Accurate calibration of a heavy liquid like lithium metatungstate should make this separation possible but doing so may be impracticable. Preparation may require a 2-step process post ashing and acid treatment. Perhaps, there may be an initial heavy liquid, sedimentation (like that used by Dr. Webber and referenced by the Working Group), or elutriation step to concentrate the chrysotile content and then a second heavy liquid separation to concentrate the amphibole component.	FDA appreciates the comment from Reviewer #4. This reviewer expects gravimetric reduction methods involving ignition and acid digestion would be as effective for cosmetics as for sample preparation of bulk materials. The reviewer thinks heavy liquid separation (HLS) might be useful albeit only for amphibole minerals; thus, Reviewer #4 suggests HLS can perhaps be investigated as an adjunct to gravimetric reduction or elutriation.

CHARGE QUESTION 8. In your opinion, is there a particular method (e.g., HLS) that shows promise and should be further developed, validated, and published as a preferred method for isolating amphibole and chrysotile particles from talc and talc-containing cosmetics?		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #5	Yes, according to me there is another method for sample preparation that shows promise and should be further developed, validated, and published as a preferred method for isolating amphibole and chrysotile particles from talc and talc-containing cosmetics. It is the "fluidized bed asbestos segregator preparation method" described by Januch et al. (2013) and used for example by Berry et al. (2919). This kind of preparation is showed in the IWGACP-WhitePaperTechnicalAppendices-December2021 FINAL (p. 103 to 106). The conclusion IWGACP is the "there have been no published studies investigating the use of the FBAS method for determining the asbestos content in talc. Talc presents some unique problems that are not present in soils, such as, (a) the similarity of density (g/cm3) for talc and some asbestos amphibole minerals, and (b) the fine particle size of cosmetic talc." Obviously, this method must be tested for cosmetics and for talc (as a raw material) before proposing it as an official method, but it looks very promising. As for the claim that the density of talc and some asbestos amphibole minerals is similar, this is not exactly true and contradicted by the data shown in Table J-1 (p 110-111) and in Figure J-3 (p. 111).	FDA appreciates the comment from Reviewer #5. This reviewer cites FBAS as a possible method and seems to agree with the IWGACP suggestion in the White Paper that FBAS would need to be subjected to laboratory research before it can be published as a method to prepare samples of talc or cosmetics for analysis.

CHARGE QUESTION 9. Do you agree that classifying amphibole mineral particles into asbestiform and non-asbestiform types using TEM images is often difficult (and the classification is inconsistently applied)?		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #3	Any amphibole particle that is thinner than 0.5 μm with an aspect ratio > 10:1 is more than likely asbestiform. The difficulties arise when particles with this aspect ratio are thicker than 0.5 μm, as they could be cleavage fragments or asbestiform bundles, and when the aspect ratio is < 10:1. The best way to determine whether the growth habit of a bundle which does not exhibit curvature or split ends is to observe nano-fibrillar bundling (individual fibrils < 100 nm diameter), best seen under SEM or high-resolution TEM. However, most particles can be classified as either asbestos or non-asbestiform with little difficulty. Issues only arise with a small sub-set of particles that are arguable, and the problem becomes less significant the more particles are observed. Setting a minimum limit on the number of particles that	FDA appreciates the comment from Reviewer #3 indicating some degree of agreement with the premise and providing insight into difficulties in classification applicable to what peer reviewer 3 refers to as "a subset of ambiguous particles". Thus, this reviewer offers a suggestion that SEM and high-resolution TEM are helpful to resolve certain ambiguous particles.

CHARGE QUESTION 9. Do you agree that classifying amphibole mineral particles into asbestiform and non-asbestiform types using TEM images is often difficult (and the classification is inconsistently applied)?		
REVIEWER	**COMMENT**	**RESPONSE**
	must be observed, which is necessary in order to have an accurate count to define a quantitative determination of content, will minimize the issue substantially. However, the intention to count all particles > 0.5 μm long is only logical if variation in length of a particle is considered to play no part in the health outcome. That implies that the disease-causing qualities are chemical, and a result of the chemistry of elements at the boundary of the particle. Cleavage fragments show much the same faces as whole crystals, including asbestiform crystals, since cleavage is along the same planes within the crystal as those that characterize the growth faces. Therefore, if chemistry results in an adverse outcome, there is likely to be the same risk from either particle. In any case, any asbestos particle which has been reduced in length by any comminution process has likely broken across the preferred basal cleavage plane, and thus practically all asbestos fibers are in some respect "cleavage fragments".	FDA agrees that SEM and high-resolution TEM would perhaps be able to assist in determining the habit of growth for certain particles not readily differentiated by TEM. For comments related to health outcome, please see peer reviewer comments and FDA responses on the health-related charge questions #13-16.
Reviewer #4	My experience in testing for asbestos is consistent with the Working Group's observation regarding morphology being inconsistently applied to either validate or invalidate the asbestiform growth habit of a mineral particle. Having read a significant number of samples, many of which I prepared from known asbestos sources, I have observed structure which may or may not be considered asbestos depending upon the morphological criteria used. The IWGACP did adequately support their position and support the reporting of EMP structures. The examples provided did support their conclusion and illustrate the potential for subjective morphological interpretation of structure images.	FDA agrees with Reviewer #4 and the IWGACP that for certain particles, the asbestiform habit is difficult to confirm or rule out viewing particle morphology by TEM and that descriptions in standards for "asbestiform" are not enabling objective determinations of amphibole habit of growth by analysts.
Reviewer #5	I do not agree with this. According to me the information and data provided are not adequate. TEM image are very useful to discriminate between "asbestiform" and "not asbestiform" if the definition of both terms have been previously detailed.	FDA appreciates the comment from Reviewer #5. This reviewer indicates that habit of growth of amphibole particles can be differentiated, given that morphology of "asbestiform" is provided to the analyst at an adequate level of detail in the method. FDA disagrees with

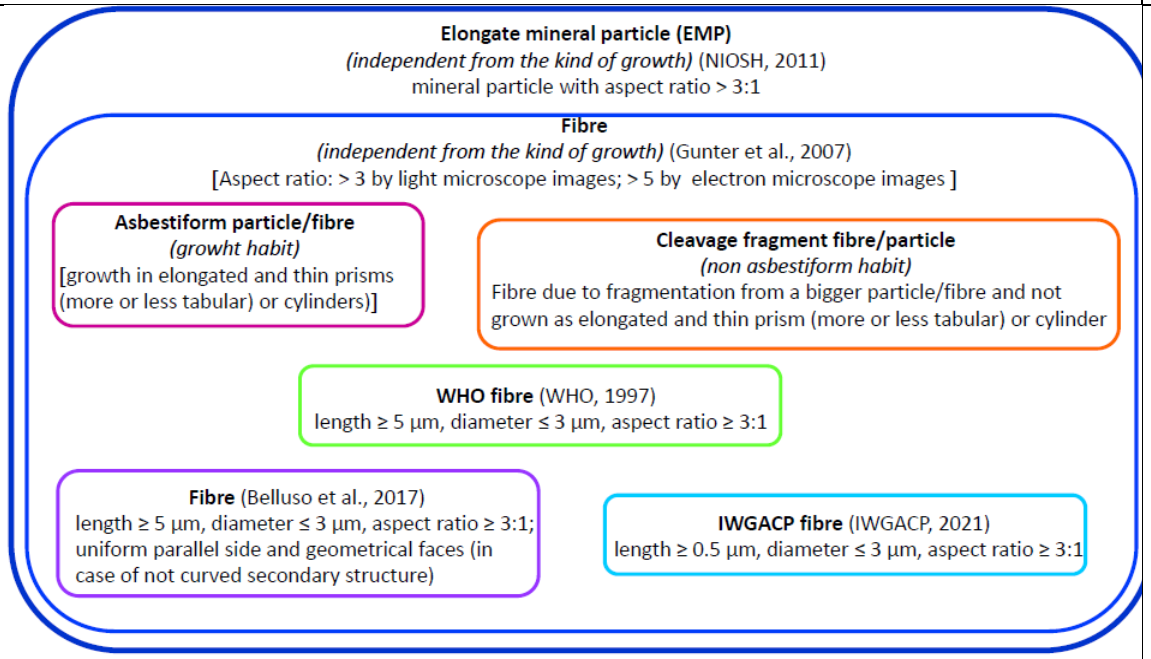
CHARGE QUESTION 9. Do you agree that classifying amphibole mineral particles into asbestiform and non-asbestiform types using TEM images is often difficult (and the classification is inconsistently applied)?		
REVIEWER	**COMMENT**	**RESPONSE**
		Reviewer #5 and finds that the habit of growth is not always readily determined using TEM images due to the difficulty discriminating between asbestos fibers and other elongate non-asbestiform particles with similar morphology.
Reviewer #5	First of all, the term "structure" used in the Fig. C.1 of the ISO 10312 (2019) and Fig. F-5 of the IWGACP-WhitePaperTechnicalAppendices-December2021 is not adequate, in fact the pictures refer to morphology of fibrils, fibrils bundles, fibers in general, and aggregate (more or less compact) of fibrils, of fibers, and fibrils/fibers and particles. The IWGACP "advises careful use of the term "fiber" because it is defined as a type of asbestos structure" (p. 19 of the IWGACP-WHITEPAPER-December2021 FINAL) but again the use of the term "structure" is not adequate: the term "fiber" must refer to the morphology/habit and not to structure.	FDA appreciates the comment from Reviewer #5. FDA agrees with the IWGACP that fiber is not a precise term to differentiate a particle having the asbestiform habit of growth. The reviewer appears to agree that the term "fiber" can designate either a morphology (size, shape) or a habit of growth. If this comment is related to the classification of asbestiform amphiboles and non-asbestiform types, we are unclear why this reviewer finds the term structure to be "not adequate". The term "structure" defined in ISO 10312 (2019) and similarly in the USEPA AHERA interim TEM method (40 CFR part 763) appears to be an adequate umbrella term for describing pertinent particles detected.

CHARGE QUESTION 9. Do you agree that classifying amphibole mineral particles into asbestiform and non-asbestiform types using TEM images is often difficult (and the classification is inconsistently applied)?		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #5	Give that, another problem is that the IWGACP provides, as second opinion and advice, to "Tabulate, at minimum, all amphibole and chrysotile particles (see 1a, 1b, 1c, and 1d) having a length ≥ 0.5 µm (500 nm) and an AR ≥ 3:1 by indicating respective length, width, and mineral type" (p. 19 and others in IWGACP-WHITEPAPER-December2021 FINAL), but if analysts use only these two-dimensional criteria, then they consider also a particle with, as an example, a length of 40 µm and a width of 10 µm as AR is 4 and therefore respects AR ≥ 3: 1, but a particle with this size is too large to reach the pulmonary alveoli.	FDA appreciates the comment from Reviewer #5 and acknowledges that these criteria place no upper bound (length, AR) on reporting particles too large to be "respirable". The IWGACP expert opinions related to dimensions, which are the focus of this comment by this reviewer, are aimed to promote comprehensive and uncensored reporting by laboratories. Please see reviewer comments and FDA responses on the health-related charge questions #13-16 regarding the criteria for dimensions related to reporting.

CHARGE QUESTION 10. Do you agree that laboratories should avoid using the term 'fiber' to describe amphibole particles and talc unless it is certain that such particles are asbestiform?		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #3	The term fiber has a purely geometric definition; one axis being longer than the other two. As a descriptor without quantitative parameters, it is purely qualitative and can be ascribed to any particle having a primary elongate axis, in the same way as "acicular" or "prismatic". While asbestiform is a fibrous habit, asbestiform particles are not the only fibers. Qualitative terms, including fiber, are best not used to avoid confusion of definition.	FDA agrees with Reviewer #3, and the IWGACP scientific opinion that the term "fiber" as used in analytical methodology to instruct laboratories to classify certain types of "structures" detected may cause confusion and is possibly a source of incorrect classification of the habit of growth of mineral particles.

CHARGE QUESTION 10. Do you agree that laboratories should avoid using the term 'fiber' to describe amphibole particles and talc unless it is certain that such particles are asbestiform?		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #4	The Group's explanation why the use of the term "fiber" should be avoided was supported and appropriate. However, the use of the term is thoroughly embedded within the environmental testing community – supported, in part, through the cross-pollination between light microscopy and electron microscopy terminologies. Overcoming the use of "fiber" will be challenging as it will almost certainly continue to be used colloquially and existing laboratories interested in engaging in any future potential talc testing will probably adapt their current benchsheets, reports, and LIMS programs. I believe it is likely the term would incorrectly be reported in future cosmetic talc results. Adoption and requirement of "EMP" and the related criteria should help facilitate a move away from the term "fiber."	FDA agrees with Reviewer #4, and the IWGACP scientific opinion to avoid using the term "fiber" as a particle descriptor for reasons provided in the White Paper. The reviewer notes that "fiber" is embedded in the environmental testing community. Thus, the reviewer suggests adoption of the term "EMP" as an umbrella term rather than "fiber".
Reviewer #5	According to me, IWGACP does not provide adequate information and/or data on this issue. If the term "asbestiform" is considered related to growth (as stated in ANSES 2015 and instead not very clear in IWGACP-WHITEPAPER-December2021 FINAL, see p. 24 of the Glossary) and given that IWGACP indicates do not distinguish between cleavage fragments and native crystals, the use of term "fiber" is adequate.	FDA appreciates the comment from Reviewer #5. This peer reviewer regards the term "fiber" to be adequate as a descriptor provided there is no intent to make a distinction between asbestiform and non-asbestiform particles. This reviewer suggests that the IWGACP did not provide adequate supporting information against using "fiber" as an umbrella term for reporting particles. FDA disagrees with Reviewer #5 and finds the term "fiber" is often used to describe any talc particle that appears to be elongate by virtue of the image obtained by TEM. FDA cautions that the term "fiber" is subjective, based on the appearance of the particle, and does not necessarily

CHARGE QUESTION 10. Do you agree that laboratories should avoid using the term 'fiber' to describe amphibole particles and talc unless it is certain that such particles are asbestiform?		
REVIEWER	**COMMENT**	**RESPONSE**
		indicate a particle is derived from a fibrous mineral or is asbestiform.
Reviewer #5	Why does the IWGACP not plan to adopt the definition of WHO fibres (1997) i.e. length ≥ 5 µm, diameter ≤ 3 µm, aspect ratio ≥ 3:1 integrated by the recent evaluation (e.g. Stayner et al., 2008) that even fibres shorter than 5 µm may be harmful, lowering the lower limit to a length ≥ 0.5 µm? The opinion of IWGACP is clear, but the information and the comments are not sufficiently consistent and sometimes non clearly explained. As an example, the report of ANSES (2015) clearly state definitions and meanings of fiber, elongated mineral fibers, asbestiform and non-asbestiform fibres, and provides indication for using each term. According to me, given that it needs to include also the fibres shorter than 5 µm and at least 0.5 µm long, it is very useful that IWGACP clearly defines any terms with the correlated characteristics and dimensions and also introduce a sketch map showing the different terms, their definitions with their partial overlapping. An example of this sketch map is pasted below.	FDA appreciates this reviewer's viewpoints on classification of mineral particles based on morphology as depicted in the figure provided by the reviewer. The IWGACP considered the WHO fiber definition (i.e., length ≥ 5 µm, diameter ≤ 3 µm aspect ratio ≥ 3:1), which places an upper limit on fiber diameter to exclude the reporting of particles that might not be respirable, but instead opted to recommend comprehensive reporting of all chrysotile and amphibole mineral particles. Also, please see reviewer comments and FDA responses on the health-related charge questions #13-16-regarding the criteria for dimensions related to reporting.

CHARGE QUESTION 10. Do you agree that laboratories should avoid using the term 'fiber' to describe amphibole particles and talc unless it is certain that such particles are asbestiform?		
REVIEWER	**COMMENT**	**RESPONSE**
		

CHARGE QUESTION 11. Do you agree that Annexes titled "Structure Counting Criteria" in ISO 10312:2019 and ISO 13794:2019 are useful to report morphology of particles of chrysotile and amphibole, including for identifying amphibole particles when it is indeterminate as to whether such particles grew in the asbestiform habit?		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #3	I agree, but see my response to Question 9. If a particle length of 0.5 μm is the criterion for counting, then it is illogical to exclude non-asbestiform particles from the count.	FDA agrees with Reviewer #3 and the IWGACP scientific opinion regarding the utility of the Annexes for reporting (but not necessarily for counting). In particular, FDA finds the Annexes helpful as they pertain to reporting particle morphology including classifying the types of structures detected by TEM.
Reviewer #4	I agree with the IWGACP's opinion on the usage of the ISO criteria to report morphology. The use of these structural terms can communicate a lot about the minerals and matrices and the potential for exposure. Having done this type of analysis on Libby, MT vermiculite-related samples, I have found the analysis to be more time-consuming than a "typical" AHERA or bulk TEM analysis. While this may not be a problem within the academic or governmental setting, it is important to the commercial testing industry and any quality assurance/control assessment program should anticipate bench-level "short cuts" to save time spent in analysis should these criteria be adopted.	FDA agrees with Reviewer #4 and the IWGACP scientific opinion. The reviewer expresses concern that classifying all detected particles based on type of structure can be time-consuming when there is a large number of particles. Thus, FDA agrees with the advice provided by the IWGACP in the White Paper that an adequate number of representative particles should be fully characterized (Scientific Opinion #5).
Reviewer #5	Yes, I agree, but only if the additions and the corrections, as I have detailed above (in the answers to questions 9 and 10) have been made.	FDA appreciates the comment from Reviewer #5. The reviewer appears to generally agree with the utility of the Annexes titled "Structure Counting Criteria" for reporting particle morphology. The charge question frames reporting of morphology of particles within the scope of indeterminate growth habit. FDA thinks that the dimensions of each

CHARGE QUESTION 11. Do you agree that Annexes titled "Structure Counting Criteria" in ISO 10312:2019 and ISO 13794:2019 are useful to report morphology of particles of chrysotile and amphibole, including for identifying amphibole particles when it is indeterminate as to whether such particles grew in the asbestiform habit?		
REVIEWER	**COMMENT**	**RESPONSE**
		particle are useful to characterize and evaluate amphiboles. Refer to FDA's responses to Reviewer #5 comments to charge questions 9 and 10.

CHARGE QUESTION 12. Do you have any other thoughts on how the dilemma of uncertainty as to habit of growth (i.e., asbestiform versus non-asbestiform) might be resolved?		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #3	As noted in my response to question 9, there is no need to expend substantial effort on a single particle of uncertain origin amongst a population of other particles whose structure is clear.	FDA appreciates the review commentary, but feels the effort expended can provide valuable information when there are only a few particles detected.
Reviewer #4	I believe any future method needs to provide the most information possible to make decisions for public health with priority given to health over mineralogical definitions. I have observed conflicts over what, morphologically, constitutes asbestos. I believe the Working Group's proposed morphological boundaries can simplify bench-level analysis. The analyst should not have to consider anything beyond certain, limited criteria and should not be put into the position of having to make questionable interpretations of what they observe or record. By avoiding the potentially subjective determination of asbestiform versus non-asbestiform the analyst can more efficiently concern themselves with recording structures >0.5 µm and >3:1 aspect ratio. Whether or not these structures are more or less significant than other can be determined through later analysis or health research. In asbestos analysis, the analyst is the instrument. Every effort must be taken to avoid primary, bench-level bias and a method which utilizes the proposed morphological requirements achieves this goal. Any opportunity where a potentially harmful structure is not counted must be avoided.	FDA agrees with the reviewer's commentary, and support of comprehensive reporting to minimize subjectivity by the analyst or analytical laboratory.
Reviewer #5	I have answered this question above.	FDA appreciates the reviewer's commentary.

CHARGE QUESTION 13. Do you agree with the IWGACP Scientific Opinion #1 to have laboratories identify/report (document) all detected particles meeting criteria 1a, 1b, 1c, 1d, and 1e in IWGACP Scientific Opinion #2 because they could be potentially harmful if inhaled during cosmetic product use?		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #1	From a health perspective it has been well documented and reflected in the present documents that all types of asbestos-containing materials, and also exposure to winchite and richterite, can cause disease. All fiber types are implicated and data documents that commercial cosmetic talc products can be contaminated with both chrysotile and amphibole. This applies to (a – c). Less clear is any role for mixed particles (d), and there is no known evidence for non-platy morphology (e) causing serious disease. However, given as seen elsewhere in the materials supplied for review, this should be recognized as having the potential to cause disease, since breakdown in the body, Atleast for (d) might yield individual asbestos fibers that could be free in tissue as if they had arrived initially as free fibers. There is less justification for (e) materials. One should consider, however, that those particles could potentially, in large enough quantities, cause non-malignant talcosis, though this has not ever been reported from home talc use. If (e) should not be reported, then overall reporting requirements from laboratories would be made a bit easier.	FDA agrees with Reviewer #1 and the IWGACP scientific opinion.
Reviewer #1	With regard to Opinion #2, my comments above fit nicely in agreement with Opinion #2 to tabulate all 1a – 1d materials. This is well justified and tracks well with strong public health principles of protection.	FDA agrees with Reviewer #1 and the IWGACP scientific opinion.
Reviewer #2	The data selected for presentation does provide information that indicates particles meeting criteria 1a, 1b, 1c, 1d, and 1e could potentially represent a health risk. There is scientific consensus that long fibers definitely contributes to asbestos-related disease. Within epidemiologic studies, exposure to short asbestos fibers especially in 1) high exposure situations and also at 2) lower exposure levels and when associated with a component of long fibers (≥ 5 μm) have been associated with lung cancer. As concluded by Boulanger, et al. 2014, in this very comprehensive review, "the toxicity of SAF (short asbestos fibers) cannot be dismissed".	FDA agrees with Reviewer #2 and the IWGACP scientific opinion.

CHARGE QUESTION 14. Since scientific studies have shown that asbestos is harmful, do you have an opinion about whether chrysotile and asbestiform amphibole particles >0.5 µm in length and aspect ratio >3:1 (i.e., short asbestos fibers) should be reported by laboratories testing talc-containing cosmetic products since they could pose a health concern?		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #1	Absolutely, short fibers of the six regulated asbestos fibers should be reported. The bulk of scientific evidence about fiber size and the ability of even smaller fibers being able to cause disease well justifies this. This comes from the early work on fiber size by Stanton and colleagues in animals where he documents even fibers less than 5 microns in his system cause disease, as well as the human data that followed. The work of Dodson and Suzuki in the United States, Bignon in France, and Kohyama in Japan all clearly document the finding of predominately short chrysotile fibers, less than 5 microns, in the majority of cases of mesotheliomas are found in the pleura. Shorter fibers should definitely be counted and reported given that they represent a significant potential health risk.	FDA agrees with Reviewer #1 and the IWGACP scientific opinion.
Reviewer #2	The potential toxicity of short fibers including regulated asbestos especially at lower exposure levels and without co-exposure to longer fibers cannot be definitely defined based on limited available data. Thus, reporting the presence of regulated asbestos fibers >0.5 µm in length and aspect ratios >3:1 both from a qualitative and quantitative perspective will provide data to better determine the propensity for short fibers to cause and/or contribute to adverse health effects.	FDA agrees with Reviewer #2 and the IWGACP scientific opinion.

CHARGE QUESTION 15. Do you agree with the IWGACP Scientific Opinion #2 that chrysotile and all amphibole particles with dimensions >0.5 µm (500 nm) and with an aspect ratio (AR) >3:1 should be reported by laboratories testing talc-containing cosmetics because they could pose a health concern?		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #1	In general, this is a correct conclusion. However, while there is excellent documentation for short chrysotile being a causative agent of disease (see response to Question 14), there is less scientific evidence to support all amphiboles beyond the five regulated amphiboles, except for winchite and richterite. There is no question the Libby amphiboles contribute to disease, and there appears to be documentation that Death Valley talc contains these two fibers. However, to date there appears to be no scientific documentation that winchite or richterite have been found in cosmetic talc samples. It could therefore be suggested that since no requirement has been in place to ever report non-regulated amphiboles, it would be reasonable to now put in place such a	FDA agrees with Reviewer #1 and the IWGACP scientific opinion. It should however be noted, as stated on page 8 of the White Paper, in footnote 13 "Some third-party laboratories (not under contract to FDA) have reported finding amphibole minerals richterite and winchite in cosmetics to FDA. These results have not been independently verified."

CHARGE QUESTION 15. Do you agree with the IWGACP Scientific Opinion #2 that chrysotile and all amphibole particles with dimensions >0.5 µm (500 nm) and with an aspect ratio (AR) >3:1 should be reported by laboratories testing talc-containing cosmetics because they could pose a health concern?		
REVIEWER	**COMMENT**	**RESPONSE**
	requirement. If after some reasonable period of time, or after some significant numbers of samples have had such a reporting requirement, none of these fibers are ever found in cosmetic talc, consideration could be given to reduce this reporting requirement. This is predicated upon sufficient widespread testing with good tests.	
Reviewer #2	The various physical and chemical characteristics that are correlated with toxicity for the six regulated asbestos fibers are not unique to these fibers alone. Similar toxicities both in animal and/or human studies have been associated, for example with erionite, man-made silicon carbide fibers and whiskers including extremely short fibers with high aspect ratios as well as winchite and richterite fibers associated with Libby vermiculite. Inclusion of these studies and in particular the association between very low cumulative fiber exposure levels of LAA and pleural toxicity would strengthen the IWGACP positions at exposure levels more equivalent to those associated with use of cosmetic talc with amphibole contamination.	FDA agrees with Reviewer #2 and IWGACP scientific opinion.

CHARGE QUESTION 16. Do you have an opinion about whether amphibole particles formed during processing and milling of talc intended for cosmetics that are not "asbestiform" in habit of growth, could pose a health concern and should be reported?		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #1	Although some of the references seem to be questionable about the scientific veracity given their origin, the overall point about the hazards of asbestos in talc is made. However, one significant citation seems to be missing, the IARC discussion of asbestos-contaminated talc. This should be cited, and clearly makes the point that if there is asbestos found in talc, then material should be treated as if it were asbestos, with all other IARC references about asbestos then being applicable.	FDA appreciates the review commentary. The White Paper and Technical Appendices cite IARC several times, but we acknowledge the discussion in Appendix E could be expanded. FDA agrees that if asbestos is found in talc or talc-containing cosmetics, that the product is a health hazard.
Reviewer #2	The report does support the observation that particles formed during processing and milling can result in the formation of increased number of EMP, particularly under 5 µm in length and therefore pose a potential health risk.	FDA agrees with Reviewer #2. The White Paper and Technical Appendices were finalized in

CHARGE QUESTION 16. Do you have an opinion about whether amphibole particles formed during processing and milling of talc intended for cosmetics that are not "asbestiform" in habit of growth, could pose a health concern and should be reported?		
REVIEWER	**COMMENT**	**RESPONSE**
	References: Lapin CA, Craig DK, Valerio MG, et al. A subchronic inhalation toxicity study in rats exposed to silicon carbide whiskers. *Fundam Appl Toxicol* 16:128-146, 1991. Johnson NF, Hoover MD, Thomassen DG, et al. In vitro activity of silicon carbide whiskers in comparison to other industrial fibers using four cell culture systems. *Am J Ind Med* 21: 807-823, 1992. Scansetti G, Piolatto G, Botta GC. Airborne fibrous and nonfibrous particles in a silicon carbide manufacturing plant. *Ann Occup Hyg*, 35: 145-153, 1992. Dufresne A, Perrault G, Sebastien P, et al. Morphology and surface characteristics of particulates from silicon carbide industries. *Am Ind Hyg Assoc J*, 48: 718-729, 1987. Baris YI, Simonato L, Artvinli M, et al. Epidemiological and environmental evidence of the health effects of exposure to erionite fibres: a four-year study in the Cappadocian region of Turkey. *Int J Cancer*, 39: 10-17, 1987. Rohs AM, Lockey JE, Dunning KK, et al. Low-level fiber-induced radiographic changes caused by Libby vermiculite. *Am J Respir Crit Care Med. Vol 177, pp 630-637, 2008*. Lockey JE, Dunning KK, Hilbert TJ, et al. HRCT/CT and associated spirometric effects of low Libby amphibole asbestos exposure. *JOEM Vol 57(1) Jan. 2015*.	December 2021, when the IWGACP was disbanded, thus FDA is unable to add the references provided by this reviewer to the documents.

CHARGE QUESTION 17. Do you agree that the tabulation of chrysotile and amphibole detected by TEM should include each particle on the TEM grid that meets the criteria for identification, and that length and width should be reported for each such particle?		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #3	Agreed. I have been able to view reports from contract laboratories that also include a rough drawing of the particle and notes regarding the analyst opinion of the nature.	FDA agrees with Reviewer #3 that each chrysotile and amphibole particle should be tabulated, showing its length and width.
Reviewer #4	Yes, the IWGACP did provide enough information and data. Counting all structures on a grid opening is a standard, required practice in the analysis of air and water samples by TEM. The question, however, refers to an entire grid. Counting and reporting/tabulating every structure on every grid could prove untenable at the magnifications appropriate to detect structures ≈0.5 μm in length. As outlined in the White Paper, appropriate stopping rules for grid openings counted or number of structures counted would need to be developed. I support and agree with the conclusion structures should be tabulated and reported by size and type.	FDA agrees with Reviewer #4 that the IWGACP opinion on tabulation by laboratories is adequately supported in the White Paper. In addressing this reviewer's concern that the question implies the entire TEM grid needs to be examined, FDA wishes to confirm that the charge question refers only to examination of the number of grid openings specified in the test method.
Reviewer #5	Yes, I agree with the IWGACP conclusions. The information are adequate. But, as stated above and below, I do not agree with all the criteria indicated for identification.	FDA agrees with Reviewer #5 that each chrysotile and amphibole particle should be tabulated, showing its length and width, and that this opinion is adequately supported in the White Paper. FDA disagrees with this reviewer and prefers that all particles that meet the criteria for identification be reported by laboratories so they can be evaluated based on their dimensions. (Also, see FDA responses to Reviewer #5 comments to charge questions 9, 10 and 11).

CHARGE QUESTION 18. Do you have an opinion or suggestion pertaining to quantification of asbestos and amphibole particles in talc and talc-containing cosmetics?		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #3	The method should require a target number of particles to be examined (which should be much greater than 100) and the limit of detection and uncertainty should be based on this target number. Particles shorter than 5 µm can be included in the calculation of asbestos percentage provided this calculation is not to be used in a quantitative estimation of risk. A second result, without such particles, should be provided for risk estimates, unless a risk profile for particles shorter than 5 µm can be established quantifiably and defended.	FDA appreciates the opinions and insights provided by Reviewer #3 on quantitation, suggesting there might be two different calculations and values, i.e., separate calculations based on particles > 0.5 µm and > 5 µm in length and that more than 100 particles be examined. If quantitation is desired or necessary, FDA agrees it is preferable to have sufficient sample quantity evaluated, especially if populations are to be binned based on length as the reviewer suggests.
Reviewer #4	I agree with the observation that the weight percent of asbestos is not be truly indicative of a potential health risk. The number of structures of concern per mass of a material would be a superior measurement. As Dr. Chatfield and others have adequately demonstrated, the majority of mass is in the larger structures – which may not have as negative health impact should someone become exposed because they can't easily be inhaled or ingested. My early work with Libby vermiculite bears out this observation. The majority of the mass in exfoliated vermiculite ore was in a distinctly non-respirable fraction which was easily picked out with tweezers and a dissection microscope. After having been suspended in water and having an aliquot withdrawn after the vermiculite ore had settle or floated, the amount of respirable fibers observed by TEM was significant. The mass of these respirable structures was negligible relative to the total mass of the original sample. It is my opinion materials like talc should be quantified by number of asbestos structures per mass, not by percent mass.	FDA agrees with Reviewer #4 that quantitation by weight percent (i.e., mass) can be misleading and that number of structures of concern per mass of material would be a better measure.
Reviewer #5	Yes, I suggested (see p. 16, third comment) the use of SEM-EDS and TEM-EDS+SAED in complementarity.	Reviewer #5 did not provide an opinion on quantitation but provided an additional suggestion on microscopy methods with which FDA agrees. SEM can be useful, but only as complementary method to TEM (IWGACP Scientific Opinion 3) due to limitations stated in the White Paper.

CHARGE QUESTION 19. In consideration of potential for variation in particle chemistry and morphology, what is a minimum number of particles for which images, spectra and SAED patterns should be provided in the laboratory report to be representative of the sample? Please provide further commentary related to this topic.		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #3	All images, and all data on every particle examined by spectra and SAED, should be accessible. Reporting only selected data leads to likely biased conclusions. The number of particles that meet the criteria for concern should be given as a percentage of the total number of particles in the fields examined. This total number of particles should be predicated on a target concentration level.	FDA agrees with Reviewer #3 and the IWGACP scientific opinion that all particles should be tabulated and that if all images, spectra and diffraction patterns are not shown in the laboratory report, this data should be accessible in records kept by the laboratory.
Reviewer #4	This is a challenging question to answer because there could, hypothetically, be some variability in the minerals present in an ore body and, as a result, present in cosmetic talc. My predominate experience is with building materials and air samples. In those analytes, homogeneity is easily determined. Additionally, they aren't cosmetics and were never intended to be applied to a person's body. It is my expectation cosmetic talc would be held to a higher standard of homogeneity for that reason and the likelihood of ingestion or inhalation is significantly increased. As such, I would suggest all structures be sketched and a minimum of 30 micrographs with SAED and EDS of the first 10 structures of each mineral type. Additionally, I would recommend every tenth structure after the first 10 of each type to be also be identified by SAED and EDS. SAED and EDS could always be performed as needed by the analyst to confirm a mineral type. Finally, I believe all micrographs should be made available to clients upon request but that a minimum of at least one representative micrograph for each mineral type present be incorporated in a final report.	FDA appreciates Reviewer 4's comments on the unknown potential for variability in accessory mineral content in ores used to produce talc and understandably given this reviewer's experience that this question would be difficult to answer. Reviewer #4 suggests a substantial number of images, i.e., minimum 30 micrographs with ED spectra and SAED patterns of first 10 structures of each mineral type to characterize the pertinent minerals detected, for representative images to be provided in laboratory reports, and for all images obtained to be accessible from laboratory records. FDA agrees that images should be representative and that the laboratory reports show all pertinent variations. FDA also believes repositories of images are

CHARGE QUESTION 19. In consideration of potential for variation in particle chemistry and morphology, what is a minimum number of particles for which images, spectra and SAED patterns should be provided in the laboratory report to be representative of the sample? Please provide further commentary related to this topic.		
REVIEWER	**COMMENT**	**RESPONSE**
		useful to show variations within groups of analogous samples as well as within a single sample.
Reviewer #5	As I detailed at page 18, second comment, 100 particles should not be the maximum number but the correct number to examine to have a good statistics. In several papers (although on other topics) the number of analyzed particle is bigger than 100: as an example, in the paper by Dong et al. (2019) 400 particles were analyzed.	FDA appreciates the Reviewer #5 comment but notes that the comment indicating over 100 particles should be analyzed appears to be more well suited to risk estimates rather than laboratory analysis to determine if chrysotile or amphibole is present, i.e., hazard identification.

CHARGE QUESTION 20. Do you agree with this scientific opinion, and do you have any additional thoughts? Related to: **IWGACP White Paper Scientific Opinion #7.** The IWGACP advised that the content and format of analytical reports should facilitate consistent and comprehensive reporting of particles (as described in IWGACP Scientific Opinions #1 and #2), in conjunction with adequate documentation of findings (see Appendix K).		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #3	It is unlikely that anyone would want to contradict this opinion. I have no additional thoughts.	FDA agrees with Reviewer #3, and the IWGACP Scientific Opinion #7.
Reviewer #4	The Working Group supported Opinion #7. I would also like to suggest that any potential method provide a stock, example benchsheet and report which laboratories could adapt to their LIMS and reporting systems. Having been involved with laboratory assessment, I appreciate the variety of final reports produced by laboratories. Providing example documents would benefit laboratories and facilitate adoption of reporting standards.	FDA agrees with Reviewer #4, and the IWGACP Scientific Opinion #7. Reviewer #4 offers a suggestion intended to help standardize tabulations provided in laboratory reports showing the chrysotile and amphibole particles detected.

CHARGE QUESTION 20. Do you agree with this scientific opinion, and do you have any additional thoughts? Related to: **IWGACP White Paper Scientific Opinion #7.** The IWGACP advised that the content and format of analytical reports should facilitate consistent and comprehensive reporting of particles (as described in IWGACP Scientific Opinions #1 and #2), in conjunction with adequate documentation of findings (see Appendix K).		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #5	As stated above and below, my opinion is in part different from that of IWGACP about the number of particle to investigate and about and about the criteria indicated for identification.	Reviewer #5 did not offer an opinion on the format and content of laboratory reports.

CHARGE QUESTION 21. Given these difficulties, do you have any thoughts that could be helpful toward future development of reference standards for microscopy analysis of talc and cosmetics?		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #3	Reference asbestos materials are available for the production of proficiency test samples. NIOSH collected several materials, which are available in a homogenized standard format from Research Triangle Institute (RTI). This includes tremolite asbestos from Lone Pine, CA and Cemetery Ridge, AZ; anthophyllite asbestos from Palm Desert, CA, and actinolite asbestos from Juneau, AK (this last may not be available as yet, but NIOSH has the raw material). "Libby Amphibole" is available from USGS. UICC chrysotile can be made available from NIOH in South Africa. The LACS and AIMS samples likely use the reference materials of the Health and Safety Laboratory of the UK Health & Safety Executive. The HSE/HSL operates the programs and distributes the samples, although the preparation of the samples may be under contract with the Laboratory of the Government Chemist. Both the HSE/HSL and LGC (who has an office in the USA) have commercial capabilities and could be approached regarding the preparation of reference standards or proficiency testing samples for the analysis of talc and talc-containing products. RTI manufactures proficiency test samples and has a reference repository of asbestos materials; they also could be approached. At least, and until properly appropriate proficiency test materials are available, laboratories should participate in the AIMS and LACS schemes.	Reviewer #3 provides a wealth of information on asbestos reference materials that might be useful for spiking into talc or cosmetics for establishing analyst proficiency. In addition, this reviewer offers suggestions for how such standards might be created and qualified and repositories might be managed (stored, distributed) by independent parties. Reviewer #3 suggests participation in existing proficiency schema until qualified standards of asbestos in talc and cosmetics become available. FDA agrees with the concept expressed for reference standard development and utilization and appreciates this information amid the foreseeable challenges.
Reviewer #4	The difficulty of doing something does not imply it ought not be done. The situation related to the lack of NIST SRMs is well known in the asbestos testing	FDA agrees with Reviewer #4's commentary on meeting the

CHARGE QUESTION 21. Given these difficulties, do you have any thoughts that could be helpful toward future development of reference standards for microscopy analysis of talc and cosmetics?		
REVIEWER	**COMMENT**	**RESPONSE**
	industry and their related assessing bodies. The absence is one of the most common complaints/frustrations received by my program and the current draft TNI standard for asbestos analysis has been edited to accommodate, as best possible, standards other than SRMs. Having these materials is critically important but, based upon the current situation, I fear NIST is unable to improve the situation by providing the required SRMs. Assuming the production of SRMs were to become a reality, I would suggest that either ore bodies be adequately typified for their known asbestos content/contamination or synthetic (spiked) materials be produced with a means where the number of asbestos structures per volume of talc can be controlled.	foreseeable challenges in developing reference standards related to talc and cosmetics and how these reference standards might be useful should these challenges be met. FDA agrees that in the ideal situation a reference standard should be derived from the ore body used to manufacture cosmetic talc and should contain a known amount of asbestos.
Reviewer #5	Yes. I think it may be possible to obtain reference standards for this use by the mixing, in suitable quantity, a pure talc (i.e. without natural fibrous contaminants) obtained by synthesis with a fully characterize asbestos that can be natural contaminants of talc. The talc synthesis is now fine-tuned: see for example the review by Claverie et al. (2017). The suitable asbestos may be characterized by TEM-EDS+SAED and SEM-EDS investigation.	FDA appreciates the Reviewer #5's suggestion to consider preparing reference standards prepared by spiking asbestos into a pure talc matrix obtained synthetically as a means to help overcome foreseeable challenges. FDA agrees that the use of a synthetic talc substance which is analogous to pure naturally sourced talc could be a proper starting point for creating reference standards spiked with well-characterized minerals of interest that typify those found associated with talc ores.

CHARGE QUESTION 22. Do you have any comments or thoughts on how to apply reference standards towards ensuring laboratory proficiency given concerns that amphibole and/or chrysotile particles are not homogenously distributed in a sample of talc or a cosmetic product?		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #3	Reference standards for use in laboratory proficiency must, of necessity, be homogenous in order to ensure that proficiency is properly and consistently determined. Inhomogeneous samples must also be homogenized before analysis. This should use the least destructive techniques available in order not to reduce the size and crystallinity of particles. It has been demonstrated that some milling techniques simply carry inhomogeneities through to the final product. Sedimentation concentration techniques will act towards homogenizing the sample before analysis.	FDA agrees with Reviewer #3 that inhomogeneity of the analyte is a factor in testing samples of talc and cosmetics, and a foreseeable challenge in creating and utilizing reference materials comprised of known quantities of chrysotile and amphibole minerals in talc and cosmetics. FDA thus appreciates the insightful commentary from this reviewer providing suggestions for how to prepare homogenous samples for interlaboratory proficiency assessments.
Reviewer #4	I do not believe simple possession of a reference sample, even with experienced laboratories, would be adequate to demonstrate or develop proficiency. Proficiency testing materials would need to be regularly produced and sent to participating laboratories for analysis and scoring. Settling or uneven distributions within individual samples can be mitigated by utilizing spiked samples or ore-based materials which have been thoroughly homogenized and requiring participant laboratories to cone and quarter or similar. When a sample arrives at a laboratory, one of their initial concerns is the homogenization of the sample if it is not already homogenous. A proficiency test sample must, likewise, be homogenized from an adequately large volume of source material before it is typified for accessory mineral content. Spikes could then be utilized and contaminate minerals taken into consideration prior to distribution.	FDA appreciates insightful commentary from Reviewer #4 acknowledging concerns about inhomogeneity in reference standards and providing suggestions for how to prepare homogenous samples for interlaboratory proficiency assessments.
Reviewer #5	I think that the not homogenous distribution of asbestos in the samples can be overcome by homogenization of the sample during his preparation and by examine more than one sample for each product. The homogenization can be obtained by using a method usually used for rock samples and named “quartering”: for quartering, see for example the paper by Panarese and Vannocci (2006).	FDA appreciates the insightful commentary from Reviewer #5 acknowledging concerns about inhomogeneity in reference standards and providing suggestions

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REVIEWER	**COMMENT**	**RESPONSE**
		for how to prepare homogenous samples for interlaboratory proficiency assessments.
Reviewer #5	Furthermore, the characterization of the reference standards should be carried out by different laboratories (at least 3) accredited by national agencies and the results should be compared and averaged.	FDA appreciates the additional commentary on how to conduct interlaboratory proficiency assessments.

CHARGE QUESTION 23. When using gravimetric reduction to prepare samples, do you have any suggestions on how to address the matter of sample size that could improve the likelihood of detecting non-homogeneous chrysotile and amphibole particles, if present in talc or cosmetics?		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #3	I have no experience in gravimetric reduction and can offer no suggestions in this regard.	FDA appreciates the response from Reviewer #3 indicating this reviewer has no suggestions on this charge question.
Reviewer #4	From what I understand of cosmetics, they are fairly homogenous when compared to building materials. Additionally, the talc would be highly processed. As such, I would suspect the sample size may be less than what is needed to test building materials – especially considering the size of the particles of interest – but I expect similar sample masses should ideally be required. What needs to be ensured is there is enough material to produce accurate results and enough remaining after preparation for analysis for potential retesting or archiving. A hypothetical limit of detection should be in EMP/mass (i.e. EMPs/gr) if the IWGACP's opinions are followed. In that case, I expect analytical sensitivities to be more like EPA water methods 100.1 or 100.2 with a sensitivity in EMPs per mass of sample (mg or gr), dependent upon the number of TEM grid openings analyzed.	FDA appreciates the thoughts from Reviewer #4 regarding the lack of data on the degree of homogeneity of chrysotile and amphibole when present in cosmetics or any desired limit of detection.
Reviewer #5	To avoid the problem of the non-homogenized sample, I suggested here above the possible method. A good approach to gravimetric reduction is in the paper by Oberta et al. (2018).	Reviewer #5 offers no suggestion on sample size. FDA appreciates the suggestion of specific scientific

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REVIEWER	**COMMENT**	**RESPONSE**
		literature that might provide insight on how to improve sample homogeneity, which will be reviewed.

CHARGE QUESTION 24. Do you have any thoughts on the implementation of a quality management system pertaining to the testing of cosmetics as advocated by the IWGACP?		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #3	There are various issues with the establishment and implementation of quality management systems. One issue is the parameters of operation of the transmission electron microscope. Electron beam damage under electron microscopy results in a conflict between the high current and beam dose preferred to produce bright images and the lower beam doses necessary to produce good diffraction patterns (Steel and Small, 1985). For example, electron beam damage has been shown to cause broadening and weakening of diffraction spots in chrysotile (Zusmann and Brindley, 1957) and damage even in more robust amphibole structures (Martin et al., 2016).	FDA appreciates the comment from Reviewer #3 related to ensuring diffraction patterns are of adequate quality for mineral identification. FDA agrees, as the reviewer suggests, that it is advisable to take precautions to avoid damage to particles from electron beams during the TEM analysis.
Reviewer #3	A fundamental tenet of ISO 17025 General requirements for the competence of testing and calibration laboratories is that laboratories appreciate, assign and report an uncertainty to their analyses. Generally, I do not see this with asbestos analysis. The example analytical report from AMA referenced in the IWGACP White Paper includes neither an uncertainty in the identification (which would be based in the calibration and uncertainty of the EDS) nor in the calculation of quantitative content. I cannot emphasize enough how poor this situation is. It must be addressed for any method to be considered "valid".	FDA appreciates the comment from Reviewer #3 highlighting uncertainty of measurements by EDS that could impact precise mineral identification based on chemistry. Given such uncertainty and potential for variation in elemental composition among minerals in the amphibole group, IWGACP noted on Table 1 of the White Paper under "Measurement and Utility" that EDS is

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REVIEWER	**COMMENT**	**RESPONSE**
		semiquantitative. As a matter of practicality for identifying amphibole using EDS and SAED, FDA agrees with the IWGACP assessment.
Reviewer #3	Finally, it is IWGACP's opinion that "The analysts should have received formal training in mineral identification and determination of asbestos, as well as in the instrumentation and methods required for the analysis." While I am in full agreement with the sentiment, it is nothing more than wishful thinking until such 'formal training" is established and approved. NIOSH established the "582" course for PCM. Perhaps they could be approached to provide similar for TEM. Otherwise, established training providers, such as McCrone, could provide details of their offerings for certification. The American Industrial Hygiene Association has established a registry program for PCM analysts and perhaps this could be extended to other analytical techniques. Additional References cited in this review but not given in the text Bloise, A., Fornero, E., Belluso, E., Barrese, E. and Rinaudo, C. (2008) Synthesis and characterization of tremolite asbestos fibres. European Journal of Mineralogy, 2008, 20, 1027–1033. Martin, J., Beauparlant, M., Sauvé, S., and Espérance, G. (2016) On the threshold conditions for electron beam damage of asbestos amosite fibers in the transmission electron microscope (TEM). Journal of Occupational and Environmental Hygiene, 12: 924–935. Richardson, D.B., Keil, A., Cole, S.R. and Dement, J. (2018) Asbestos standards: Impact of currently uncounted chrysotile asbestos fibers on lifetime lung cancer risk. American Journal of Industrial Medicine, 61(5): 383–390. Spurny, K.R., Stöber, W., Opiela, H. and Weiss, G. (1980) On the problem of milling and ultrasonic treatment of asbestos and glass fibers in biological and analytical applications. American Industrial Hygiene Association Journal, 41(3): 198-203.	FDA agrees with Reviewer #3 and the IWGACP and appreciates the insightful commentary suggesting formal training by experts administered and certified under the auspices of independent parties would help ensure reliability of findings from microscopy analysis for asbestos in cosmetics. FDA also appreciates the references provided by Reviewer #3 in support of the commentary, which will be reviewed.

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REVIEWER	**COMMENT**	**RESPONSE**
	Steel, E.B., and Small, J.A. (1985) Accuracy of transmission electron microscopy for the analysis of asbestos in ambient environments. Analytical Chemistry, 57: 209–213. Zusmann, J., and Brindley, G.W. (1957) Electron diffraction studies of serpentine minerals. American Mineralogist, 42: 133–153.	
Reviewer #4	Skilled training and proficiency are of utmost importance. I share the opinion that basic analytical expertise is not dependent upon a specific educational background but that thorough in-depth training and technical competence are must-haves. Assuming laboratories are regularly provided with sufficiently challenging proficiency testing samples, a robust quality assurance and control program is in place and training is comprehensive and completely documented, I believe a laboratory will adequately perform analysis of cosmetic talc. I also believe an accreditation requirement like that seen in the environmental testing industry would be required but one which is better suited to the needs of the FDA.	FDA agrees with Reviewer #4 and the IWGACP and appreciates the insightful commentary highlighting the importance of training and the use of samples tailored to microscopy analysis for asbestos in talc/cosmetics to establish proficiency and thereby ensure reliability of analytical findings in the realm of asbestos analysis.
Reviewer #5	As I indicated below, 2 implementations could be very useful. 2. The TEM operator must be a trained and experienced microscopist in TEM imaging of minerals, but also trained and experienced in SAED both in the acquisition of suitable diffraction patterns and in their measurement and processing of the obtained data (a crystallographic basis it is necessary). 3. Since the simple stage holder is not sufficient, all TEM laboratories must have double tilt stage holder. The double tilt stage holder must have both tilt axes in the plane perpendicular to the axis of the electronic beam.	FDA agrees with Reviewer #5 and appreciates the thoughts on training of microscopists performing asbestos analysis and proper application of SAED to avoid recognized potential for misidentification in the analysis of talc and talc-containing cosmetics.

2. FDA Response to Specific Observations – White Paper and Appendices		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewers #1, #4, and #5	Reviewers provided a number of editorial comments to the White Paper and Technical Appendices.	The FDA appreciates the reviewers careful review of the IWGACP White Paper and Technical Appendices that were finalized in December 2021, at which time the IWGACP was disbanded.