Environmental Sciences Laboratory

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DEC 1 2000

November 30, 2000

Dr. Mary S. Wolfe
Director, ETP OD-NL
Building 101, Room B348
NIEHS
Alexander Drive
P.O. Box 12233, A3-07
Research Triangle Park, NC 27709

FAXED 11/30/00

RE: National Toxicology Program / RoC / Talc (Asbestiform and Nonasbestiform)

Dear Dr. Wolfe:

I am writing concerning the above reference matter. Our Laboratory will be submitting written comments by December 1st. In addition, we are requesting an oral presentation concerning the nomination.

If you have any questions or comments, please feel free to contact me.

Sincerely yours,

[redacted]

cc: CW Axten, Ph.D.
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A Submission on the

Mineralogy and Experimental Animal Studies of Tremolitic Talc

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December 1, 2000

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Executive Summary

The nomenclature of asbestiform talc is not specific enough to define a class of carcinogens. The proper nomenclature should be fibrous talc and transitionals. Microscopic analyses indicate the fibrous particulates in talc are not surrogates for asbestos. This fact is further substantiated by the results of several animal studies which indicate significant differences in that fibrous talc and transitionals lack the carcinogenic potency of asbestos fibers. As such, fibrous talc and transitionals do not meet the criteria for inclusion in the NTP Report on Carcinogens and should be removed from further consideration.

Introduction

The nomenclature of asbestiform talc is not specific enough to define a class of carcinogens. An understanding of the mineralogy of tremolitic talc is required to evaluate whether this assemblage of minerals can cause cancer in humans or experimental animals. This is particularly important if you wish to justify the assumption that talc is a surrogate for asbestos as was done in the Report on Carcinogens (ROC Report) Background Document for Talc Asbestiform and Non-Asbestiform. The ROC document reviews the medical and scientific literature and offers a premise for concluding that "talc asbestiform" materials are either "known to be a human carcinogen" or "reasonably anticipated to be a human carcinogen". (Summary of Review Group 1 & 2, ROC, 2000). The two review groups are of differing opinion concerning the evaluation of the information within the background report. Although the summaries are remarkably similar, no explanation for the difference in evaluation is offered, we are of the opinion that neither review group's claim is justified on the basis of the available information for tremolitic talc. Furthermore, the assumption that asbestiform talc is a surrogate for asbestos has not been justified in the ROC document and we will show that such an assumption is not scientifically justifiable.

The medical and scientific literature that the ROC used to describe "talc asbestiform" largely refers to tremolitic talc. This complex assemblage of minerals contains three phases (three different minerals), which can occur as asbestos minerals and two additional minerals that can occur in fibrous form. The ROC relies on relating these

phases to the carcinogenic risks associated with the commercial asbestos minerals to strengthen their case that asbestiform talc is a human and animal carcinogen. We will describe the tremolitic talc mineral assemblage and show that this extrapolation to asbestos is not justified. Examples from experimental animal studies will be used to emphasize the relevance of the mineralogy to carcinogenic risk.

Mineralogy of Tremolitic Talc

New York State tremolitic talc is an assemblage of five principal minerals, which can vary in abundance and particle size to form the various commercial grades (Table 1). Specific grades have properties useful in the fabrication of various products including ceramics and paints. Each grade contains three phases - anthophyllite, tremolite and serpentine – which can exist as asbestos or non-asbestos minerals but asbestos is not typically found in talc (Table 2). The two-amphibole minerals occur more commonly in nature in a nonasbestos habit, although each can occur as asbestos. Commercial deposits of these asbestos minerals have been rare and small and together they represent the least important of the commercial asbestos minerals (Ross, in press). The serpentine asbestos mineral is chrysotile – another serpentine mineral is antigorite, a platy particle. In addition, tremolitic talc can contain two fibrous particulates – fibrous talc sometimes referred to as agalite and an intergrowth of talc and anthophyllite referred to as an intermediate or transitional.

Each of the phases that can occur either as asbestos mineral or as a fibrous particulate was examined and characterized using polarized light microscopy, continuous scan x-ray diffraction and analytical transmission electron microscopy. A variety of tremolitic talc samples and reference standards were used for comparison. NYTAL400, a fine particle size grade of tremolitic talc, which is rich in fibrous particulates, was selected for analysis. Reference standards of the following minerals were selected for comparison:

- NYTAL 400 obtained from Gouverneur Talc Company, Inc., 1837 State Highway 812, Gouverneur, NY 13642.
- Tremolite Asbestos, Korea obtained from John Addison, Cottingham, Hull, United Kingdom.
- Tremolite Nonasbestos Respirable (NTP Animal) obtained from RT Vanderbilt, Inc., 30 Winfield Street, P.O. Box 5150, Norwalk, Ct 06856-5150.
- High Fiber Concentrate obtained from RT Vanderbilt, Inc., 30 Winfield Street, P.O. Box 5150, Norwalk, Ct 06856-5150.
- Anthophyllite Asbestos, UICC, Paakkila, Finland.
- Anthophyllite Asbestos, Anglo Dutch, Republic of South Africa, obtained from Prof DR Bowes.
- Anthophyllite Asbestos, Svedlovsk Region, Russian Federation.

Tremolite

Examination by TEM shows that tremolite particles in the NYTAL 400 tremolitic talc sample range from 20 micrometers to 5 micrometers in length and 1 to 4 micrometers in width with aspect ratios of 6 to 4. The sides of the particles are generally rough and not parallel with irregular to squared off terminations. The width is similar to the thickness indicating the particles are prismatic in shape. The particles are usually too thick to be electron transparent even at 200 keV accelerating voltages. Bright-field images (Figure 1) show the particles to be featureless in areas that were electron transparent.

Selected area electron diffraction patterns of tremolite particles (Figure 2) showed no evidence of disorder or the presence of additional phases or alteration. By tilting on the c-axis open planar fractures can be seen parallel to the c-axis (Figure 3). Selected area electron patterns indicate the open fractures are the {110} cleavage planes.

Fibrous Talc and Transitionals

Examination by TEM shows that fibrous talc particles in the NYTAL 400 tremolitic talc. Fibrous talc is identified in the image by its curved edges, bent and twisted shapes and frayed ends as in flax. It ranges from very thin ribbons with high aspect ratios (Figure 4) to equidimensional mats (Figure 5). Fibrous talc intergrown with anthophyllite appears as relatively straight lath-shaped particulates – commonly with small curved portions of talc-rich material separating from the larger particle at the

sides and ends. In bright-field images long linear features run along the length of the particles (Figure 6). These features are due to diffraction contrast from a talc and anthophyllite intergrowth, these fibrous particulates are the transitional.

Transitionals arise from the alteration of anthophyllite to talc; they are part anthophyllite and part talc intimately intergrown. The compositions of both phases are almost identical so that only an excess of OH^- is needed for the alteration, which easily migrates through the structure. The crystal structures of both phases also are similar so that there is an orientation relationship maintained between anthophyllite and talc. This relationship can be seen in [100] electron diffraction patterns of the transitionals where diffraction from both phases is present (Figure 7). The [100] zone shows layer lines with $l = 3n$ that are intense relative to those with $l \neq 3n$. The addition of the second phase, talc, with its characteristic psuedohexagonal [001] zone axis pattern results in diffraction spot triplets in the $l = 3n$ layer lines. These triplets are characteristic of anthophyllite and talc intergrowths, transitionals, with an interface parallel to (010).

Platy Talc

Talc is a sheet silicate and when growing freely naturally grows fastest parallel to the plane of the sheet as platelets. Sliding between the sheets gives talc its characteristic low hardness and lubricating properties. In the NYTAL 400 talc also occurs as platelets, generally less than 5 micrometers in diameter (Figure 8). A hexagonal arrangement of spots is characteristic of the diffraction pattern (Figure 9).

Serpentine

Serpentine occurs as a platy mineral identified mainly by the high Mg/Si ratio in energy dispersive spectroscopy (EDS) patterns (theoretically 1.5). The serpentine phase is antigorite or lizardite, most likely antigorite, both have a platy habit. No rolled tubes indicative of the chrysotile serpentine mineral (the asbestos variety) were observed.

Anthophyllite

Anthophyllite in the NYTAL 400 sample occurs as tabular crystals similar to popsicle sticks with the large flat face indexed as (100) (Figure 10). The length of the particle is parallel to the c-axis, the width is parallel to the b-axis and the thickness is parallel to the a-axis. This are the same common crystal faces expected in hand-specimen sized anthophyllite crystals. The particles are invariably thin and in most cases electron transparent from one side to the other. Electron diffraction patterns contain no extra spots due to talc alteration (Figure 11 – compare with Figure 7).

The longest particle measured on the sample grid had a length of 200 micrometers and a width of 3 micrometers for an aspect ratio of 67. Aspect ratios of other anthophyllite particles were smaller, ranging down to 2. The width of the smaller particles appeared to be constant at about 2 to 3 micrometers indicating the smaller aspect ratio particles were fragments of larger ones.

The terminations of the anthophyllite particles are generally right angles. Small amounts of alteration material adhering to the terminations indicate the particles break along planes of alteration parallel to (001). Long particles also split along (010) again along bands of alteration. These are seen in images as bands of material that have different diffraction contrast conditions than the adjacent anthophyllite.

Quartz

Quartz in the NYTAL 400 sample occurs as rare irregular shaped featureless particles generally several micrometers in diameter. These were identified by EDS spectra with only Si and O present.

Tremolitic Talc and Experimental Animal Studies

The tremolite present in tremolitic talc are cleavage fragments and should not be referred to as asbestos or asbestiform (Langer et al 1991). Smith et al 1979 evaluated the carcinogenic activity of tremolitic talc, tremolite non-asbestos and tremolite asbestos by intrapleural injections in hamsters. Only tremolite asbestos produced tumors (Table 3, Figure 12) and this is not present in tremolitic talc. The phases present in the tremolitic talc used by Smith et al 1979 were similar to Table 1 in this report with tremolite non-asbestos, talc fibers, talc plates and transitionals (Smith, 1974).

More recently, Davis et al 1991 evaluated six tremolite samples in rats by intraperitoneal injection (see Nolan et al 1991 for a review). Each tremolite sample was prepared as a respirable size range sample. The three-asbestos/asbestiform tremolites produced mesotheliomas in almost all animals. Davis et al 1991 goes on to conclude:

> Two samples of non-fibrous tremolite produced respirable dust samples containing numerous elongated fragments with aspect ratios greater than 3:1, which therefore fitted the definition of respirable fibers. Both these samples produced relatively few tumors, although one had more long "fibers" than did the brittle tremolite that produced 70% tumors. This study has therefore demonstrated that different morphologic forms of tremolite produce dusts with very different carcinogenic potential (p. 489).

Therefore, fibrous morphology alone does not define whether a mineral is carcinogenic or not (Nolan et al, 1991). Stanton et al 1981 reported on 72 experiments relating an index of fiber morphology to carcinogencity. Although the fiber morphology produced some correlation with carcinogenicity it was not without exceptions. For example, two tremolite asbestos samples containing fewer long thin fibers than a fibrous talc sample produced tumor probability of 100% while the fibrous talc produced no tumors (Table 4) (Nolan and Langer, 1993 for a review). Two other platy talc samples tested by Stanton et al 1981 also did not produce

tumors while four other platy talcs produced 1 tumor each corresponding to a tumor probability of 7% or less. The two tremolite asbestos samples which caused tumors are not found in tremolitic talc while fibrous talc which did not produce tumors would be found in tremolitic talc.

Again, there was no increase in the number of tumors in this location, although this procedure appears to have a similar sensitivity as the intraperitoneal injection technique.

The primary animal data set used to classify non-asbestiform talc as an animal carcinogen is the inhalation study conducted by the NTP (NTP 1993). This appears to be a well-conducted and reported study of non-asbestiform talc in rats and mice. The exposure levels (6 and 18 mg/m3) correlate well with the lung burdens in rats although the data for mice are not shown. The concentration of talc in the lungs of the rats increases linearly with dose and time, until 18 months. The evidence for carcinogenic activity is confined to the rat, e.g. the mouse studies were negative. In the rat a significant increase in lung tumors was observed in females, but not males, at 18mg/m3 but not at 6 mg/m3.

However, pheochromocytomas (tumors comprised of chromaffin cells of the adrenal medulla) were increased in both males and females at both exposures. This type of tumor in rats has little relevance to humans because it is related to an epigenetic mechanism as a result of chronic stress related to pulmonary pathology (Tishler et

al., 1988, 1994, 1996, 1999). Chromaffin cell proliferation appears to be under the control of neural signals, which explains tumor formation with the anti-hypertensive drug reserpine (Sietzen et al., 1987). Proof of this mode of action has been offered by Tishler et al. (1994), who showed that chromaffin cell proliferation induced by reserpine could be abolished by adrenal denervation. Pheochromocytomas in rats have also been induced in rats by common food components, e.g. vitamin D, lactose (milk sugar) and xylitol probably as a result of altered calcium homeostasis (Tishler et al., 1999).

Because this type of tumor is such a nonspecific effect and not related to non-asbestiform talc *per se*, it would be interesting to determine how the animal exposures (8 and 16 mg/m3) compare with those encountered by humans. Such information could then be used for margin of exposure analyses, especially since talc is not genotoxic (see below).

Hamsters have also been exposed by inhalation to nonasbestiform talc (talc baby powder) (Wehner et al., 1979). Again, no treatment related tumors were observed, but the study was of too short a duration to make a definitive statement about carcinogenicity.

There was one subcutaneous injection study of talc in mice. No tumors were observed. This is an important study because many solid materials, both fibrous

and nonfibrous particulates cause tumors using this technique and not finding any neoplasms is biologically significant.

The NTP report mentions two intraperitoneal injection studies of non-asbestiform talc in rats, both of which were negative for tumor induction. These are in addition to the negative studies reported earlier for tremolitic talc and some of the various mineral phases of tremolitic talc in rats and hamsters. These are particularly significant result because this technique (route of exposure) is highly sensitive to the induction of tumors (typically mesotheliomas), particularly with fibrous particulates, both naturally occurring and synthetic. In fact, many researchers feel that this technique is overly sensitive and that positive results may not indicate that the mineral phase has a carcinogenic potential for humans. On the other hand, a negative result should be viewed as meaning that it has minimal or no carcinogenic potential. In addition, it needs to be remembered that this technique results in a large and direct exposure to the ovary and surrounding tissues. If talc can cause tumors in this organ, it seems reasonable to expect that tumors would have been found in this exaggerated exposure condition. The negative results of these studies are buttressed by a study in rats where non-asbestiform talc was injected directly into the ovary with no tumor formation (Hamilton et al., 1984).

There was one intrathoracic injection study in mice, which showed a non-significant increase in lymphoid tumors (3/47), and adenocarcinomas (2/47) compared to 0/48 in the concurrent controls. The lymphoid tumors are not biologically significant

because they are not found with other types of fibrous and nonfibrous particulates, including asbestos. The adenocarcinomas are also an unusual response; the typical response is induction of mesotheliomas, none of which were observed.

While the ROC background document attempts to provide a definitive argument for classifying talc as carcinogenic in humans, the summary is not complete in its survey of the medical and scientific literature. For example, the most recent reference in Table 4-6 is 1977. There have been several informative and relevant inhalation studies of fibrous particulates including asbestos in the last 23 years that are not included. The studies undertaken and reported since 1977 represent the state-of-the-art for the inhalation studies of synthetic vitreous fibers in rats and hamsters where different types of asbestos were used as a positive control. If these well-known studies are missing, has other data also been omitted? Furthermore the NTP did not even mention its' own ingestion studies in rats and hamsters of several types of asbestos and non-asbestos tremolite. Finally, why are the talc studies conducted by Stanton using intrapleural instillation and those of Pott using intraperitoneal injection, both of which were negative for tumors, not included in the Table? The review of the medical and scientific literature needs to be re-reviewed and brought up-to-date.

Probably the least justifiable assumption in the ROC background report is the claim that asbestos is a "surrogate for talc". No mineralogical or biological basis has been offered for this assumption. Our review of the medical and scientific literature

indicates the tremolitic talc contains a class of minerals, which are sufficiently different to be considered as a separate and distinct class of minerals from asbestos (see above). It appears that the NTP relies on asbestos-related experimental animal studies to support its claim that talc is carcinogenic in animals because the data specific to asbestiform and non-asbestiform itself is so weak. The weakness of the data may simply reflect that lack of carcinogenic potential in the talc (asbestiform and non-asbestiform) which the ROC report is recommending as either known or probably a human carcinogen.

Genotoxicity

Determining the genotoxicity for particulates and fibers is always problematic because most fibers are relatively insoluble and therefore do not have the same potential to interact with DNA as chemicals. However, it is clear from the data that asbestiform and non-asbestiform talc has not been shown to be genotoxic or clastogenic either *in vitro* or *in vivo*. In contrast, asbestos has been shown to be clastogenic in several types of *in vitro* systems and some *in vivo* ones. The problem is that while the ROC background report states that talc, with or without asbestiform fibers, is not genotoxic, asbestos is and by inference, talc should also be considered positive, in spite of the evidence to the contrary. This is another weakness in the talc as a surrogate for asbestos argument.

Other Relevant Data

The discussion, in this particularly important part of the document, on deposition, clearance and retention is less than thorough. For example, there is no mention of the possibility of dissolution within the body, aspects of surface chemistry or the biological differences between asbestiform and non-asbestiform talc. The report seems to make the argument that because talc particles are found in the lungs and lavage samples from individuals many years after exposure, this means that a potential carcinogenic response is possible. This is a particularly weak argument. For example, using this argument, a coal-miner would be expected to show cancer because coal particles are found in his/her lung or sputum. Well-conducted studies of miners have shown no evidence of coal-related lung cancer, even in the presence of severe pneumoconiosis and high lung burdens. The ROC background report lacks a scientific balance and a modern approach.

Similarly, the document seems to suggest that because talc particulates have been found in ovarian tissues, in both cancerous and normal ovaries, that this indicates cause/effect. At best this is an observation and only of limited value in establishing etiology. One would have to examine ovarian tissue from a large number of individuals, exposed and non-exposed, to make this claim for an etiological role for talc in ovarian cancer. In fact, such a study has been done, and there was no correlation (Heller et al., 1996a, b see ROC Report for reference).

As another example, it is commonly known that asbestos bodies can be found in the lung and lymph nodes of most individuals living in urban environments, there is no evidence to show that such individuals are at an increased risk for asbestos-related cancer, nor do many researches believe these are meaningful risk factors. The most persuasive evidence that talc is not a significant hazard to the ovary is the intraperitoneal injection and intra-ovarian injection studies of huge amounts of talc in rodents. If talc were carcinogenic in this tissue, surely one or more of these studies would have shown a positive result. The ROC background report should be revised to reflect the importance of these animal studies and improve the scientific balance of the report.

Very importantly, in discussing the possible mechanisms of talc toxicity (6.2.2), there are a number of significant reports in medical and scientific literature showing inflammation and resulting production of cytokines and growth factors are important in the mechanism of particulate induced cancer. However, the preeminent investigators in this field, e.g. Driscoll, Kane, Oberdorster, Mossman, etc. are not referenced or their work considered in the document. The ROC report is weak on a state-of-the-art review of mechanisms of fibrous and non-fibrous particulate induced cancer.

Summary

In summary, the document fails to make a case that talc, either asbestiform or non-asbestiform, meets the criteria for inclusion in the NTP Report on Carcinogens. The standard for inclusion of a material into the NTP Report on Carcinogens should be a clearly supported by sound science and judgment establishing the material as a carcinogen. To "list" talc on the basis that asbestos is a "surrogate for talc" is without mineralogical or biological merit and should be rejected.

To the extent that the ROC document relies on asbestos to justify the claim that tremolitic talc is carcinogenic the NTP needs to reconsider their approach. The logic, used within the ROC document, contains conflicts in that the six commercial asbestos minerals are well defined and regulated by OSHA and other regulatory agencies. Such minerals are not exempt from the standard because they occur in association with talc, anymore than they would be exempt because they are used to fabricate a building material. To the extent that commercial asbestos minerals occur in association with talc, exposure would carry the same cancer risk. If the ROC wishes to go beyond simply classifying asbestos as a carcinogen and define other mineral phases present in tremolitic talc as carcinogens they should define the phases that they claiming are carcinogenic – not rely on claims of similarity to asbestos – and produce convincing evidence of carcinogenic effects in human and experimental animals.

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Table 1: Material Safety Data Sheet reports on the composition of tremolitic talc.

	CAS#	% by Weight
Tremolite (nonasbestiform)	14567-73-8	40-60
Talc	14807-96-6	20-40
Serpentine	12135-86-3	15-30
Anthophyllite (nonasbestiform)	17068-78-9	1-10
Quartz	14808-60-7	0.32

Table 2: Ideal formulas for the six regulated asbestos minerals and talc.

Mineral Name	Ideal Chemical Formula	Mineralogical Family/Group
Talc	$Mg_3Si_4O_{10}(OH)_2$	Sheet Silicate
Anthophyllite	$(Mg,Fe^{2+})_7[Si_8O_{22}](OH)_2$	Amphibole Family
Chrysotile	$Mg_3[Si_2O_5](OH)_4$	Serpentine Group
Riebeckite (Crocidolite)	$Na_2Fe_2^{3+}(Fe^{2+},Mg)_3[Si_8O_{22}](OH)_2$	Amphibole Family
Grunerite (Amosite)	$(Mg,Fe^{2+})_7[Si_8O_{22}](OH)_2$	Amphibole Family
Tremolite	$Ca_2Mg_5[Si_8O_{22}](OH)_2$	Amphibole Family
Actinolite	$Ca_2(Mg,Fe^{2+})_5[Si_8O_{22}](OH)_2$	Amphibole Family

Table 3: Results of the interpleural injection of hamsters with tremolitic talc, tremolite non-asbestos and tremolite asbestos (Smith et al, 1979).

	Tumors/survivors[1] Dose: 25 mg			Tumors/survivors[1] Dose: 10mg		
	350 days	**500 days**	**600 days**	**350 days**	**500 days**	**600 days**
Tremolitic Talc	0/35	0/27	0/20	--	--	--
Tremolite Non-Asbestos	0/31	0/15	0/3[2]	0/34	0/14	0/6[3]
Tremolite Asbestos	3/20	5/6	5/1	0/13	1/6	3/2

1 Numerator = cumulative number of hamsters with tumors related to treatment. Denominator = number of survivors.
2 2 additional animals survive.
3 6 additional animals survive.

Table 4: Selected samples from Stanton et al (1981) grouped by mineral name[1]

Mineral	Tumor incidence	Tumor probability (% ± SD)	Log f/μg[†]	Number fibers/μg ≤0.25μm x > 8μm	Total number fibers/μg
Tremolite Asbestos					
1	22/28	100	3.14	1,380	1.41×10^5
2	21/28	100	2.84	692	6.86×10^4
Talc (Asbestiform & Non-Asbestiform)					
1	1/26	7±6.9	--	0	1.26×10^5
2	1/29	4±4.3	--	0	1.26×10^5
3	1/30	4±3.8	--	0	7.43×10^5
4	1/29	5±4.9	--	0	1.90×10^5
5	0/30	0	--	0	2.67×10^5
6	0/30	0	3.3	1,995	3.76×10^5
7	0/29	0	--	0	9.75×10^5

Figure 1: Tremolite particle, 6 μm by 1 μm. (Plate 727)

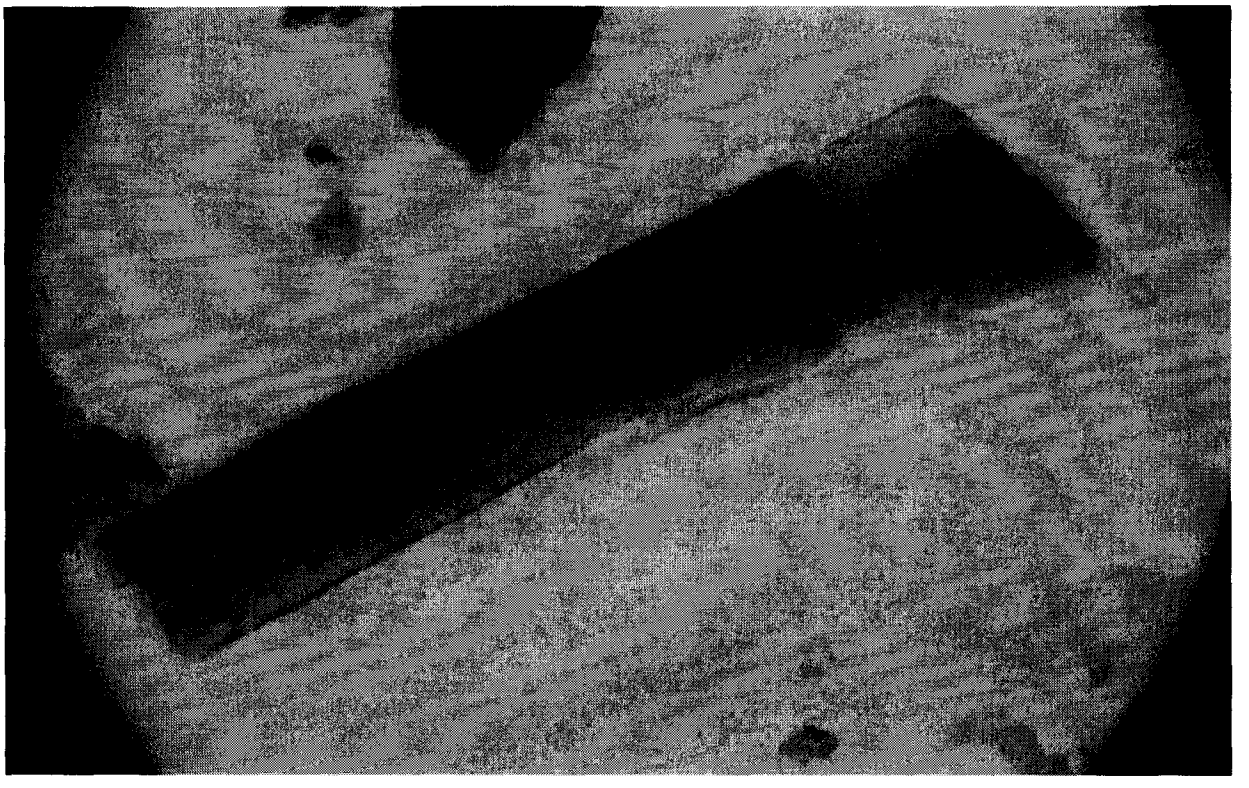

Figure 2: [100] Zone Axis, Selected Area Electron Diffraction Pattern (Plate 724)

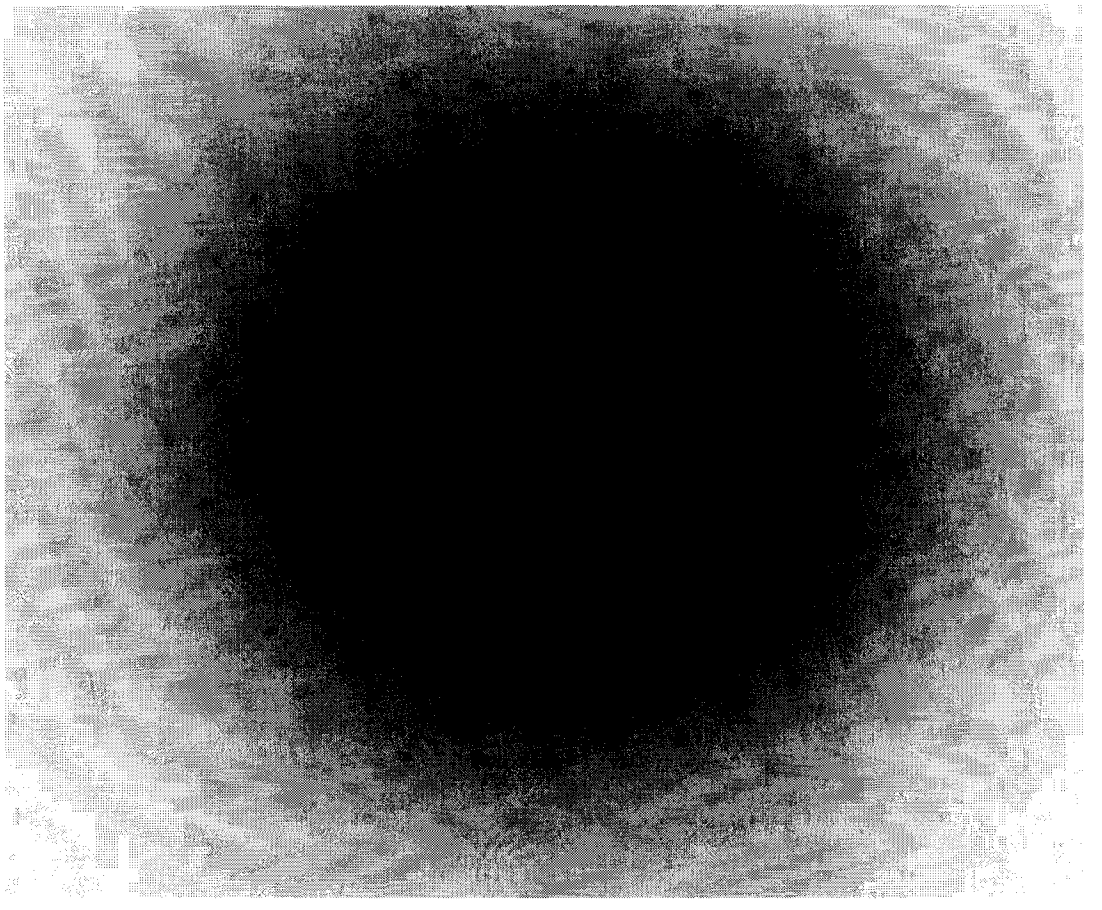

Figure 3: Open Fractures parallel to the c-axis are {110} cleavage planes (Plate 729)

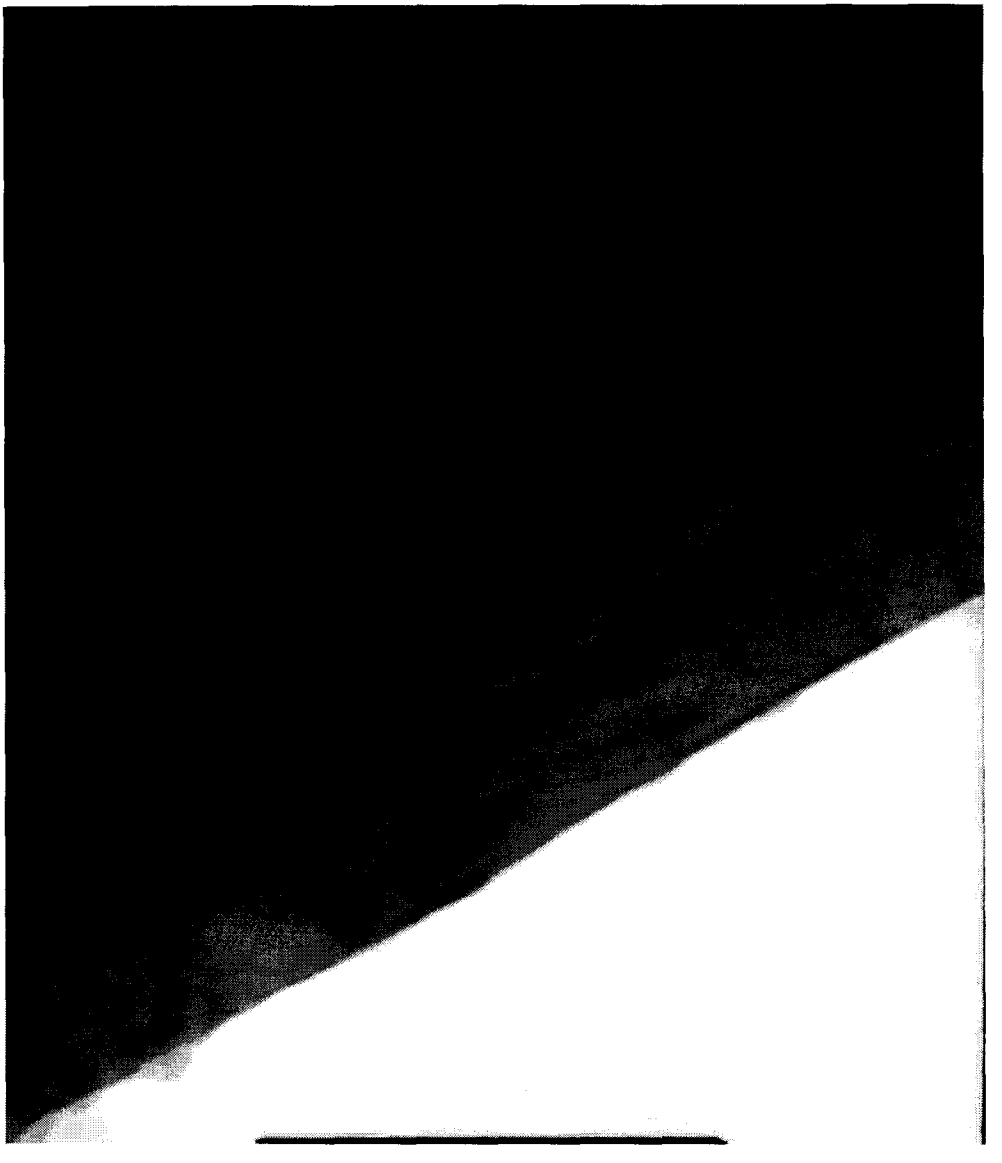

Figure 4: Curved fibrous talc particle with high aspect ratio. (Plate 730)

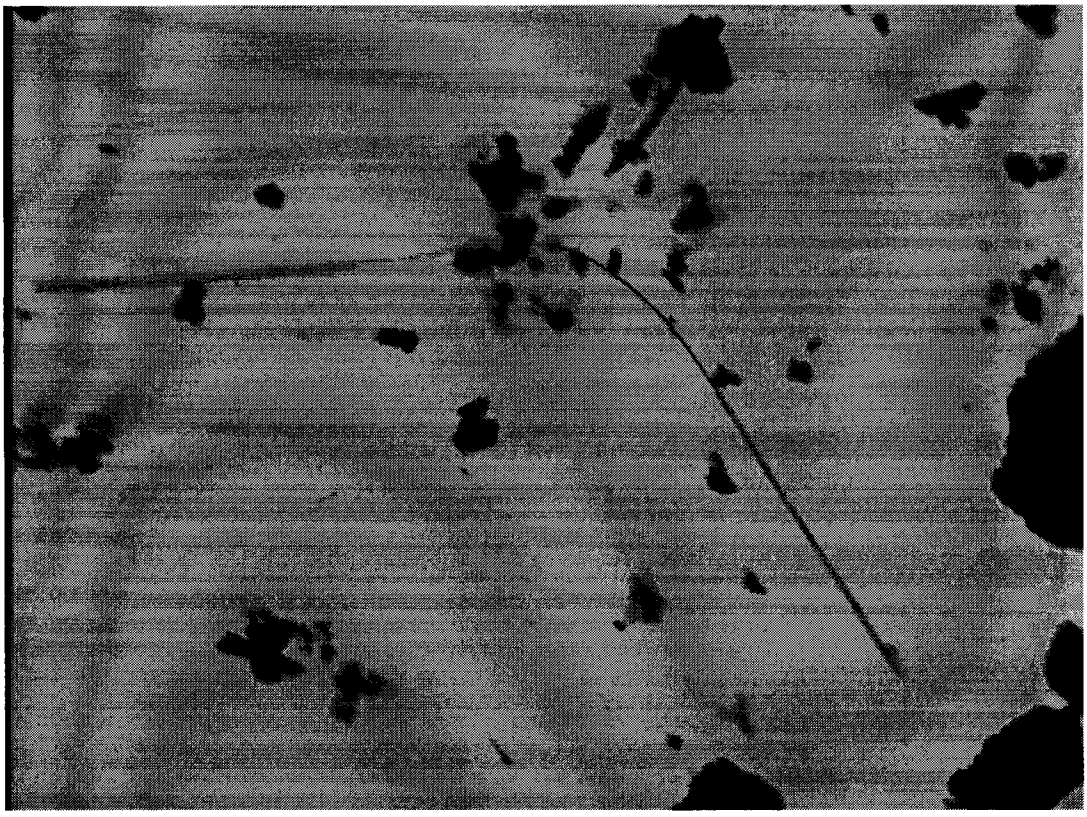

Figure 5: Fibrous talc particle (Plate 531)

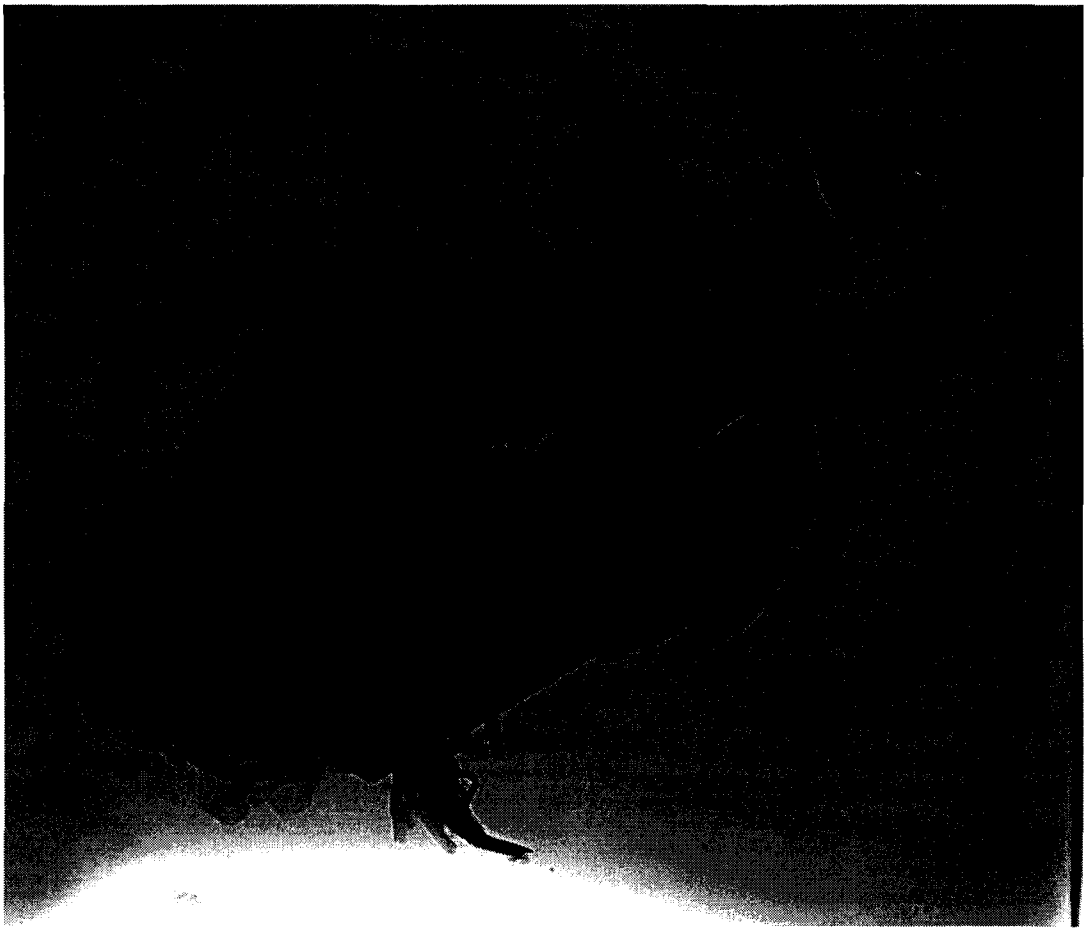

Figure 6: "Transitional" showing linear features from the intergrowth. (Plate 686)

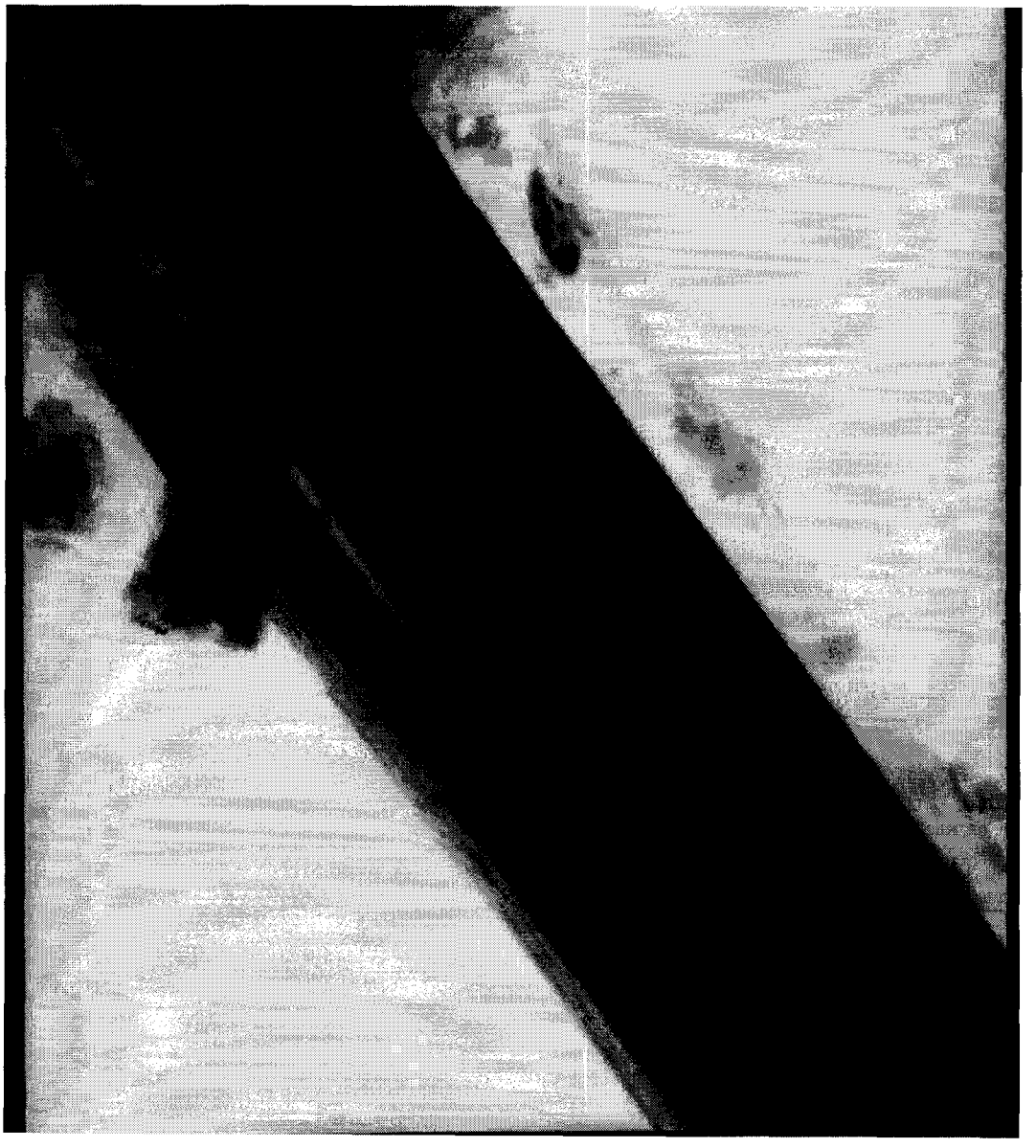

Figure 7: [001] Zone Axis showing both anthophyllite and talc spots in "Transitional" particle. (Plate 562)

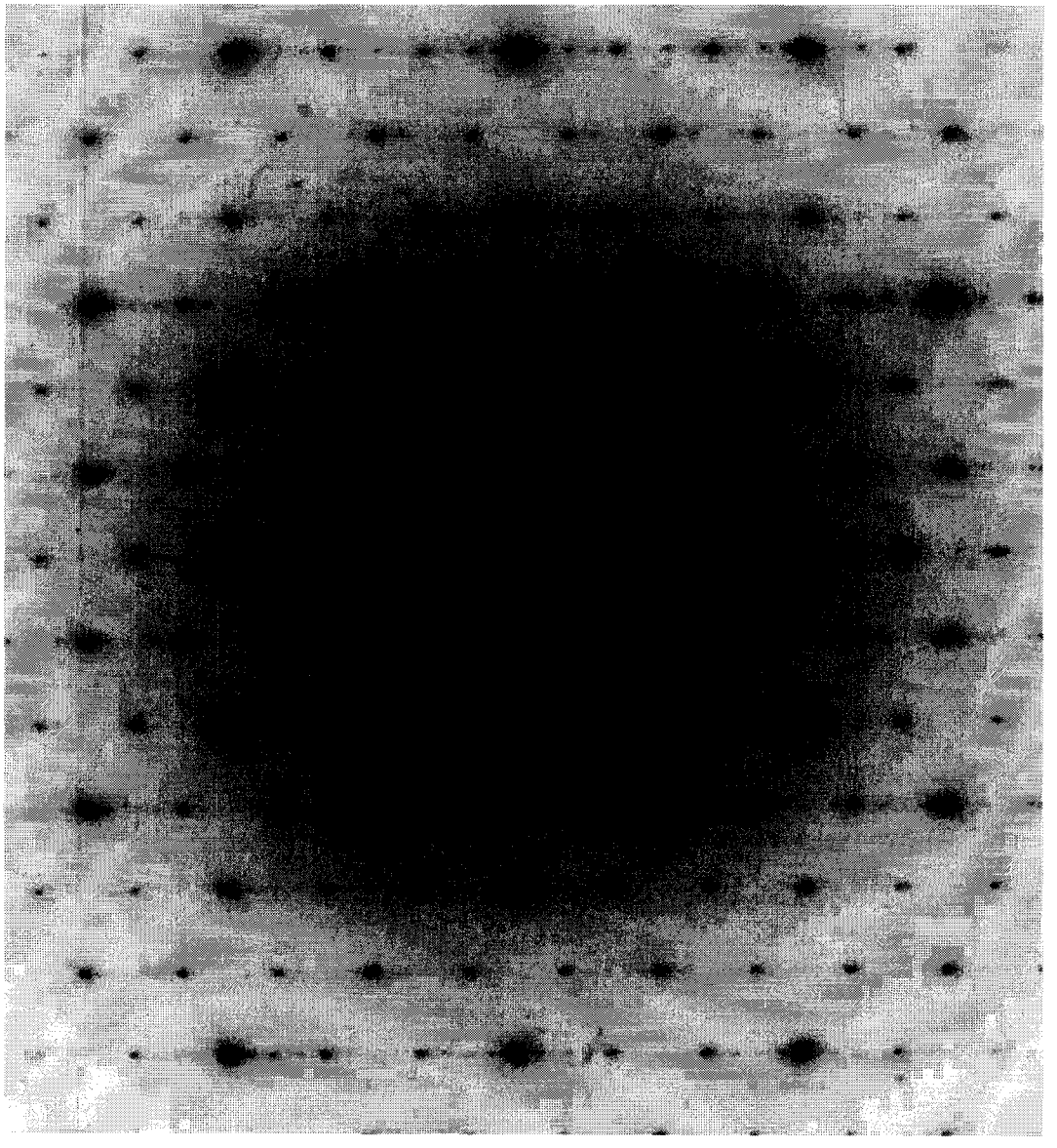

Figure 8: Talc Plate (Plate 706)

Figure 9: [001] Zone Axis from Talc Plate (Plate 707)

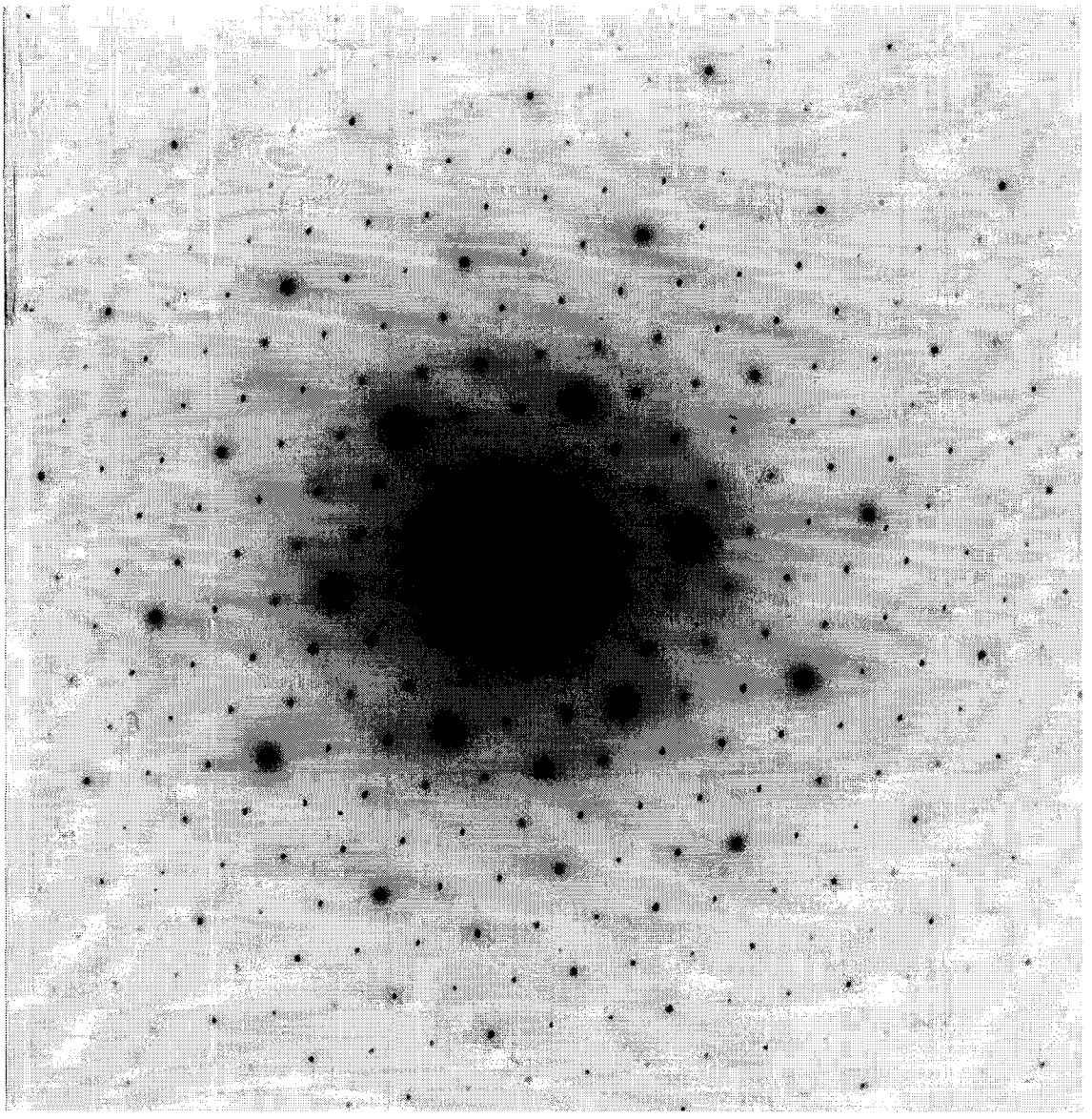

Figure 10: Bright Field electron micrograph of an anthophyllite particle. The width is 0.5 micrometers and the length is 6 micrometers with an aspect of 12. (Plate 709)

Figure 11: Selected area electron diffraction pattern of the [100] zone axis. Very weak spots from intergrown talc are also present. (Plate 711)