

Vista Chemical Company

15990 North Barker's Landing Road
Post Office Box 19029

Houston, Texas 77224
Phone (713) 531-3200

TGG: JOL: ~~MMG~~: RF

XF: Desk

July 25, 1988

VISTA

Dr. Gerald Vaughn
2417 W. Gallaher Ferry Drive
Knoxville, TN 37932

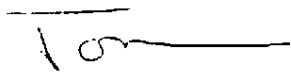
Dear Gerald:

I never got you a copy of the JOM article regarding the toxicity of various aluminas. We would appreciate your thoughts on this article relative to what you understand about our small particle work.

I've also enclosed a copy of a 1981 article for the JNCI which has some reference to aluminum oxides.

I'll be sending you drafts of the MSDS and labels for alumina fibers by mid-week.

Sincerely,


Thomas G. Grumbles, C.I.H.
Environmental Quality Manager

dlj

Enclosures

VVV 000014393

Alumina-related Pulmonary Disease

VVV 000014394

Bertram D. Dinman, MD, ScD

A review of experimental studies suggests that the catalytically active low temperature transitional forms of alumina produces irreversible fibronodular change only when administered by intratracheal insufflation. Other aluminas not catalytically active but also broadly identified as "gamma" for different reasons also appear capable of inducing pulmonary fibrosis in the same model. Under conditions of human exposure, occupational exposure to a broad range of aluminas indicates—at most—minimal pulmonary nodular response.

Assessment of biomedical studies of the toxicity of Alumina in the lung is complicated by inconsistencies in the nomenclature used to describe chemical and physical variants of this compound. The biologic literature can be evaluated only to the extent that investigators have clearly identified the individual alumina species studied. Only with careful physical-chemical delineation of these physical-chemical entities is it possible to place experimental and human data in perspective so as to understand the biologic and health implications of exposure to aluminas.

To complicate the situation further, various biologic models have been developed as surrogates for the study of human interactions with chemical agents. With the evolution of such model systems, a broader understanding of their utility and limitations is revealed. Although biologic mechanisms of action may be demonstrated by such experimental systems, their applicability to the human condition is frequently limited, eg, because of high dose regimens and nonphysiologic portals of entry or administration. Such reservations have been extensively discussed in connection with studies of carcinogenesis; similar reservations are equally applicable to investigations of pulmonary response to dusts, or vapor, or gases. But within these constraints, and in conjunction with clinical investigations, such models can assist in elucidation of human responsivity and risk. Thus,

within this frame of reference, this report will attempt to place in perspective studies using both experimental models and human encounters with this group of aluminum, oxygen, and hydrogen-containing compounds, the aluminas.

Experimental Studies of Alumina's Actions in the Lungs

On the basis of an examination of those reports which provide sufficient chemical and physical specifications, it is possible to identify aluminas previously studied in terms of present day knowledge. These specific aluminas are summarized in Table 1.

Gardner et al¹ reported that *inhalation* of a gelatinous alumina (designated γ -HX1010), presently known to be gelatinous boehmite, apparently did not produce deleterious pulmonary alterations when administered to guinea pigs in doses of approximately 40 to 120 mg/m³. Among its other properties, gelatinous boehmite usually possesses an extremely high surface area (250 to 500 m²/g).

Gardner administered by inhalation at doses of 21 to 33 mg/m³ a second alumina which he identified as C-730. His description of the mode of preparation indicates that this alumina was gibbsite; heated at atmospheric pressure, this aluminum trihydroxide dehydrates mainly to the χ transitional form, a catalytically active alumina. Once more, no pathologic alterations ensued following *inhalation* exposure.

The benign outcomes of the studies of Gardner et al¹ stand in stark contradiction to the findings of King and associates²: in their laboratory, this same HX1010 gelatinous boehmite (referred to as γ -AlOOH) produced extensive nodular and diffuse confluent fibrosis. It is important to note that King et al² administered this alumina via *intratracheal insufflation*.

Because of this major difference in response, further efforts in King's laboratory by Stacy et al³ culminated in more extensive and systematic intratracheal insufflation studies of several aluminas (Table 1). Stacy and co-workers,⁴ using the same gelatinous boehmite (γ -AlOOH, HX1010) replicated King's results, ie, moderately severe pulmonary fibronodular change.

From the Department of Industrial Environmental Health Sciences, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA 15261 (address correspondence to Dr Dinman)...
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TABLE 1
Review of Experimental Data with Contemporary Evaluation of Alumina Species

Investigator	Agent		Crystalline Packing Arrangement	Route of Administration	Particle Size, μm	Surface Area, m^2/g	Catalytic Activity	Dose, mg	Response
	Investigator Designation	Identity (1987)							
Gardner et al ¹	C-730, activated	χ transitional	γ	Inhalation	?	250-?	+	21-33/ m^3	No harmful effects
	HX1010	Gelatinous boehmite	γ^*	Inhalation	0.02	250-350	-	35-105/ m^3	No harmful effects
King et al ²	$\gamma\text{-AlOOH}$ HX1010	Gelatinous boehmite	γ^*	Intratracheal insufflation	0.02-0.04	250-350	-	100	+3 to +5/5 fibrosis†
Stacy et al ⁴	$\gamma\text{-AlOOH}$ HX1010	Gelatinous boehmite	γ^*	Intratracheal insufflation	0.02-0.04	250-350	-	50	+3/5 fibrosis†
	$\gamma\text{-Al}_2\text{O}_3$ HX1010 at 850°C	η transitional	γ	Intratracheal insufflation	0.02-0.04	60-?	+	50	+5/5 fibrosis†
	$\gamma\text{-AlOOH}$ Cera hydrate ⁶	Boehmite	γ	Intratracheal insufflation	3	0.6	-	50	0 fibrosis†
	$\alpha\text{-Al}_2\text{O}_3$ HX1010 at 1,200°C	$\alpha\text{-Al}_2\text{O}_3$ (corundum)	α	Intratracheal insufflation	0.1-0.8‡	3	-	50	+1/5 fibrosis†
	$\gamma\text{-Al}_2\text{O}_3$	γ transitional	γ	Intratracheal insufflation	0.005-0.04	95-105	+	35	+3/5†
Klosterkötter ⁵	$\gamma\text{-Al}_2\text{O}_3$	γ transitional	γ	Inhalation	0.005-0.04	95-105	+	3300/ m^3	Alveolar proteinosis†

* This alumina is only minimally crystalline.

† System of fibrosis grading of King et al.³

‡ Estimated by review of electron micrographs of Stacy et al.⁴

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Next, this gelatinous boehmite was heated to 850°C; the dehydration formed what Stacy referred to as $\gamma\text{-Al}_2\text{O}_3$. However, present knowledge⁶ indicates that the product of dehydration at this temperature results largely in the formation of the η transitional form, a catalytically active aluminum oxide (cf "Technical Note"). Nevertheless, intratracheal insufflation of what was probably the η transitional Al_2O_3 resulted in severe pulmonary fibronodular alteration.

The third alumina studied by Stacy was the thermal dehydration product of the same gelatinous boehmite HX1010 heated to 1,200°C which led to the formation of α -aluminum oxide (Fig. 1) (see also Fig. 2) or corundum. These crystals were then ground to a smaller particle size, which appeared to range from 0.1 to 0.8 μm . When administered intratracheally, $\alpha\text{-Al}_2\text{O}_3$ provoked a minimal but consistent degree of fibronodular lung pathology.

The fourth alumina investigated was the highly crystalline, large particle size (ie, 3.0 μm mean diameter) $\gamma\text{-AlOOH}$ boehmite (referred to as Cera hydrate⁶). This catalytically inactive alumina given intratracheally at similar doses as the other aluminas was inert in the lungs.

These data of the London-Post Graduate School clearly indicate (cf Table 1), within the context of the intratracheal insufflation model, that (1) exposure to the catalytically active η transitional form results in severe fibronodular alteration; (2) exposure to certain catalytically inactive aluminas (viz, $\alpha\text{-Al}_2\text{O}_3$ and gelat-

inous boehmite) produces a lesser but broader range of fibronodular change; and (3) in view of the broad range of reactivity to variously described γ -aluminas (ie, zero response with $\gamma\text{-AlOOH}$ boehmite, extending to severe alterations with η transitional form), and (4) in view of a minimal but consistent response to a fine α -alumina, (5) it is inconsistent to associate γ -aluminas with pulmonary hazard. (6) This position is reinforced by the probability that the London School never exposed their animals to any specific γ -aluminum oxide (ie, γ -transitional).

Since the London investigators' experiments^{3,4} were based upon intratracheal insufflation dosings, Klosterkötter⁵ attempted to study the effect of inhalation of what was believed to be the most biologically active of these aluminas, a relatively well-defined γ transitional form Al_2O_3 . However, because his dosage was so extremely large, ie, 33 g/ m^3 for each of 285 days, this massive overloading produced what would presently be considered as alveolar proteinosis, a nonspecific response to large pulmonary dust loadings. Accordingly, the implications of his experiments for only the most excessive human exposures to γ transitional Al_2O_3 should still be considered as questionable.

Regarding these experiments, it is indeed ironic that, of the multiple forms of aluminas investigated, a specific fibronodular response apparently has never been produced by the only one specific γ -alumina, ie, the γ transitional form. In more precise terms, a fibronodular response can only be said to have resulted from intra-

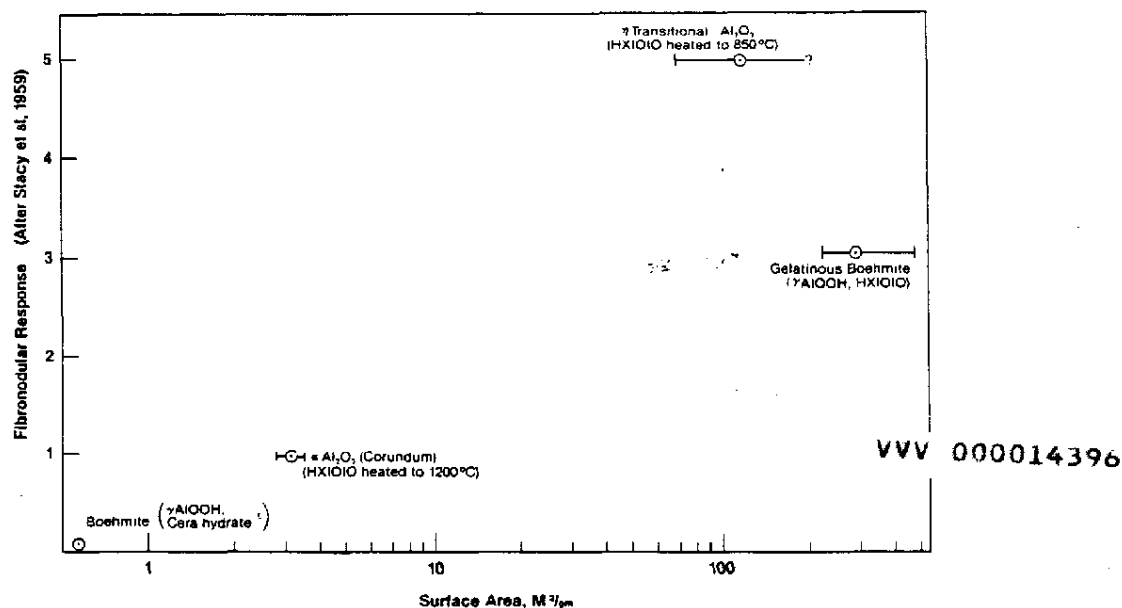


Fig. 1. Correlation of Surface Area of Aluminas with Pulmonary Fibrosis Graded According to Stacy et al.⁴

tracheal insufflation of (1) *catalytically active, low temperature range transitional*, and/or (2) *relatively high surface area aluminas*. In order to clarify the biomedical literature, we would propose that the reference to γ -aluminas be discontinued, and that this *intratracheal* model's effect be specifically associated with these two alumina species and their properties.

More recent inhalation studies of aluminum oxide reported the production of nonspecific polymorphonuclear response characteristic of a wide variety of cytotoxic and nonpathogenic particulates. By contrast, Al_2O_3 did not provoke increased alveolar macrophage response,⁷ suggesting only minimal potentials for chemotactic or fibronectin release and injury associated with such events. Although more studies of the alumina's effect upon alveolar macrophages are indicated, presently available data do suggest a relatively efficient elimination from the lung⁸ and a low degree—if any—of fibrogenicity. Other investigations of corundum (α - Al_2O_3) indicated an inability to evoke lung tissue acid phosphatase, which has been associated with development of fibrogenic response.⁹

Occupational Exposure to Aluminas

Unfortunately, most reports of occupational exposure to aluminas unmixed with other dusts have not provided specifics sufficient to adequately define the qualitative nature of worker exposures. Much of this stems from the failure of biomedical investigators to appreciate these multiple variations in alumina's physical and chemical forms. Moreover, workplace characterization is complicated by the reality that production and use of specific aluminas varies in response to marked demands and/or technologic changes at various times and places.

Furthermore, in the production of aluminas, relatively few employees are exposed to alumina dust. Such dust exposures that do occur are found in the vicinity of kilns at grinding, screening, transport, and packing operations. Given these facts, it is understandably difficult to characterize precisely the quantitative as well as qualitative nature of employee exposures in the course of alumina production.

Studies of alumina refineries in which one would encounter aluminas unmixed with other dusts are relatively uncommon; however, a recent study of alumina refinery workers reported by Townsend et al.¹⁰ represents such exposures. This alumina chemical refinery employing 1,109 potentially exposed workers has been engaged in the production of various aluminas, predominantly the chemical grades. Production data available showed that since 1958 these workers have processed 244,500 tons of the low temperature transitional aluminas (viz, η , γ , χ) representing 2.9% of the total aluminas produced since that time. Accordingly, exposure to the intratracheally bioreactive low temperature range transitional alumina species has been occurred here on an intermittent basis from 1952 until 1982. A search for pulmonary fibrosis and pneumoconiosis in this population yielded essentially negative results¹¹; the major change reported was a slight but significant decrement in ventilatory function among nonsmoking workers exposed to excessive total dust levels. The observed changes were consistent with a minor degree of nonspecific chronic industrial bronchitis associated with excessive, protracted nuisance dust exposure, (ie, 100 mg-years for more than 20 years).

Other reports of occupational exposure to aluminas unmixed with other dusts occur in connection with pottery production. In that industry, α -aluminum oxide is used to support green, unfired pottery and flatware.¹²

Because of the ease with which this stable form of corundum $\alpha\text{-Al}_2\text{O}_3$ becomes airborne, exposure of workers in this industry has been the subject of multiple epidemiologic and clinical investigations in the United Kingdom.^{12,14} None of these investigators have found evidence of pneumoconiosis or chronic respiratory disease.

Reports of exposure to an otherwise uncharacterized alumina which is probably unmixed with other dusts have been provided by Szczekocki and co-workers.¹⁵ Although their interests lay in whole body absorption and excretion of aluminum, they briefly note in their clinical evaluations that 49 workers engaged in the reloading of aluminum oxide showed no roentgenographic evidence of pneumoconiosis.

Alumina exposures in aluminum smelters are mixed, involving such other pulmonary irritants as hydrogen fluoride and inorganic fluoride particulates, as well as low levels of sulfur dioxide. The difficulty inherent in the study of mixed exposures among aluminum smelter workers has been commented upon by Saia et al.,¹⁶ who reported pulmonary opacities of a minor degree in cast-iron foundries where mixed exposures similarly occurred.¹⁷ Similarly, small irregular opacities of category 1/0—or at most, 1/1—have been found among workers exposed to coal dust¹⁸ and man-made mineral fibers.¹⁹

Putting aside the confounding variables involved in mixed dust exposures present in aluminum reduction, changes in the character of smelting type aluminas which have evolved since the 1950s are of interest. With the introduction of flash and fluid phase calciners in the alumina refining industry, lower temperatures and faster flow-throughs are achieved. Thus, by calcining aluminas at a lower temperature, more of the higher temperature transitional forms (cf Technical Note and Fig. 2) and less α -alumina are produced; in addition, among the high temperature transitional aluminas (eg, γ , κ , θ , and δ), surface areas larger than that associated with α -alumina are formed (cf Technical Note and Fig. 3). This is advantageous, as these high temperature transitional aluminas used as smelting feedstock make more effective adsorptive media when they are used to scrub airborne smelter effluents. Thus, as economics drove this rapid, lower temperature calcination throughout the industry, increasing percentages of transitional γ , κ , δ , and θ aluminas have come to be the major component of the aluminas used in aluminum smelting. At present, smelting grade aluminas—which comprise 90% of the world's alumina production—may contain as little as 1% of α -aluminum oxide, although more usually 80% to 90% of smelting aluminum will consist of the high-temperature transitional forms κ , δ , and θ .

Under such operating conditions, which have gradually applied since midcentury, evaluation of lung changes in aluminum smelter operators since that time could shed light upon the pulmonary reactivity of the γ transitional-laden smelting grade aluminas. At present, population studies of smelter employees indicate either minimal¹⁵ or absent fibronodular disease^{20,21} nor excess mortality²² associated with pneumoconiosis. In most of these studies, smelter workers have predominantly been

exposed to the high temperature range transitional aluminum oxide aluminas since the late 1960s. In none of the foregoing aluminum reduction operations did cell room attendants evidence changes consistent with alterations seen by King et al.³ or Stacy and co-workers⁴ with intratracheal insufflation of the low temperature (η) transitional alumina. In contrast to population studies, individual case reports from smelters note lung fibrosis²³ or fibronodular alteration.²⁴ Ultimately, the strength of these associations must be borne by the weight of available evidence.

Discussion

The biomedical literature dealing with the aluminas suffers from imprecisions regarding the nature of the agent component of the host-agent interaction. Because they most clearly identify which aluminas were investigated, the London intratracheal insufflation reports are valuable. In the case of the Stacy group's reports,⁴ a *gradation of response to similar doses of several different aluminas is demonstrated*, despite the disputatious route of administration. Had all these dosings led to severe or uniform response to the aluminas, a more plausible case for total disregard of these data might be appropriate. That there was a broad range of response to these agents suggests reason for serious consideration of their findings. A re-examination of the King group's³ data therefore is useful to the extent one understands the limitations of their model's implications for human exposure conditions.

We suggest that an association between pulmonary fibrogenicity, surface area, and catalytic activity (Table 1) is apparent upon consideration of the characteristics of these aluminas. Examination of King and Stacy's range of pulmonary response as related to surface area (Fig. 1) suggests an association between these two variables among the noncatalytic aluminas. We would propose that increased thermodynamic instability and enhanced bioreactivity of these compounds occur as surface area increases (cf Technical Note). (Of interest in this connection is Timbrell's recent report,²⁵ which correlates surface area with the pulmonary bioreactivity of various mineral forms of asbestos.)

Regarding the catalytic activity of the low temperature transitional forms of alumina (ie, η , χ , γ), enhancement of pulmonary bioreactivity resulting from their thermodynamically active catalytic character is also suggested by Fig. 1. It would be reasonable to suggest that this property is responsible for that increment of lung damage beyond that due to the surface area factor.

Because of gaps in knowledge at the time Stacy and co-workers⁴ performed their experiments, they could not be aware that they probably had not dosed with the specific gamma transitional alumina form. Aside from inadvertent confusion in the literature, this is not a serious shortcoming from the biomechanistic viewpoint, since the low temperature transitional alumina η possesses catalytic and surface area characteristics common to the other low temperature transitional forms γ and χ .

✓ All of the foregoing reports of King, Stacy and associates must be considered within limitations imposed by intratracheal insufflation models; the massive dosing and overwhelming of defense mechanisms represents a "forcing" model reminiscent of megadose carcinogenesis experiments. A parallel is exemplified by the large dose animal studies with halogenated aliphatics: although alternate metabolic pathways are elucidated by such investigations,²⁸ their relevance to the human exposure conditions is problematic. Although alumina at such doses which negate tracheal-bronchial clearance may produce effects as a consequence of catalytic activity or surface area related thermodynamic instability, usual human exposure conditions produce neither such lung doses, disablement of clearance mechanisms, or significant pathology. Thus, as with the halogenated aliphatics, although alternate pathways and pathologies can be induced experimentally, under usual conditions of chronic human exposure, these phenomena are largely of academic interest.

In contrast, the inhalation model approaches more closely the exposures encountered at work. Studies using this model to evaluate alumina's pulmonary bioreactivity demonstrate that even the most thermodynamically active forms χ^1 and γ^5 do not cause fibronodular change. Yet the results of Klosterkötter⁵ serve to caution against uncritical application of the inhalation model. Klosterkötter explicitly recognized that the doses he employed (ie, 33 g/m³ for eight hours a day for 285 days) represent an exposure level which was intolerable for his laboratory personnel.⁵

Ultimately, in assessing human health hazards, well designed studies of working populations potentially at risk assume considerable importance.

Review of occupational exposures to (1) catalytically active large surface area, low temperature transitional aluminas (χ , η , γ) in aluminum chemical refineries; (2) high temperature γ , κ , δ , and θ transitional aluminas encountered in smelters since the late 1960s; and (3) high-fired α -aluminum oxide as found in potteries suggest that of all these aluminas demonstrate minimal—if any—fibrogenic potentials in man. It is ironic that, although concerns regarding γ -alumina's pulmonary fibrogenicity have persisted (eg, in the standard-setting process²⁷) since the London studies, (1) a specific γ -alumina, ie, the transitional form, was probably not

actually studied by that group and (2) the other so-called γ -aluminas exhibited inconsistent biologic responses (eg, the nonreactivity of γ -AlOOH Cera hydrate⁹ v the fibrogenic response to γ -AlOOH HX1010 gelatinous boehmite). The final irony is reflected in the observation that the only true exposure to a specific γ transitional alumina (ie, by Klosterkötter) via inhalation does not produce a specific pulmonary fibronodular response, but rather the nonspecific alveolar proteinosis.

All the foregoing data place in high relief the proposition that it is only through critical assessment of both experimental and human experience with environmental agents that we may understand such compounds' role in disease induction. On the basis of in vitro and in vivo experimental and workplace studies under conditions of human exposure, it is clear alumina's fibrogenicity is quite low regardless of which specific alumina is examined.

Technical Note: Physical, Chemical, and Structural Nomenclature, Identification, and Behavior of Aluminas

The Physical and Chemical Bases for Confusion

The oxides, hydroxides, and oxyhydroxides of aluminum have been given a multiplicity of designations since aluminum oxyhydroxide was first chemically analyzed and identified by Vauquelin in 1802. Investigators gave different names to the same chemical compound or mineral form (cf Table 2); this led to confusion as different physical properties, eg, crystalline structure, were assigned to the same compound. For example, the minerals gibbsite and diaspor, identified in the first and third decades of the 19th century, were later confused with their isomorphs, which were given the names boehmite and bayerite in the 1920s. To compound this multiplicity of appellations, the name hydrargillite was applied by the Europeans to gibbsite.

Duplicative and inconsistent terminology ensued when Greek letter prefixes were attached to various aluminas for unrelated reasons or behaviors. Rankin and Merwin²⁸ in 1916 assigned the Greek letter prefix β to a high temperature alumina later shown to contain alkali or alkaline earth atoms. Haber²⁹ in 1925 divided

TABLE 2
Comparison of Physical and Chemical Nomenclature Applied to the Alumina Minerals

Preferred Chemical Formula and Name ²⁴	Mineral Name ²⁵	Formerly Applied Designation ²⁴	American System ^{24, 27}	European System ²⁸	X-ray Crystallograph Classification ²⁴
Al(OH) ₃ , alumina trihydroxide	Gibbsite or Hydrargillite	Alumina trihydrate Aluminum hydroxide	α , γ	γ	γ
	Bayerite	Alumina trihydrate Aluminum hydroxide	α , β	γ	α
	Nordstrandite	Randomite	—	γ	β
AlOOH aluminum oxyhydroxide	Boehmite	Alumina monohydrate	α , γ	γ	γ
	Diaspor	Alumina monohydrate	α , β	α	α
Aluminum oxide	Corundum	α -Alumina	α	α	α

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aluminum oxide into an α and γ series, depending upon the product of the oxide's calcination. Subsequently, Edwards et al.³⁰ assigned the prefix α to the more abundant hydroxide, whereas the less abundant alumina was given the β prefix; both appellations were applied without regard for structure.

Later, as these aluminum compounds were used in industrial processes, different nationally based variant nomenclatures—North American or European—were used to describe the same compounds. The resulting confusion in chemical and mineral nomenclature is amply demonstrated by Table 2.

This ambiguous situation was further complicated when Ulrich³¹ in 1925 found that progressive heating of the hydroxide gave rise to a previously undescribed form which he called γ . This material was later found by Stumpf et al.³² to be but one of the several alumina transition forms χ , η , and γ (Fig. 2). However, before these specific, individual forms were defined, the Greek prefix γ , attached by Ulrich to these forms, came to be applied via common usage to all three low temperature calcination products of aluminum oxides and oxyhydroxides, ie, η , χ , and γ . It was not until 1950 that Stumpf et al.³² restricted the prefix γ to one specific thermally induced transition form derived from gibbsite and boehmite formed between 500 and 850°C (Fig. 2). In succeeding years, the identification of each of these thermal transitional reorderings was established and Greek alphabetical prefixes were given to these specific forms (Fig. 2).

However, it must be recognized that what appears to be a straightforward sequence of individual, defined

phases or polymorphs of aluminum oxides represents in reality thermodynamically unstable states of structural reorderings of the hydroxide lattice. Although these states are reasonably reproducible, even within a solid, there may occur simultaneously various domains characterized by different degrees of structural reorderings. The type of transition form and the sequence of transformation depends upon variables such as the structure of the precursor, rate of heating, particle size, and components or contaminants in the atmosphere. Accordingly, unless details of all such variables are reported, critical evaluation and interexperimenter comparisons of biologic response are unreliable.

The structural and compositional differences among these several transition forms, e.g., between η and γ forms, are small and difficult to distinguish. In attempting to identify precisely these low temperature transitional forms, η , χ , and γ , we are faced with a double dilemma. Not only are these transitional states identified with difficulty, but structural analysis cannot precisely quantify the ratio between the amorphous and crystalline states within a specific specimen. Ultimately, in considering these low temperature transition forms, one faces the reality that these aluminum oxides represent highly dynamic reorderings of crystalline structure and amorphous elements temporally and spatially distributed in a nonhomogeneous, random fashion. It should be readily apparent why, despite general acceptance of the Munster Symposium³³ recommendation giving each transitional form an individual, specific Greek prefix designation (Fig. 2), present industrial/commercial nomenclature often fails to differentiate between

Conditions	Conditions Favoring Transformations	
	Path a	Path b
Pressure	> 1 atm.	1 atm.
Atmosphere	moist air	dry air
Heating Rate	> 1°C/min.	< 1°C/min.
Particle Size	> 100 microns	< 10 microns

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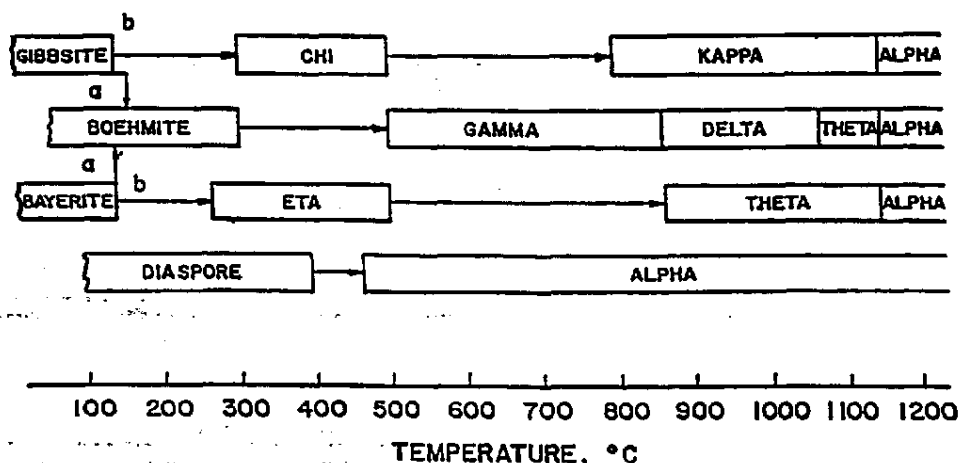


Fig. 2. Decomposition sequence of aluminum hydroxides. The transition forms (chi, eta, gamma, kappa, delta, theta) represent states of thermally induced structural reordering associated with dehydration. The χ , γ , and η forms have been generically referred to in the past as γ -alumina.³⁴

these low temperature transition forms. Given these multiple ambiguities arising from a highly dynamic system, we recommend that, rather than attempting to ascribe biologic effects to individual aluminum oxides, eg, to the γ form, the transition forms η , χ , and γ collectively be referred to as *low temperature transitional aluminas*.

To complete the confusion, international crystallographic convention prefers application of the prefix α to the closest packed—especially hexagonal—structures; the γ prefix is given generically to the cubic packed structures.³⁴ (Nordstrandite (β - $\text{Al}(\text{OH})_3$) possesses a crystalline packing arrangement intermediate between gibbsite (γ) and bayerite (α) and therefore is designated β .)

In summary, it should be readily apparent that the prefix γ has been applied for a multiplicity of reasons both to crystalline alumina minerals as well as to the transitional form.

In addition to the foregoing relatively well-defined crystalline minerals, various syntheses of aluminum hydroxides produce colloidal aluminas which easily coagulate to a two-phase system gel, ie, a highly dispersed colloidal solid with molecular water occupying capillary interstices. In particular, one of these gelatinous aluminas, gelatinous boehmite, is pertinent to our concerns. It demonstrates minimal crystalline structure, consisting of molecular water situated between the elemental structure layers. This leads to an enlargement of the basal spacings of boehmite. These gels can be dried to extremely fine (10^{-9} μm) and porous particulates possessing extremely large surface areas, as large as 500 m^2/g .³⁴

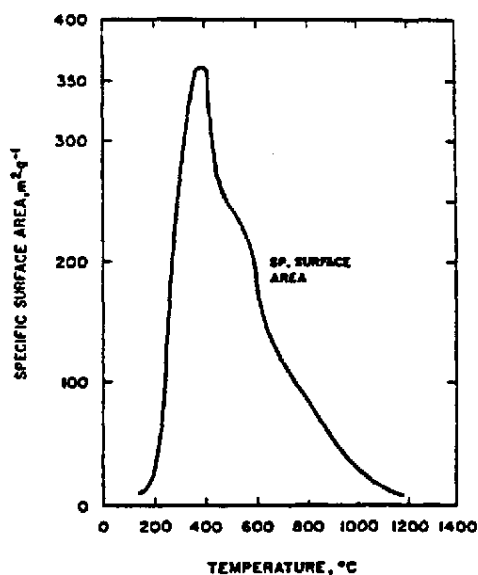


Fig. 3. Specific surface area changes resulting from heat treatment of $\text{Al}(\text{OH})_3$.³⁴

Functional Properties of Those Aluminas of Potential Biologic Interest

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Regarding α and γ designations derived from the crystallographic convention, no apparent common properties with biologic implications are presently known to occur. Because they are applied to a diverse and large number of aluminas (Table 2), with different chemical and physical forms, any lack of commonality of biologic behavior is not unexpected.

Concerning the thermally induced transitional forms (Fig. 2), the physical-chemical properties of these forms may be of importance in biologic systems. Heating alumina minerals *under specific conditions* (Fig. 2) induces these transition forms; such forms characteristically demonstrate a progressive disorganization and reorganization of crystalline structure as temperature rises through the 250 to 850°C range. Structurally, lattice voids and a network of submicroscopic cracks and spaces open.³⁴

The newly formed surfaces presented by these fissures and voids result in large surface areas characteristic of the low temperature transitional forms (Fig. 3). Concomitant with the loss of water resulting from the combination of OH^- ions ($\text{OH}^- + \text{OH}^- \rightarrow \text{H}_2\text{O} + \text{O}$), exposed Al^+ sites are formed; these act as Lewis acid sites, ie, electron acceptors. Furthermore, certain retained OH^- ions act as proton donors, Brønsted acid sites. Depending upon the local composition, O^- or OH^- ions may also function as Brønsted or Lewis bases. The aggregate of these physical-chemical alterations occurring during thermal transformation is believed responsible for catalytic activity of these alumina transition forms.³⁵ The γ , η , and χ transition forms maximally manifest these crystalline disorderings; they likewise manifest the maximum catalytic activity among these transitional forms.

As an additional consequence of these thermal transformations leading to the transitional aluminas, at approximately 300 to 600°C a marked increase in surface area occurs³⁴ (Fig. 3). This is a result of the loss of over 30% of the mass without change in the external dimensions of the crystals. With continued heating of these transitional aluminas beyond 850°C, crystalline order begins to be re-established and chemical stoichiometry is restored. With these balances restored, catalytically active sites diminish and ultimately disappear. The voids and channels are diminished and surface area becomes markedly decreased (Fig. 3). This reordering and thermodynamic stabilization reaches a maximum with the formation of α - Al_2O_3 , corundum.³⁴

As a consequence of the dehydration, a remarkably large surface area forms. Concurrent with the rise in surface area, there is proportionate increase in surface thermodynamic instability.³⁶ It is not unreasonable to suggest that the combination of chemical activity (ie, the acid-base character of the low temperature transitional alumina surfaces) and the large surface area per se are important factors controlling bioreactivity.

Relation of Particle Dimension to Carcinogenicity in Amphibole Asbestoses and Other Fibrous Minerals^{1,2}

Mearl F. Stanton,^{3,4} Maxwell Layard,^{5,6} Andrew Tegeris,⁷ Eliza Miller,^{3,8} Margaret Elizabeth Morgan,^{7,9} and Alroy Smith⁵

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ABSTRACT—In 72 experiments, durable minerals in the form of particles on respirable size and of wide chemical and structural varieties, were implanted in the pleurae of outbred female Osborne-Mendel rats for periods of more than 1 year. The incidence of induced malignant mesenchymal neoplasms correlated well with the dimensional distribution of the particles. The probability of pleural sarcoma correlated best with the number of fibers that measured 0.25 μm or less in diameter and more than 8 μm in length, but relatively high correlations were also noted with fibers in other size categories having diameters up to 1.5 μm and lengths greater than 4 μm . Morphologic observations indicated that short fibers and large-diameter fibers were inactivated by phagocytosis and that negligible phagocytosis of long, thin fibers occurred. The wide variety of compounds used in these experiments suggested that the carcinogenicity of fibers depended on dimension and durability rather than on physicochemical properties.—JNCI 1981; 67:965-975.

Work in several laboratories has indicated that diverse varieties of minerals are carcinogenic when applied directly to the pleura of the rat or hamster in the form of microscopic fibers, i.e., particles with dimensional aspect ratios of 3:1 or greater (1-9). The same minerals are much less carcinogenic when applied at equal weight and size in nonfibrous form. Further, preliminary experiments indicate that carcinogenicity correlates best with increasing numbers of fibers having both diameters of 0.25 μm or less and lengths of more than 8 μm and that the correlation diminishes with fibers of greater diameter or lesser length. Consequently, a reasonable conclusion is that the long, thin, fibrous structure is critical to the carcinogenicity of these minerals. Studies on fibrous samples within very narrow dimensional ranges would be valuable in the establishment of this hypothesis, but these ideal samples are not available. Consequently, we are faced with the correlation of carcinogenicity with fiber samples of widely mixed dimension. The purpose of this report is to correlate our best estimate of fibrous dimension with carcinogenicity for all those minerals that we have studied that are both durable and within the size range of respirable particles. This involves 72 experiments with minerals of wide chemical and structural variety. Of special interest are the data on the amphibole asbestoses: amosite, tremolite, and crocidolite, though estimates of the dimensions of the asbestoses are especially liable to error. Chrysotile, although as carcinogenic as the amphiboles at comparable dimensions, could not be included since it has proved difficult to be measured with any degree of precision.

MATERIALS AND METHODS

None of the methods were appreciably different from those described in earlier papers (4, 6, 9-11). Consequently, only modifications of methods are detailed here. A standard 40-mg dose of particles uniformly dispersed in hardened gelatin was applied by open thoracotomy directly to the left pleural surface of 12- to 20-week-old, outbred female Osborne-Mendel rats. In each experiment, 30-50 rats were treated and followed for 2 years, at which time the survivors were killed. All rats were necropsied and all lesions examined histologically. A positive response was the occurrence of pleural sarcomas that resembled the mesenchymal mesotheliomas of man, developing after the 1st year (12). Three types of controls were considered: untreated rats, rats that received thoracotomies but no pleural implant, and rats with pleural implants of nonfibrous material. There were two types of spontaneous tumors that could cause confusion: the fibrosarcomas of left mammary glands and the subcutaneous fibrosarcomas induced by suture material. Vigilance and early surgical removal accounted for most mammary tumors; the use

ABBREVIATIONS USED: alumin=aluminum oxide; attapul=attapul-gite(s); crocid=crocidolite(s); dawson=dawsonite(s); halloy=halloysite(s); UICC=International Union Against Cancer; wollaston=wollastonite(s).

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² The guidelines for the care and use of laboratory animals were followed as set forth by the Committee on Revision of the Guide for Laboratory Animal Facilities; by the Guide for the Care and Use of Laboratory Animal Resources, the National Research Council; and by the National Institutes of Health.

³ Laboratory of Pathology, Division of Cancer Biology and Diagnosis, National Cancer Institute (NCI), National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services, Bethesda, Md. 20205.

⁴ Deceased.

⁵ Biometry Branch, Division of Cancer Cause and Prevention, NCI.

⁶ Address reprint requests to Dr. Layard at his present address: Veterans Administration Medical Center, 3801 Miranda Ave., Palo Alto, Calif. 94304.

⁷ Pharmacopathics Research Laboratories, Inc., 9705 North Washington Blvd., Laurel, Md. 20810.

⁸ Present address: 5524 Trent St., Chevy Chase, Md. 20015.

⁹ Present address: Triangle Resource Industries, P.O. Box 599, Laurel, Md. 20707.

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of synthetic, biodegradable, polyglycolic acid sutures largely eliminated suture sarcomas. An equivocal diagnosis for the origin of a tumor was necessary in less than 1% of the tumors. The probability of pleural sarcoma in each experiment was calculated by an actuarial life table method that accounts for early deaths without pleural sarcoma and provides a good means of making quantitative comparisons of one experiment with another. Details of this method are given in (13, 14).

The fibrous materials used in these experiments were mostly commercial products that were submitted by the manufacturers from an interest in their potential carcinogenicity. Consequently, they were used as received and were not especially refined except in our efforts to separate particles by size. None of the preparations appeared overtly contaminated by other materials when examined in the electron microscope. A few of the small-fibered subfractions of the fibrous materials were obtained by ball milling in a steel ball mill and consequently were contaminated with fragments of steel. In general, subfractions were obtained by simple gravimetric methods in aqueous media to separate fibers of different dimensions. These maneuvers included sedimentation, centrifugation, and filtration, which in some instances were also responsible for the reduction of the size of the particles but did not otherwise alter the particles physically or chemically. Eleven chemically and structurally different groups of fibers were available for study, and samples studied are listed in text-figure 1 and table 1. Six major groups of particles had multiple dimensional ranges; these include: crocidolites (samples crocid 1-13), glasses (glass 1-22), aluminum oxide whiskers (alumin 1-8), talcs (talc 1-7), dawsonites (dawson 1-7), and wollastonites (wollaston 1-4). Seven additional types of particles had only one or two dimensional ranges. These were the amphibole asbestoses tremolite (tremolite 1, 2) and amosite, the clays attapulgite (attapul 1, 2) and halloysite (halloy 1, 2), crystals of silicon carbide and potassium titanate (titanate 1, 2), and nickel titanate (titanate 3). All of these materials have been described elsewhere (4, 6, 10, 11, 15-18), but the following information is pertinent.

Crocidolite (crocid 1-13).—These 13 samples of South African crocidolite (an amphibole asbestos) were from four different sources. Samples crocid 1, 3, and 9 were prepared in our laboratory from a single sample of hand-cobbed, unmilled ore. The ore sample was hand milled without exposure to any metallic materials and reduced to the approximate size of commercial crocidolite. Samples crocid 6, 7, 8, 11, 12, and 13 were all prepared in our laboratory by various milling, sedimentation, and flotation methods from a single lot of standard UICC crocidolite designated crocid 5. Differences in dimension were the result of different milling times. Crocid 5, the original UICC sample, has been characterized in (19, 20-23). Samples crocid 4 and 10 were specimens prepared in a commercial laboratory from a single separate sample of

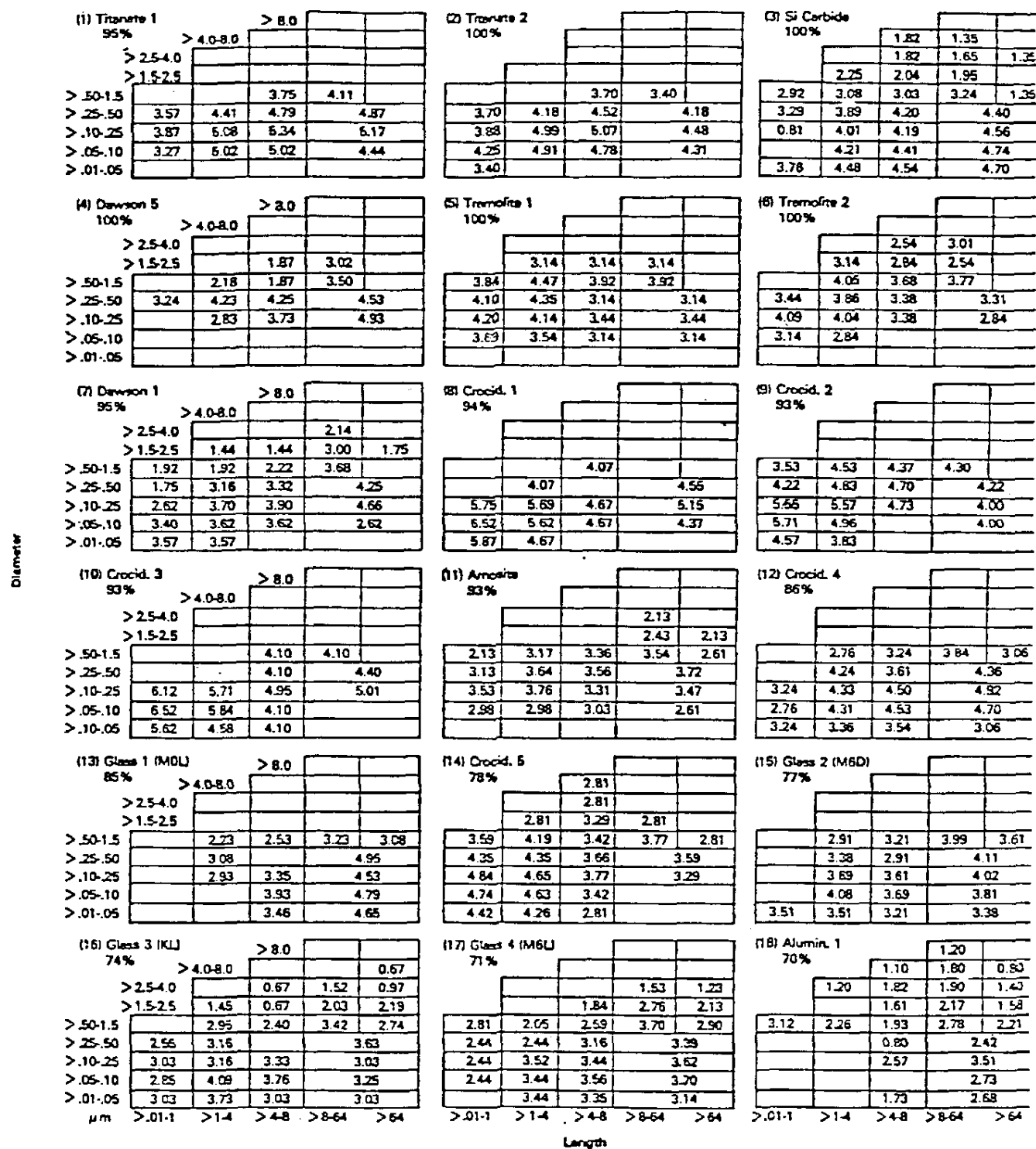
South African crocidolite and separated by centrifugation to obtain mutually exclusive size ranges from the same sample (24). The remaining sample, crocid 2, was obtained from Dr. J. C. Wagner (Medical Research Council Pneumoconiosis Unit, Penarth, Wales) as representative of the material used by him in his original experiments (25). It was our impression that any mechanical manipulation of these samples could both reduce the size of the particles by fragmentation and effectively increase the size of the particles by clumping. For this reason, probably the dimensional measurements on crocidolite are the least representative of all the fibers measured.

Glass (glass 1-22).—The first 18 of the 22 glasses were borosilicate glasses that have been previously reported and can be recognized from those publications by their letter designations (4, 10). Glasses 12, 14, 15, and 18 were preparations of typical large-diametered insulation glass fibers that were coated with a phenol-formaldehyde binder. In the early experiments, glass 18 was used as a control and also served as a vehicle for the implants. Glasses 19 and 20 were preparations of large-diametered fibrous glass that was leached to remove all elements except SiO_2 . These two glasses were exceptionally fragile and contained many irregular fragments. Glasses 21 and 22 were large-diametered extruded fibers with a microcrystalline aluminum oxide content greater than 80% (glass 21) and with a microcrystalline zirconium oxide content greater than 90% (glass 22).

Aluminum oxide (alumin 1-8).—The 8 samples of aluminum oxide were all crystalline sapphire whiskers prepared by General Technologies Corporation, Reston, Va., or by Thermokinetics Fiber Incorporated, Nutley, N.J. (15-18, 26). All of the samples were processed and selected for dimensional ranges. Of the samples, 3 were exceptionally noteworthy. Sample alumin 8 was non-fibrous, sample alumin 3 was exceptionally fine but tended to cluster in nonfibrous balls, and sample alumin 4 contained whiskers of aluminum nitride as well as aluminum oxide.

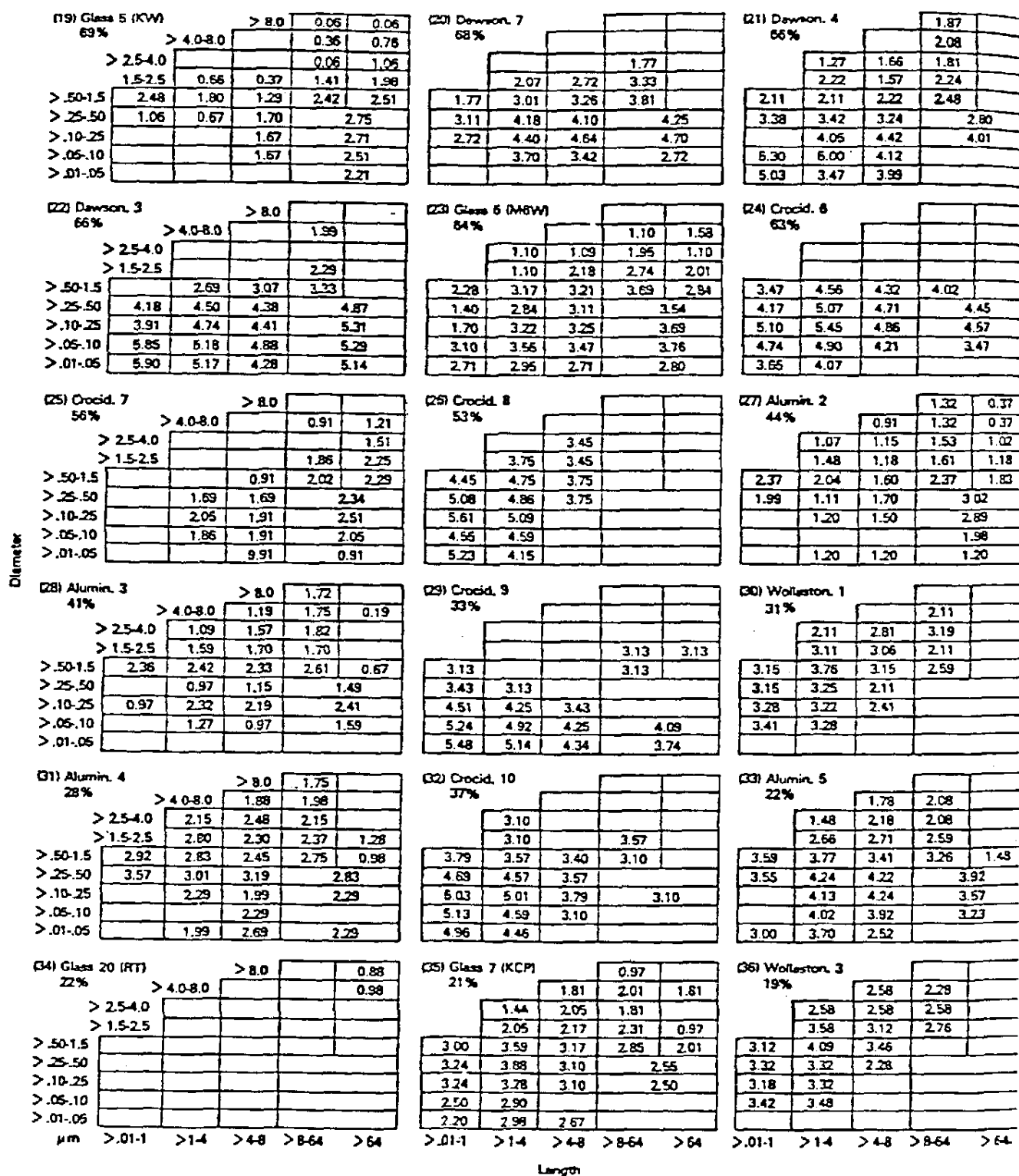
Talcs (talc 1-7).—All seven talcs were refined raw materials for commercial products. Each was from a separate and diverse source and selected to include all extreme ranges of dimension. Platelike structure was consistent and was considered in the calculation of the volume (15-18).

Dawsonite (dawson 1-7).—The 7 dawsonite samples (crystalline dehydroxy sodium aluminum carbonate $[\text{NaAl}(\text{OH})_2\text{CO}_3]$) were from several sources. The characteristics and synthesis of dawsonite can be found in (27, 28). Samples dawson 2 and 3 were synthetic crystals prepared by a commercial company (for dawson 2) and by the Bureau of Mines, U.S. Department of Interior (for dawson 3). Sample dawson 4 was a natural crystalline dawsonite from the Olduvai Gorge, Tanzania. The remaining 4 samples (dawson 1, 5, 6, and 7) were synthetic crystals from a second commercial company. These 4 samples were especially crystallized and sorted to achieve narrow ranges of size.

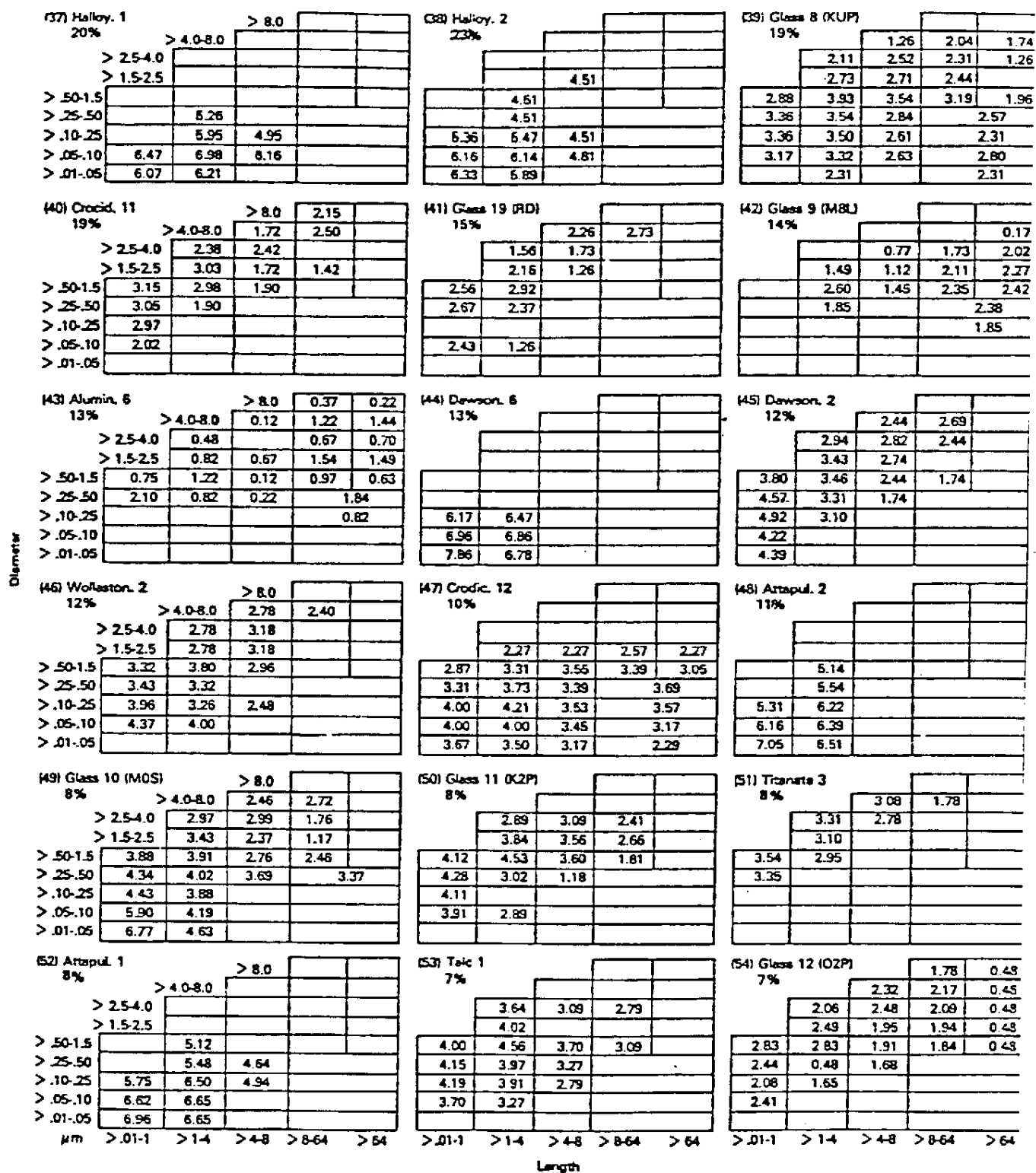


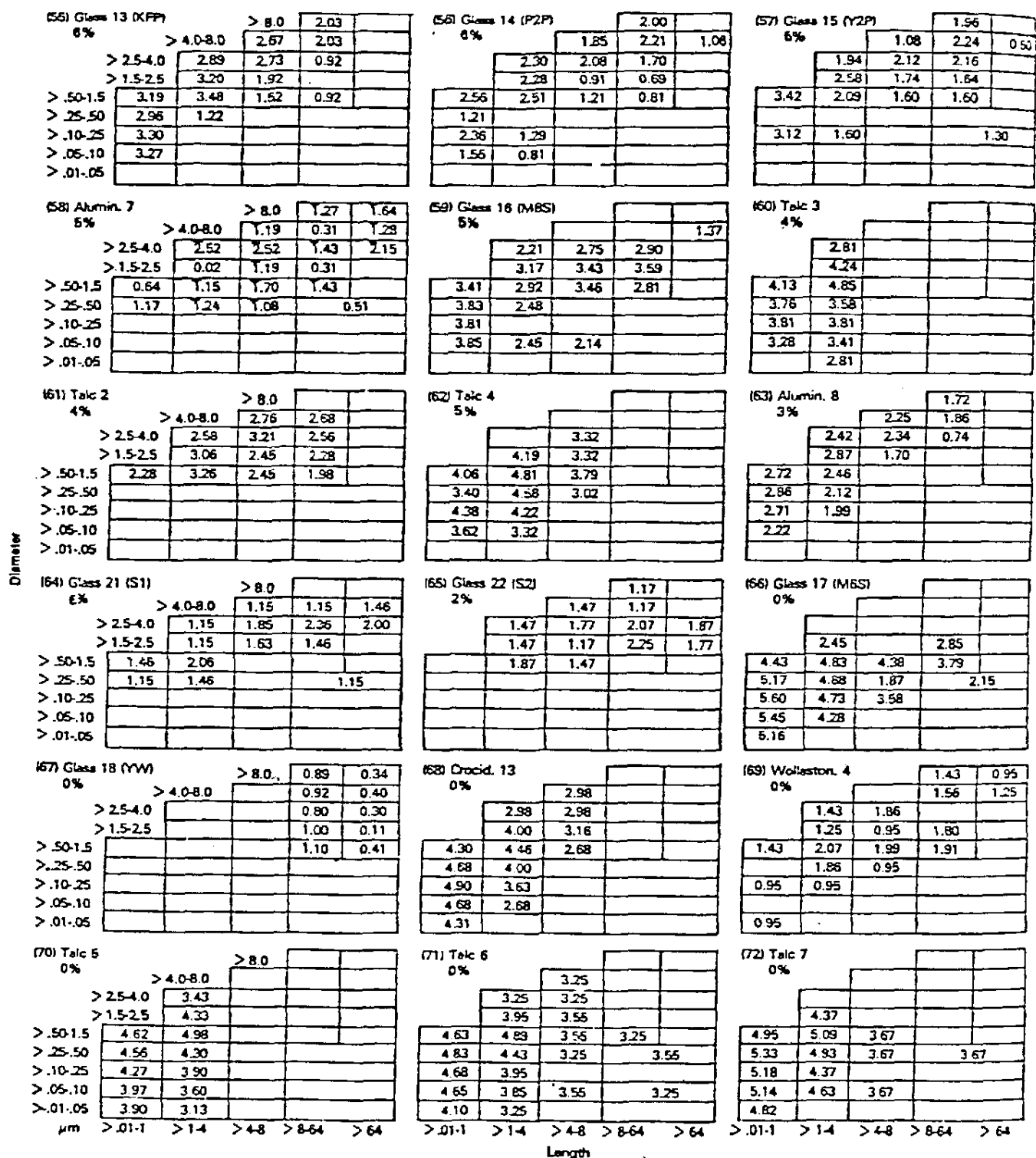
TEXT-FIGURE 1.—Fiber distribution by common log of the number of particles per microgram in each of 34 dimensional categories.

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TEXT-FIGURE 1 (continued).—Fiber distribution by common log of the number of particles per microgram in each of 34 dimensional categories.





TEXT-FIGURE 1 (continued).—Fiber distribution by common log of the number of particles per microgram in each of 34 dimensional categories.

TABLE 1.—Summary of 72 experiments with different fibrous materials

Expt No.	Compound	Actual tumor incidence	Percent tumor probability $\pm$ SD	Common log fibers/ μ g. $\leq 0.25 \mu$ m $\times$ $> 8 \mu$ m	Expt No.	Compound	Actual tumor incidence	Percent tumor probability $\pm$ SD	Common log fibers/ μ g. $\leq 0.25 \mu$ m $\times$ $> 8 \mu$ m
1	Titanate 1	21/29	95 $\pm$ 4.7	4.94	37	Halloy 1	4/25	20 $\pm$ 9.0	0
2	Titanate 2	20/29	100	4.70	38	Halloy 2	5/28	23 $\pm$ 9.3	0
3	Si carbide	17/26	100	5.15	39	Glass 8	3/26	19 $\pm$ 10.3	3.01
4	Dawson 5	26/29	100	4.94	40	Crocid 11	4/29	19 $\pm$ 8.5	0
5	Tremolite 1	22/28	100	3.14	41	Glass 19	2/28	15 $\pm$ 9.0	0
6	Tremolite 2	21/28	100	2.84	42	Glass 9	2/28	14 $\pm$ 9.4	1.84
7	Dawson 1	20/25	95 $\pm$ 4.8	4.66	43	Alumin 6	2/28	13 $\pm$ 8.8	0.82
8	Crocid 1	18/27	94 $\pm$ 6.0	5.21	44	Dawson 6	3/30	13 $\pm$ 6.9	0
9	Crocid 2	17/24	93 $\pm$ 6.5	4.30	45	Dawson 2	2/27	12 $\pm$ 7.9	0
10	Crocid 3	15/23	93 $\pm$ 6.9	5.01	46	Wollaston 2	2/25	12 $\pm$ 8.0	0
11	Amosite	14/25	93 $\pm$ 7.1	3.53	47	Crocid 12	2/27	10 $\pm$ 7.0	3.73
12	Crocid 4	15/24	86 $\pm$ 9.0	5.13	48	Attapul 2	2/29	11 $\pm$ 7.5	0
13	Glass 1	9/17	85 $\pm$ 13.2	5.16	49	Glass 10	2/27	8 $\pm$ 5.6	0
14	Crocid 5	14/29	78 $\pm$ 10.8	3.29	50	Glass 11	1/27	8 $\pm$ 5.5	0
15	Glass 2	12/31	77 $\pm$ 16.6	4.29	51	Titanate 3	1/28	8 $\pm$ 8.0	0
16	Glass 3	20/29	74 $\pm$ 8.5	3.59	52	Attapul 1	2/29	8 $\pm$ 5.3	0
17	Glass 4	18/29	71 $\pm$ 9.1	4.02	53	Talc 1	1/26	7 $\pm$ 6.9	0
18	Alumin 1	15/24	70 $\pm$ 10.2	3.63	54	Glass 12	1/25	7 $\pm$ 5.4	0
19	Glass 5	16/25	69 $\pm$ 9.6	3.00	55	Glass 13	1/27	6 $\pm$ 5.7	0
20	Dawson 7	16/30	68 $\pm$ 9.8	4.71	56	Glass 14	1/25	6 $\pm$ 5.5	0
21	Dawson 4	11/26	66 $\pm$ 12.2	4.01	57	Glass 15	1/24	6 $\pm$ 5.9	1.30
22	Dawson 3	9/24	66 $\pm$ 13.4	5.73	58	Alumin 7	1/25	5 $\pm$ 5.1	0
23	Glass 6	7/22	64 $\pm$ 17.7	4.01	59	Glass 16	1/29	5 $\pm$ 4.4	0
24	Crocid 6	9/27	63 $\pm$ 13.9	4.60	60	Talc 3	1/29	4 $\pm$ 4.3	0
25	Crocid 7	11/26	56 $\pm$ 11.7	2.65	61	Talc 2	1/30	4 $\pm$ 3.8	0
26	Crocid 8	8/25	53 $\pm$ 12.9	0	62	Talc 4	1/29	5 $\pm$ 4.9	0
27	Alumin 2	8/27	44 $\pm$ 11.7	2.95	63	Alumin 8	1/28	3 $\pm$ 3.4	0
28	Alumin 3	9/27	41 $\pm$ 10.5	2.47	64	Glass 21	2/47	6 $\pm$ 4.4	0
29	Crocid 9	8/27	33 $\pm$ 9.8	4.25	65	Glass 22	1/45	2 $\pm$ 2.3	0
30	Wollaston 1	5/20	31 $\pm$ 12.5	0	66	Glass 17	0/28	0	0
31	Alumin 4	4/25	28 $\pm$ 12.0	2.60	67	Glass 18	0/115	0	0
32	Crocid 10	6/29	27 $\pm$ 13.5	3.09	68	Crocid 13	0/29	0	0
33	Alumin 5	4/22	22 $\pm$ 9.8	3.73	69	Wollaston 4	0/24	0	0
34	Glass 20	4/25	22 $\pm$ 10.0	0	70	Talc 5	0/30	0	0
35	Glass 7	5/28	21 $\pm$ 8.7	2.50	71	Talc 6	0/30	0	3.30
36	Wollaston 3	3/21	19 $\pm$ 10.5	0	72	Talc 7	0/29	0	0

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They represent an excellent size distribution for comparison.

Wollastonite (wollaston 1-4).—Wollastonite is a naturally occurring crystalline fiber of monocalcium silicate (15-18). Four separate samples of this substitute for asbestos were received from the same Canadian mine. These were graded commercially according to size by the designation A, B, D, and F. It was apparent at low-power magnification that only grade F was completely fibrous and that these fibers were relatively large.

Tremolite (tremolite 1, 2).—The second type of amphibole asbestos studied was tremolite, a material that has a close affinity to the talcs. Both of these samples were from the same lot of asbestos and were in the optimal range of size for carcinogenesis. Comparison of these fibers indicated that they were distinctly smaller in diameter than the tremolite fibers used by Smith et al. (29).

Amosite.—The third amphibole asbestos studied was a single sample of South African amosite from the UICC standard reference samples. No efforts were made

to alter this as received, and descriptions of this sample as published should apply (19, 21, 22).

Attapulgit (attapul 1-2).—Of the natural fibers, the clay attapulgit was of particular interest because of its use in many household items that generate respirable dust. Two different samples of this complex hydrated magnesium silicate were obtained from sources in Attapulgis, Decatur County, Georgia. Both samples were considerably refined, and by electron microscopy they were seen to be composed entirely of short fibers of consistently small diameter (30). These refined clays were considered by the U.S. Bureau of Mines to be 90% or greater in purity, with the remaining 10% being quartz.

Halloysite (halloy 1-2).—Halloysite is a natural fibrous hydrated aluminum silicate, which is respirable and of minute size. The 2 samples were obtained from Dr. Walter Parham, who recovered them from the raw water supply of Hong Kong. On examination these samples were seen to have a tendency for clumping in water. In an effort to disperse the minute fibers, the second sample was sonicated and treated with sodium

hexametaphosphate. Clumping persisted in this second sample, and little difference was seen between the 2 samples.

Silicon carbide (si carbide).—One metallic crystalline whisker other than alumin was prepared by the General Technologies Corporation. Silicon carbide was a single sample, which was of exceptionally fine, uniform dimension.

Potassium octatitanate (titanate 1-3).—In addition to the synthetic crystals of dawsonite, aluminum oxide, and silicon carbide, 2 samples of fibrous crystalline potassium octatitanate (titanate 1 and 2) were tested. These were obtained from two different suppliers but they represent a single source. Because of the potential carcinogenicity of metallic nickel, the control for these 2 samples was nonfibrous, finely ground nickel titanate (titanate 3).

The 72 experiments represent all of the experiments done in a single dose range and with durable minerals and particles in the respirable range. Additional controls outside of these limits are mentioned in "Results."

Fiber measurements.—An aliquot of each of the 72 experimental mineral samples was placed on a Formvar-covered, slotted grid with an opening measuring 1×2 mm. This grid was air dried and first examined under the light microscope. If the fibers appeared satisfactorily distributed, a photomontage of the entire grid was made at a final magnification of ×3,000. The slotted grid was then placed in a Siemens electron microscope, Elmiskop 1-A, and the entire grid was scanned at low magnification. From this scan, an area that seemed to represent a typical distribution of particles in the specimen was selected for counting. At a final magnification of about ×5,000–100,000, a second photomontage was made of that section of the grid selected to include particles typical of the sample. This selected area, which generally measured about 350×150 μ m, was then located on the lower magnification montage of the grid and examined to determine whether the area chosen was truly representative of the entire grid. Finally, all fibers in the area were counted and measured individually. For the diameters, a comparative scale at the final magnification was used to measure magnified diameters that measured less than 1 mm. In most cases, the selected area counted included at least 1,000 fibers, but the actual number varied with the overall size of the particles.

Subsequently, with the aid of the IBM system 370 computer, assuming the fibers to be of cylindrical shape and using the density of the material, we were able to estimate the weight of the counted samples and the number of particles of a given dimension in the 40-mg dose administered. For the purpose of calculation, particles were grouped into 34 dimensional ranges as indicated in text-figure 1, and the number of particles per microgram in each category was calculated. Duplicate counts on the montages were done on most samples and were surprisingly similar, as were counts on different areas of the same montage. However, when studies of repeat samples from the original fibers were

made, considerable variation in counts occurred. Clearly, the method is subject to several errors; calibration of the electron microscope, deviation of particles from the assumed cylindrical shape, and sampling errors, especially where large particles are concerned, represent the major problems. Nevertheless, the estimates are probably valid to within one order of magnitude. Consequently, the counts are reported as the common log with the characteristic of the log representing the probable limit of accuracy (text-fig. 1).

RESULTS

Controls have been discussed in previous publications (4, 6, 9–11), but they were approached here in a slightly different way. In addition to untreated controls we studied rats in which open thoracotomy was performed and a noncarcinogenic material was either applied to the pleura or implanted in the lung. These 3 groups (table 2) were rats from numerous experiments that were of the same species, sex, and age and that were housed in the same quarters. The incidence of clearly apparent pleural neoplasms in untreated, aged outbred Osborne-Mendel female rats was essentially nonexistent. However, a few pleomorphic sarcomas that might be confused with pleural tumors occurred in the left thorax of both treated and, to a lesser degree, untreated controls. Although these tumors involved the thickness of the chest wall, in most cases the tumors appeared to be derived either from mammary gland fibroadenoma or from suture granuloma in the subcutaneous tissues. But there remained a few tumors for which no definite origin could be determined and which were histologically comparable with pleural sarcomas. In both the experimental groups and the control groups these questionable tumors were counted as pleural sarcomas. These essentially confusing tumors observed in the controls need to be taken into account in the assessment of the carcinogenicity of the experimental materials. The incidence of pleural sar-

TABLE 2.—Incidence of pleural sarcomas in outbred female Osborne-Mendel control rats

Time, wk	Untreated ^a	Noncarcinogenic pulmonary implants ^a	Noncarcinogenic pleural implants ^a	Combined controls ^a
12–52	1/113	0/49	0/47	1/209
53–65	0/15	2/26	1/72	3/113
66–78	0/26	4/50	3/64	7/140
79–91	0/68	1/70	2/85	3/223
92–104	0/26	1/72	10/294	11/392
105–120	0/98	1/162	1/36	2/296
121–130	1/66	0/3		1/69
131–143	0/27			0/27
144–156	0/27			0/27
156	1/22			1/22
Total	3/488	9/432	17/598	29/1,518
Percent	0.6	2.1	2.8	1.9

^a No. dead with pleural sarcomas/No. dead without pleural sarcomas.

comas in all 3 control groups combined, calculated by the life table method (13), was $7.7 \pm 4.2\%$. Comparison of this incidence with the pleural sarcoma incidence in the 72 individual experiments showed that the incidence of pleural sarcomas in a particular experimental group was significantly greater than that in the combined control group only if it exceeded 30% (see expts 1-29 in table 1).

In regard to the controls, some negative experiments with intrapleural implants not used as controls should be mentioned. These experiments included intrapleural implants that did not conform to the type of materials under consideration because the particles were either nondurable (cotton lint, gypsum, and carrageenan), were of greater than respirable size (steel shavings, steel wool, vermiculite, polyurethane, tungsten carbide, and infusorial earth), or were exclusively nonfibrous (polyacrylic nitrile, antigorite, silicon dusts, and several glasses). None of these experiments had an incidence of pleural sarcoma that was significantly greater than the 7.7% incidence of the combined control group.

From the summarization of the 72 experiments in table 1 and text-figure 1, even cursory examination of the fiber distribution suggested that particles in the relatively thin- and long-dimensional categories were associated with higher tumor probabilities. This observation was confirmed by the statistical correlation and regression techniques that were used in previous papers (4, 9, 10). The logit transformation (13) was applied to the estimated tumor probabilities (p) according to the formula: $\text{Logit} = \ln \{p/(1-p)\}$, where $\ln$ denotes the natural logarithm. The 34 dimensional categories indicated in text-figure 1 were arbitrarily grouped into 11 size categories, and the simple correlation coefficients of the logit of tumor probability with the common logarithms of numbers of particles per microgram in each of these categories was calculated (see table 3). The maximum correlation coefficient, 0.80, was with particles equal to or less than $0.25 \mu\text{m}$ in diameter and greater than $8 \mu\text{m}$ in length. There was no correlation with particles equal to or less than $4 \mu\text{m}$ in length or with particles greater than $1.5 \mu\text{m}$ in diameter, but relatively good correlations were noted with log numbers of fibers in categories greater than $4 \mu\text{m}$ in length and up to $1.5 \mu\text{m}$ in diameter, with correlation coefficients of 0.45-0.80.

The possibility of the existence of relationships between the particle size distributions and tumor prob-

abilities, which are not disclosed by the simple correlation coefficients in table 3, was explored by multiple regression methods. These methods were used to find the best-fitting function of the form: $\text{logit} = a + b_1 x_1 + \dots + b_k x_k$, where $x_1, \dots, x_k$ represent the common logs of numbers of the particles per microgram in the size categories of table 3, and $a, b_1, \dots, b_k$ are the regression coefficients to be estimated. The analysis indicated that the addition of further dimensional categories to the category with diameter equal to or less than $0.25 \mu\text{m}$ and with length greater than $8 \mu\text{m}$ did not significantly improve the explanation of the variation in tumor probability. The regression equation for the single variable (x) representing the common log of number of particles per microgram with diameters equal to or less than $0.25 \mu\text{m}$ and lengths greater than $8 \mu\text{m}$ was:

$$\ln[p/(1-p)] = -2.62 + 0.9305x \\ \quad \quad \quad (0.24) \quad (0.0834)$$

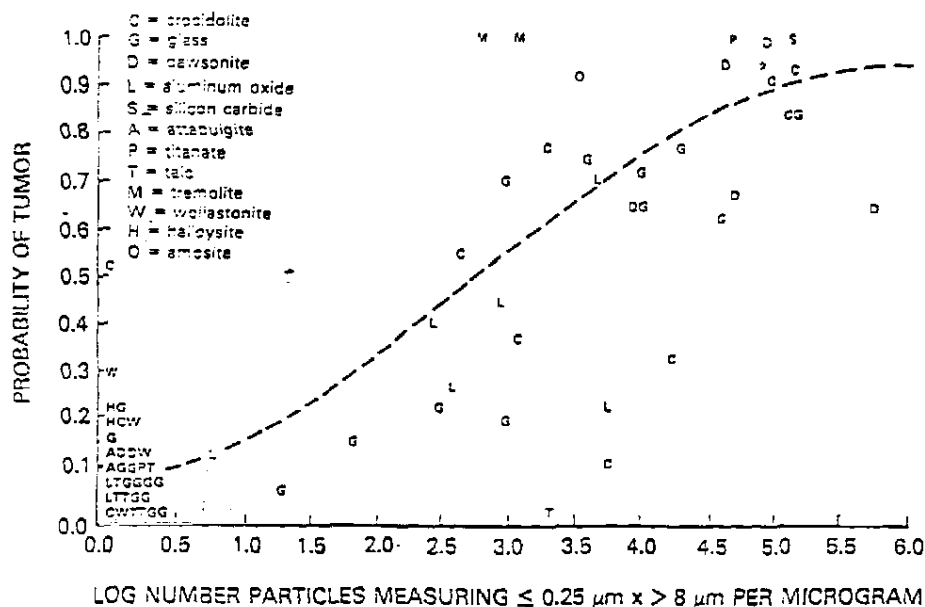
The numbers in parentheses beneath the regression coefficients are their estimated standard deviations. The relationship expressed by the above equation is highly significant ($P < 0.0001$). The estimated regression curve is illustrated in text-figure 2.

The fact that the use of additional dimensional categories did not significantly improve the fit of the regression equation does not indicate lack of carcinogenicity in other categories. The regression of logit of tumor probability on common log of numbers of particles in other categories with a diameter up to $1.5 \mu\text{m}$ and a length greater than $4 \mu\text{m}$ would also indicate a highly significant relationship. The difficulty here is that the numbers of particles in adjacent size categories were highly correlated. Better definition of the critical range of carcinogenicity would require more narrowly defined samples (i.e., particles in a narrower dimensional range). What is perhaps more likely than the existence of a narrow range of sizes within which particles are carcinogenic and outside of which they are not is that the probability of tumor falls as particle diameter increases and length decreases.

Of the 72 experiments, 7 had tumor incidences that deviated markedly from those predicted by the estimated regression line. These were: experiments 5 (tremolite 1), 6 (tremolite 2), 26 (crocid 8), 29 (crocid 9), 33 (alumin 5), 47 (crocid 12), and 71 (talc 6) (see table 1 and text-fig. 2). For the first 3 of these experiments the observed responses were higher than the predicted responses, but the high responses can in part be explained by the fact that there were substantial numbers of fibers in size categories adjacent to the category used in the regression equation. For the remaining 4 experiments, the observed response was substantially lower than the expected response; although no apparent explanation existed for these deviations, they were possibly due to inaccuracies in the assessment of functional particle size. In preparations of amphibole asbestoses (which included the crocidolites and tremolites), we observed that both

TABLE 3.—Correlation coefficients of logit of tumor probability with common logarithm of number of particles per microgram in different dimensional ranges

Fiber diameter μm	Fiber length, μm		
	≤ 4	$> 4-8$	> 8
> 4	—	-0.28	-0.30
$> 1.5-4$	-0.45	-0.24	0.13
$> 0.25-1.5$	0.01	0.45	0.68
≤ 0.25	0.20	0.63	0.80



TEXT-FIGURE 2.—Regression curve relating probability of tumor to logarithm of number of particles per μg with diameter $\leq 0.25 \mu\text{m}$ and length $> 8 \mu\text{m}$.

clumping and fragmentation of the particles were greater than those in the other minerals, and estimates of particle size distribution in duplicate samples varied most for amphibole asbestoses.

DISCUSSION

The results show that a wide variety of compounds that seem to have only dimension and durability in common are carcinogenic for the pleura of the rat. Our conclusions regarding those dimensional categories that correlate strongly with probability of pleural tumor remain essentially the same as in previous studies, namely, that probability of pleural sarcoma correlates best with fibers that measure $\leq 0.25 \mu\text{m} \times > 8 \mu\text{m}$, but that relatively high correlations were also observed with fibers in other categories having a diameter up to $1.5 \mu\text{m}$ and a length greater than $4 \mu\text{m}$. A more refined estimate of critical carcinogenic dimension may be possible if the parameters of the experiments were changed. A different animal species, lower dose, more precise means of fiber measurement, more accurate volumetric calculations, and samples with narrower dimensional ranges all might be determining factors in better assessment of the particle dimensions critical to carcinogenicity. However, we should keep in mind two points: *a) the dimensional limits are probably far from absolute, and b) we are dealing with cancer in the rat and thus extrapolation to man may not be precise.*

It is clear from the histologic studies of these experiments and of previous studies that our data offer an explanation more for the lack of carcinogenicity of short fibers and thick fibers than for the carcino-

genicity of long, thin fibers. Sections of preneoplastic pleural lesions show avid phagocytosis of both short fibers and large-diameter fibers but negligible phagocytosis of long, thin fibers. Consequently, in these experiments we may simply be measuring the efficiency of phagocytosis. Doubtless, we have little real knowledge of the way that long, thin fibers can cause cancer, but as Rous (31) once said, "Since what we think largely determines what we do, it is well that we think something." In the spirit of this quote, it might be profitable to consider potential mechanisms of cancer production by long, thin fibers. Of first importance are those hypotheses in which the progenitor of the cancer cell is not directly affected by the fiber. The long latent period would suggest that a generalized alteration either in local milieu or systemic environment might be at fault. In this regard, the abundant collagen in the preneoplastic pleural scars should be noted. Consideration of a relationship between this phenomenon and "solid-state" carcinogenesis is attractive, though the reduction of plastic sheets to small particles tends to reduce carcinogenesis. Mechanisms of solid-state carcinogenesis have been thoroughly reviewed by Brand (32), and little more need be added.

Any hypothesis concerning fibers must take into account the fact that both short fibers and thick fibers are less carcinogenic than fine, long fibers. Since dose was fixed in weight, but was different in dimension for all experiments, one might consider the surface area as a possible factor. If this were the case then fibers from the same pool that were modified only by shortening should be equal in tumor-producing capacity. Clearly, this is not true in the following experiments: 13 (glass 1, MOL) vs. experiment 49 [glass 10, MOS see (4, 10)].

and in experiment 24 (crocid 6) and experiment 25 (crocid 7) vs. experiment 40 (crocid 11), experiment 47 (crocid 12), and experiment 68 (crocid 13). However, in these examples the phagocytosis variable cannot be ruled out.

A provocative explanation relates to the ability of fine, long fibers to penetrate cells without killing them. That this can occur is evident from *in vitro* studies (33). However, simple penetration of cells by mycelia of fine dimension (a notable aspect of contamination of cell cultures by fungi) rarely produces transformation of cell cultures and thus is unlikely to produce cancer. However, mineral fibers differ from fungi in their rigidity as well as chemical content, and one easily could conceive of physical differences between the mineral fibers and mycelia that might be critical.

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Insulation Peril?

Health Studies Suggest Asbestos Substitutes Also Pose Cancer Risk

While Data Aren't Definitive,
Some Fine-Fiber Products
Have Scientists Concerned

Companies Question Findings

By **BARRY MEYER**
Staff Reporter of THE WALL STREET JOURNAL

Two decades and thousands of deaths after asbestos insulation was found to be a killer, recent health studies suggest that certain other insulation products, sometimes used as substitutes for asbestos, may also present a lung-cancer threat.

A blue-ribbon scientific panel assembled by the World Health Organization is set to consider next month whether those materials—glass fibers, mineral wool and ceramic-based fibers—pose a cancer threat to tens of thousands of workers world-wide. A decision that any or all of them do would force the affected manufacturers to label their products as possible cancer risks. It would also doubtless trigger regulatory action in the U.S. and elsewhere and spark lawsuits against a \$3 billion domestic industry that now gets little oversight.

Just how such fibers might cause cancer—and at what exposure levels—is unclear. But "if the question is, 'Do other (insulation) fibers besides asbestos cause cancer?' the answer is yes," says Philip Enterline, a University of Pittsburgh epidemiologist hired by U.S. insulation producers several years ago to study their products' hazards.

Mineral-Wool Workers

His studies show, Mr. Enterline told an international scientific conference last October, that mineral-wool factory workers have an increased lung-cancer risk. He also found a recent spate of lung-cancer deaths among glass-fiber workers exposed to fine-diameter fibers, but he said such data were too preliminary to draw any scientific conclusions. Mr. Enterline says he is also concerned about ceramic fibers, for which health data are sparse.

Makers of the materials under scrutiny all defend their products' safety. And researchers such as Mr. Enterline believe that most currently used insulating products don't appear to threaten homeowners and are less toxic than asbestos. Because of improved plant controls, some independent scientists say, any danger to current plant workers may also be low.

Nonetheless, the specter of a health crisis even vaguely resembling the asbestos disaster is sparking a furor in the insulation industry. Company scientists are scrambling for evidence to defuse Mr. Enterline's findings; some insulation producers are building defenses against future damage claims; and the safety issue is at the heart of a battle between producers of competing types of insulation.

Manville 'Concerned'

"There's no question we're concerned," says William Reitze, a health official for Denver-based Manville Corp. Bankrupted by asbestos-related death claims and punitive damage awards, Manville recently ordered its salesmen of glass-fiber products to certify in writing that they have divulged Mr. Enterline's findings to customers.

Exposure to asbestos has been linked to fatal lung cancers and other disabling respiratory diseases. Some 40,000 death and injury claims have been filed against Manville and other asbestos producers by plant workers, insulators and others. Most uses of asbestos are currently banned by federal regulations.

Glass-fiber and some other insulation products have long been known to cause skin rashes and respiratory irritation. But such materials and asbestos, several scientists say, also share a potentially fatal trait: All contain masses of small, inhalable fibers that can lodge in human lungs. Under one current scientific theory, the cancer-producing potential of any fiber is a function of its size rather than its chemistry. The most suspect: fibers that are thin, long and durable.

Scientific concern about such "fine" insulation fibers is growing. Hans Weill, a pulmonary specialist at Tulane University, says chest X-rays of insulation-plant workers exposed to fine fibers exhibit more minor abnormalities than do X-rays of workers exposed to larger fibers. Fine-fiber workers are also showing a pattern of decreased lung capacity, says Dr. Weill, who cautions that his work is preliminary.

Use Is Growing

Such warnings come as insulation producers increase fine-fiber output largely for products blown under pressure into walls and ceilings of homes and commercial buildings. Use of fine fibers is growing because they provide greater insulation than larger-sized fibers, and at lower cost, says William Setts, president of Manville's glass-fiber division.

The safety debate is putting glass-fiber producers on the defensive. At a tense two-hour meeting last month with Mr. Enterline, health officials from Manville, Owens-Corning Fiberglas Corp. and CertainTeed Corp. challenged the scientist's methods and facts. They said they hope to prove that workers' deaths from lung cancer aren't related to fiber exposure, that they may instead have resulted from other toxic compounds in the workplace or the environment.

"That is what we are trying to accomplish. Whether that turns out or not we have to see," says Robert Doban, a senior vice president at Owens-Corning, the nation's largest glass-fiber producer.

The company's response to Mr. Enterline's findings is exemplified by measures it has taken at its Newark, Ohio, glass-fiber plant. Mr. Enterline had found that workers and former workers at the plant—and at a few other plants among 11 he studied in the glass-fiber industry—had a higher-than-expected lung-cancer rate 20 years or more after their first exposure. In recent months, Mr. Doban says, a team of company engineers has scoured Newark plant records going back four decades in an effort to determine what cancer-causing agents might have been used at the facility. Retired plant personnel were questioned for the same purpose, Mr. Doban says.

Armed with their own findings regarding the Newark plant, Owens-Corning officials challenged Mr. Enterline's findings when they met with the scientist last month. Mr. Doban said company records showed sporadic use of asbestos at the Newark plant. Jon Konzen, the company's medical director, said the Newark plant had frequently been used to test glass-fiber manufacturing techniques involving any number of potentially toxic compounds.

"There were things that went on at Newark that never saw the light of day anywhere else," Dr. Konzen said.

'They're in a Jam'

The ruddy-faced Mr. Enterline isn't deterred. After the meeting, he noted that mineral-wool producers were raising similar objections to his work, but he said they hadn't supported their objections scientifically. Of the insulation industry's current plight, he remarks: "They're in a jam and they just don't know what to do."

Some companies are shoring up legal defenses. Besides requiring salesmen to disclose Mr. Enterline's findings on glass fiber, Manville recently ordered the destruction of all outdated insulation safety pamphlets, says Mr. Setts, the company official. In asbestos-related cases, large punitive damage awards had been meted out against Manville for failing to publicly disclose its up-to-date knowledge of asbestos hazards.

Industry workplace practices are also changing. For instance, Chicago-based

USG Corp., the nation's largest producer of mineral-wool products, recently banned cigarette smoking by insulation-plant workers. The move, says a USG spokesman, reflects scientific concern that smoking might intensify any lung-cancer threat posed by mineral wool. Plant workers have also been issued uniforms, the spokesman says, to prevent workers from carrying insulation fibers home on their clothing. Lung-cancer deaths in asbestos workers' families have been linked to such exposure.

Quandary for Union

The lack of definitive health data on insulation hazards is creating a quandary for workers and product users. "At this point we haven't taken any position on glass fiber because we feel the jury is still out," says James Golden, a health official with the Sheet Metal Workers International Association. On the other hand, Mr. Golden says, union officials are concerned by the lack of data. The reason: Most scientists believe that cancers develop 20 years or more after the first exposure to a carcinogen. "Some of these fibers haven't been around long enough to study their effects on humans," Mr. Golden says.

Ceramic fibers are a case in point. Sales of products using the durable fibers have boomed since the mid-1970s, reaching an estimated \$100 million last year, according to industry officials. They are used mainly in linings for industrial furnaces and as asbestos substitutes.

Health research, however, has lagged behind sales. Thus far, the two major animal studies of the materials' cancer-causing hazards have yielded mixed results. Moreover, given the latency period for lung cancer, industry scientists acknowledge that it may be too early to detect developing cancers in workers through traditional X-ray screening tests.

"The latency issue is one that has to be addressed," says Edward Horvath, medical director of occupational health for Standard Oil Co., the nation's largest maker of ceramic-based-fiber products. Dr. Horvath estimates it may take several years for such cancers, if any, to develop in exposed workers.

Banned by Navy

Some major users of such products aren't waiting. The U.S. Navy, for example, recently banned shipboard use of ceramic fibers, according to a Navy spokesman. The move, says the spokesman, came after manufacturers voluntarily related products to note that in an animal study, some ceramic fibers had produced cancerous tumors.

Along with a possible cancer threat, ceramic-based fibers pose other health problems. In a published 1986 study by Browning-Ferris Industries, for instance, the Houston-based waste-management concern warned that ceramic-based fibers used to line industrial furnaces quickly break down into cristobalite, a form of silica linked to silicosis, a fatal lung disease common among quarry and tunnel workers. Charles E. Fryman, Standard Oil's manager of industrial hygiene, says ceramic-fiber producers are aware of the cristobalite hazard and have long urged workers to use masks when removing ceramic insulation from furnaces. They have also called attention to the cristobalite risk on their labels.

Mr. Fryman acknowledges, however, that the cristobalite levels detected in the Browning-Ferris study exceeded levels predicted by manufacturers. As a result, he says, Standard Oil recently urged that improved face masks be used by workers removing ceramic insulation.

Concerns over insulation safety are also fueling a war between makers of competing products. Take the case of Richard Munson, president of National Consumer Products Marketing Inc., an Auburn, Calif.-based company that sells cellulose-based insulation, a competitor to glass fiber in the home-insulation market.

Mr. Munson founded and sponsors a group called Victims of Fiberglass, which recently placed advertisements in several U.S. newspapers carrying bold headlines that read: Consumer Warning—Manmade Asbestos (Fiberglass) Insulation in Your Attic Will Cause Lung Cancer.

Mr. Munson is also publicizing the work of a consultant he hired to measure fiber sizes contained in a blown-insulation product sold by the Valley Forge, Pa.-based CertainTeed. The consultant found that most of the products' fibers were small enough to be inhaled.

CertainTeed officials say that insulation workers are only briefly exposed to such fibers and thus don't face a health danger. Glass-fiber company officials also charge Mr. Munson with running a scare campaign. "It's obvious he has a conflict of interest," says Mr. Setts, the Manville official.

"There's no question that I have a conflict of interest," Mr. Munson says, "but so does Manville." As for any lung-cancer threat from cellulose-based insulation, epidemiologist Enterline says he isn't aware of any evidence suggesting one.

Several independent scientists say that current health data don't indicate that the insulation materials under study pose a lung-cancer threat to homeowners. "The unstudied population I'm most concerned about are people putting in insulation," says Ernest E. McConnell, a toxicologist with the federal National Toxicology Program.

Regulatory Action Likely

Whatever the case, U.S. regulatory action on glass and other insulating fibers is likely. Richard Lemen, a top official at the federal National Institute for Occupational Safety and Health, says the agency, based on Mr. Enterline's report, is reviewing whether to recommend stricter workplace exposure limits. Sir Richard Doll, a leading British epidemiologist, says he believes exposures to all insulating fibers should be held to the same level as exposure to asbestos. Glass and other insulating fibers are currently regulated in the U.S. as so-called "nuisance," or nonhazardous, dusts.

Both industry and academic institutions are planning new studies of insulation-fiber safety. Scientists who witnessed the asbestos disaster are intent on averting any similar tragedy. Says Irving Selikoff, a leading asbestos expert at New York's Mount Sinai School of Medicine: "All the resources we built to study asbestos should be drawn on now."