TO: T. G. Grumbles

FROM: M. M. Goodreau
DATE: April 13, 1989

Interoffice Communication

SUBJ: **CATAPAL ALUMINA**

VISTA

Regulations under the OSHA Hazard Communication Standard and SARA Section 313 require you to have precise information on the definition, nomenclature, and CAS number of your product to determine its regulatory status. Within Vista the terms alumina, aluminum oxide, aluminum hydroxide, etc. are used for Vista's CATAPAL Alumina's. This wide variation in nomenclature use has caused some confusion when determining the regulatory status of our alumina's. We have researched this issue to clarify the regulatory status of CATAPAL Alumina's. The following classifications and resultant regulatory requirements have been developed.

CATAPAL G and GST (calcined and ground calcined alumina) and Whiskers are believed to most accurately be defined as aluminum oxide's with the CAS number 1344-28-1. Table I (attached) shows other pseudonyms listed in the TSCA inventory for this material.

All other LCCP produced CATAPAL Alumina's are believed to be most accurately be defined as Boehmite with the resultant CAS number 1318-23-6.

CATAPAL G and GST aluminas and whiskers, defined as aluminum oxide, CAS No. 1344-28-1, are listed both by name and CAS number on the SARA Section 313 list of Toxic Chemicals. Emissions of aluminum oxide must be reported annually to the EPA. In addition, suppliers of products containing 313 chemicals must annually inform their customers of the presence of 313 chemicals in a product.

Aluminum oxide (Catapal G and GST aluminas and whiskers), CAS No. 1344-28-1, is listed both by name and CAS number in the OSHA Z-Tables and the ACGIH TLV's with a PEL/TWA of 10 mg/M^3 total dust. Because it is listed in these reference sources it is a chemical on OSHA's "floor list" of hazardous chemicals, subject to all provisions of OSHA's Hazard Communication Standard (HCS).

The products described by the CAS No. 1318-23-6 <u>are not</u> subject to SARA Section 313. As to whether they are subject to the OSHA HCS depends on Vista's independent hazard evaluation. The other "alumina's" listed in Table I are not listed by name or CAS number in OSHA's Z-Tables or ACGIH TLV's. They are, however, considered to be "nuisance particulates" which are listed by both reference sources with a PEL/TWA of 10 mg/m^3 total dust. OSHA has recently stated that "nuisance particulates" are hazardous as defined by the OSHA HCS as a result of their being listed in these reference sources. OSHA continued to say that you may perform an independent

hazard evaluation and may determine the nuisance particulate in question to be non-hazardous. Until the independent evaluation is completed, the material is assumed to be hazardous, and subject to all provisions of OSHA's HCS. After much discussion and a review of available toxicology data, we have determined that all CATAPAL alumina products, excluding CATAPAL G, GST, and Whiskers, are nonhazardous as defined by the OSHA hazard communication standard.

If I can provide further clarification on this subject, please contact me.

M. M. Goodreau

dlj
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cc: J. R. Drumwright, D. L. Cohen, W. L. McClain, G. Hoenes, W. S. Tuzinkiewicz

M. G. Hayes, K. L. Fogg-LCCP, J. T. Fenton-Ponca City

TABLE I: PSEUDONYMS AND CAS NUMBERS

1344-28-1	Al_2O_3 alumina aluminum oxide (as listed in the TSCA inventory) alumina, calcined - aluminum oxide
1318-23-6	$AlHO_2$ or $Al(OH)O$ or $Al_2O_3 \cdot H_2O$ Boehmite (as listed in the TSCA inventory) Pseudoboehmite
24623-77-6	aluminum hydroxide oxide (as listed in the TSCA inventory) $Al(OH)O$ or $AlHO_2$
21645-51-2	AlH_3O_3 or $Al_2O_3 \cdot 3H_2O$ or $Al(OH)_3OH)_3$ aluminum hydroxide (as listed in the TSCA inventory) alumina trihydrate aluminum trihydroxide aluminum hydrate hydrated alumina hydrated aluminum oxide

VISTA

Vista Chemical Company
P.O. Box 19029
Houston, TX 77224

MATERIAL SAFETY DATA SHEET

1. PRODUCT IDENTIFICATION

MANUFACTURER'S NAME	Vista Chemical Company		
ADDRESS	P.O. Box 727, Westlake, LA 70669		
TRADE NAME	VISTA CATAPAL® Alumina		
SYNONYMS	Boehmite, Al_2O_3 H_2O		
CAS NUMBER	1318-23-6		
REGULAR TELEPHONE NO.	(318)494-5403	EMERGENCY TELEPHONE NO.	(318)494-5142

2. HAZARDOUS INGREDIENTS

MATERIAL OR COMPONENT	%	HAZARD DATA
Aluminum Hydroxide Oxide	75	Nuisance Dust Inhalation Hazard

3. PHYSICAL DATA

BOILING POINT (°F)	Not applicable	SPECIFIC GRAVITY (H_2O = 1)	Not applicable
VAPOR PRESSURE (mm Hg.)	Not applicable	MELTING POINT	Not applicable
SOLUBILITY IN WATER	Nil	VAPOR DENSITY	Not applicable
APPEARANCE AND ODOR	White powder, odorless.		

4. FIRE AND EXPLOSION DATA

FLASH POINT (TEST METHOD)	Not applicable		AUTOIGNITION TEMPERATURE		Not applicable
FLAMMABLE LIMITS IN AIR, % BY VOL.		LOWER	Not applicable	UPPER	Not applicable
EXTINGUISHING MEDIA	Non-flammable material.				
SPECIAL FIRE FIGHTING PROCEDURES	Non-flammable material.				
UNUSUAL FIRE AND EXPLOSION HAZARD	Not applicable. This is an inert material and will not produce a dust explosion				

VVV 000010508

5. HEALTH HAZARD INFORMATION

FIRST AID

EYES: Flush with large amounts of water for at least 15 minutes. If irritation occurs, seek medical aid.

SKIN: Flush with water.

INHALATION: If exposed to excessive amounts, remove to fresh air.

INGESTION: Seek medical advice.

NATURE OF HAZARD

EYES: May cause physical irritation if exposed to large amounts of dust.

SKIN: No hazard under normal circumstance.

INHALATION: May cause physical irritation to upper respiratory tract. This material is a nuisance dust and as such does not produce significant organic disease or toxic effect with reasonable exposures.

INGESTION: No hazard under normal circumstances.

EFFECTS OF OVEREXPOSURE:

ACUTE OVEREXPOSURE: Physical irritation.

CHRONIC OVEREXPOSURE: Physical irritation. No known long-term toxic effects.

THRESHOLD LIMIT VALUE (TLV)

Vista recommends this material be treated as a nuisance dust.
1985-86 ACGIH TLV: 10 mg/m^3 of total dust and 5 mg/m^3 respirable dust.
OSHA PEL: 15 mg/m^3 of total dust and 5 mg/m^3 respirable dust.

TOXICITY DATA

SKIN CONTACT: Rabbit skin LD_0: 4 g/Kg
Rabbit skin irritation index: 0.2 (max. score possible is 8.0)

EYE CONTACT: Rabbit eye irritation index: 6 (max. score possible is 110)

INHALATION: Rats survived exposure to a concentration of 83 mg/l for one hour.

INGESTION: Acute oral LD_{50} in rats: 20 g/kg

VVV 000010509

SPECIAL PRECAUTIONS: AVOID INHALATION

6. REACTIVITY DATA

CONDITIONS CONTRIBUTING TO INSTABILITY

Stable and non-volatile material.

INCOMPATIBILITY
Not applicable.

HAZARDOUS DECOMPOSITION PRODUCTS

Not applicable.

CONDITIONS CONTRIBUTING TO HAZARDOUS POLYMERIZATION

Not applicable.

7. SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

Material should be picked up mechanically and placed in drums, bins, or other appropriate containers.

NEUTRALIZING CHEMICALS
Not applicable.

WASTE DISPOSAL METHOD
May be disposed of in a landfill according to local, state and federal regulations.

8. SPECIAL PROTECTION INFORMATION

VENTILATION REQUIREMENTS

Mechanical ventilation should be used to control dust levels below the PEL and TLV.

SPECIFIC PERSONAL PROTECTIVE EQUIPMENT

RESPIRATORY (SPECIFY IN DETAIL):
NIOSH approved air-purifying dust respirator.

EYE: Chemical goggles.

GLOVES: Not needed.

VVV 000010510

OTHER CLOTHING AND EQUIPMENT:
Not needed.

9. SPECIAL PRECAUTIONS

HAZARD CLASSIFICATION INFORMATION

IMO HAZARD CLASS AND NUMBER	US DOT HAZARD CLASS
No hazard classification	No hazard classification
UN NUMBER	**US DOT IDENTIFICATION NUMBER**
Not applicable	Not applicable

TRANSPORTATION AND STORAGE

USUAL SHIPPING CONTAINERS	ELECTROSTATIC ACCUMULATION HAZARD
Railroad Hopper Cars Tank Trucks Bags	None
	STORAGE/TRANSPORT PRESSURE Ambient
STORAGE TRANSPORT TEMPERATURE	**LOADING/UNLOADING TEMPERATURE**
Ambient	Ambient
	VISCOSITY AT LOADING/ UNLOADING TEMPERATURE Unknown

HANDLING AND STORAGE MATERIALS AND COATINGS

SUITABLE	UNSUITABLE
Carbon Steel Mild Steel Aluminum	Abrasion in handling systems may occur.

Alumina-related Pulmonary Disease

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.

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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 al[1] 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/m^3. Among its other properties, gelatinous boehmite usually possesses an extremely high surface area (250 to 500 m^2/g).

Gardner administered by inhalation at doses of 21 to 33 mg/m^3 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 al[1] stand in stark contradiction to the findings of King and associates[3]: in their laboratory, this same HX1010 gelatinous boehmite (referred to as γ-Al00H) produced extensive nodular and diffuse confluent fibrosis. It is important to note that King et al[3] administered this alumina via *intratracheal insufflation.*

Because of this major difference in response, further efforts in King's laboratory by Stacy et al[4] 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-Al00H, HX1010) replicated King's results, ie, moderately severe pulmonary fibronodular change.

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[3]	γAlOOH HX1010	Gelatinous boehmite	γ*	Intratracheal insufflation	0.02–0.04	250–350	–	100	+3 to +5/5 fibrosis†
Stacy et al[4]	γ-AlOOH HX1010	Gelatinous boehmite	γ*	Intratracheal insufflation	0.02–0.04	250–350	–	50	+3/5 fibrosis†
	γ-Al_2O_3 HX1010 at 850°C	η transitional	γ	Intratracheal insufflation	0.02–0.04	60–?	+	50	+5/5 fibrosis†
	γ-AlOOH Cera hydrate®	Boehmite	γ	Intratracheal insufflation	3	0.6	–	50	0 fibrosis†
	α-Al_2O_3 HX1010 at 1,200°C	α-Al_2O_3 (corundum)	α	Intratracheal insufflation	0.1–0.8‡	3	–	50	+1/5 fibrosis†
Klosterkötter[6]	γ-Al_2O_3	γ transitional	γ	Intratracheal insufflation	0.005–0.04	95–105	+	35	+3/5†
	γ-Al_2O_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]

Next, this gelatinous boehmite was heated to 850°C; the dehydration formed what Stacy referred to as γ-Al_2O_3. However, present knowledge[5] 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, α-Al_2O_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) γ-AlOOH boehmite (referred to as Cera hydrate®). 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, α-Al_2O_3 and gelatinous 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 γ-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, Klosterkötter[6] 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-

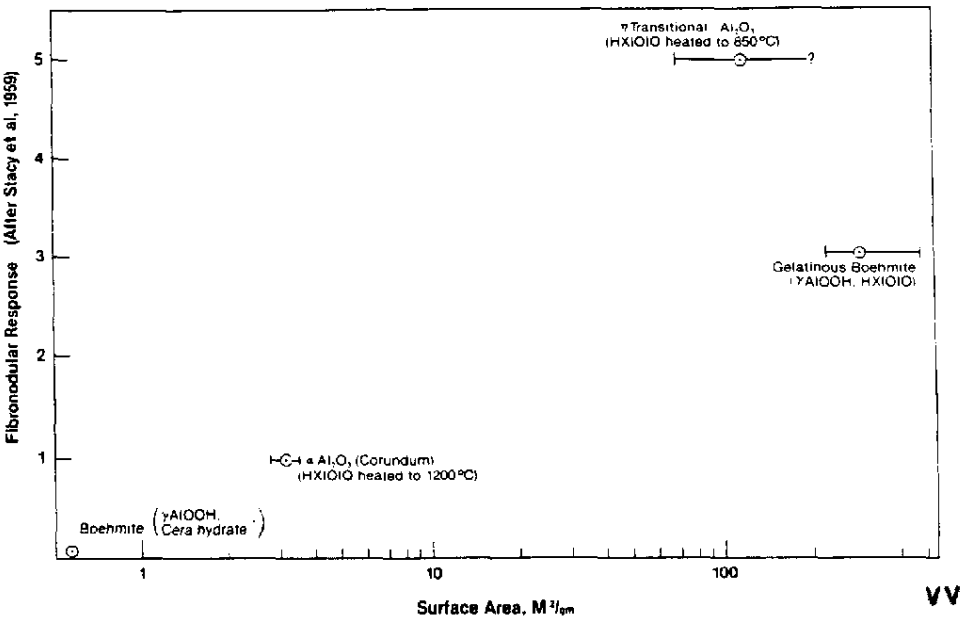

Fig. 1. Correlation of Surface Area of Aluminas with Pulmonary Fibrosis Graded According to Stacy et al.[4]

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 chemotaxic 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 lung[8] 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 results[11]; 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 α-Al_2O_3 becomes airborne, exposure of workers in this industry has been the subject of multiple epidemiologic and clinical investigations in the United Kingdom.[13,14] 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 dust[18] 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-aluminas 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 minimal [16] or absent fibronodular disease[20,21] nor excess mortality[22] 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-workers[4] with intratracheal insufflation of the low temperature (η) transitional alumina. In contrast to population studies, individual case reports from smelters note lung fibrosis[23] 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's[3] 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-workers[4] 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,[26] 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[6] do not cause fibronodular change. Yet the results of Klosterkötter[6] serve to caution against uncritical application of the inhalation model. Klosterkötter explicitly recognized that the doses he employed (ie, 33 g/m^3 for eight hours a day for 285 days) represent an exposure level which was intolerable for his laboratory personnel.[6]

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 process[27]) 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 hydrate[5] *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 diaspore, 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 Merwin[28] in 1916 assigned the Greek letter prefix β to a high temperature alumina later shown to contain alkali or alkaline earth atoms. Haber[29] in 1925 divided

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

Preferred Chemical Formula and Name[33]	Mineral Name[32]	Formerly Applied Designation[34]	American System[35, 37]	European System[29]	X-ray Crystallograph Classification[34]
$Al(OH)_3$, 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
	Diaspore	Alumina monohydrate	α, β	α	α
Aluminum oxide	Corundum	α-Alumina	α	α	α

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 appelations were applied without regard for structure.

Later, as these aluminum compounds were used in industrial processes, different nationally based varient 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 Ulrich[31] 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[39] 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[39] 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 Symposium[33] recommendation giving each transitional form an individual, specific Greek prefix designation (Fig. 2), present industrial/commercial nomenclature often fails to differentiate between

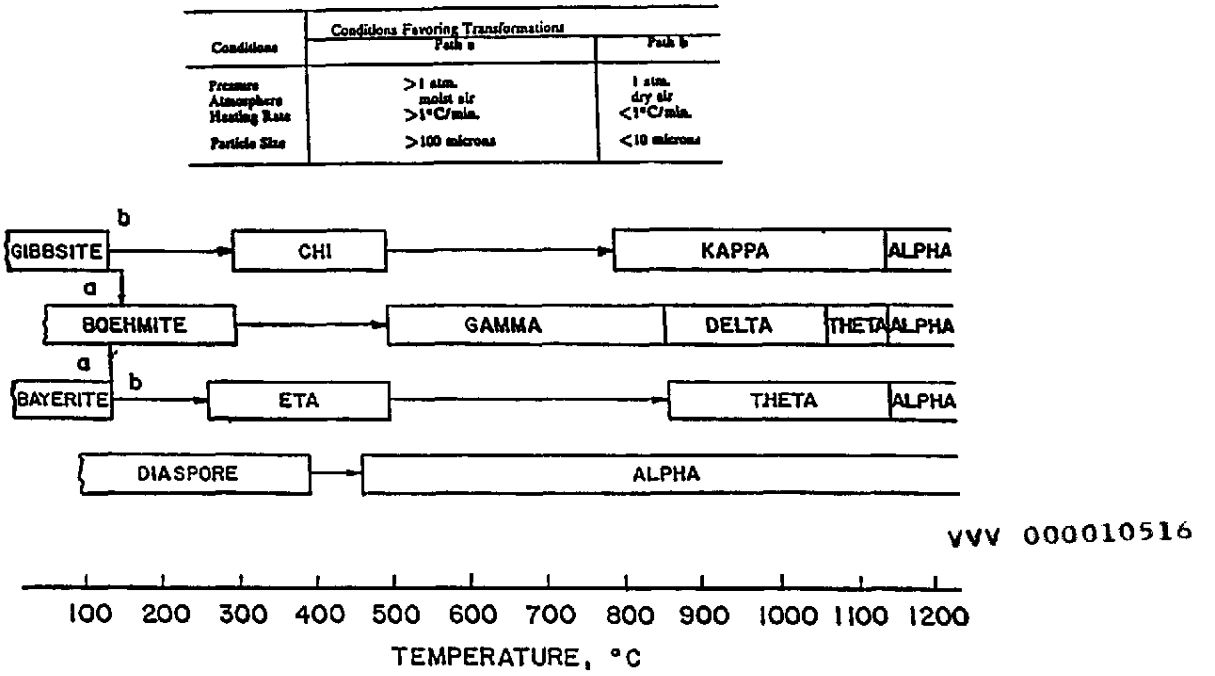

Fig. 2. Decomposition sequence of aluminum hydroxides. The transition forms (chi, eta, gamma, kappa, delta, theta) represent states of thermally induced structural reordering associated with dehydration. The χ, γ, and η forms have been generically referred to in the past as γ-alumina.[34]

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-$Al(OH)_3$) 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^{-2} μm) and porous particulates possessing extremely large surface areas, as large as 500 m^2/g.[34]

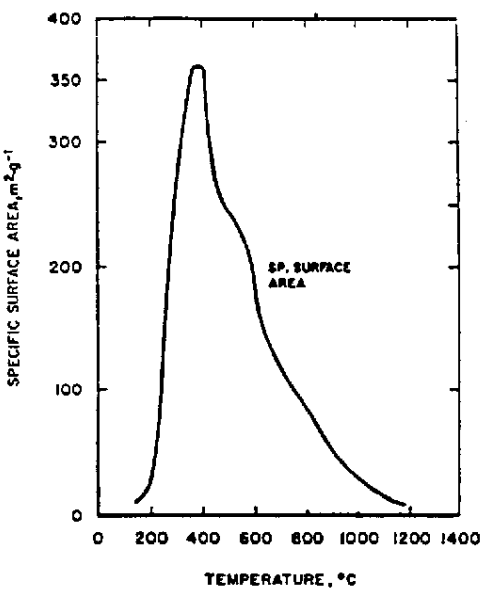

Fig. 3. Specific surface area changes resulting from heat treatment of $Al(OH)_3$.[34]

Functional Properties of Those Aluminas of Potential Biologic Interest

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 ($OH^- + OH^- \rightarrow H_2O + O$), 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 occurs[34] (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.

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