NATIONAL CENTER FOR DRUGS AND BIOLOGICS
FOOD AND DRUG ADMINISTRATION
PUBLIC HEALTH SERVICE
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Panel on Review of Allergenic Extracts
Category IIIA Reclassification, Final Report
December 1983

The Panel on Review of Allergenic Extracts was re-established on March 2, 1982 by a notice in the FEDERAL REGISTER (47 FR 8763). The Panel was reconvened to reclassify all assigned products previously designated by review panels or FDA as "Category IIIA". Category IIIA applies to those licensed products judged to fall under the description of 21 CFR 601.25 (e)(3), meaning that the available data were sufficient to classify as safe and effective, but that the products should remain on the market pending further testing. The Category IIIA designation was based on a favorable potential benefit-to-risk judgment. Regulations removing the Category IIIA option and establishing Section 601.26 were published in the FEDERAL REGISTER of October 5, 1982 (47 FR 44062). The products assigned to this Panel are the Polyvalent Bacterial Vaccine (with no U.S. Standard of Potency) licensed to Cutter Laboratories (42 FR 58266) and all products classified in Category IIIA in the report of the Panel on Review of Allergenic Extracts final report of March 13, 1981, as announced in the April 21, 1981 FEDERAL REGISTER (46 FR 22808).

The Commissioner of Food and Drugs appointed the following Panel members:

Chairman, Paul M. Seebohm, M.D., Professor, Department of Internal Medicine, Executive Associate Dean, College of Medicine, University of Iowa, Iowa City, Iowa.

Elliot F. Ellis, M.D., Professor and Chairman, Department of Pediatrics, State University of New York at Buffalo, Childrens Hospital, Buffalo, New York.

Clifton T. Furukawa, M.D., Clinical Associate Professor of Pediatrics, University of Washington, Seattle, Washington.

Ralph Hale, M.D., Clinical Assistant Professor of Internal Medicine, Kansas University Medical Center, Wichita, Kansas.

David A. Levy, M.D., Professor of Immunology & Infectious Diseases, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, Maryland.

Floyd J. Malveaux, M.D., Ph.D., Associate Professor of Medicine and Chairman of Allergy, Howard University Hospital, Washington, D.C.

Thomas E. Van Metre, Jr., M.D., Associate Professor of Medicine, Johns Hopkins University, Physician in Charge, Allergy Clinic, Johns Hopkins Hospital, Baltimore, Maryland.

The Consumer Liaison Representative was Mrs. Barbara Mae Layman, 261 Ringgold Street, Waynesboro, Pennsylvania. The Industry Liaison Representative was Lowell Zeleznick, Ph.D., Director, Research and Development, New Products Evaluation, Allergan Pharmaceuticals, Inc., Irvine, California. Robert E. Reisman, M.D., Clinical Professor of Medicine and Pediatrics, State University of New York, served as a consultant to the Panel. Clay Sisk, Office of Scientific Advisors & Consultants, National Center for Drugs and Biologics served as Executive Secretary.

The Panel held reclassification meetings on November 19-20, 1982, February 18-19, 1983 and June 3-4, 1983.

In the October 5, 1982 announcement, interested persons were requested to submit any new data for consideration by the review panel. A data submission was received from Miles Pharmaceuticals, Division of Miles Laboratories, West Haven, Connecticut, in support of their "Allpyral" line of alum-precipitated allergenic extracts. A letter was received from Center Laboratories, Port Washington, New York, calling attention to information in support of the safety of aluminum, a component of their "Center-Al" line of alum-precipitated allergenic extracts.

Regarding the criteria for effectiveness, the October 5, 1982 notice stated that it will be the obligation of the Panel conducting the reclassification review to reexamine the scope of evidence currently available regarding the effectiveness of allergenic extracts and determine what the current practices are for the responsible assessment of their effectiveness. Furthermore, the Panel was charged with determining whether these contemporary standards are readily applicable to each type of product under review. The standards should be consistent with available technology and readily obtainable through the use of clinical and laboratory methodology that has already been recognized by the general scientific community as practical and applicable to the products under review.

The Panel was asked to recommend which products should be designated under §601.25(e)(1), called "Category I" and §601.25(e)(2), called "Category II." An option was provided under §601.25(e)(2)

for those products recommended to be designated as safe and presumptively effective and to remain on the market pending completion of further testing because there is a compelling medical need and no suitable alternative therapeutic, prophylactic, or diagnostic agent that is available in sufficient quantities to meet current medical needs. This option was called "Category IIA."

The Panel submitted the following recommendations:

A. STANDARDS FOR PRODUCT CATEGORIZATION

The Code of Federal Regulations, Title 21, Section 601.25 (d)) defines the standards for safety, effectiveness and labeling that are to be used by review panels in determining their recommendation for the continued or discontinued marketing of currently marketed biologics. It states that proof of safety should consist of adequate tests to show the biological product is safe, including results of significant human experience during use. In the case of allergenic extracts, there has been significant human experience which generally has demonstrated that they are safe when prudently administered. Serious and fatal reactions have occurred following errors in dosage in association with their use in both diagnosis and treatment. The number of such adverse reactions has been few considering the millions of doses given annually over a period of some 70 years. There are, however, concerns about the potential toxicity of substances that may be added to allergenic extracts to modify absorption or in some other manner affect their antigenicity. Currently, aluminum is an ingredient about which there is the greatest safety concern because of its alleged association with oncogenesis in animals and pathologic findings in humans with Alzheimer's disease.

Except for alum-precipitated allergenic extracts, safety was not judged to be a significant factor in the evalution of Category IIIA products when they are used in accordance with proper labeling instructions concerning the possibility of severe anaphylactic reactions.

In contrast to safety, proof of effectiveness for the diagnosis and treatment of immunoglobulin E-mediated (IgE-mediated) allergies was the major consideration for the reclassification of the Category IIIA products into Category I or II. In its reports of March 13, 1982, report the Panel required evidence of adequate clinical investigation to classify a product into Category I. Chapter 601.25 (d)(2) provides several exceptions for the requirement of controlled clinical investigations when such investigations are not reasonably applicable to the biologic product or essential to the validity of the investigation and states that an alternate method of investigation is adequate to substantiate effectiveness.

Alternate methods suggested are:

> "Serological response evaluation in clinical studies and appropriate animal and other laboratory assay evaluations may be adequate to substantiate effectiveness where a previously accepted correlation between such data and clinical effectiveness already exists."

For example, if in fact clinical improvement in hayfever were found to relate to the blood level if IgG antibody to a particular allergen, then one might relate the capacity of an allergen to induce IgG antibody in a human to its clinical effectiveness. Although such a correlation between antigenicity of an allergen to clinical effectiveness

has not been established, it is true that allergens shown to be effective in controlled clinical trials also induce specific IgG antibodies.

Serological responsiveness might be used as a minimum requirement in the reclassification of IIIA products. Allergens without antigenicity are not likely to be clinically effective.

The regulation continues: "Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing."

The Panel considered definitions of these latter methods.

"Partially controlled" could mean the patient is blinded to the identity of the study materials, but the physician is not, or vice versa. It could also mean that the patient's pre-treatment condition is compared to his condition during treatment and/or his post-treatment condition.

An "uncontrolled study" could mean a clinical trial in which all patients took the same treatment; and the outcome was evaluated by the physician-observers based on the degree of improvement reported by the patients.

A "documented clinical study" by a "qualified expert" could be a report of cases which appeared to be improved or not improved as a result of their treatment. Such studies could be either partially controlled or uncontrolled as stated above. The two components of this method were regarded as indistinguishable, that is, the quality of the expert must be judged by the quality of the documented study and vice versa. A valid study appearing in a peer-reviewed journal and describing a series of patients who are reactive to allergens and in whom

injection therapy results in clinical improvement would constitute the most important evidence for effectiveness.

After considering the above criteria and the guidance in the preamble of the October 5, 1982 FEDERAL REGISTER, the Panel developed the following guidelines for recommending that a Category IIIA product be reclassified into Category I rather than Category II for diagnosis of IgE-mediated allergic disease:

(a) The accumulated evidence indicates that the extract is safe.

(b) The extract is derived from a well-defined source material.

(c) The extract has definable or measurable constituents and is capable of being standardized.

(d) The extract has been demonstrated to be effective by skin testing in appropriately allergic and nonallergic subjects and/or by radioallergosorbent testing (RAST) with appropriate sera.

(e) In lieu of (d) it is acceptable if the extract is closely analogous to products shown to be effective.

(f) The product is properly labeled.

For Category I for use in immunotherapy of IgE-mediated allergic disease, the above criteria for diagnosis must first be met. In addition, an extract must be also demonstrated to be effective for immunotherapy by a valid clinical study or by analogy with products for which effectiveness has been shown.

Category II was recommended for those products judged as not meeting the above criteria. In reviewing the conditions in §601.26(c)(2) the Panel does not believe this section applies to any of the products

and diseases under review. Therefore, no products are recommended for Category IIA.

B. POLLEN ALLERGENIC EXTRACTS

1. Pollen extracts for diagnosis. Most pollen allergenic extracts employed frequently for diagnosis of allergic disease were classified in Category I for diagnosis in the previous Panel report because published studies indicated that they were effective for diagnosis. The remainder were classified in Category IIIA for diagnosis because they had not been shown to be effective for diagnosis by a valid controlled published study. All of these Category IIIA for diagnosis extracts have been accepted by practicing allergists or by the authors of standard allergy textbooks as effective for diagnosis. They fall into two groups which are identified in Tables 1 and 2.

a. Group A. Group A is comprised of extracts of pollens which are related botanically to pollens in extracts which were classified in Category I for diagnosis in the previous Panel report. A good example is southern ragweed (Ambrosieae bidentata) extract which is closely related to various ragweed extracts in Category I for diagnosis. The Panel is of the opinion that the most appropriate diagnostic allergenic extract for a patient allergic to a specific pollen species is generally an extract of that specific species of pollen. Thus, for an allergic patient living where southern ragweed grows and who is actually allergic to southern ragweed pollen, an extract of southern ragweed pollen is appropriate and should be available for use in diagnosis. Though, by definition, extracts of pollens in Category IIIA for diagnosis have not been proven effective, many of those pollens are related

to others which have been proven effective in a valid study. The Panel presumes that the Category IIIA diagnostic extracts listed in Table 1, if they were properly standardized, could be proven effective for the diagnosis of patients sensitive to those specific pollens if valid studies were done. However, such studies may never be accomplished because of the small demand for most if not all of the extracts in Category IIIA for diagnosis in Table 1.

RECOMMENDATION. The Panel recommends that when properly standardized, those pollen extracts previously placed in Category IIIA for diagnosis and listed in Table 1 be reclassified into Category I for skin test diagnosis.

b. Group B. Group B is comprised of extracts of those pollens which are not related botanically to pollens in extracts classified in Category I for diagnosis in the previous Panel report. A good example is the extract of common cattail (Typha latifolia). In these instances, there is no published evidence which indicates that pollens in these families are responsible for IgE mediated allergic diseases with symptoms of respiratory tract allergy such as hay fever. Neither is there evidence that positive skin tests and/or radioallergosorbent tests can be obtained with the specific pollen extract. The Panel is of the opinion that the field of allergy would be served best by taking such extracts off the market until there are studies which demonstrate that positive skin tests in patients are correlated with evidence of symptoms of respiratory tract allergy after exposure to the pollen. Such studies would demonstrate also that IgE-mediated respiratory allergy to these pollens does, in fact, exist.

RECOMMENDATION. The Panel recommends that pollen extracts listed in Table 2 which were in Category IIIA be reclassified into Category II for skin test diagnosis.

2. Pollen extracts for immunotherapy. Few pollen extracts were classified in Category I for immunotherapy in the previous Panel report because only these few had been shown to be effective for immunotherapy in appropriately controlled published studies. Many were classified in Category IIIA for immunotherapy. These Category IIIA extracts had not been shown to be effective by controlled studies but rather they have been accepted by allergists and by the authors of standard allergy textbooks as effective for diagnosis and immunotherapy. In some instances, they have been proven effective for diagnosis in a valid study. The extracts which were in Category IIIA for immunotherapy fall into two groups which are identified in Tables 1 and 2.

a. Group A. Group A is comprised of extracts classified in the previous report in Category I for diagnosis, plus those classified previously in Category IIIA for diagnosis which are now recommended for reclassification into Category I for diagnosis of IgE-mediated allergic diseases such as hayfever and asthma. The Panel presumes that any properly standardized extract which is effective for such skin test diagnosis and, which contains an adequate amount of the significant allergens, is safe when properly employed and could be proven effective for immunotherapy by a valid clinical study. The Panel recognizes that controlled studies have not been done with these extracts because such studies are difficult, costly and time-consuming. Where a weed (e.g.,

short ragweed), a grass (e.g., timothy and orchard), or a tree (e.g., mountain cedar) pollen extract has been tested in an appropriate manner, it has been shown to be effective for immunotherapy.

RECOMMENDATION. The Panel recommends that the extracts listed in Table 1 which were previously in Category IIIA for immunotherapy be reclassified into Category I for immunotherapy.

b. Group B. Group B is composed of extracts classified in the previous report in Category IIIA for diagnosis and now recommended for reclassification in Category II for immunotherapy. For these extracts (listed in Table 2) the Panel has found no appropriate, published evidence which indicates that these pollens are responsible for IgE-mediated allergic diseases with symptoms of respiratory tract allergy. Neither is there evidence that positive skin tests and/or radioallergosorbent tests can be obtained with the specific pollen extract. The Panel is of the opinion that the field of allergy would be served best by taking such extracts off the market until properly controlled studies are accomplished which prove that they are effective for diagnosis. Such studies should demonstrate also that IgE-mediated respiratory tract allergy to these pollens does, in fact, exist. When and if proven effective for skin test diagnosis, these extracts could be placed in Category I for immunotherapy as were the extracts in Table 1.

RECOMMENDATION. The Panel recommends that the extracts listed in Table 2 which were previously in Category IIIA for immunotherapy be reclassified in Category II for immunotherapy.

The Panel recognizes that the list of pollen extracts reviewed is not inclusive of all marketed products, partially because of the various systems of classifications that have been used. Therefore, the Panel recommends that the FDA Office of Biologics Research and Review accept similar evidence as mentioned above in considering the inclusion of other extracts of pollens in the individual manufacturer's license.

TABLE 1

Pollen Extracts Recommended for Category I[1/]

Taxonomic Classification	Common Name	Previous Category Recommendations: Diagnosis	Previous Category Recommendations: Immunotherapy
COMPOSITAE FAMILY	COMPOSITE, SUNFLOWER		
Ambrosieae	Ragweed Tribe		
Ambrosia artemisiifolia			
syn. A. elatior	short ragweed	I	I
A. trifida	giant ragweed	I	IIIA
A. bidentata	southern ragweed	IIIA	IIIA
A. psilostachya	western ragweed	I	IIIA
A. confertiflora syn. franseria confertiflora or tenuifolia	false or slender ragweed	IIIA	IIIA
A. acanthicarpa syn. Franseria acanthicarparpa	bur ragweed	IIIA	IIIA
A. deltoidea syn. F. deltoidea	rabbit bush	IIIA	IIIA
A. dumosa syn. Franseria dumosa	burroweed	IIIA	IIIA
A. ambrosiaides syn. Franseria Ambrosiaides	canyon ragweed	IIIA	IIIA
(Taxonomic Name not Supplied)	wooly ragweed	IIIA	IIIA

1/ Category I for skin test diagnosis and immunotherapy.

TABLE 1--con.

Pollen Extracts Recommended for Category I

Taxonomic Classification	Common Name	Previous Category Recommendations: Diagnosis	Previous Category Recommendations: Immunotherapy
COMPOSITAE FAMILY--con.	COMPOSITE, SUNFLOWER		
Iva	Ragweed Tribe		
Iva xanthifolia syn. cyclachaena xanthifolia	burweed marsch elder	I	IIIA
I. annua syn. ciliata	rough marsh elder	I	IIIA
I. frutescens	high tide bush	IIIA	IIIA
I. microcephala		IIIA	IIIA
I. angustifolia		IIIA	IIIA
I. toxensis		IIIA	IIIA
I. axillaris	poverty weed	IIIA	IIIA
I. acerosa		IIIA	IIIA
I. nevadensis		IIIA	IIIA
I. ambrosiaefolia		IIIA	IIIA
Hymenoclea	winged ragweed	IIIA	IIIA
Dicoria		IIIA	IIIA
Xanthium	clicoria cocklebur	IIIA	IIIA
Anthemideae	Tansy Tribe		
Arthemisia	common sage brush	I	IIIA
A. filifolia	sand sage brush	I	IIIA

TABLE 1--con.

Pollen Extracts Recommended for Category I

Taxonomic Classification	Common Name	Previous Category Recommendations: Diagnosis	Previous Category Recommendations: Immunotherapy
COMPOSITAE FAMILY--con.	COMPOSITE, SUNFLOWER		
Anthemideae	Tansy Tribe		
Artemisia californica	coastal sage brush	I	I
A. ludoviciana	prairie sage	I	IIIA
A. frigida	pasture sage	I	IIIA
A. caudata	tall wormwood	I	IIIA
A. annua	annual sage	I	IIIA
Other Artemisia species		none	none
Insect Pollinated Composites			
Heliantheae	sunflower	IIIA	IIIA
Solidago	goldenrod	IIIA	IIIA
Callistephus	aster	IIIA	IIIA
Chrysanthemum	chrysanthemum	IIIA	IIIA
Dahlia	dahlia	IIIA	IIIA
Calendulua	zinnia	IIIA	IIIA
Cosmos	cosmos	IIIA	IIIA
Eupatorium	dog fennel	IIIA	IIIA
Taraxacum	dandelion	IIIA	IIIA
Helenium	sneezeweed	IIIA	IIIA

TABLE 1—con.

Pollen Extracts Recommended for Category I

Taxonomic Classification	Common Name	Previous Category Recommendations	
		Diagnosis	Immunotherapy
AMARANTHACEAE FAMILY	AMARANTH		
Amaranthus retroflexus	common, rough, or redroot pigweed	I	IIIA
A. Palmeri	carelessweed, Palmer's amaranth	I	IIIA
A. spinosus	spiny amaranth	I	IIIA
Other Amaranthus species		None	None
Acnida tamariscina	western water hemp	I	IIIA
CHENOPODIACEAE FAMILY	CHENOPOD, GOOSEFOOT		
Salsola pestifer	Russian thistle	I	IIIA
Salsola species			
Kochia scoparia	burning bush, Mexican firebush, summer cypress	I	IIIA
Chenopodium album	lamb's-quarter	I	IIIA
Chenopodium species		None	None
Atriplex species	saltbush	IIIA	IIIA
Beta vulgaris	sugar beet	I	IIIA
CANNABINACEAE FAMILY	HEMP		
Cannabis	hemp	I	IIIA
Humulus lupulus	hop, common	I	IIIA
H. japonica	hop, Japanese	I	IIIA

TABLE 1--con.

Pollen Extracts Recommended for Category I

Taxonomic Classification	Common Name	Previous Category Recommendations	
		Diagnosis	Immunotherapy
PLANTAGINACEAE FAMILY	PLANTAIN		
Plantago lanceolata	English plantain	I	IIIA
P. major		IIIA	IIIA
P. rugel		IIIA	IIIA
POLYGONACEAE FAMILY	BUCKWHEAT		
Rumex acetosella	sheep or red sorrel	I	IIIA
R. crispus	dock, curley	IIIA	IIIA
R. obtusifolius	dock, bitter	IIIA	IIIA
R. hymenosepalus	canaigre	IIIA	IIIA
GRAMINEAE FAMILY	GRASS		
Festuceae Tribe			
Bromus mollis	brome, soft chess	I	IIIA
B. inermis	smooth brome	I	IIIA
B. carinatus	California brome	I	IIIA
B. secalinus	brome chess	I	IIIA
B. rigidus	ripgut grass	I	IIIA
Other *Bromus* species		None	None
Festuca elatior	meadow fescue	I	IIIA
F. rubra	red fescue	I	IIIA
F. ovina	sheep fescue	I	IIIA

TABLE 1—con.

Pollen Extracts Recommended for Category I

Taxonomic Classification	Common Name	Previous Category Recommendations: Diagnosis	Previous Category Recommendations: Immunotherapy
GRAMINEAE FAMILY--con.	GRASS		
Festuceae Tribe			
Dactylis glomerulata	orchard, cocksfoot	I	I
Poa pratensis	June, meadow	I	IIIA
P. compressa	Canada bluegrass	I	IIIA
P. annua	annual bluegrass	I	IIIA
P. trivialis	rough bluegrass	I	IIIA
Hordeae Tribe			
Agropyron repens	quackgrass, couchgrass	I	IIIA
A. Smithii	western wheatgrass	I	IIIA
Triticum aestivum	wheat	I	IIIA
Hordeum jubatum	foxtail barley	I	IIIA
H. murinum	mouse barley	I	IIIA
Lolium perenne	perennial ryegrass	I	IIIA
L. multiflorum	Italian ryegrass	I	IIIA
L. tementulum	darnel	I	IIIA
Secale cereale	rye	I	IIIA
Aveneae Tribe			
Holcus lanatus	velvet, Yorkshire fog	I	IIIA
Avena fatua	wild oat	I	IIIA

TABLE 1--con.

Pollen Extracts Recommended for Category I

Taxonomic Classification	Common Name	Previous Category Recommendations: Diagnosis	Previous Category Recommendations: Immunotherapy
GRAMINEAE FAMILY--con.	GRASS		
Aveneae Tribe			
A. barbata	slender wild oat	I	IIIA
A. sativa	cultivated oat	I	IIIA
Koeleria cristata	western June grass	I	IIIA
Agrostideae Tribe			
Phleum pratense	timothy	I	I
Agrostis alba	redtop	I	IIIA
Chlorideae Tribe			
Cynodon Dactylon	Bermuda	I	IIIA
Boutaloua	grama	IIIA	IIIA
Phalarideae Tribe			
Anthoxanthum oderatum	sweet vernal	I	IIIA
Phalaris minor	Mediterranean canary	I	IIIA
P. arundinacea	reed canary	I	IIIA
P. canariensis	canary	I	IIIA
Paniceae Tribe			
Digitaria sanguinalis	crab	I	IIIA
Paspalum	dallis	I	IIIA

TABLE 1--con.

Pollen Extracts Recommended for Category I

Taxonomic Classification	Common Name	Previous Category Recommendations: Diagnosis	Previous Category Recommendations: Immunotherapy
GRAMINEAE FAMILY--con.	GRASS		
Andropogoneae Tribe			
Sorghum halepense	Johnson	I	IIIA
S. vulgare	sorghum	IIIA	IIIA
Tripsaceae Tribe			
Zea Mays	maize, Indian corn, corn	I	IIIA
CONIFERAE FAMILY	CONIFER		
Cupressinae	Junipers, Cypresses and Cedars		
Juniperus sabinoides (mexicana)	mountain cedar	I	I
J. virginiana	red cedar	IIIA	IIIA
J. bermudiana	Bermuda cedar	IIIA	IIIA
J. Pinchotii	red-berried juniper	IIIA	IIIA
J. osteosperma	Utah juniper	IIIA	IIIA
J. monosperma	one-seeded juniper	IIIA	IIIA
Other Junipurus species		None	None
Chamaecyparis Lawsoniana	Port Orford cedar or cypress	IIIA	III
Cupressus arizonica	Arizona cypress	I	IIIA
C. sempervirens	Italian or Mediterranean cypress	I	IIIA

TABLE 1--con.

Pollen Extracts Recommended for Category I

Taxonomic Classification	Common Name	Previous Category Recommendations: Diagnosis	Previous Category Recommendations: Immunotherapy
CONIFERAE FAMILY--con.	CONIFER		
Cupressinae	Junipers, Cypresses and Cedars		
C. lusitanica	Mexican or Portugese cypress	I	IIIA
C. macrocarpa	Monterey cypress	I	IIIA
C. torulosa	Indian incense cedar	I	IIIA
Cryptomeria japonica	Japanese cedar	I	IIIA
Libocedrus dacurrens	incense cedar	IIIA	IIIA
Thuja	white cedar, arborvitae	IIIA	IIIA
Abietineae	Pines, spruces, and firs		
Picus	pine	IIIA	IIIA
Picea	spruce	IIIA	IIIA
Abies	firs	IIIA	IIIA
Tauga	hemlock	IIIA	IIIA
Taxodineae	Bald cypress and sequoias	IIIA	IIIA
Taxineae	Yews	IIIA	IIIA
CASUARINACEA FAMILY	BEEFWOOD		
Casuarina	Australian pine	I	IIIA
SALICACEEAE FAMILY	WILLOW, POPLAR		
Salix	willow	IIIA	IIIA

TABLE 1—con.

Pollen Extracts Recommended for Category I

Taxonomic Classification	Common Name	Previous Category Recommendations: Diagnosis	Previous Category Recommendations: Immunotherapy
SALICACEEAE FAMILY	WILLOW, POPLAR		
Populus albus	poplar, white or silver	I	IIIA
P. tremuloides	poplar, aspen	I	IIIA
P. deltoides	poplar, cottonwood	I	IIIA
P. nigra	poplar, Lombardy	I	IIIA
JUGLANDACEAE FAMILY	WALNUT, HICKORY		
Juglans californica	California black walnut	I	IIIA
J. nigra	black walnut	I	IIIA
J. cinerea	butternut	IIIA	IIIA
J. regia	English walnut	IIIA	IIIA
Other *Juglans* species			
Carya pecan	pecan	I	IIIA
C. ovata	shellbark hickory	I	IIIA
C. glabra	whiteheart hickory	I	IIIA
C. myristicaeformis	nutmeg hickory	I	IIIA
Other *Carya* species		None	None
BETULACEAE FAMILY	BIRCH		
Betula	birch	I	IIIA
Alnus species	alder	IIIA	IIIA

TABLE 1--con.

Pollen Extracts Recommended for Category I

Taxonomic Classification	Common Name	Previous Category Recommendations: Diagnosis	Previous Category Recommendations: Immunotherapy
BETULACEAE FAMILY--con.	BIRCH		
Carpinus	American hornbean, ironwood	IIIA	IIIA
Ostrya species	ironwood, hop-hornbeam	IIIA	IIIA
Corylus	hazelnut, filbert	IIIA	IIIA
MYRICACEAE FAMILY	BAYBERRY		
Myrica cerifera	wax myrtle	IIIA	IIIA
FAGACEAE FAMILY	BEECH, OAK		
Quercus species	oak	I	IIIA
Fagus grandifolis	American beech	IIIA	IIIA
F. sylvatica	European beech	IIIA	IIIA
ULMACEAE FAMILY	ELM		
Ulmus americanus	American elm	I	IIIA
U. rubra	slippery elm	I	IIIA
U. glabra	English elm	I	IIIA
U. pumila	Chinese elm	I	IIIA
U. crassifolia	cedar or scrub elm	I	IIIA
U. serotina	September or red elm	I	IIIA
U. racemosa	cork elm	I	IIIA
U. alata	winged elm	I	IIIA

TABLE 1--con.

Pollen Extracts Recommended for Category I

Taxonomic Classification	Common Name	Previous Category Recommendations: Diagnosis	Previous Category Recommendations: Immunotherapy
ULMACEEAE FAMILY--con.	ELM		
Planera	water elm	I	IIIA
Celtis occidentalis	hackberry	IIIA	IIIA
C. tala	Argentine hackberry or tala	IIIA	IIIA
OLEACEAE FAMILY	OLIVE		
Fraxinus americana	white ash	I	IIIA
F. pennsyvanica	red ash	I	IIIA
F. texana	green ash	I	IIIA
F. velutina	mountain ash	I	IIIA
F. oregona	Oregon ash	I	IIIA
Other Fraxinus species		None	None
Olea eruopaea	olive	I	IIIA
Ligustrum	privet	IIIA	IIIA
PLATANACEAE FAMILY	SYCAMORE		
Platanus occidentalis	common native sycamore	I	IIIA
P. orientalis	oriental plane tree	I	IIIA
P. acerfolia	London plane tree	I	IIIA
P. racemosa	western sycamore	I	IIIA
HAMAMELIDACEAE FAMILY	SWEET GUM		
Liquidambar styraciflua	sweet gum	IIIA	IIIA

TABLE 1—con.

Pollen Extracts Recommended for Category I

Taxonomic Classification	Common Name	Previous Category Recommendations: Diagnosis	Previous Category Recommendations: Immunotherapy
ACERACEAE FAMILY	MAPLE		
Acer saccharinum	silver maple	I	IIIA
A. negundo	box elder, Manitoba maple	I	IIIA
A. rubrum	red maple	I	IIIA
A. platanoides	Norway maple	I	IIIA
A. pseudoplatanus	sycamore maple	I	IIIA
A. saccharum	sugar maple	I	IIIA
TILIACEAE FAMILY	LINDEN		
Tilia americana	American linden (lime, basswood)	I	IIIA
T. europaea	European linden	I	IIIA
MIMOSACEAE FAMILY	MIMOSA		
Acacia	Acacia	IIIA	IIIA
Prosopis juliflora (syn. *glandulosa*)	mesquite, kiawe	I	IIIA
SIMARUBACEAE FAMILY	AILANTHUS		
Ailanthus altissima	tree of heaven	I	IIIA
MORACEAE FAMILY	MULBERRY		
Broussonetia papyrifera	paper mulberry	I	IIIA
Morus alba	white mulberry	I	IIIA
Morus rubra	red mulberry	I	IIIA
Maclura pomifera	osage orange	I	IIIA

TABLE 1--con.

Pollen Extracts Recommended for Category I

Taxonomic Classification	Common Name	Previous Category Recommendations	
		Diagnosis	Immunotherapy
URTICACEAE FAMILY	NETTLE		
Urtica dioica (syn. U. gracilis)	great nettle	I	IIIA
U. urens	dwarf nettle	I	IIIA
Parietaria officinalis	wall pellitory	I	IIIA

TABLE 2

Pollen Extracts Recommended for Category II

Taxonomic Classification	Common Name	Previous Category Recommendations	
		Diagnosis	Immunotherapy
CYPERACEAE FAMILY	SEDGE		
Carex	sedge	IIIA	IIIA
JUNCACEAE FAMILY	RUSH		
Luzula	wood rush	IIIA	IIIA
TYPHACEAE FAMILY	CATTAIL		
Typha latifolia	common cattail	IIIA	IIIA
T. augustifolia	narrow leaf cattail	IIIA	IIIA
ARECACEAE FAMILY	PALM[1/]		
Phoenix dactylifera	date palm	IIIA	IIIA
Sabal	cabbage palm	IIIA	IIIA

1/ (Following completion of the Panel Review, letters were received from two physicians in Palm Springs, California in support of palm pollen extracts, stating that strongly positive skin reactions to palm pollen extracts occur and that palm pollen sufficiently disperses in the environment to cause symptoms. This suggests that it may be appropriate to designate palm pollen extracts in Category I. As with other new information which is submitted following the Panel meetings, the FDA will consider available data before making final category designations.)

C. EXTRACTS OF MAMMALIAN AND AVIAN ORIGIN

1. Extracts of mammalian origin for diagnosis. The mammalian extracts most frequently employed for diagnosis of allergic diseases (i.e., cat, dog and horse) were classified in Category I for diagnosis in the original Panel report because studies acceptable to the Panel indicated that they were effective and safe for diagnosis of IgE-mediated allergies.

The remainder of these mammalian Category IIIA extracts are employed for diagnosis less often than cat, dog and horse extracts. Because they had not been shown to be safe and effective for diagnosis by studies judged adequate by the Panel, most of them were classified in Category IIIA for diagnosis except those from processed furs which were in Category IIIB. These Category IIIA diagnostic extracts tend to fall into two groups.

a. Group A. Group A is composed of extracts whose composition and allergenicity have been examined in some detail. The composition and allergenicity of extracts of cow, guinea pig, mouse, rabbit, and rat hair, hair and dander and/or pelt have been studied in some detail, as noted in the Panel's original report. There is conclusive evidence that extracts in this group contain one or more potent allergens and that each is capable of inducing a typical IgE-mediated wheal and flare skin reaction in individuals with a well-documented history of allergy to the particular animal species in question. However, none of the reported studies aimed at proving their efficacy for diagnosis is without fault. Nevertheless, the Panel is of the opinion that properly standardized preparations of extracts from these five animal species

would be proven safe and effective for diagnosis of specific allergic sensitivity in appropriate patients. However, such studies may not be accomplished because the demand for these extracts is relatively limited and because the high cost of these studies would make them impractical. The Panel is of the opinion that, if properly manufactured and standardized, their safety and efficacy would be equivalent to these extracts previously classified in Category I for diagnosis.

b. Group B. Group B is composed of extracts whose composition and/or allergenic potency is largely unknown. The allergenicity of some of them has been demonstrated in only a small number of specifically sensitive individuals according to descriptions in a few published reports of uncontrolled studies or in one or another allergy textbooks, that is, it is based on anecdotal evidence.

For most of these extracts, it would be difficult to assemble enough individuals who are sufficiently sensitive to the animal in question to conduct an adequate study of their safety and efficacy. Nevertheless, by analogy with extracts in Category I for diagnosis, the Panel is of the opinion that, if properly manufactured and standardized, safety and efficacy would be equivalent to those previously classified in Category I for diagnosis.

There are exceptions to this statement, namely, with reference to human dander extracts, human hair extracts and extracts of leathers. The published evidence for the existence of IgE-mediated sensitivity of humans to allergens of human origin is not convincing. Likewise, the

evidence for the efficacy of these extracts for diagnosis of specific sensitivity to human allergens is equivocal. Leathers are prepared from animal skins by tanning or a similar denaturing process which results in the incorporation of various chemicals into the skins. Therefore, where it actually exists, sensitivity to leather may be due to these additives and not to the native mammalian proteins.

RECOMMENDATIONS. The Panel recommends that, with the exception of extracts of human dander, human hair and leathers, properly standardized extracts of the mammalian species in the above Group A and Group B be reclassified into Category I for diagnosis (Table 3). Breeds may be specified although there is little evidence justifying this. It is recommended that extracts of human dander, human hair and leathers be reclassified into Category II for diagnosis (Table 4).

c. Extracts of processed furs. In the Panel's original report, extracts of processed furs were classified in Category IIIB for diagnosis. It is the opinion of the Panel that there is no new evidence to suggest that processed furs are the source of species-specific allergenic substances. The Panel recognized that some of the extracts listed in Table I might be prepared from processed furs even though data originally submitted by the manufacturers did not identify the source materials as processed furs and, thus, this is emphasized in Table 3.

2. Extracts of mammalian origin for immunotherapy. No mammalian extracts were classified in Category I for immunotherapy in the Panel's original report because none had been shown to be safe and effective

for immunotherapy in studies acceptable to the Panel. Recent placebo-controlled studies of immunotherapy for allergy to cats and/or dogs, including one that has been reported as an abstract (Ohman, J. L., Double Blind Trial of Immunotherapy in Cat Induced Asthma, Journal of Allergy and Clinical Immunology, 71 (Supplement):91, 1983) and another in progress in Scandinavia suggest significant clinical improvement following administration of an extract of known potency.

Moreover, extracts of cat, dog and horse have been shown previously to be effective for diagnosis and were placed in Category I for diagnosis. They were regarded as probably effective for immunotherapy and were placed in Category IIIA for immunotherapy. Extracts that were classified in Category IIIA for diagnosis in the Panel's original report were also classified in Category IIIA for therapy. The Panel recognized that the appropriate studies have not been done (and may never be done) with most of these extracts because such studies are difficult, costly and time-consuming. The Panel believes that if the presently available evidence for safety and efficacy of cat extract is confirmed by additional evidence, then any properly standardized, potent mammalian extract that is effective for diagnosis likely would be proven effective for immunotherapy if an adequate placebo-controlled study were conducted.

RECOMMENDATION. The Panel recommends that extracts of the mammalian species that previously were in Category I for diagnosis or are now being reclassified into Category I for diagnosis be reclassified in Category I for immunotherapy (Table 3). Breeds may be specified but, as for diagnosis, there is no evidence to justify a requirement for breed identification. Mammalian extracts that are now classified in

Category II for diagnosis should be reclassified into Category II for immunotherapy (Table 4).

3. Extracts of avian origin for diagnosis. Extracts of eight avian species (canary, chicken, duck, goose, parakeet, parrot, pigeon and turkey) are employed with varying frequencies for diagnosis in patients with allergic diseases. These extracts were classified in Category IIIA for diagnosis in the Panel's original report because reports of acceptable studies indicating their safety and efficacy were not available to the Panel.

There is reported anecdotal evidence that various feather extracts can induce positive skin test reactions in individuals who are clinically sensitive to birds, such as birds kept as pets in their homes. The Panel regards this as an indication of the existence of IgE-mediated allergy to the avian species. However, there is inadequate evidence on the composition and allergenic potency of these extracts and on their safety and efficacy for diagnosis. The Panel is, nevertheless, of the opinion that if properly standardized extracts were available they would prove safe and effective for diagnosis. The Panel is also of the opinion that the field of allergy would be well served if adequate studies were conducted with standardized feather extracts.

RECOMMENDATION. The Panel recommends that defined avian extracts now classified in Category IIIA for diagnosis be reclassified into Category I for diagnosis. Poorly defined extracts such as a mix of "feathers and lint" and "mixed feathers" should be reclassified into Category II for diagnosis.

4. Extracts of avian origin for immunotherapy. No avian extracts were classified in Category I for immunotherapy in the Panel's original report because none had been shown to be safe and effective for immunotherapy. In fact, there is a gross lack of information about their use in treatment of proven allergy to the feathers of one or another avian species. Nevertheless, the Panel presumes that if potent, properly standardized feather extracts can be proven effective for diagnosis of allergic sensitivity in such patients, then by analogy with extracts of other defined inhalant allergens, placebo-controlled clinical studies might demonstrate that feather extracts are safe and effective when employed properly for immunotherapy. The Panel regards it as imperative that a clinical trial of at least one standardized feather extract be conducted to prove this assumption. However, feather extracts in general have been accepted by allergists and by the authors of early standard allergy textbooks as effective for immunotherapy, and the Panel believes that they should continue to be available for this use.

RECOMMENDATION. The Panel recommends that extracts of defined avian species previously classified in Category IIIA for immunotherapy should be reclassified into Category I for immunotherapy (Table 5). Poorly defined extracts such as the mix of "lint and feathers" and "mixed feathers" should be reclassified into Category II for immunotherapy (Table 6).

TABLE 3

Mammalian Extracts Recommended for Category I

Extract

Beaver (not processed fur)

Camel (not processed fur)

Cat

Chinchilla (not processed fur)

Cow

Deer

Dog

Elk

Fox (not processed fur)

Gerbil

Goat

Guinea pig

Hamster

Hog

Horse

Leopard (not processed fur)

Mink (not processed fur)

Monkey

Mouse

Muskrat (not processed fur)

Rabbit (not processed fur)

TABLE 3--con.

Mammalian Extracts Recommended for Category I

Extract
Racoon (not processed fur)
Rat
Skunk
Squirrel (not processed fur)

TABLE 4

Mammalian Extracts Recommended for Category II

Extract
Human dander
Human hair
Leathers

TABLE 5

Avian Extracts Recommended for Category I

Extract
Feathers, canary
Feathers, chicken
Feathers, duck
Feathers, goose
Feathers, parakeet
Feathers, pigeon
Feathers, turkey

TABLE 6

Avian Extracts Recommended for Category II

Extract
Feather, lint, mixed
Feathers, mixed

D. MOLD ALLERGENIC EXTRACTS

1. Mold extracts for diagnosis. Six mold allergenic extracts which are employed frequently for diagnosis of allergic diseases were classified in Category I for diagnosis in the previous Panel report because appropriate controlled published studies indicated that they were effective for diagnosis. These extracts were of the mold genera listed below.

Alternaria

Cladosporium (Hormodendrum)

Helminthosporium

Aspergillus

Penicillium

Mucor

No attempt was made by the Panel to determine which species or strains of these mold genera were to be employed in the Category I diagnostic extracts.

The remainder of the mold extracts listed were classified in Category IIIA for diagnosis. Although many of these Category IIIA extracts have been accepted as effective for diagnosis by practicing allergists and by the authors of allergy textbooks, the Panel was unable to find appropriate published evidence which unequivocally proved that these specific mold extracts were actually effective for diagnosis. The difficulty related in part to finding proof that clinical exposure to a specific mold produced symptoms of allergic disease which were due to that specific mold. Whereas there was abundant evidence which indicated

that exposures to other airborne allergens such as pollens and animal allergens produced symptoms of allergic diseases, it was difficult to prove that an individual patient was exposed to a specific species or genera of mold in his natural environment and that this exposure induced the symptoms of allergic disease which were present in the patient at a particular time. As with certain pollens, examination of the ambient air indicated that a patient usually sustained exposure to multiple molds at the same time. Therefore, in the absence of conclusive evidence of diagnostic effectiveness, the Panel based its judgments concerning the classification of mold extracts on knowledge (1) of the immunology and aerobiology of molds, (2) of the data concerning positive skin tests and RAST in patients living in environments in which airborne molds are abundant from time-to-time, and (3) of evidence that such patients may suffer allergic symptoms when specific molds can be detected in the environment in high density.

Table 7 lists mold extracts for which there is evidence of both clinical exposure to the mold genera and positive skin tests in allergic patients to extracts of various species of the mold genera. The Panel recommends that allergenic extracts of these molds be placed in Category I for diagnosis.

Table 8 lists mold extracts for which the Panel so far has not seen sufficient evidence of both clinical exposure to the mold genera and positive skin tests to extracts of the various species of the mold genera. The Panel recommends that allergenic extracts of these molds be placed in Category II for diagnosis unless or until appropriate evidence of effectiveness is found.

2. Mold extracts for immunotherapy. No mold extracts were classified in Category I for immunotherapy in the previous Panel report because the Panel found none which had been shown to be effective for immunotherapy in valid controlled published clinical trials. Those extracts listed in Table 7 were classified in Category IIIA for immunotherapy because they had been accepted by practicing allergists and standard textbooks as effective for diagnosis and immunotherapy. The Panel has recommended that those extracts in Table 7 be classified in Category I for diagnosis. As stated previously, when certain pollen extracts have been tested adequately, they have been shown to be effective for immunotherapy. The Panel presumes that any properly standardized sufficiently potent mold extract which is effective for skin test diagnosis and is safe when properly employed for immunotherapy might be proved to be effective for immunotherapy by appropriate controlled studies. The Panel recognizes that such studies have not been done with these extracts because such studies are difficult, costly and time-consuming and standardized mold extracts have not been available for testing.

RECOMMENDATION. The Panel recommends that extracts listed in Table 7 be reclassified in Category I for immunotherapy.

The mold extracts listed in Table 8 have been recommended for Category II for diagnosis for the reasons listed on the previous pages. The Panel recommends that extracts listed in Table 8 be reclassified in Category II for immunotherapy.

TABLE 7

Mold Extracts Recommended for Category I

	References which Demonstrate Exposure to Mold Genera	References which Demonstrate Positive Skin Test to Mold Species
Alternaria tenuis	1, 3, 9, 11	2, 5, 11
Aspergillus clavatus	1, 3, 9, 11	10
Aspergillus fumigatus	1, 3, 9, 11	2, 9, 11
Aspergillus glaucus	1, 3, 9, 11	2, 11
Aspergillus nidulans	1, 3, 9, 11	2, 11
Aspergillus niger	1, 3, 9, 11	2, 9
Aspergillus sydowi	1, 3, 9, 11	2
Aspergilus terreus	1, 3, 9, 11	2, 11
Botrytis cinerea	1, 3, 11	2, 11
Candida albicans	1, 11	11
Cephalosporium acremonium	3, 8, 11	8*, 9*, 11
Cephalothecium roseum	1, 11	9, 10, 11
Chaetomium globosum	1, 3, 11	2, 11
Cladosporium fulvum	1, 3, 9, 11	4, 11
Cladosporium herbarum	1, 3, 9, 11	4, 11
Curvularia spicifera	3	2, 5
Epicoccum nigrum	1, 3	2
Fusarium vasinfectum	1, 3, 9, 11	2
Fusarium roseum	1, 3, 9, 11	11
Gliocladium fimbriatum	3	2

*Positive skin tests to these mold genera only

TABLE 7--con.

Mold Extracts Recommended for Category I

	References which Demonstrate Exposure to Mold Genera	References which Demonstrate Positive Skin Test to Mold Species
Helminthosporium interseminatum	1, 3, 9, 11	2
Monilia sitophilia	1, 3, 11	2, 9, 11
Mucor plumbeus	1, 3, 11	9, 11
Mucor racemosus	1, 3, 11	2, 11
Mucor spinorus	1, 3, 11	11
Mycogone sp.	3	2
Nigrospora sphaerica	3, 11	2, 11
Paecilomyces variota	3	2
Penicillium biforme	1, 3, 9, 11	2
Penicillium carmino-violaceum	1, 3, 9, 11	2
Penicillium intricatum	1, 3, 9, 11	2
Penicillium luteum	1, 3, 9, 11	2
Penicillium notatum	1, 3, 9, 11	2, 11
Penicillium rubrum	1, 3, 9, 11	9
Phoma herbarum	1, 3, 11	2
Phoma betae	1, 3, 11	11
Pullularia pullulans	1, 3, 11	2, 11
Rhizopus nigricans	1, 3, 9, 11	2, 11
Rhodotroula glutinis	1, 3	2
Saccharomyces cerevisiae	1, 9, 11	2, 10, 11
Spondylocladium sp.	3, 9	5

TABLE 7--con.

Mold Extracts Recommended for Category I

	References which Demonstrate Exposure to Mold Genera	References which Demonstrate Positive Skin Test to Mold Species
Sporobolomyces, roseum	3, 11	11
Stemphylium botryosum	1, 3, 11	2, 5
Trichoderma viride	1, 3, 11	2, 11
Trichothecium roseum	11	11

TABLE 8

Mold Extracts Recommended for Category II

Absidia capillata

Achorion schoenleini

Acrothecium spp.

Anacystis

Beauvaria bassiana

Bispora antennata

Chlanydomyces diffusus

Chlorella

Colletotrichum

Cryptococcus sp.

Cryptococcus diffluens

Cryptococcus laurentii

Cryptococcus terreus

Cunninghamella elegans

Dematium nigrum

Epidermophyton

Epidermophyton floccosum (inguinale)

Epidermophyton rubrum

Fomes sp.

Geotrichum

Geotrichum (Oospora)

Geotrichum oidium

Lycopodium

Microsporum

TABLE 8—con.

Mold Extracts Recommended for Category II

Microsporum audouinii

Microsporum canis (lanosum)

Microsporum gypseum

Monotospora lanuginosa

Mycelia sterilia

Mycogone sp.

Mycotypha dichotoma

Neurospora crassa

Oidiodendrum sp.

Oidiodendrum oospara

Papularia arundinis

Phycomycetes

Phycomyces blakesleeanus

Pleospora sp.

Podaxis sp.

Poria sp.

Scopulariopsis

Scopulariospsis brevicaulis

Sporotrichum

Sporotrichum pruinosum

Stachybotrys atra

Streptomyces

Streptomyces griseus

TABLE 8--con.

Mold Extracts Recommended for Category II

Syncephalastrum racemosum

Tetracoccosporium

Thamnidium elegans

Trichophyton

Trichophyton cutaneum

Trichophyton gypseum

Trichophyton interdigitale

Trichophyton mentagrophytes

Trichophyton purpureum

Trichophyton rubrum

Trichophyton (achorion) schoenleinii

Trichophyton tonsurans

Trichophyton yiolaceum

Typhula

Verticillium albo-atrum

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Basidiomycetes: Rusts, smuts, and mushroom spores. Since the Panel completed its original report, there has been additional information dealing with allergy to basidiomycetes:

Symington (Ref. 1) reported on eight workers in a food manufacturing company who had rhinorrhea, dyspnea and wheezing with preparation of dried mushroom soup. Five had varying degrees of positive immediate skin tests to dried mushroom extract and four had positive inhalation challenge tests. Precipitating antibodies could not be detected.

Two abstracts were presented at the meeting of the American Academy of Allergy, Montreal, Canada, March 1982. Lehrer (Ref. 2) reported that an extract of spores of the mushroom Chlorophyllum molybetium collected from the field caused positive skin tests in 12 of 66 atopic patients with perennial allergic symptoms; 5 of the 12 patients had a positive RAST as well. An extract made from the mycelial form, grown in vitro, did not cause positive skin test reactions. Using crossed radioimmunoelectrophoresis, 7 of 23 precipitating antigens were shown to bind IgE from patients' sera. In New Orleans, spores from basidiomycetes can account for up to 20-30% of the total spore and pollen count, and allergic symptoms in some patients appear to be related to this exposure, although a firmly established cause and effect relationship has not been proved.

Santilli, et al. (Ref. 3) reported that they were able to elicit immediate skin reactions with extracts of basidiospores (including Agaricus,

Coprinus, Fuligo, Lycoperdon, Scleroderma, Ustilago and sooty mold) in individuals who have allergic symptoms, including asthma, coincident with high environmental spore counts.

In two Japanese journals (Refs. 4 and 5) two cases of asthma from occupational exposure to spores (Cortinellus shitake and Lentinus edodus) were reported. The disease was not the mushroom workers' lung type of extrinsic allergic alveolitits with precipitins.

This additional evidence allows the following mushrooms to be included in the list of identified basidiomycetes which will produce allergic reactions: Lentinus, Agaricus, Lycoperdon, Scleroderma, and Fuligo.

No reports were found on the use of extracts of basidiomycetes in immunotherapy.

It should be noted that there are 10,000 to 20,000 more members of the basidiomycete class that are yet to be studied and evaluated. For industrial exposure as in the above references, material present at the industrial plant may be the best source material to extract, so commercial allergenic extract will not be as useful or specific (e.g., it may be a dust of the product rather than of the spore of the mushroom).

RECOMMENDATIONS: (a) The basidiomycetes extract groups listed in Table 9 should be in Category I for diagnosis if spores are used as the source material. Other members of the class should not be included generically, since it appears that this group of substances has a low degree of cross-reactivity and data on other members are not available.

(b) Even though there are no data, other than a few anecdotal comments, about immunotherapy with extracts of members of this group,

by analogy with other airborne allergens and if spores are used as the source material then these extracts should be in Category I for immunotherapy.

TABLE 9

Basidiomycete Spore Extracts Recommended for Category I

Barley smut - *Ustilago bordei*
- *Ustilago nuda*

Corn smut - *Ustilago zeae*

Millet smut - *Ustilago crameri*

Oat smut - *Ustilago avenae*

Rye smut - *Urocystis occulta*

Sorghum smut - *Sphacelotheca sorghi*
- *Sphacelotheca cruenta*

Wheat smut - *Tilletia tritici*
- *Tilletia levis*
- *Ustilago tritici*

Rust - *Puccinia graminis tritici*

Mushroom - *Agaricus*, *Cantharellus*, *Chlorophyllum*, *Coprinus*,
- *Frustulatum*, *Fuligo*, *Hypholoma*, *Lintinus*, *Lycoperdon*,
- *Pleurotus*, *Scleroderma*

Jelly fungus - *Dacromyces*

Yeast - *Tilletiopsis*

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E. MISCELLANEOUS INHALANT ALLERGENIC EXTRACTS

For the allergenic extracts of the miscellaneous inhalant substances, the Panel relied on the data in the Panel's original report. Generally, an extract previously placed in Category IIIA for diagnosis is reclassified into Category I for diagnosis when there is adequate evidence that the substance is allergenic (Table 9). Among the extracts originally in Category I for diagnosis, there are a few which can also be recommended for Category I for immunotherapy (Table 10). However, the remainder of the extracts in Category I for diagnosis have been recommended for Category II for therapy because (1) there are no published reports of their use and (2) avoidance of the offending allergen is sufficient. For completeness, Table 10 also includes several extracts which were in Category I in the Panel's original report. Table 11 lists extracts of miscellaneous substances which are recommended for Category II.

For grain elevator dust, grain mill dust and grain dust mix, several conditions were recommended to provide better assurance of a safe, more consistant product. Fine dust which has been airborne and which has settled on high rafters should be the original source material. Locations where only one or two species of grains are processed are inappropriate. As soon as possible after storage, the material should be screened, defatted, and stored at freezing temperatures or otherwise handled to limit the presence of weevils, mites, other insects, endotoxins, and mycotoxins until ready to be extracted. Dialysis and acetone precipitation may be useful in the manufacturing process.

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TABLE 10

Miscellaneous Inhalant Allergenic Extracts

Recommended to Remain Licensed

Extract	Category Recommendations[1/] Skin Test Diagnosis	Immuno-therapy
Algae	I	I
Castor bean	I	II
Cotton linters	(I)	I
Cottonseed	(I)	(II)
Derris root	I	(II)
Dust, grain elevator (grain mill dust or grain dust mix)	I	I
Flaxseed	(I)	(II)
Gum Guar	I	II
Gum Arabic or Acacia	I	II
Gum India (Karaya)	(I)	II
Gum Tragacanth	(I)	II
Ipecac	I	II
Monsanto enzyme (B. Subtilis, Novoenzyme)	I	II
Orris root	I	II
Pyrethrum	I	II

1/ Category I recommendations in parenthesis were in Category I in the Panel's original report. Category II recommendations in parenthesis were in Category IIIB in the original report.

TABLE 10--con.

Miscellaneous Inhalant Allergenic Extracts

Recommended to Remain Licensed

Extract	Category Recommendations[1/] Skin Test Diagnosis	Immuno-therapy
Silk, raw	(I)	I
Tobacco leaf (unmodified)	(I)	II
Wood dust, cedar and red cedar	(I)	II
Wood dust, cocabola	(I)	II
Wood dust, red oak	(I)	II
Wood dust, white oak	(I)	II
Wood dust, padauk	(I)	II

1/ Category I recommendations in parenthesis were in Category I in the Panel's original report. Category II recommendations in parenthesis were in Category IIIB in the original report.

TABLE 11

Miscellaneous Inhalant Allergenic Extracts

Recommended for Category II

For Diagnosis and Immunotherapy

Almond hulls

Chicle

Chicory

Coconut fiber

Cotton

Cotton, aged

Cotton gin dust

Fern spores

Flax fiber

Gum carbo

Hemp dust

Jute

Kapok

Lavendar

Lycopodium

Malt

Psyllium seed

Rapeseed

Rose spp.

Sea moss

Senna

Sisal

TABLE 11--con.

Miscellaneous Inhalant Allergenic Extracts

Recommended for Category II

For Diagnosis and Immunotherapy

Tobacco leaf, cured

Wood dusts:

- Busal
- Beech
- Birch
- Cottonwood
- Elm
- Fir
- Fir, Douglas
- Fir, red
- Fir, white
- Hemlock
- Mahogany
- Maple
- Pine, white
- Pine, yellow
- Redwood
- Spruce
- Tamarack (larch)
- Walnut

F. HOUSE DUST EXTRACTS

House dust extracts are prepared from source materials which have not been precisely defined and, therefore, fail to meet the first requirement the Panel established to qualify for Category I classification. By their nature, house dust extracts are not of constant composition. Because of this inconsistency, it is not possible to assure that any two batches of house dust are alike. Furthermore, it is doubtful that this will ever be possible unless collection and extraction methods can be devised which will produce batches of known composition so that standards can be developed. The chemical composition of house dust extracts has not been determined. They are known to contain multiple antigens, but an antigen unique to house dust has not been shown conclusively.

Nevertheless, there is adequate evidence for the need in practice of an extract with the characteristics of house dust. It is generally recognized that there is a small proportion of patients who give clear-cut histories of allergy to house dust and who react to house dust extract by skin and/or serological tests, but who do not have positive skin test reactions to available extracts of several known allergenic components of house dust. The reasons for this are not clear. While it is the goal of the conscientious allergist to be as specific as possible in diagnosing and treating the allergies of each patient, in practice it is not feasible to perform all of the diagnostic testing necessary to do this. Therefore, house dust extracts fulfill a need in the diagnosis and treatment of allergic disease. However, there is no standard of potency for house dust extracts. They are currently produced on a W/V or PNU

basis. Extracts with equal W/V or PNU designations may differ in biologic activity by more than a thousandfold. This is a major fault which will be considered in the Panel's recommendations.

The safety of house dust extracts as used in diagnosis and therapy has not been studied systematically, but extensive marketing experience and human use appear to have demonstrated their safety.

The specificity and sensitivity of these extracts for the diagnosis of IgE-mediated allergy to components of house dust cannot be established unless and until standardized preparations are available.

The effectiveness of house dust extracts in the treatment of sensitivity to house dust cannot be established for the same reason.

Recommendations:

House dust extract is recommended to be placed in Category I for skin test diagnosis notwithstanding the fact that the source material is not well defined and each product is a mixture varying from batch-to-batch.

By a 6 to 1 vote of the Panel members house dust extract was recommended for Category I for use in immunotherapy. The dissenting opinion reflected several concerns of the Panel. Although there are some reports in the literature which suggest that house dust extract may be useful in therapy, other reports show it to be ineffective. Because of a lack of knowledge of the components used in the reported studies, these data could not be applied to current production batches of house dust extracts.

Several recommendations are repeated from the original Panel report.

(1) Collection. Various environments are suitable for the collection of these source materials. The collector should maintain a record of the actual location from which each sample of source material was collected. The sites and method of collection of the source material, for example, by vacuuming, should be approved by the FDA.

(2) Processing. Upon receipt of the source material from the supplier, it should be inspected by the manufacturer and should meet standards for this product established by the FDA. When required, it should be sieved upon receipt from the supplier to remove contaminating debris.

(3) Storage. The source material should be stored under conditions approved by the FDA. Particular attention should be given to the temperature and humidity during storage, and to the duration of storage.

(4) The manufacturer must indicate the general nature of the source on the label. For example, "a mixture of mattress and carpet dust". Only extracts made from source materials obtained from houses or similar establishments (e.g. hotels) or their appurtenances should be labeled "house dust extract." Due to the observed wide variation in potency which may occur from batch-to-batch, a warning should appear on the label. For example: "Warning, potency may vary from batch-to-batch, therefore, equivalent doses measured by W/V or PNU may differ. This must be considered when changing a patient to a new lot number."

Based on its previous review of this subject and discussions at the most recent Panel meeting, the Panel added the following conditions:

a. No house dust source material should be collected from areas where pet animals, particularly cats or dogs, are kept.

b. House dust source material should not be collected from areas where detergents or pesticides have been used within the previous two weeks.

c. House dust source material should have low levels of mite and other insect infestation detectable upon microscopic examination.

d. House dust source material should be stored in a manner to inhibit bacterial, mold, and insect growth.

e. House dust extracts should be tested for mycotoxins, particularly aflatoxin.

f. House dust extracts should be limited to low levels of endotoxin as specified by the FDA.

g. No extraneous additives should be used to "fortify" these extracts.

It is also suggested that a sufficient number of lots of extract should be skin tested to assure consistency and to ultimately determine whether there is a clinical syndrome which can be attributed to house dust per se and in which people are skin test-positive at relatively high dilutions of these extracts.

G. INSECT EXTRACTS

Insect extracts were reviewed again in the same groups as in the original Panel report, i.e., extracts for insect sting allergy, extracts for insect bite allergy, and extracts for insect inhalant allergy.

1. Extracts for allergy to insect venom. The only insect extract for immunotherapy of insect sting allergy in Category IIIA in the original Panel report was the extract of the whole body of the fire ant. Venoms of the winged hymenoptera such as bees, wasps, yellow jackets and hornets were marketed as safe and effective products after the initial Panel review and were not addressed by the Panel. Whole body extracts of the winged hymenoptera were placed in Category IIIB based on published evidence of their ineffectiveness. However, limited observations mentioned in the original Panel report suggest that whole body extract of the fire ant may be effective in the diagnosis and treatment of fire ant-sensitive individuals. Observation of a control group of untreated individuals is lacking and corraborative immunological studies are not available. Nevertheless, because of the published evidence it is recommended that whole body fire ant extracts be placed in Category I for immunotherapy.

2. Extracts for allergy to insect bites.

a. Fleas. Reactions from flea bites are primarily large local reactions. As mentioned in the original Panel report, many of these reactions are delayed in onset as is the reaction found when skin testing with flea extract. There is no present documentation that reactions to flea bites have an IgE pathogenesis. It is recommended that flea

extracts be placed in Category II for diagnosis and therapy as currently labeled for use in IgE-mediated allergic disease. One Panel member believed the extract should remain on the market for use in the diagnosis of delayed hypersensitivity to the flea bite.

b. Mosquito. The original Panel report concluded that mosquito extracts may have some diagnostic value in confirming the delayed local reactions which some individuals have had following mosquito bites, but that an IgE pathogenesis for this type of reaction has not been established. It is recommended that mosquito extracts be placed in Category II for diagnosis and therapy as currently labeled for use in IgE-mediated allergic disease. One Panel member believed the extract should remain on the market for use in the diagnosis of delayed hypersensitivity to the mosquito bite.

c. Deerfly. Deerfly extract was placed in Category I for skin test diagnosis in the original Panel report. Based on studies reviewed in the earlier report, it is recommended that deerfly extract now be placed in Category I for immunotherapy.

d. Bedbugs. Based on studies cited in the original Panel report, extracts of bedbugs are recommended for Category I for skin Test diagnosis. (Bedbug extracts are in Category IIIB for therapy in the original Panel report).

e. Kissing bug. Kissing bug (Triatoma) extracts were placed in Category I for skin test diagnosis in the original Panel report. There is evidence in one study which suggests that an extract of the salivary glands of this insect is effective for immunotherapy (Ref. 1). Therefore, it is recommended that kissing bug extract be placed in Category I for immunotherapy.

3. Extracts for inhalant allergy to insects.

a. Caddis fly. Caddis fly extract was placed in Category I for skin test diagnosis in the original Panel report. Based on the studies reviewed in that report, it is recommended that caddis fly extract be placed in Category I for immunotherapy.

b. May fly. May fly extract was in Category I for skin test diagnosis in the original Panel report. Based on the studies reviewed there, it is recommended that May fly extract be placed in Category I for immunotherapy.

c. Aphid. Aphid extracts were placed in Category I for skin test diagnosis in the original Panel report. Use in therapy is analogous to the above extracts. It is recommended that aphid extract be placed in Category I for immunotherapy.

d. Bee. The evidence supporting the use of whole body extract in inhalant allergy to bees was discussed in the original Panel report. If whole bee body extract is permitted to be marketed for this purpose, then the labeling should indicate that extensive studies have shown that it is not effective for bee sting allergy despite widespread previous use for this purpose. It is recommended that whole body bee extracts labeled for use in the diagnosis and treatment of inhalant allergy be placed in Category I.

e. Cockroach. Cockroach extracts were in Category I for skin test diagnosis in the Panel's original report. They were in Category IIIB for immunotherapy, however the FDA Office of Biologics has proposed a change based on new evidence available in manuscript and published as the abstract (Ref. 2). In 11 patients, the symptom and medication scores decreased significantly following immunotherapy for two years.

The sensitivity of basophil histamine release declined on the average 350 fold during the same period. It is unclear if the same lot of antigen was used for all assays and the use of controls was not documented. Nevertheless, the Panel now recommends Category I for immunotherapy.

f. Mite (Dermatophygoides). The extensive literature dealing with house dust mite was discussed in the Panel's original report where it was recommended that specific mite extracts be placed in Category I for skin test diagnosis. The Panel now recommends that the house dust mite extracts of D. fariniae be placed in Category I for immunotherapy as there is growing evidence of their efficacy.

g. Moths and butterflies. Extracts of moths were in Category I for diagnosis in the Panel's original report while extracts of butterflies were in Category IIIB. Evidence from a study in Japan (Ref. 3). indicates that butterfly extracts are effective for diagnosis in patients who experience symptoms upon significant exposure to butterflies. The Panel recommends that extract of butterfly be placed into Category I for diagnosis. There was insufficient evidence to justify reclassification of extracts of moths and butterflies from Category IIIB for immunotherapy.

h. Other extracts for inhalant allergy to insects. The recommendations for the other extracts for insect inhalant allergy, listed in Tables 11 and 12, are based on information in the Panel's original report. The Panel recommends that when there is evidence that the insect is the cause of IgE-mediated allergic reactions in humans, these other extracts be placed in Category I for diagnosis.

Although exposure to many of these insects is rare, occupational contacts account for much of the reported evidence. These other extracts should be placed in Category II for immunotherapy because of a lack of evidence that the products are effective or safe. Where the Panel could find no information that a specific insect is responsible for an allergic reaction, the extract has been recommended to be placed in Category II for both diagnosis and immunotherapy.

REFERENCES

(1) Marshall, N. A., and D. H. Street, "Allergy to Triatoma protracta, I. Etiology, Antigen Preparation, Diagnosis and Immunotherapy," Journal of Medical Entomology, 19:248-252, 1982.

(2) Kang, B., J. Johnson, B. S. Chang and J. L. Chang, "Blocking Antibody and Efficacy of Immunotherapy in Cockroach Asthma," Journal of Allergy and Clinical Immunology, 69:132, 1982.

(3) Kino, T., and S. Oshima, "Allergy to Insects in Japan," Journal of Allergy and Clinical Immunology, 61:10-16, 1978.

TABLE 12

Insect Extracts

Recommended to Remain Licensed

Extract	Category Recommendations[1/] Skin Test Diagnosis	Immuno-therapy
Aphid	(I)	I
Bedbugs	I	(II)
Bee, honey (whole body)	(I)[2/]	I[2/]
Beetles (identified)	(I)	(II)
Butterfly	I[3/]	(II)
Caddis fly	(I)	I
Crickett	I	(II)
Cicada/locust	I	(II)
Cockroach, American	(I)	I
Cockroach, German	(I)	I
Cockroach, Oriental	(I)	I
Daphnia	(I)	(II)
Deer fly	(I)	I
Fire ant	(I)	I
Flea, water (daphnia pulex)	(I)	(II)

1/ Category I recommendations in parenthesis were in Category I in the original panel report. Category II recommendations in parenthesis were in Category IIIB in the original panel report.
2/ For inhalent insect allergy.
3/ Extract of butterflies was in Category IIIB in the original report.

TABLE 12--con.

Insect Extracts

Recommended to Remain Licensed

Extract	Category Recommendations[1/]	
	Skin Test Diagnosis	Immuno-therapy
Fruit fly	I	(II)
House fly	(I)	(II)
Kissing bug	(I)	I
Leafhopper	I	(II)
May fly	(I)	I
Mexican bean weevil	I	I
Mite (Dermatophygoides farinae)	(I)	I
Mite (Dermatophygoides farinae)	(I)	I
Mite (D. pteronyssinus)	I	I
Moth	I	(II)
Moth, miller	I	(II)
Mushroom fly	(I)	I
Screwworm fly	I	(II)
Sow bugs	I	(II)
Spider	I	(II)

1/ Category I recommendations in parenthesis were in Category I in the original panel report. Category II recommendations in parenthesis were in Category IIIB in the original panel report.

TABLE 13

Insect Extracts

Recommended for Category II[1/]

For Diagnosis and Therapy

Flea

Flea, Dog

Flea, Cat

Flea, mixed

Mosquito

Spider mix

1/ This table does not include extracts listed in Category IIIB in the original panel report.

H. FOOD EXTRACTS

In conducting the reclassification of food extracts, the Panel noted carefully its original and current charge to review the safety and effectiveness of the assigned products for use according to the way they are labeled. There was no new information submitted by the manufacturers for the Panel to consider in its reclassification of Category IIIA food extracts.

Food extracts for skin test diagnosis. Many food extracts were considered in the previous Panel report to be effective as an aid in the diagnosis by skin test of IgE-mediated allergic disease. In considering the evidence in that report and in other articles (Refs. 1 through 6) and in applying the standards of effectiveness recommended by the Panel in this report for the reclassification of the Category IIIA extracts, most food extracts are recommended for Category I for this use. Applying these standards, each extract should: (1) be obtained from a well defined source; (2) be capable of being standardized as shown by identifiable and measurable allergenic constituents (which remain intact during the dating period); and (3) be shown to induce positive skin test reactions in individuals with IgE-mediated food allergy and negative reactions in those persons without such allergies. Many food extracts were recommended for Category I, even if they were derived from exotic foods unlikely to be consumed by humans on more than a sporadic basis. Requirement number (2) is not presently fulfilled with the great majority of food extracts but is theoretically possible with many of them.

Almost all mixtures and processed foods, e.g. Angostura Bitters, soft drinks (e.g., Coca-Cola, 7-Up) and simple chemicals (e.g., vinegar), were classified into Category IIIB in the original Panel report. Three products reviewed in the original report, beechnut, roasted coffee bean and licorice extracts, were not clearly defined and were originally placed in Category IIIB. However, if the FDA can ascertain that a discrete plant substance rather than a processed form is the source material, extracts of these substances should be reclassified in Category I for skin test diagnosis.

The recommendations for the reclassification of food extracts for skin test diagnosis of IgE-mediated allergy are listed in Tables 14 and 15. Table 15 lists four food extracts previously classified in Category IIIA which are recommended for Category II for skin test diagnosis. Three of these (beef heart, cod liver, and grapefruit peel) represent extracts of anatomical parts of an approved food, i.e., beef, cod, and grapefruit, and therefore are considered redundant. The fourth, black/white pepper, is a mixture.

Because the Panel believes that the use of allergenic extracts as defined in its previous report have been demonstrated to be effective only for use in connection with IgE-mediated allergy, the Panel recommends that the labeling of allergenic extracts of foods should clearly state that they are intended for use in the diagnosis of this type of disease only. Furthermore, the labeling should indicate that allergies to food substances may be of ingestant and, in some cases, inhalant nature.

Food extracts for immunotherapy. The Panel recommends that all food extracts be reclassified into Category II for immunotherapy of IgE-mediated allergic disease when exposure to the food is by ingestion. The reasons for this decision are: (1) there is no generally acceptable evidence supporting the use of allergenic extracts of foods as therapeutic agents, either orally or parenterally, for ingestant IgE-mediated allergy, while in contrast such studies do exist for several inhalant allergens; (2) avoidance of allergens to which an individual is sensitive is a fundamental principle in allergy management (this is usually possible for most food allergens most of the time); and (3) food extracts are more likely than other classes of extracts to induce a systemic anaphylaxis when used in immunotherapy. This latter conclusion is based on the evidence reviewed in the original Panel report.

Several physicians and members of the public appeared before the Panel in support of the use of allergenic extracts of foods in the treatment of "food intolerances." Representatives of the Society for Clinical Ecology, the American Academy of Otolaryngic Allergy, and the Pan American Allergy Society spoke at one of the Panel meetings and submitted information (References 7 through 44)

mostly relating to the use of allergenic extracts of food substances by "provocation" testing and "neutralization" treatment. They stated that food intolerance is primarily nonIgE-mediated, and may have both immediate and delayed clinical and immunological features. They also stated that for patients with food intolerance who as a practical matter can not avoid the offending foods, they support the use of allergenic extracts of foods in ameliorating and preventing a variety of conditions which they believe are caused by food. Examples of these conditions as described in their documentation include otitis media, hyperkinetic syndrome in children, behavioral abnormalities, asthma, milk intolerance, headaches, and laryngeal edema.

It was noted by the Panel that most of the discussions by the speakers from the three societies and the written material they supplied to the Panel had to do with techniques employed by some physicians in their medical practices but did not represent evidence from studies supporting allergenic extracts as made and labeled commercially and as under review by the Panel. Seven of these references were on "environmentally triggered" conditions unrelated to allergenic extracts of foods

and unrelated to any topic within the charge to the Panel. Eight references were on "mechanisms involved," none of which contained evidence of an immunological relationship between a specific food extract and its labeled use in treatment. Three of the references were commentaries on other reviews of the use of food extracts. Several other references contained reports of case histories or testimonials of individual physicians rather than controlled studies. The few articles that were in some manner referred to as reporting controlled studies did not contain information demonstrating that any specific, well-characterized food extract being reviewed by the Panel is safe and effective for use in immunotherapy as labeled by the manufacturers.

The Panel's charge is to consider the evidence pertaining to the approved labeled indications of allergenic extracts. "Neutralization" treatment of food intolerances following "provocation" testing is an unapproved use of these products. The Panel has nevertheless considered all of the evidence submitted to determine whether it supports the approved indications of food extacts for IgE-mediated allergy. The evidence submitted does not purport to prove the effectiveness of food extracts for the immunotherapy of IgE-mediated allergy. In some instances the data did not even relate to allergenic extracts or to an immunological relationship between a food extract and its labeled use. The material submitted by the three societies therefore does not alter the Panel's conclusion that food extracts should be placed in Category II for immunotherapy.

TABLE 14

Food Extracts Recommended for Category I for Skin Test Diagnosis[1/]

Abalone: *Haliotidae* species

Alfalfa leaves: *Medicago sativa*

Allspice: *Pimenta officinalis*

(Almond: *Prunus amygdalus*)

Anchovy: *Engraulis encrasicholus*

Anise: *Pimpinella anisum*

Anise seed

(Apple: *Malus pumila*)

Apricot: *Prunus armeniaca*

Arrowroot: *Maranta arundinacea*

Artichoke: *Cynara scolymus*

(Asparagus: *Asparagus officinalis*)

(Avocado: *Persea americana*)

(Banana: *Musa paradisiaca sapientum*)

(Barley: *Hordeum vulgare*)

Barracuda: *Sphraena barracuda*

Basil: *Clinopodium vulgare*

Bass

Bass, Black: *Micropterus* species

Bass, Florida red

Bay leaf: *Laurus nobilis*

Bean, broad: *Vicia faba*

1/ Extracts in parenthesis were in Category I for skin test diagnosis in the original panel report.

TABLE 14--con.

Food Extracts Recommended for Category I for Skin Test Diagnosis

Bean, castor

Bean kidney, red kidney: Phaseolus vulgaris

Bean, kola

Bean, lima: Phaseolus limensis

Bean, mung

Bean, navy

(Bean, pinto)

(Bean, string/green

Bean, string/wax

Bean, yellow/wax

Beechnut: Fagus sylvatica

Beef meat: Bos species

Beet: Beta vulgaris

Beet, sugar, vegetable

Blackberry: Rubus occidentalis

Black-eyed pea: Vigna sinensis

Blueberry: Vaccinium corymbosum, pennsylvanicum

or other species

(Blue fish: Pomatomus saltatrix)

Boysenberry: Rubus ursinatus loganobaccus

Brains, calves

(Brazil nut: Bertholletia excelsa)

TABLE 14—con.

Food Extracts Recommended for Category I for Skin Test Diagnosis

Broccoli: *Brassica oleracea italica*

Brussel sprouts: *Brassica oleracea gemmifera*

(Buckwheat: *Fagopyrum sagittatum*)

Cabbage: *Brassica oleracea capitata*

(Cacao, whole bean: *Theobroma cacao*)

(Cantaloupe: *Cucumis melo cantalupensis*)

Caraway seed: *Carum carvi*

Cardamom: *Elettaria cardamomum*

(Carp, *Cyprinus corpio*)

Carrot: *Daucus carota*

(Casein)

(Cashew nut: *Anacardium occidentale*)

Catfish

Catfish, bullhead

Catfish, channel

Cauliflower: *Brassica oleracea botrytis*

Celery, *Apium graveolus*

Chard: *Beta vulgaris cicla*

Cherry

Cherry, bing: *Prunus avium*

Cherry, choke

Cherry, red sour: *Prunus cerasus*

(Chestnut: *Castanea dentata*

TABLE 14--con.

Food Extracts Recommended for Category I for Skin Test Diagnosis

Chicken meat: *Gallus gallus*

Chicle

Chicory: *Chichorium intybus*

Chili pepper

Chives: *Allium schoenoprasum*

Cinnamon: *Cinnamomum zeylanicum*

Citron: *Citrus medica*

(Clams, hard shell - *Venus mercenaria*

soft shell - *Mya arenaria*)

Cloves: *Caryophyllus aromaticus*

Coconut: *Cocos nucifera*

(Codfish: *Gadus callarius*)

Collards: *Brassica oleracea acephala*

Coffee: *Coffea arabica* (roasted bean)

(Corn: *Zea mays*)

(Corn, sweet: *Zea mays saccharata*)

(Cotton seed: *Gossypium* species seed)

(Crab: *Crustacea* species)

Cranberry: *Vaccinium macrocarpon*

Crappie: *Pomoxis* species

Crawfish: *Cambarus virilis* and *bartoni*

Croaker

TABLE 14--con.

Food Extracts Recommended for Category I for Skin Test Diagnosis

Cucumber: *Cucumis sativus*

Cumin seed: *Cuminum cyminum*

Currants: *Ribes* species

Currant, Red: *Ribes rubrum*

Dandelion leaf: *Taraxacum officinale*

Date: *Phoenix dactylifera*

Dill: *Anethum graveolens*

Dill seed or leaves

Duck meat: *Anas platyrhynchos*

(Egg, white: (Chicken, *Gallus galluse*))

(Egg, whole)

Egg, yolk

Eggplant: *Solanum melongena*

Elk meat: *Cervus canadensis*

Endive: *Cichorium endivia*

Fig: *Ficus carica*

Filbert nut (Hazelnut): *Corylus* species

Fish, white

(Flounder)

Frog meat: *Rana* species

(Garbanzo (chick-pea; *Cicer arietinum*)

Garlic: *Allium sativa*

Ginger: *Zingiber officinale*

TABLE 14--con.

Food Extracts Recommended for Category I for Skin Test Diagnosis

Goat meat: *Capra* species

Goose meat

Gooseberry: *Ribes hirtellum*

(Grape: *Vitis* species)

(Grape, concord: *Vitis labrusca*)

(Grape, Rieber: *Vitis vinifera*)

(Grape, tokay)

(Grape, white)

(Grape, white seedless)

Grapefruit: *Citrus paradisi*

(Gum, acacia: *Acacia senegal*)

(Gum, karaya)

Gum, chicle

(Gum, tragacanth: *Astragalus* species)

Haddock: *Melanogrammus aeglefinus*

Halibut: *Hippoglossus* species

Herring: *Clupea* species

Hickory nut: *Carya* species

(Hops: *Humulus* species)

Horseradish: *Armoracia rusticana*

TABLE 14--con.

Food Extracts Recommended for Category I for Skin Test Diagnosis

Huckleberry: Gaylussacia baccata

Juniper berry: Juniperus communis

Kale: Brassica oleracea acephala

Kohlrabi: Brassica oleracea caulorapa

Kola nut: Cola acuminata

(Lactalbumin, alpha, cow)

(Lactoglobulin, beta, cow)

Lamb (sheep) meat: Oris vigrei

Leek: Allium porrum

Lemon: Citrus limonia

Lentil: Lens culinaris

Lettuce: Lactuca sativa capitata (iceberg)

Lettuce leaf: Lactuca sativa crispa (leaf)

Licorice: Glycyrrhiza glabra

Lime: Citrus aurantifolia

Liver, beef

Liver, chicken

Liver, pork

Lobster: Homarus americanus

Loganberry: Rubus ursinus loganobaccus

Mace: Myristica fragrans

(Mackerel: Scomber scombrus)

TABLE 14--con.

Food Extracts Recommended for Category I for Skin Test Diagnosis

Malt

(Mango: *Mangifera indica*)

Maple, syrup/sugar: *Acer saccharum*

Marjoram: *Majorana hortensis*

(Melon, honeydew)

(Milk, cow's (whole): *Bos* species milk)

Milk, goat's: *Capra* species milk

Millet grain

Mullet: *Mugil cephalus*

Mulberry, red: *Morus rubra*

Mulberry, black: *Morus nigra*

Mushroom: *Basidiomycetes* (with species defined)

Mustard greens: *Brassica juncea*

Mustard seed: *Brassica hirta*

Nectarine: *Prunums persica*

Nutmeg: *Myristica fragrans*

Oat, whole ground: *Avena sativa*

Okra: *Hibiscus esculentus*

Olive, black: *Olea europaea* - ripe

Olive, green: *Olea europaea* - green

Onion: *Allium cepa* varieties

(Orange: *Citrus sinensis*)

Oregano: *Origanum vulgare*

TABLE 14--con.

Food Extracts Recommended for Category I For Skin Test Diagnosis

(Oyster: Ostrea virginica)

Oyster plant/salsify: Tragopogon porrifolius

Papaya: Carica papaya

Paprika: Capsicum annuum

Parsley: Petroselinum cirspum

Parsnip: Pastinaca sativa

Pea, black eyed

(Pea, green English: Pisum sativum)

(Peach: Prunum persica)

(Peanut: Arachis hypogaea)

(Pear: Pyrus communis)

(Pecan: Carava illinoensis)

Pepper, black: Piper nigrum

Pepper, Cayenne: Capsicum annuum

Pepper, green: Capsicum frutescens

Pepper, sweet: Capsicum frutescens

Peppermint: Mentha piperita

(Perch: Perca flavescens)

(Perch, lake)

(Perch, sea)

Persimmon: Diospyros virginia

Pheasant: Phasianus torguatas

TABLE 14--con.

Food Extracts Recommended for Category I for Skin Test Diagnosis

Pigeon (squab): Columbidae species

Pickerel: Esox species

Pike: Esox lucius

Pike, walleye: Perca

Pimento: Pimenta officinalis

(Pineapple: Ananas comosus)

Pistachio nut: Pistacia vera

Plum: Prunus domestica

Plum, blue

Plum, red

Poke greens: Phytolacca americana

Pollock

Pomegranate: Punica granatum

Pompano: Trachinotus carolinus

Poppy seed: Papaver somniferum

Pork

(Potato, red Irish: Solanum tuberosum)

Potato, sweet: Ipomoea batatas

(Potato, white Irish: Solanum tuberosum)

Prune, fresh

Psyllium seed: Plantago pysllium

Pumpkin: Cucurbita pepo

Quail: Colinus virginianus

TABLE 14--con.

Food Extracts Recommended for Category I for Skin Test Diagnosis

Quince: *Cydonia oblonga*

Quince seed

Rabbit: *Lepus* species

Radish: *Raphanus sativus*

Raspberry: *Rubus* species

Raspberry, black: *Rubus occidentalis*

Raspberry, red: *Rubus idaeus*

Red snapper: *Lutjanus campechanus*

Rhubarb: *Rheum rhaponticum*

(Rice: *Oryza sativa*)

Rice, wild

Rosemary: *Rosmarinus officinalis*

Rutabaga: *Brassica napobrassica*

Rye: *Secale cereale*

Safflower seed: *Carthamus tinctorius*

Sage: *Salvia officinalis*

(Salmon: *Oncorhynchus* species)

Sardine: *Sardina pilchardus*

Savory: *Satureia hortensis*

(Scallops: *Pecten irradians*)

(Sesame seed: *Sesamum indicum*)

(Shad: *Alosa sapidissima*)

TABLE 14--con.

Food Extracts Recommended for Category I for Skin Test Diagnosis

(Shrimp: *Peneus setiferus*)

Smelt: *Osmerus mordax*

Snail: *Helicidae* species

(Sole: *Achirus fasciatus*)

Sorghum: *Sorghum vulgare* species

(Soybean: *Glycine max*)

Spearmint: *Mentha spicata*

(Spinach: *Spinacea oleracea*)

Squash, acorn

Squash, banana

Squash, summer

Squash, tomato

Squash, turnip

Squash, water cress

Squash, zucchini (Italian)

Squirrel: *Sciurus* species

Strawberry: *Fragaria* species

Sunfish (bluegill): *Lepomis* species

Sunflower seed: *Helianthus* species

Swiss chard: *Beta vulgaris cicla*

Swordfish: *Xiphias gladius*

(Tangerine: *Citrus nobilis*)

Tapioca: *Manihot esculenta*

TABLE 14--con.

Food Extracts Recommended for Category I for Skin Test Diagnosis

Tea: Thea sinensis (if variety is defined)

Thyme: Thymus vulgaris

(Tomato: Lycopersicon esculentum)

Trout: Salvelinus (if species is defined)

Trout, Gulf or speckled

Trout, lake: Salvelinus namaycush

Trout, rainbow: Salmo irideus

Tuna: Thunnus species

Turkey (meat): Agriocharis ocellata

Turmeric: Curcuma longa

Turnip: Brassica rapa

Turnip greens

Vanilla bean: Vanilla planifolia

Venison (deer): Odocoileus species

(Walnut, black: Juglans nigra)

(Walnut, English: Juglans regia)

Watercress: Lepidium sativum

(Watermelon: Citrullus vulgaris)

(Wheat, whole: Triticum species)

Whitefish: Coregonus clupeiformis

Whiting: Merlangus merlangus

Yam: Dioscorea alata

Yeast, Bakers' (if species is defined)

Yeast, Distillers' (if species is defined)

TABLE 15

Food Extracts Recommended for Category II for Skin Test Diagnosis[1/]

Beef heart

Codliver

Grapefruit peel

Pepper, black/white: Piper nigrum

[1] This table does not include food extracts which were in Category IIIB in the original panel report.

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I. ALUM-PRECIPITATED ALLERGENIC EXTRACTS

Alum-precipitated allergenic extracts and adjuvants were discussed extensively in the original Panel report. In addition to the conclusions in that report, more recent information on the possible role of aluminum in dementia has been reviewed during meetings of the Panel. McLachlan and DeBoni (McLachlan, D. R. and V. DeBoni, "Aluminum in Human Brain Disease - An Overview," Neurotoxicology, 1:3-16, 1980) reviewed the role of aluminum in brain disease, examining the circumstantial evidence implicating aluminum as a possible cytotoxic factor in processes associated with neurofibrillary degeneration of the Alzheimer type. They emphasized that at least two important areas require intensive further investigation: the biological state of aluminum within the nucleus and the chemical identification of the polypeptide subunits of the Alzheimer paired helical filaments. There seems no doubt that aluminum occurs in elevated concentration in a number of abnormal brain conditions, however, the critical question of whether it is pathogenetic or the result of disease remains unanswered.

Although higher brain levels of aluminum in patients have been associated with dementia, evidence of its causal relationship is still circumstantial and the Panel did not find sufficiently compelling evidence to recommend a change in the permitted levels of aluminum in allergenic extracts. However, the Panel recommends that the labeling of alum-precipitated allergenic extracts should include a warning that they should not be used in patients with Alzheimer's disease, Down's Syndrome or renal impairment.

The Panel has reviewed evidence dealing with the use of aluminum-containing adjuvants in immunotherapy for allergic disease. In some instances, immunological and clinical evidence reviewed in the original Panel report suggests results comparable to those following the use of aqueous extracts. The margin of difference is not great and falls far short of the enhancing effect which might be expected from the larger nominal doses of extract that can be administered with alum. Nevertheless, the principle embraced by adjuvant therapy is sound and its further development should be encouraged.

Alum-precipitated Allergenic extracts, (Center-Al™), Center Laboratories, Inc., Port Washington, New York. These alum-precipitated allergenic extracts are prepared from aqueous extracts by formation of an aluminum hydroxide precipitated complex. They are licensed for use in immunotherapy only. The conclusions and recommendations of the original Panel report concerning comparable safety and efficacy remain unchanged. However, on further review by the Panel, the data still do not support conclusively the claims of clinical or immunological superiority of Center-Al over aqueous allergenic extracts. The Panel therefore recommends that each alum-precipitated allergenic product for which Center Laboratories, Inc., is licensed be placed in the same generic category as the corresponding aqueous product.

Alkaline-pyridine extracted alum-precipitated allergenic extracts (Allpyral™), Dome Laboratories, Division of Miles Laboratory, West Haven, Connecticut. Allpyral™ products are prepared from nondefatted source materials by an alkaline extraction procedure employing pyridine. Comments made earlier about the safety of alum-precipitated

extracts apply as well to Allpyral™ extracts. In addition, special consideration ought to be given to the safety and particularly the effectiveness of these altered allergens although, based on uncontrolled clinical observations, there appears to be at least no greater risk to their use in therapy than to the use of the corresponding aqueous allergenic extracts. After 30 years of experience with over 200 million doses of Allpyral™ extracts, there is to date no clinical evidence to suggest an increased incidence of oncogenic or neuropathic conditions among the patients receiving this form of treatment as noted in the previous Panel report.

Data on effectiveness were reviewed in the Panel's original report. More recently the immunogenicity of Allpyral™ grass pollen extract (containing both orchard and timothy) was tested in Sweden (by Drs. Lars Belin and Kjell-orvar Pegelow). A report of this study (provided by Dome Laboratories) revealed the effect of treatment on 40 patients during a 3-year course of treatment. Specific IgE antibody levels rose initially and later fell, and specific IgG antibody levels increased during and fell following treatment. This suggests that this Allpyral grass extract is immunogenic in allergic patients.

In the Panel's original report, evidence was reviewed for five Allpyral grass pollen extracts, the allergenicity of which was apparently not destroyed by the alkaline-pyridine extraction process. These were orchard (cocksfoot), timothy, meadow fescue, perennial rye, and velvet (Yorkshire fog). Allpyral extracts of these five grass pollens are recommended for Category I. Similar evidence is not available for other Allpyral pollen, mold, dust or animal extracts.

The Panel's original report recommended that Allpyral™ short ragweed pollen extract should be placed in Category IIIB, because the bulk of the evidence available at that time suggested that this extract was not effective. With the demonstrated loss of antigen E of short ragweed by the alkaline-pyridine extraction process, there is the concern that active antigens in other pollens, molds, etc. might likewise be destroyed in the preparation of their respective Allpyral products. However, since these active fractions have not been identified for most allergens, it is difficult to be sure whether they are affected by the Allpyral process or not. Although patients receiving Allpyral have generally been reported to have been improved, there is inadequate evidence to put these preparations into the same category as their aqueous counterparts. The Panel recommends that the remaining Allpyral extracts be placed in Category II unless new evidence is furnished that the allergens are not destroyed in the extraction process.

J. PLANT OLEORESINS

Considering the almost universal susceptibility of man to contact dermatitis given sufficient exposure to chemical and plant organic compounds, it is recommended the Category IIIA plant oleoresin extracts currently available for patch testing be placed in Category I and made available for clinical diagnosis.

On the other hand, oral immunotherapy has only been tested and proven to be effective for a urushiol standardized preparation. Extracts of poison ivy and poison oak should be placed into Category I for oral immunotherapy if the conditions in the original Panel report are met, that is, if the product is shown to contain an adequate amount of urushiol and an effective dosage schedule is substantiated by appropriate effectiveness data. It is recommended that all other oral oleoresin products be placed in Category II. (Injectable poison ivy, oak, and sumac extracts for use in immunotherapy were in Category IIIB in the original Panel report.)

K. BACTERIAL VACCINE AND BACTERIAL ANTIGENS WITH NO U.S. STANDARD OF POTENCY

The Federal Register November 8, 1977 (42 FR 58266), summarized the Panel on Review of Bacterial Vaccines and Antigens with No U.S. Standard of Potency Report and the FDA's response. The final order was published January 5, 1979 (44 FR 1544).

Cutter Laboratories, Hollister-Stier Division's Mixed Respiratory Bacterial Vaccine (MRV) (licensed as "Polyvalent Bacterial Vaccines with No U.S. Standard of Potency") which was in Category IIIA has continued to be offered for sale and was assigned to this Panel for reclassification. As stated on page 58317 in the November 8, 1977 notice, the Category IIIA products could "remain on the market and their licenses remain in effect on an interim basis provided that: (1) group A streptococcal organisms and their derivatives, where present, are removed, and (2) satisfactory potency standards are developed and acceptable standards are developed and acceptable data based on scientifically sound studies (as recommended in the panel report) be submitted to demonstrate efficacy in humans."

Although the manufacturer removed the group A streptococcal organisms and began some preliminary studies for MRV, since 1977 there has been no better definition of indications for the use of this product. Neither are there recognizable criteria for selection of patients or dosage. No double-blinded controlled studies have been performed or even started since the Panel made its recommendations in 1977.

With no demonstrated effectiveness, the Panel with one dissenting vote recommends that Cutter Laboratories, Polyvalent Bacterial Vaccines with "No U.S. Standard of Potency" be reclassified from Category IIIA to Category II. One Panel member recommends Category I for diagnosis and immunotherapy because in his experience a rare patient will react with an immediate skin test response and seemingly will benefit from immunotherapy.