
Immunopathogenesis of fish allergy: identification of fish-allergic adults by skin test and radioallergosorbent test

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Background: As the consumption of fish increases in the United States, the importance of allergic reactions to fish has become clear. Since most previous studies on fish allergy have focused on children reacting mainly to codfish, there is a need to investigate allergic reactions to other fish in adults.

Objective: To identify fish-allergic adults, and to assess cross-reactivity among different species of fish by RAST inhibition.

Methods: Thirty-nine individuals who reported fish allergy were selected for study; 32 (82%) were atopic as defined by two or more positive skin tests to common inhalant allergens and a history of allergic reactions and 33 (85%) experienced allergic symptoms within 30 minutes after ingesting fish. The most frequently reported symptoms were hives (69%), itching (69%), and wheezing/chest tightness (54%). Study subjects were skin tested with fish extracts and their sera assayed for IgE antibodies to different fish species.

Results: Thirty-six (92%) of the subjects tested had a positive skin test to at least one of 17 fish extracts tested; 9/35 (26%) reacted to all 17 extracts. Of the atopic (two or more positive skin tests to common inhalant allergens plus a personal and/or family history of allergy) and nonatopic fish-tolerant controls, 20/26 (77%) reacted by skin test to one or more fish extracts tested; the most prevalent positive reaction was to anchovy (73%). A significant correlation ($P < .01$) was observed between skin test reactivity of fish-allergic subjects to most fish extracts and fish RAST reactions. Radioallergosorbent inhibition testing demonstrated significant cross-reactivity among pollack, salmon, trout, and tuna; and between mackerel and anchovy.

Conclusion: These results suggest that fish-allergic subjects may be clinically sensitive to more than one species of fish. Skin test reactivity to fish by itself is not an adequate criterion for the confirmation of clinically relevant fish allergy; consequently, fish-allergic subjects with positive skin tests to several fish species should exercise caution when eating fish until tolerance can be demonstrated by double-blind, placebo-controlled food challenge, at the patient's earliest convenience.

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INTRODUCTION

IgE-mediated reactions to seafood, particularly fish and crustacea, are

among the most commonly encountered food allergies.¹⁻³ Not surprisingly, seafood allergy is more prevalent in areas where fish is a major component of the diet (for example, Scandinavia, Portugal, and Spain) than

in regions where fish is not eaten routinely. Codfish allergy is the best studied;^{4,5} reactions to most other fish species have not been well studied.

Gad c l, the major cod allergen, is a parvalbumin believed to be similar in structure to those present in many fish species.⁶ Physicians therefore usually recommend that fish-allergic individuals eschew all species of fish although there is not uniform agreement among clinicians. For example, results from two studies suggest that children with histories of codfish allergy can ingest other species without risk.^{7,8}

A recent double-blind, placebo-controlled food challenge (DBPCFC) study of fish-allergic children concluded that all the subjects could eat some species of fish.⁹ In fact, the majority (80%) of blinded food challenges were negative. It is important to note, however, that when a negative blinded challenge was followed by an open challenge, 21% of the test subjects had a positive reaction. It is noteworthy that this high rate of false-negative fish-challenge tests exceeded that particular group's previous experience with other food challenges which had resulted in only 1.8% false-negative challenges.¹⁰ The ability of fish allergic individuals to eat additional fish species without risk clearly warrants further study.

Despite the fact that fish is considered one of the most important food allergens in adults, most studies of fish allergy have been performed in children. In this study, our objectives were to identify fish-allergic adults and to assess cross-allergenicity among different species of fish using that population.

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STUDY SUBJECTS AND METHODS

Study Populations

Thirty-nine subjects (27 women and 12 men, mean age 36.4 years) with histories of adverse reactions following ingestion of fish were recruited from allergy clinics at Tulane University, Case Western Reserve University, or the Medical Center of Louisiana at New Orleans Hospitals, or by newspaper advertisement. All protocols were reviewed and approved by the Institutional Review Committee on the Use of Human Subjects and informed consent was obtained from each subject prior to study. Subjects were given a screening questionnaire to determine information on their general health; presence of allergic diseases, in general, and fish allergy, in particular. The latter included information on the time since they had last eaten any species of fish (1 week to 20 years) and the time since their last adverse reaction to fish (1 week to 10 years). Eighteen atopic (eight women, mean age 32.7 years) and eight nonatopic (five women, mean age 38.1) non-fish sensitive adults served as controls.

Skin Tests

Thirty-five subjects were prick skin tested with 16 commercial fish extracts: channel catfish (*Ictalurus punctatus*), herring (*Clupea harengus*), black bass (*Centropomus striatus*) (Greer Laboratories); anchovy (*Engraulidae* spp.) (Allergy Labs of Ohio); cod (*Gadus callarius*), flounder (*Pleuronectes* spp.), halibut (*Hippoglossus* spp.), salmon (*Salmo solar*), tuna (*Thunnus* spp.) (Center Laboratory); haddock (*Melanogrammus aeglefinus*), mackerel (*Scomber japonicus*), lake perch (*Perca flavescens*), snapper (*Sebastodes* spp.), sole (*Parophrys cetulus*), trout (*Falmo gaironeri*), and whitefish (*Coregonus* spp.) (Hollister-Stier). Catfish, sardine and bass extracts were tested at 1:20 wt/vol concentration, all others were tested at 1:10 wt/vol concentration. Individuals were also tested with 12 common inhalant allergens (Greer): ragweed mix (1:20 wt/vol), Johnson and Bermuda

grass (1:20 wt/vol), oak (1:20 wt/vol), *D. farinae* (1:50 wt/vol), cockroach mix (1:10 wt/vol), cat and dog epithelia (1:20 wt/vol), *Alternaria tenuis* and *Aspergillus fumigatus* (1:20 wt/vol), and *Cladosporium herbarum* (1:40 wt/vol). Extracts of four species of crustacea (shrimp [*Penaeus setiferus*], lobster [*Panulirus argus*], crawfish [*Procambarus clarkii*], and crab [*Callinectes sapidus*]) were tested at 10.0 mg/mL (dry weight); and Alaskan pollack (*Theragra chalcogramma*), 10.0 mg/mL dry weight, prepared in our laboratory were also tested. For the purposes of this study, a positive skin test response was defined as a mean wheal diameter of 3 mm or greater to the test antigen in subjects who react to the positive control (1 mg/mL histamine diphosphate) and negative to the diluent control (50% glycerol in phosphate buffered saline [PBS]). Results were recorded 15 minutes after testing.

Fish Extracts

Uncooked finfish fillets (anchovy, mackerel, rainbow trout, salmon, and tuna) and crustacea were purchased from a local (New Orleans, LA) seafood store. Crustacea were boiled for 15 minutes prior to extraction. Alaskan pollack was obtained from Seafest/JAC Creative Foods, Motley, MN. Extracts were prepared separately by blending 500 g seafood in 1 L 0.01 M PBS (pH 7.2) in a commercial Waring blender (New Hartford, CT) for one to three minutes at room temperature. Mixtures were extracted overnight at 4 °C under constant stirring. Extracts were centrifuged (70,000 g); supernatants were concentrated on an Amicon-YM1 filter (Amicon, Danvers, MA; mwco <1kD) and were re-centrifuged (180,000 g). Dry weight determinations were performed in the following manner. One-tenth milliliter of the fish extract in duplicate along with 0.1 mL duplicate aliquots of buffer were placed in pre-weighed beakers and water evaporated in an oven. The amount of material remaining was determined and corrected for the weight contribution of buffer. The final figure reflects the dry weight of extract. Aliquots

were stored at -20 °C until use in skin testing. For preparation of skin test reagents of Alaskan pollack and the four crustacea, extracts were sterile filtered; and the filtrates were assessed for sterility. For skin testing, extracts were diluted 1:1 with sterile glycerol to a final concentration of 10 mg/mL.

Commercial extracts of bass, catfish, codfish, haddock, perch, sardine/herring, snapper, sole, and whitefish were dialyzed against 0.1 M borate buffer (pH 8.0), concentrated by dialysis with Ficoll 400 (Pharmacia LKB, Upsala, Sweden) and stored at -20 °C until use. Protein concentrations were measured using a commercially available phenol reagent method (Sigma Diagnostics, St. Louis, MO).

RAST, RAST Inhibition and Total IgE Determinants

Cyanogen bromide-activated paper discs¹¹ coated with fish extract (50 µg protein/disc) or shrimp (1.0 mg dry weight extract/disc) were incubated overnight (duplicate samples) with 100 µL undiluted serum. After washing with saline (0.9%), 100 µL ¹²⁵I-labelled anti-IgE (15,000 cpm/disc; Kallestad, Chaska, MN) was added and incubated overnight. Discs were washed and bound label was counted in a gamma counter (Gamma 5500; Beckman, Irvine, CA). Results are expressed as mean percent bound of total radioactivity added; a positive value is defined as ≥3% of total radioactivity added.

Radioallergosorbent test inhibition was performed as described previously,¹² using anchovy, mackerel, pollack, salmon, trout, tuna, and shrimp extracts. Peanut extract was the negative control. Fifty microliters of a serum pool (composed of equal volumes of five fish RAST positive sera) plus 50 µL of 10-fold increasing concentrations (beginning at 0.8 or 5 µg/mL) of extract were tested for inhibition. Duplicate inhibitions were performed and mean values were determined. The dose that inhibits 50% RAST (ID₅₀) was determined graphically.

Total serum IgE levels were measured using a Kallestad QuantiCLONE kit (Chaska, MN).

Statistical Analyses

Chi-square analysis was used to compare the different fish species' skin test and RAST reactivity.

RESULTS

Reported signs and symptoms after ingestion of fish among the fish-sensitive population tested are summarized in Table 1. The most frequently reported signs/symptoms were pruritus and hives (69%), wheezing/chest tightness (54%), and angioedema (51%). Thirty-three (85%) of the subjects reported that their allergic reaction had occurred within 30 minutes following fish ingestion, two (5%) within 30 to 60 minutes, and four (10%) after one hour.

Twenty of the fish-sensitive subjects (51%) complained of allergic reactions to other seafood, primarily shrimp (49%) and crawfish (36%) (Table 2). Eleven (28%) of the fish-sensitive study participants had histories of hypersensitivity reactions to other foods including milk (10%), egg (8%), celery (5%), and pea (5%). Asthma was reported by 17 (44%), allergic rhinitis by 24 (62%), and atopic dermatitis by 14 (36%). Nine of seventeen (53%) asthmatic subjects experienced pulmonary symptoms including chest tightness or wheezing after fish ingestion; however, only one reported pulmonary symptoms as the only symptom. Nine (23%) subjects had no history of other atopic diseases.

Subjects' history and skin test and RAST reactivity to different species of

Table 1. Reported Signs and Symptoms of 39 Fish-Sensitive Subjects

Sign/Symptom	No (%)
Pruritus	27 (69%)
Hives	27 (69%)
Asthma, wheezing	21 (54%)
Angioedema	20 (51%)
Dyspepsia, cramps	7 (18%)
Vomiting	3 (8%)
Shock	3 (8%)
Fainting	2 (5%)

Table 2. Reactivity of 39 Fish- Sensitive Subjects to Other Seafood

	Positive History	Positive Skin Test	Positive RAST*
<i>Arthropoda crustacea</i>			
Crab	10 (26%)	13 (33%)	ND†
Crawfish	14 (36%)	13 (33%)	ND
Lobster	7 (18%)	11 (28%)	ND
Shrimp	19 (49%)	16 (41%)	5/14 (36%)
<i>Mollusca bivalvia</i>			
Oyster	7 (18%)	ND	ND

* Positive RAST = percent bound >3.
† ND = not determined.

fish are presented in Table 3. By history, the most frequently implicated fish were catfish (62%), trout (59%), snapper (41%), and perch (38%). Six (15%) experienced symptoms to a single species of fish, seven (18%) to two, five (13%) to three, and 21 (54%) to four or more species.

Thirty-two of 39 (82%) subjects reacted by skin test to at least two common inhalant allergens. Thirty-six (92%) had a positive reaction to at least one commercially available fish extract; however, four reacted only to anchovy. Fifteen of 35 (43%) had positive skin tests to more than ten fish extracts; nine (26%) reacted to all fish extracts tested. Anchovy (63%), mackerel (51%), whitefish (51%), and perch (51%) extracts produced the most positive reactions.

Skin test reactivity of the fish-tolerant control subjects (18 atopics and 8 non-atopics) are summarized in Table 4. The greatest number of fish-tolerant subjects reacted to anchovy; 6/8 (75%) nonatopics reacted only to anchovy. Whereas 13/18 (72%) atopic controls reacted to anchovy. Three of the atopic control subjects had positive skin tests to two fish extracts; and four to three fish extracts.

Radioallergosorbent test reactivity with sera of skin-test positive subjects (Table 3) was observed to cod (66%), haddock (72%), and bass (58%); in contrast, tuna and anchovy RAST were positive in only 18% and 13% of skin test positive subjects, respectively. Mean RAST reactivity of skin test positive and negative fish-allergic subjects

is shown in Table 5. The highest levels of RAST reactivity in skin test positive subjects were to cod (19%), bass (17.8%), and haddock (17.1%); the least was to mackerel (5.2%), tuna (4.5%), and anchovy (1.8%). In general, a significant correlation existed between RAST and skin test reactivity ($P < .001$ to $.0002$) for most species of fish that were tested; most skin test reactors had positive RAST responses. No correlation was found between skin and RAST values to anchovy, sole, tuna, or mackerel. Skin test verses RAST comparison for three species of fish of different orders are presented in Figure 1. Three of the 39 fish-allergic subjects (8%) had negative skin tests and RAST to all fish. Mean total serum IgE was 504.2 IU/mL (range 3.5 to 8,150 IU).

Radioallergosorbent test inhibitions demonstrated significant cross-reactivity among salmon, pollack, trout, and tuna; as well as between mackerel and anchovy. Trout RAST was inhibited 86% by salmon, 67% by pollack, and 45% by tuna (Fig 2). Mackerel RAST was inhibited 76% by anchovy, 47% by salmon, and 26% by tuna (Fig 3). Although the homologous shrimp extract inhibited shrimp RAST by 90%, none of the fish species tested significantly inhibited shrimp RAST, even at the highest concentrations (4 to 25 mg/mL) tested (data not shown). Peanut, an unrelated negative control, did not significantly inhibit fish or shrimp RAST.

DISCUSSION

Fish are recognized as an important cause of immediate food hypersensitivity reactions.^{1-4,8,9} With the exception of codfish allergy, however, allergy to most species of fish has not been well studied. Further, most studies of fish allergy have focused on children.^{4,7-9,13} Fish allergy in adults has not been well studied and there are only infrequent reports in the literature.^{2,14-16}

Since 1921, when Prausnitz and Küstner described the first controlled passive transfer experiment,¹⁷ it has been accepted that fish hypersensitiv-

Table 3. Reactivity by Species of 39 Fish-Sensitive Subjects

Fish Species	Positive History	Positive Skin Test	Positive RAST*
Anchovy	28% (11/39)	63% (22/35)	13.8% (4/29)
Bass	36% (14/39)	43% (15/35)	58.3% (7/12)
Carp	10% (4/39)	ND†	ND
Catfish	62% (24/39)	40% (14/35)	52.4% (11/21)
Cod	31% (12/39)	46% (16/35)	66.7% (8/12)
Flounder	33% (13/39)	31% (12/39)	57.1% (12/21)
Haddock	5% (2/39)	43% (15/35)	72.7% (8/11)
Halibut	10% (4/39)	31% (12/39)	ND
Herring/Sardine	28% (11/39)	43% (15/35)	40.9% (9/22)
Mackerel	10% (4/39)	51% (18/35)	39.1% (9/23)
Orange roughy	3% (1/39)	ND	ND
Perch	38% (15/39)	51% (20/39)	54.2% (13/24)
Pollack	5% (2/39)	51% (18/35)	57.1% (12/21)
Redfish	3% (1/39)	ND	ND
Salmon	33% (13/39)	41% (16/39)	54.2% (13/24)
Snapper	41% (16/39)	43% (15/35)	52.4% (11/21)
Sole	3% (1/39)	44% (17/39)	63.6% (14/22)
Trout	59% (23/39)	43% (15/35)	50% (11/22)
Tuna	33% (13/39)	38% (15/39)	18.5% (5/27)
Whitefish	26% (10/39)	51% (18/35)	76.5% (13/24)

* Positive RAST = percent bound >3.

† ND = not determined.

Table 4. Skin Test Reactivity by Species of Fish-Allergic and Non-Fish-Allergic Control Subjects

Fish Species	Fish-Sensitive Subjects	Atopic Controls	Nonatopic Controls
Anchovy	66% (23/35)	72% (13/18)	75% (6/8)
Flounder	33% (13/39)	22% (4/18)	0% (0/8)
Herring/sardine	46% (16/35)	6% (1/18)	0% (0/8)
Mackerel	60% (21/35)	6% (1/18)	0% (0/8)
Tuna	46% (18/39)	28% (5/18)	0% (0/8)

ity is immediate. The finding that the majority of our study subjects experienced symptoms within 30 minutes after fish ingestion is compatible with an IgE-mediated mechanism. Positive skin test reactions and RAST to fish extract, demonstrating the presence of the IgE-antibody's reactivity, clearly support this concept. Four subjects reported development of symptoms more than one hour following ingestion of fish. Although most systemic allergic reactions from ingested food occur within 30 minutes, reactions occurring several hours after ingestion have also been reported.¹⁸

The clinical spectrum of food allergy ranges from intestinal distur-

bance to anaphylaxis.^{1-3,14,15} In our study, cutaneous or pulmonary manifestations were the most frequently reported symptoms after exposure to fish. Only one subject reported pulmonary manifestations as the sole symptom following fish ingestion or exposure to the cooking process; all others experienced more than one symptom. All three of the subjects who reported anaphylaxis following ingestion of fish experienced cutaneous, pulmonary, or gastrointestinal symptoms prior to frank shock.

Diagnosis of most food allergies by skin testing with food extracts is an unresolved issue. Some studies recommend skin tests as a major diagnostic

method,¹⁰ while others consider it non-specific and unreliable.^{19,20} Positive food skin tests in the absence of clinical allergy are seen in up to 65% of atopics;²¹ thus, diagnosis of food allergy requires both accurate interpretation of history as well as test results, such as skin testing and RAST. In many instances, uncertainty remains and further testing is necessary to ascertain the link between food ingestion and clinical symptoms. Currently, the double-blind, placebo-controlled food challenge is the most accurate method to diagnose food allergy.^{10,22,23}

Generally, skin test positivity to fish extracts is thought to correlate well with allergic manifestations following ingestion of fish;^{4,9,10,24} however, this belief is principally based on results from studies of codfish-sensitive subjects and using a highly purified codfish allergen. Our results demonstrated a low concordance between skin tests and history of fish-allergic subjects. For example catfish and trout, the two most frequently reported offending species by subjects' history, did not result in the anticipated number of skin test responses for this population. Anchovy and mackerel had a high rate of skin test positivity although only a few clinical allergic reactions were reported to these species. Some fish extracts (especially anchovy) elicited positive skin tests in fish tolerant subjects. A major problem with seafood allergy is that subjects' history may not be reliable, may be biased, or based on inaccurate knowledge of the fish species eaten. Accurate identification of the ingested fish is particularly problematic, since a variety of common names for the same species are used in different parts of the country.^{1,25} For example, king mackerel may be sold as black salmon or kingfish; kingfish may also be called king whiting, but is often sold as ground mullet or gulf whiting.¹

A recent study did not demonstrate skin test reactivity in non-fish-sensitive subjects suggesting that fish extracts have a high specificity.⁹ In contrast, our results suggest strongly that some fish extracts (ie, anchovy) may nonspecifically elicit a positive skin

Table 5. RAST Reactivity of Fish-Sensitive Subjects

Fish Species	Skin Test- Positive Mean % Label Bound	Skin Test- Negative Mean % Label Bound
Anchovy	1.8%* (21†)	1.0% (6)
Bass	17.8% (8)	1.3% (4)
Catfish	10.4% (12)	1.4% (7)
Cod	19.0% (8)	1.1% (4)
Flounder	15.4% (10)	3.5% (12)
Haddock	17.1% (8)	1.3% (3)
Herring/sardine	6.8% (12)	1.3% (9)
Mackerel	5.2% (18)	1.3% (3)
Perch	13.4% (19)	1.2% (5)
Pollack	9.1% (14)	1.0% (5)
Salmon	10.1% (14)	1.7% (10)
Snapper	10.5% (13)	1.2% (6)
Sole	11.5% (15)	4.1% (7)
Trout	8.9% (14)	1.2% (6)
Tuna	4.5% (15)	1.8% (12)
Whitefish	14.4% (17)	1.1% (6)

* Mean percent bound.
† Number of sera tested. Since only a limited number of discs were available for some species of fish, only selected sera could be tested.

test response. Overall, the concern has been raised that histamine contamination of fish extracts can cause false-positive results. Fish skin test reagents have been shown to contain the highest levels of histamine among 26 food extracts tested;²⁶ thus, some fish extracts may contain sufficient quantities of histamine to induce positive skin tests

in some individuals. With the exception of flounder, all other fish species eliciting positive skin test responses in controls have been implicated in scombroid or histamine fish poisoning;^{1,28} thus, quantitation of histamine levels in fish extracts should be performed. Alternately, positive skin tests reactions to tuna, flounder, mackerel, and herring in atopic controls without a history of fish allergy may be interpreted as subclinical or latent allergy.^{19,27} The results of our study suggest that commercial fish extracts may not be reliable diagnostic tools in subjects with suspected fish allergy.

Only three of the 39 (8%) subjects with a significant history of fish allergy were skin-negative and RAST-negative to all species tested. Multiple skin test sensitivity to different fish species in fish-allergic individuals is a frequent clinical observation commonly attributed to possible cross-reactivity among fish species.^{8,9,29} Based on clinical histories from our fish-sensitive patients, the majority of subjects reacted to several species. Radioallergosorbent test inhibition studies support the presence of common antigens among different species of fish.^{8,9,30} This is supported by the recent studies of James and co-workers which reports the presence of a 12.5-kD, Gad c 1-like protein in several different fish species analyzed.³¹ Our inhibition experiments demonstrated that common epitope structures occur not only between dif-

ferent species but among various orders. In contrast to our observations, other studies suggest that evidence of cross-reactivity by skin prick test and IgE antibody reactions do not necessarily correlate with clinical fish allergy.⁹

Tuna was consistently the least effective inhibitor of the fish RASTs performed; other studies have reported similar findings.⁸ The major fish 13-kD allergen, which is analogous to Gad c 1, has been demonstrated in several fish species,⁹ but is absent in tuna immunoblots, possibly suggesting tuna's lack of inhibitory potency. These findings support the clinical impression that tuna, one of the most frequently consumed fish in the United States, has less allergenic activity than other fish species.¹ Recent evidence suggests this maybe a result of food processing.³²

Although half the sensitive subjects reported reactivity to other seafoods, including shrimp or crawfish, cross-sensitization between finfish and shellfish is unlikely, since they belong to different phyla. The reported sensitivity to crustacea by some of our subjects probably reflects concomitant hypersensitivities, which are frequently observed in atopic subjects, since cross-reactivity between finfish and crustacea could not be demonstrated by RAST inhibition.

In this study, we demonstrated that most fish-sensitive subjects are atopic, have positive skin test reactions to fish extracts, and have elevated circulating fish-specific IgE antibodies. Almost half of the fish-sensitive subjects reacted to the majority of fish species tested. Radioallergosorbent test inhibitions showed that different species of fish from different orders share allergenic epitopes. Some of the commercial fish extracts apparently elicited false-positive skin test reactions; this requires further investigations. Further, caution should be employed when using only skin test reactivity as the basis for diagnosis of fish allergy, especially in individuals with no prior history. Based on these results, fish-sensitive subjects may be clinically sensitive to

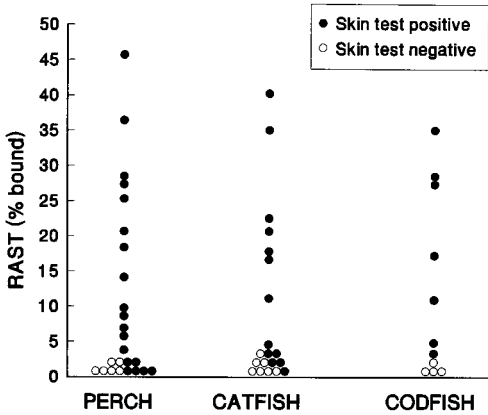


Figure 1. Relationship between fish-specific skin test and RAST. The correlation was significant for perch ($P < .0063$), catfish ($P < .0045$), and codfish ($P < .0005$).

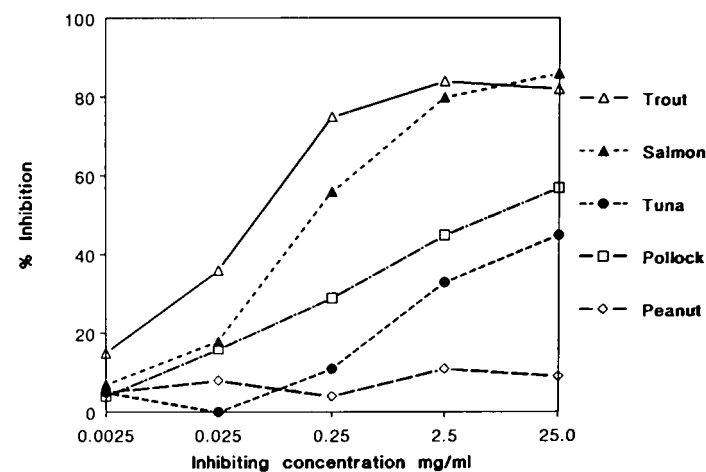


Figure 2. Inhibition of trout RAST with trout, salmon, tuna, pollack, and peanut (negative control).

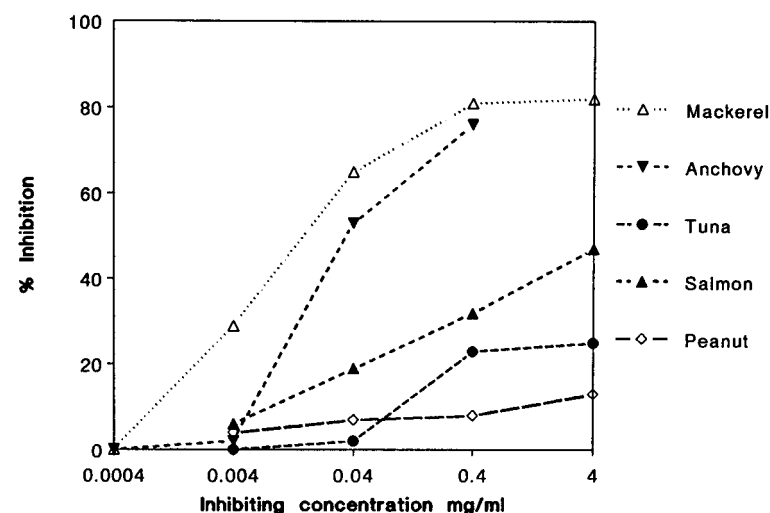


Figure 3. Inhibition of mackerel RAST with mackerel, anchovy, tuna, salmon, and peanut (negative control).

several different species. Our data imply that fish-allergic individuals should be advised to eat fish cautiously until specific sensitivities can be confirmed by challenges, unless they have histories of severe reactions in which case they should be advised to avoid all fish until challenge studies can be undertaken.

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PAF ANTAGONIST MODIFIES AIRWAY HYPERRESPONSIVENESS

Using a randomized, double-blind, placebo controlled, cross-over study design the authors determined the effect of an orally active, specific platelet activating factor-receptor antagonist on methacholine airway responsiveness.

Subjects were 13 stable nonsteroid treated extrinsic asthmatic adults treated with active drug (Y-24180) and placebo for 2-week periods with a 2-week wash-out period between treatments. Methacholine PD₂₀ FEV₁, using a tidal breathing protocol, was determined immediately before and at the end of each treatment period.

There were no statistically significant differences in baseline FVC or FEV₁ before and following administration of active drug or placebo. There was a significant ($p = 0.005$) improvement in airway responsiveness following treatment with Y-24180 compared to placebo and the authors state that these results suggest an important role for platelet activating factor in asthmatic airway hyperresponsiveness.

—JGE

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