

CLIAC Committee:

RE: Allergy Blood Tests-Need to make specific IgE a regulated analyte

Decisions on which manufacturer's test for specific IgE antibodies is used is usually based upon cost irregardless of the accuracy and precision of such tests. Presently in the U.S. there are three major manufacturers of such tests plus a number of laboratories utilizing in house developed tests. The literature clearly shows major deficiencies in the accuracy and precision of some of these tests yet they continue to be utilized as there are no factors in place to control their accuracy. Physicians ordering these tests rarely know the difference, often have no choice in these matters due to managed care utilization of one laboratory or the other, and the possibility and related costs of incorrect diagnoses and treatments are rather substantial.

The FDA has approved tests on predicate device standards almost wholly with data supplied from the manufacturers themselves which impedes progress as is all a company has to do is supply data which says the device in question gives equivalent answers to some already approved device using similarly obtained data. The possibility is strong that the previously approved devices functioned poorly which results in use of a standard that guarantees mediocrity in this field.

Here I briefly recount some recent studies which verify the status of several of these tests and suggest that the only real solution is to make the measurement of specific IgE antibodies a regulated analyte. These tests are used not only to identify sensitization to various allergens but recently the quantity of these antibodies an individual produces has been shown to be related to their likelihood of reacting to the same upon exposure. Thus, regulation should also include their ability to quantitatively measure these antibodies as claimed in their approval by the FDA process.

These tests essentially all use solid phased allergens to capture specific IgE antibodies from serum samples and interpolate the response using total IgE assays linked to the W.H.O. standard. Problems arise due to the quality of the allergen preparations, the mechanics of the assays themselves (amount of solid phased ligand, chemistries used, incubation times, washing procedures, etc.), and the software employed to yield results. With this many variables it is surprising that even similar results on identical samples are sometimes achieved with these different procedures.

Total IgE is a regulated analyte and most surveys and studies reveal a rather close concordance of results on an inter-laboratory and inter-procedure basis. In fact, the measurement of total IgE in spite of the varied techniques is one of the best immunometric assays available. Sadly, the non regulated specific IgE assays show a very different picture. Here specific IgE assays have been treated as a non regulated analyte that laboratories can and do participate in CAP survey samples. The results of the different assays are quite disparate but no body seems to care. This is probably because very few people have access to these results and in particular physicians don't know enough to ask. Complicating this is the fact that the survey results are compared by log

related classes determined quite arbitrarily even though the major three assays utilized in the US all report out their results in quantitative terms (KUa/L). This log related class system (classes I-VI usually) actually serves to hide the fact that different assays give very different and non comparable results. For example, the difference between a class I and II might represent only a few tenths of a unit while a difference between a class IV and V represents a very large amount of units. In addition, most of these assays are run in singlicate. Given the rather large variation even with the same repeated sample for some these assays raises the possibility that these singlicate measurements are likely to be in error.

Applicable Data:

The CAP survey results and a number of recent studies have clearly pointed out the unacceptable variability of these different assays. I believe the most comprehensive of these points out that some assays couldn't even detect several dilutions of the same sample. This paper compared 12,708 results from different laboratories using four different procedures. Results were compared to an ideal standard (slope of one for serial dilutions on a semi-log plot) and revealed that while one procedure was quite accurate with good precision, the others gave noncomparable and quite variable results.

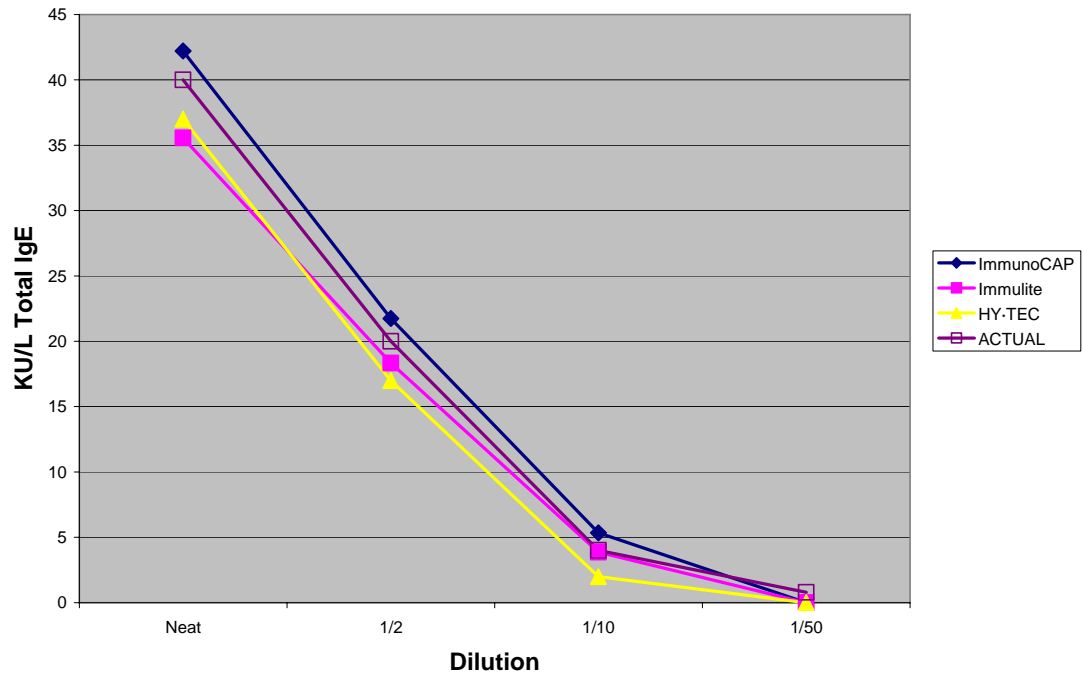
Recently, we sent blinded humanized chimeric IgE antibody samples directed against two different allergens to laboratories to be analyzed by the three different major procedures used in the US. All three procedures claim to give quantitative results and are FDA approved for the same. The laboratories were asked to determine the total IgE and specific IgE of each sample. The expected results in dilutions of these samples, if an assay was performing correctly, would be that the total IgE would equal the specific IgE in each sample. The findings were very clear and reflected similar results from the CAP surveys. Here all the total IgE values in these samples correlated closely with each other and with the expected values. However, the specific IgE assays revealed very different results. One assay reported up to ten times more specific IgE than was present in the sample and another reported much less specific IgE than total IgE in these samples. One procedure reported identical results for both the specific IgE and total IgE in these samples. The results were very similar for both allergen specificities for these assays.

Conclusions:

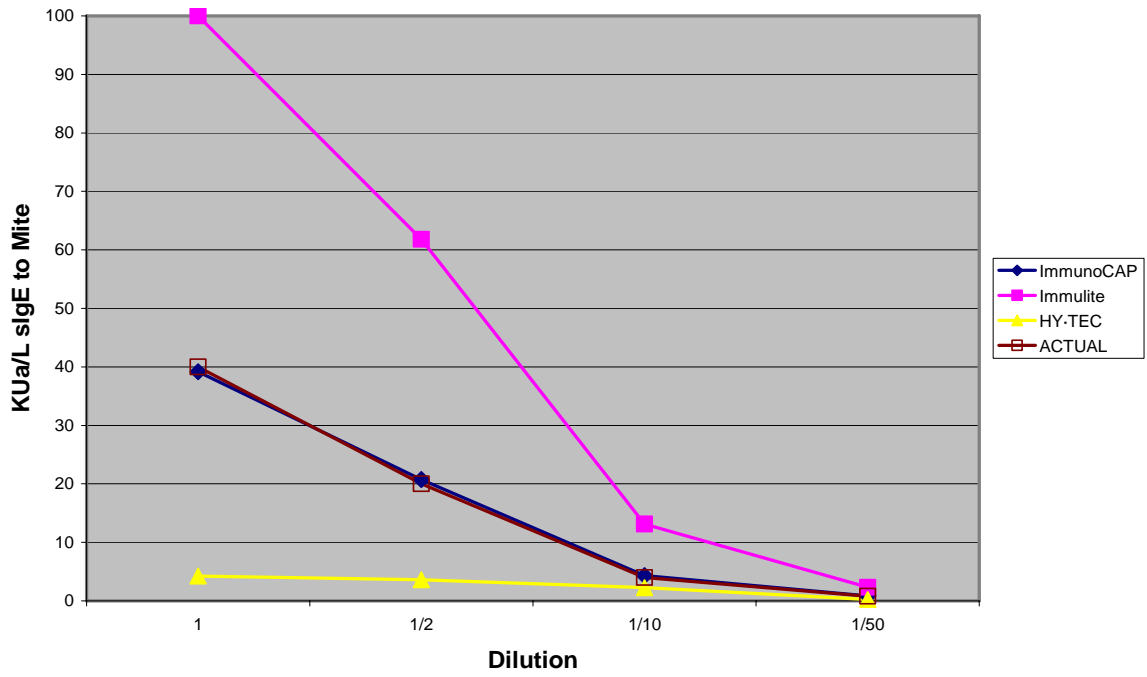
This is an unacceptable situation promulgated by the lack of regulating this analyte which in all likelihood leads to incorrect diagnoses in this field with resulting over and under treatment of conditions that have a number of chronic health consequences. Thus, it is recommended that specific IgE tests become a regulated analyte as soon as possible and that this regulation be instigated on a quantitative basis for those assays claiming quantitative abilities.

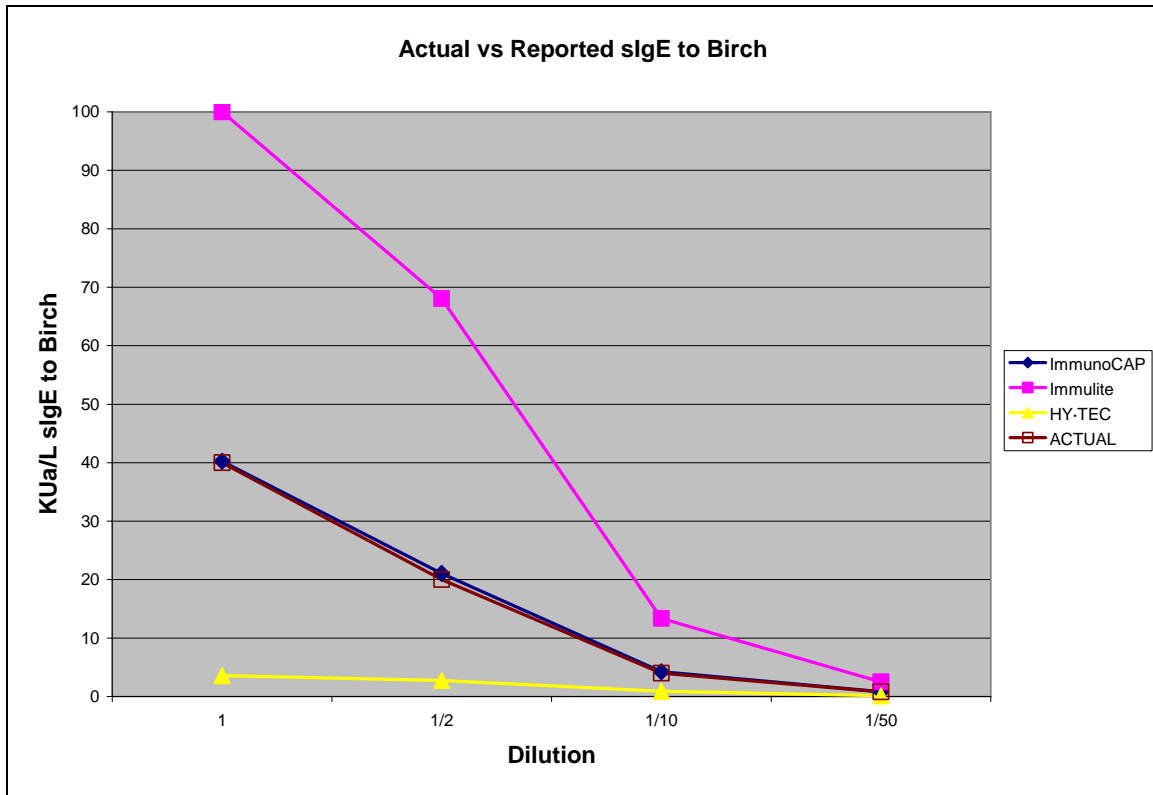
P. Brock Williams, Ph.D. 913-768-7072; pbrockwil@aol.com, 11840 Woodland Road, Olathe, KS 66061. U. of Missouri Medical School, at Kansas City.

Actual vs Reported Total IgE of Chimeric Antibodies



Actual vs Reported sIgE to Mite





References:

P. Brock Williams, Barnes James H, Szeinbach Sheryl L, Sullivan T.J. Analytic precision and accuracy of commercial immunoassays for specific IgE: Establishing a standard. *J Allergy Clin Immunol* 2000;105:1221-30.

P. Brock Williams, Ahlstedt Staffan, Barnes James H, Soderstrom Lars, Portnoy, Jay.. Are our impressions of allergy test performance correct? *Ann Allergy Asthma Immunol* 2005;91:26-33.

Szeinbach Sheryl L, Barnes James H, Sullivan Timothy, P. Brock Williams. Precision and accuracy of commercial laboratories' ability to classify positive and/or negative allergen specific IgE results. *Ann Allergy Asthma Immunol* 2001;86:373-381.

Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol.* 1997;100:444-451.

Celik-Bilgili S, Mehl A, Verstege A et al. The predictive value of specific immunoglobulin E levels in serum for the outcome of oral food challenges. *Clin Exp Allergy* 2005; 35: 268-273.

Simpson A, Soderstrom L, Ahlstedt S, Murray CS, Woodcock A, Custovic A. IgE antibody quantification and the probability of wheeze in preschool children. *J Allergy Clin Immunol* 2005; 116: 744-749.

Soderstrom L, Kober A, Ahlstedt S et al. A further evaluation of the clinical use of specific IgE antibody testing in allergic diseases. *Allergy* 2003;58: 921-928

G, Pastori E, Portalupi S, Temporito R. In vitro allergy diagnosis: comparison of a new method of fully automated determination of specific IgE, using Immulite 2000 compared with UniCAP 100. *Europ Ann Allergy Clin Immunol* 2003; 35: 285-294.

Schuurman J, Perdock GJ et al. Production of a mouse/human chimeric monoclonal antibody to the house dust mite allergen Der P2 and its use for the absolute quantification of allergen-specific IgE. *J Allergy Clin Immunol* 1997; 99: 545-550.

I have a much more extensive reference list that can be provided by request.