

Correspondence

How much is too much . . . And in what setting?

To the Editor:

I read with interest the article regarding threshold dosing by Ballmer-Weber et al¹ published in the April 2015 issue of the *Journal*. Establishment of threshold dosing for food allergy would be ideal for individual patients, and it is of vital importance for populations as pointed out by the authors.

Interesting though is the juxtaposition of this article with the article by Brockow et al² and its accompanying editorial³ just a few pages later in the same issue.

The article by Brockow et al² shows that adjuvants such as alcohol, aspirin, and exercise augment the severity of allergic reactions in wheat-allergic individuals.² The idea of adjuvant factors is not new and not unique to wheat allergy.⁴ In fact, one simply has to look at oral immunotherapy studies for food allergy to show that stable, tolerated daily amounts of food antigen can elicit a reaction in the setting of adjuvant factors. For example, Varshney et al⁵ showed that with peanut oral immunotherapy, subjects can be tolerating a stable daily dose, yet develop symptoms of an allergic reaction to that tolerated dose in the setting of a febrile illness, exercise, menses, and even when they take the dose on an empty stomach.

One can easily see then the slippery slope of establishing a defined ED10 for a population from these studies, which is that the ED10 is established in a “sterile,” controlled setting. Subjects are given food, often blinded and mixed into a matrix, and then monitored with a watchful eye examining for any small reaction. This may (and I would argue is likely to) be very different from everyday field encounters of allergens and reactions. Thus, an established ED10 for a population may be artificially high once that same dose is allowed to be consumed in the field, where patients are likely to be on nonsteroidal anti-inflammatory drugs, have viral illnesses, indulge in exercise, or be drinking alcohol in conjunction with ingestion.

In addition to this, ED10 values are typically established using the cumulative dose eliciting a reaction during graded challenges with 15- to 20-minute intervals. As Blumchen et al⁶ cogently point out in their article on establishing ED10 for peanut, this does not reflect real-world experience and may also make the ED10 artificially high because many patients have a reaction up to 2 hours after ingestion. In fact, using a 120-minute interval in their challenges, these authors found that the median time to onset of initial objective symptoms was 55 minutes. Thus, by simply adding time between doses

during a challenge, the authors may have found a lower ED10 than reported here.

Although I do not wish to downplay the importance of this article or the need for establishing an ED10, I do believe that the topic must be understood in a realistic fashion. Establishing an ED10 for a population will help in shaping future regulations for labeling, and allow patients to not have to wade through myriads of products that have warning labeling just to cover companies for any possible legal action, rather than to truly inform patients. However, by establishing an ED10 using controlled challenges, we may be setting an artificially high value.

In their rostrum in 2002,⁷ some of the same authors in the current report suggest adding an uncertainty factor of 10 to account for some of the unknown factors, citing toxicology literature; however, it seems difficult to attempt to account for these factors.

In the end, if we are fortunate enough to one day have an ED10 (or an ED5 or ED1 for that matter), and labeling regulations become standardized on the basis of this, we must still be cognizant that the real-world environment may not mimic our selected testing environment.

Jay A. Lieberman, MD

From the Department of Pediatrics, The University of Tennessee Health Sciences Center, LeBonheur Children's Hospital, Memphis, Tenn. E-mail: jlieber1@uthsc.edu.
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