

# Potency variability in diagnostic allergen extracts: is there an optimal strength?

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Ideally, allergen skin testing should be used as a confirmatory validation of conclusions about the presence of specific hypersensitivity already derived on the basis of the appropriate patient history. The significance of positivity must be gauged in light of the history and not taken *prima facie*. The pitfall of interpreting reactions from too concentrated an extract has been well established for intradermal skin testing as early as 1934 by Rackemann and Simon, and revalidated by Lindblad and Farr in 1961.<sup>1,2</sup> But what about prick skin tests? The European Academy of Allergology & Clinical Immunology in a position paper on skin testing stated that prick skin tests are the preferred technique and that intradermal testing for pollen had no role in accurate diagnosis.<sup>3</sup> But is it also possible to use too potent of an extract for prick skin testing?

In this issue, Larenas-Linnemann and colleagues report on titrated prick skin tests using Bermuda grass and cat dander from diverse geographic locations: United States, Europe, and Mexico from US sources as well as local Mexican acquisition.<sup>4</sup> This paper represents a clinical *in vivo* companion piece to an *in vitro* potency of the source extracts compared with the Center for Biologics Evaluation and Research/Food and Drug Administration references report published elsewhere last year.<sup>5</sup> In that report, the authors found that the total protein content was less than the reference standard, as was relative potency measured by enzyme-linked immunosorbent assay inhibition for Bermuda and Fel d 1 content for the cat extracts. The exception was one European cat dander extract containing almost twice the Fel d 1 content compared with the US reference. Generally, the European extracts contained 4-fold to 6-fold less potency than the US standard, and the local Mexican extracts contained 10-fold less potency. The current paper supports the *in vitro* data with similar findings based on prick skin testing. These combined findings are reassuring that *in vivo* and *in vitro* assays mirror each other and supports the contention that laboratory analyses are appropriate surrogates for determining potency of allergen extracts.

What is less reassuring is the not unexpected finding of extraordinary variability of extract potency depending on the source. This variability was demonstrated years ago with US pollen extracts and recently reinforced concerning European extracts by Larenas-Linnemann and Cox.<sup>6,7</sup> The differences in strength are dependent in part on the source material, the extraction process, and decisions on reconstitution based on arbitrary in-house reference standards. All of these vary from one manufacturer to another. International standardization

guidelines would answer some of these issues. Parenthetically, standardized extracts are not inherently more potent than conventional extracts based on weight per volume (w/v) or protein nitrogen units.<sup>8</sup>

Returning to the other issue raised by the current paper: Can an extract for diagnostic prick skin testing be too potent? As pointed out by the authors, this depends in part on the rationale for the testing: epidemiology vs clinical management, with the latter being the major indication for most practicing allergists. The current paper can be taken to imply that US extracts are too potent, rather than that European or Mexican extracts are too weak—a question of viewpoint. Is there a “gold standard” that can be used as a yardstick? Many would say no. Nasal challenge with anterior manometry provides an objective measure of response to exposure, but the caveat is that the challenge may be superphysiologic and not reflect natural conditions.<sup>9</sup> Two articles have addressed optimal cutoff values for prick skin testing using receiver operating characteristic curves for sensitivity and specificity. Pastorello and associates<sup>10</sup> suggested a wheal area of 32 mm<sup>2</sup> (0.57 mm mean diameter) for seasonal allergens and 31 mm<sup>2</sup> (0.56 mm mean diameter) for *Dermatophagoides pteronyssinus*.<sup>10</sup> Zarei and coworkers found the optimal cutoff for cat dander to be a 6-mm wheal.<sup>11</sup> The former study was performed in Italy, and the latter in California. Studies like these are perhaps the only way the issue of appropriate extract potency can be determined objectively. Considering the paucity of such studies, we have a long way to go.

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