Open Letter to Phytochemists

Inspired by papers delivered at the recent conference at Kew on the systematics and biology of Leguminosae, I reiterate a plea issued previously[1]. Those of us attempting to understand the effects of herbivores on plants and the responses of plants to herbivory are dependent on the work of chemists, natural products chemists, phytochemists, and pharmacologists for the identification of the secondary compounds in plants. However, secondary compounds do not occur in Latin binomials, and herbivores do not eat Latin binomials.

Secondary compounds occur in plant parts. A report of a new alkaloid in *Xus albus*, even assuming the plant to be correctly identified, is absolutely useless to the animal–plant biologist (except perhaps in giving some later phytochemist a clue as to what to look for in diagnosing a toxic diet). There is no excuse for the numerous papers that do not clearly identify the plant part from which the chemical was obtained. It takes one sentence to report it and only a few seconds to determine it. Secondary compounds are not evenly distributed in kind or quantity throughout the plant (in space and often in time as well). Animals respond accordingly.

It is easier to understand why the phytochemist is reluctant to determine content per unit of tissue, but let me simply beg for such information. Most secondary compound effects on animals are dosage dependent[2]. Without statements of concentration, we are powerless to interpret refusals of foods containing these chemicals. Furthermore, artificial diets testing the compounds cannot be realistic unless the concentrations are known from real dietary items. Even statements of the approximate concentration enormously increase the value of a chemical identification.

Seeds and their contained chemicals are of particular interest to me, and seed chemistry data are gross offenders. Seedcoats are from 1 to 70% of the dry weight of a seed[3] and are usually made of largely inert cellulose–lignin–tannin complexes; at the least, secondary compounds found in the seedcoat are not repeated in the seed contents and vice versa. When a bag of seeds is ground up and analyzed, concentrations of secondary compounds as then measured are extremely misleading. The animals that eat seeds almost invariably discard, avoid, or defecate the seedcoat undigested. The kind and concentration of secondary compounds in the seed contents normally matter to the animal, and this information is almost never recorded. Please do it.

The time is ripe for a person with a strong flair for organization to initiate and develop an international museum of secondary compounds. Such a "museum" would perform all those analogous functions provided by more conventional museums of organisms. The burgeoning population of workers on the interface between animals and plants are desperate for a technology or a system that will cut through the contemporary block to the identification, characterization, and provision of secondary compounds for experimental and feeding studies. Secondary compounds are, after all, practically the entire basis for the enormous and complex structure of the interaction between herbivores and plants, which makes them largely responsible for the diversity of plant and animal life on this planet.

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[1] D. H. Janzen, *Ann. Missouri Bot. Gard.*, **64**, 706 (1978).
[2] D. H. Janzen, *Phytochemistry*, **16**, 223 (1977).
[3] D. H. Janzen, *Ecology*, **58**, 921 (1977).

Propoxyphene Bioavailability

A recent letter[1] by Mr. Chmielewski on "Propoxyphene Bioavailability" in the Open Forum indicated that no technical information was forthcoming from the authors after written requests. As we certainly have no reason for not responding to any inquiry, we checked our files and discovered that Mr. Chmielewski's request, along with six other requests, had been filed as sent. However, there were no copies of correspondence indicating that these requests were answered. We have recently sent the requested information to the requestors with our regrets for the delay. We thank Mr. Chmielewski for bringing this matter to our attention.

In regard to some conclusions drawn from the aforementioned Open Forum letter, we would like to make the following comments:

1. The research lots reported[2] in our bioavailability article were 100,000 capsule lots (one-tenth full size manufactured lots), which were manufactured on the exact equipment to be used for the full-sized marketed lots.
2. The research lots in question met all current existing FDA requirements and could have been submitted as part of an abbreviated NDA and been marketed.
3. The research lot that was bioinequivalent was not marketed for that very reason. We firmly believe that it is better to test for the bioequivalence of products before they are put on the market rather than after marketing.
4. The research lot that passed bioavailability testing was not marketed. The tablet dosage form was marketed instead.

Our original article was not published with political motivation. The data were sent to the FDA well before publication. The intent of the article was to point out that existing FDA requirements for approval of propoxyphene capsules were, in our opinion, inadequate. Furthermore, Mr. Chmielewski's request that only marketed generic formulations be tested for bioinequivalence would indicate that he is in favor of marketing products without any bioavailability testing. We do not believe that the blind approach of testing for bioequivalence only after the products have been marketed will improve the quality of the products on the market. It is quite possible that there are existing marketed generic formulations of propoxyphene capsules that are bioinequivalent. However, since there is little, if any, testing of this product for bioinequivalence, we sincerely doubt that any publications will be forthcoming.

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[1] D. H. Chmielewski, *J. Pharm. Sci.*, **67**(9), IV (1978).
[2] K. A. DeSante, R. G. Stoll, D. G. Kaiser, and A. R. DiSanto, *ibid.*, **66**, 1713 (1977).