Therapeutic Gain or Therapeutic Ratio?

The advent of the triptans, serotonin 5-HT_{1B/1D} agonists, was a major boon for patients and doctors alike. The practical clinical imperative to make a decision about triptan use in individuals and the desire to better understand the pharmacologic underpinnings of therapeutics has driven interested clinicians to compare the agents in the class. With a view to clinical utility and an emphasis on scientific rigor, meta-analyses of triptan studies have been conducted to compare the triptans, in part because head-to-head comparative studies are not available for all triptans.

Like all other research techniques, meta-analysis inevitably requires a series of methodologic choices. For acute migraine trials, one key issue is the end point selected for comparing drugs; in our meta-analysis, we provided data on a series of end points to give clinicians the opportunity to compare drugs across a range of measures and to select the end points they consider most important. Another issue is selecting a strategy to control for factors that vary from trial to trial. These studies have one treatment group in common—the placebo group. The placebo arms in each study can offer insight into interstudy variability and an opportunity to partially control for this variability. There are 2 major approaches for using the placebo arm to control for interstudy variability. These approaches make different assumptions about the relationship between active drug and placebo. “Therapeutic gain” assumes an additive relationship; the placebo response rate is subtracted from response rate for active drug. The measure, number needed to treat (NNT), is the reciprocal of therapeutic gain, and relies on the same additive assumption. Therapeutic ratio assumes a multiplicative relationship; the response rate to active drug is divided by the placebo rate. A recent article in this journal argues that estimates of therapeutic ratio are more statistically robust because values will be “nearer to its mean” than those of therapeutic gain. We were surprised in this regard that the article made only summary calculations that did not take into account study size and were, thus, inaccurate. Furthermore, we were not able to find the inclusion and exclusion criteria the authors used in their analysis. The Tables seem to include a wide variety of studies not necessarily conducted according to a similar design or including similar study populations, or even administering the same formulation. Moreover, there are factual errors in Table 1: 3 placebo-controlled almotriptan 6.25-mg studies are quoted, but only 2 exist; and the placebo value for one of the 12.5-mg studies is wrong.

The authors seem divided on the fundamental premise of therapeutic gain. They describe several meta-analyses that used therapeutic gain or NNT as objective and worthy, yet conclude that therapeutic gain should not be calculated. This conclusion is mathematically incorrect, and at odds with mainstream approaches to meta-analysis as well as clinical common sense. Response rates to placebo and active treatment are determined similarly. In essence, the unit of measure is the proportion of subjects who respond. Subjects are randomized to one or the other treatment and the individual responses counted. The measurement made is the number of responses, not the treatment employed. The measurement is made on an internal scale, and the range of transformations can be employed.

It is perfectly appropriate to calculate either therapeutic gain or ratio from a statistical perspective. Is there a biological or clinical reason to prefer one measure to the other? Therapeutic gain assumes an additive effect of active drug above that of placebo, while therapeutic ratio assumes a multiplicative effect. Given a 60% response to active drug and a 30% response to placebo, therapeutic gain tells us that 30% more people respond to active drug than placebo. Therapeutic ratio tells us that twice as many people respond to active drug than placebo.

Though either approach is appropriate, most clinicians find therapeutic gain more intuitive. The therapeutic effect of an active drug adds to the benefit of placebo. The therapeutic ratio is less intuitive and is subject to misinterpretation. It is not easy to understand what it means for a drug to be 2 or 3 times more effective than placebo. Further, if the placebo rate approaches 50%, the upper bound on the therapeutic ratio is 2. If there is no biological imperative
to prefer therapeutic ratio, any statistical advantage is irrelevant. Use of therapeutic gain versus therapeutic ratio is a methodologic choice, and we chose therapeutic gain for the reasons outlined above. For the reader who prefers therapeutic ratio, in the most recent triptan meta-analysis the results and relative differences were virtually identical whatever measure was used: therapeutic ratio, therapeutic gain, or NNT.\textsuperscript{3,6}

When the calculations made in the article by Fox et al are examined, it seems undesirable that data were pooled across routes of administration and formulations. We made the assumption that a clinician had decided to give an oral triptan and sought to summarize data on safety and efficacy that would inform the choice of an oral triptan. It might be legitimate to contrast one route of administration with another to help inform the choice of a tablet versus a nasal spray, for example, but that was not our objective. As the route of administration of placebo (and perhaps the effectiveness of placebo) varies among these studies, it would be more difficult to adjust for within-study differences. Given the relative paucity of data, the methodological issues, and the nature of the clinical problem, we feel comfortable with our decision to evaluate oral triptans.

Though therapeutic gain or therapeutic ratio provide appropriate methods for adjusting for interstudy differences, we reject the notion that therapeutic ratio has important advantages. Therapeutic gain, or its reciprocal, NNT, offers a widely used, simple, intuitively attractive, mathematically sound comparison that clinicians can readily apply to the everyday management of migraine. For the reader who prefers therapeutic ratio, the results are fundamentally the same. In our view, headache clinicians and scientists should focus on understanding the mechanisms and delivering better treatments to those with headache and not on methodological issues in meta-analysis that do not influence statistical results or clinical practice.

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**Response From Fox et al**

Our article addressed the relative merits and demerits of 2 methodologies; namely, therapeutic ratio (TR) and therapeutic gain (TG).\textsuperscript{1} The dataset that we used is presented fully in Table 1 (for almotriptan and its placebo, see “Acknowledgments”). We made no comparisons between alternative migraine therapies, and our article is not a meta-analysis. Small differences among alternative databases are inconsequential for this sort of comparison of methodologies.

We think that Goadsby et al are being too uncritical in stating, “These studies [in their meta-analysis]
have one treatment group in common—the placebo group.” The placebo response rates are an important source of heterogeneity among clinical trials of acute therapies for migraine, and we have underscored this phenomenon in a manuscript that has been submitted to *Headache*.

We pooled across routes of administration so as to introduce as much variability as possible into our dataset. This is a conservative approach. To have done otherwise would have risked the error that unduly narrow ranges of TR might result from limits on the range of efficacy observations.

The skews introduced into the datasets by transforming active response rates into TG and number needed to treat (NNT) also interest us. Placebo-derived heterogeneity drive these measures in opposite directions in regards to relative efficacy. Posters on this topic were exhibited at last year’s American Headache Society (AHS) scientific meeting.2-6

In short, the TR is widely used in medicine and should not necessarily be ignored in headache research. Only to the extent of an abstract, separately publishing placebo data,7 did we refer to the meta-analysis of Ferrari et al.8-13

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**Eletriptan Issues**

Dr. Tepper and colleagues have utilized the Merck-Medco pharmacy management database to perform a retrospective analysis that examines the rate of coprescription of medications which might potentially interact with triptans.1

We are concerned that this article contains information concerning concomitant use of CYP3A4 inhibitors that is not consistent with the safety profile or product labeling for Relpax (eletriptan HBr).
We first will highlight 3 of the key methodologic shortcomings in the study. We then briefly report data that demonstrate the tolerability and wide margin of safety of eletriptan, even when coadministered with the most potent CYP3A4 inhibitors.

**FLAWS IN STUDY METHODOLOGY**

**Confusion of CYP3A4 Substrates With CYP3A4 Inhibitors.**—Dr. Tepper and colleagues cite (in reference 6) an article by Michalets as the source of Table 3, which purports to show CYP3A4 inhibitors. Yet, Table 1 of the Michalets’ article lists only 24 drugs as CYP3A4 inhibitors. It appears that the authors misread Table 1 in the Michalets’ article, and thus confused drugs that are substrates of CYP3A4 with drugs that are clinically significant inhibitors of CYP3A4. It should also be noted that CYP3A4 substrates have no effect on the metabolism of eletriptan itself.

The authors then use this much larger list of “inhibitors” (N = 67, instead of 24) to perform an analysis, the results of which indicate that “46%” of patients took a triptan with a CYP3A4 inhibitor. This result is inflated and inaccurate.

**Inappropriate K<sub>i</sub> Criterion for What Qualifies as a “Potent” Inhibitor.**—The authors cite (in reference 5) an article by Thummel and Wilkinson as the justification for using a K<sub>i</sub> of less than 25 µM as the criterion for what constitutes a “potent” inhibitor. Nowhere in the Thummel article is 25 µM used as a criterion level to define an inhibitor as being “potent.” In fact, on page 396, Thummel and Wilkinson appear to suggest that a K<sub>i</sub> of ≤1 µM may be the appropriate criterion level for “potent” CYP3A4 inhibitors. Thummel then refers to Table 1 on page 397 where 7 drugs are listed as having K<sub>i</sub> values of ≤1 µM. These potent inhibitors are saquinavir, indinavir, ritonavir, miconazole,itraconazole, ketoconazole, and clotrimazole. No published literature that we are aware of suggests that a K<sub>i</sub> of ≤25 µM is an appropriate standard for a “potent” CYP3A4 inhibitor. The result of this broad definition is that the authors list 28 drugs in Table 2 as being “potent inhibitors,” and thus they cite (on page 47) a potent inhibitor plus triptan coprescription rate of “18%.” Again, the results that are reported are inflated and inaccurate.

**Coprescription Does Not Indicate Concomitant Use, But Only Possible Use Within the Same General Time Period.**—Inhibition of the CYP3A4 enzyme requires concurrent use and at doses sufficient to achieve a clinically meaningful degree of inhibition. (The Thummel and Wilkinson review emphasizes the importance of this point.) Nonetheless, the “coprescription” results reported by the authors depend on redefining “coprescription” to include receiving a prescription for a potent inhibitor at any time “during the time period between 2 successive triptan prescriptions.” The authors properly caution that coprescription “does not necessarily mean that patients would have taken the contraindicated drug simultaneously…” Unfortunately, they then proceed to employ this relaxed definition of “coprescription” to conclude that a high rate of actual concomitant use of triptans and CYP3A4 inhibitors occurred.

Because of the methodologic shortcomings summarized above, the authors’ prescription database analysis fails to provide useful information important to clinicians, who would like to know 2 things: (1) if I prescribe eletriptan, how likely is it that my patient might take 1 of only 7 potent CYP3A4 inhibitors that are listed in the “Warnings” section of the eletriptan prescribing information; and (2) if my patient does take one of these potent inhibitors, will there be any effect on the tolerability or safety of eletriptan?

The authors have not answered the first question, since the article contains an expansive list of medications, the majority of which can be used with eletriptan. Regarding the second question, the high tolerability and safety margin of eletriptan is confirmed by data in patients who had documented concurrent use of a potent CYP3A4 inhibitor. The analysis, which compared adverse event rates in patients during long-term therapy who took eletriptan both with and without a concurrent CYP3A4 inhibitor, found no difference (Figure; data on file, Pfizer, Inc). As a stringent test of eletriptan tolerability, we examined (right panel) the impact of coadministration of the most potent CYP3A4 inhibitors in patients taking the 80-mg dose of eletriptan. As can be seen (Figure), even the most potent CYP3A4 inhibitors had no consistent effect on the tolerability of high-dose eletriptan, either in terms
of overall frequency of adverse events or in their severity. Furthermore, no instances of drug-related serious adverse events occurred in patients coadministered a CYP3A4 inhibitor.

Finally, to confirm its margin of cardiovascular safety, even at very high doses and plasma concentrations, Pfizer conducted a separate challenge study where eletriptan was administered intravenously to patients undergoing diagnostic coronary angiography. The plasma concentrations of eletriptan in this study were more than 6 times the peak levels achieved by a 40-mg oral dose coadministered with a potent CYP3A4 inhibitor. High-dose intravenous challenge with eletriptan was associated with coronary vasoconstriction that was mild and had no clinically meaningful difference from placebo.

After a rigorous review of the scientific evidence, the Food and Drug Administration dismissed the vast majority of CYP3A4 inhibitor drugs in its approval of eletriptan. As such, the “Warnings” section of the label recommends that eletriptan not be taken within 72 hours of only 7 potent CYP3A4 inhibitors. Eletriptan can be taken safely with many other medications including those commonly used in a migraine population such as selective serotonin reuptake inhibitor antidepressants, oral contraceptives, hormone replacement therapy, and those medicines used in the prophylactic management of migraine (eg, calcium channel blockers, beta-blockers). Across an extensive clinical trials database involving over 11000 patients and 70000 migraine attacks, eletriptan has been shown to be highly effective and well tolerated with a wide margin of safety.

Jayasena Hettiarachchi, MD
Carolyn Sikes, PhD
Pfizer, Inc.
New York, NY

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Response From Author

I undertook this research from the perspective of a clinician who frequently prescribes triptans, is concerned for patient safety and so seeks to avoid potential drug-drug interactions. As a first step in determining the maximal proportion of patients who could be expected to possess at least some risk of an interaction, I requested access to the Medco database. I then assessed the frequency of co-prescription of triptans with medications whose pharmacologic properties could lead to potential interactions with triptans: SSRIs, MAOIs, propranolol, cimetidine, ergots, and CYP3A4 inhibitors.

Included in our survey were potent CYP3A4 inhibitors that have been cited in several authoritative monographs (Thummel KE, et al. Annu Rev Pharmacol Toxicol 1998;38:389-430; Dressler GK et al. Clin Pharmacokinet 2000;38:41-57; Michalets EL, et al. Pharmacotherapy 1998;18:84-112). I also selected those CYP3A4 inhibitors listed as “Do not use” with eletriptan by the European Union regulatory authorities, presumably the most potent of the CYP3A4 inhibitors. At the time of my survey, the FDA had not
yet approved eletriptan and released its own list of contraindicated CYP3A4 inhibitor medications.

In summary, I sought simply to calculate the likelihood of coprescription. This was not intended to be a study of co-administration or treatment outcome, but rather a “first pass” attempt to determine whether coprescription of all the available triptans with various other types of medication might occur at a frequency sufficient to warrant further study to assess the risk of associated adverse events. Our results clearly establish that co-prescription of triptans with SSRIs or CYP3A4 metabolized medications occurs at high frequency, although it does not establish, nor was it ever intended to establish, co-administration, outcome, or risk.

The FDA-approved prescribing information does list seven proscribed potent CYP3A4 inhibitors with eletriptan, and these are not the same potent CYP3A4 inhibitors as those prohibited by the European Union in their prescribing information. The American prescribing information also goes on to state, “Eletriptan should not be used within 72 hours with drugs that have demonstrated potent CYP3A4 inhibition and have this potent effect described in the CONTRAINDICATIONS, WARNINGS OR PRECAUTIONS sections of their labeling.” Instead of simply debating the relative potency of CYP3A4 metabolized medications, I urge Drs. Hettiarchchi and Sikes to provide clinicians with a peer-reviewed article that evaluates the safety of eletriptan when co-administered with potent CYP3A4 inhibitors, with adverse events divided according to body system, severity and seriousness. At the time of this writing, these data have not been made public, except in limited, non-peer reviewed, forms such as their letter.

Stewart J. Tepper, MD
The New England Center for Headache
778 Long Ridge Road
Stamford, CT 06902

Worsening of Headaches on Topiramate? A Low Cerebrospinal Fluid Pressure Syndrome?

Topiramate is a newer antiepileptic medication, which recently has shown efficacy as a migraine preventive in a large placebo-controlled trial. In the last several years, the use of topiramate for migraine prevention has increased substantially in both headache specialty clinics and general neurology clinics. As more patients are treated with topiramate, it appears that a small subset develop a worsening of their baseline headache or a new type of headache altogether while on the medication. This has occurred in about 30 patients of 300 personally treated with topiramate.

Initially, it was difficult to determine why the headaches worsened or changed on topiramate. Recognizing that topiramate inhibits some isoenzymes of carbonic anhydrase (not unlike acetazolamide) and thus could theoretically reduce cerebrospinal fluid (CSF) pressure, I asked the patients who had a worsening of their headaches about a positional component to their head pain. In most instances, the patient could recognize that this new, more severe headache was better in a supine position and worse in a sitting or standing position. In this event, the patient would be instructed to lower their dose of topiramate slightly (25 mg) or taper off the drug; within several days almost all would return to their baseline, with alleviation of the positional head pain. This suggested that topiramate was inducing a low CSF pressure headache in these individuals and that the effect of topiramate on CSF pressure was short lasting and dose dependent.

It has yet to be documented in the literature how successful topiramate is in reducing CSF pressure in patients with headache. Based on clinical observation, however, it seems that in a subset of migraineurs topiramate can alter CSF pressure enough to induce a low CSF pressure-type headache. In some of my own patients, the positional headache started with topiramate doses of 25 or 50 mg per day. To help prove that topiramate can indeed alter CSF pressure, a case history is presented.

A 30-year-old woman who was on topiramate (100 mg per day for 6 months) for chronic daily headache and who had a positional component to her headache underwent a lumbar puncture. She was on no other medication known to have an effect on CSF pressure. Opening CSF pressure was 8.5 cm H₂O. Topiramate was discontinued, and a second lumbar pressure was completed 1 week later. The opening pressure
was now 18.5 cm H₂O, clearly within the normal CSF pressure reference range.

This patient suggests that in some individuals topiramate can have dramatic effects on CSF pressure. For a subset of patients with headache, such as those with pseudotumor cerebri, this may be an advantage, but for others the lowering of CSF pressure could cause a new form of headache or an acute worsening of well-controlled migraine. It is important to be aware of this phenomenon, as, in the future, increasing numbers of patients undoubtedly will be placed on topiramate for migraine prevention.

Todd D. Rozen, MD
Michigan Head Pain & Neurological Institute
3120 Professional Drive
Ann Arbor, MI 48104

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Female Migraineurs Who Usually Blink in Flash Photos and Those Who Usually Do Not

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Female Migraineurs Are Much More Likely to Blink in a Flash Photograph Than Controls

I usually blink when I have a flash photograph taken and wondered whether other migraineurs have the same tendency. To determine this, I asked 60 consecutive women, aged 55 years or younger, whether they usually blink when they have a flash photograph taken, resulting in their eyes being closed in photographs.

Of the group of 45 migraineurs, 32 (71%) reported usually blinking. The Table provides information on the mean ages of blinkers and nonblinkers and their migraine subtypes. Of the 15 nonmigraineurs (mean age, 38.7 years; range, 22 to 48), only 1 (6.7%) reported blinking. To preliminarily assess whether this much lower rate of blinking is also found in a general population of men and women, I asked a professional photographer to estimate what percentage of people usually blink when he takes 2 or 3 pictures of individuals or small groups. He estimated the percentage of blinkers to be 15% (Alan Ross, personal communication, February 2003).

So it seems that female migraineurs may be much more likely to blink in a flash photograph than nonmigraineurs. It would be of interest to confirm these findings in a larger female and also a male population. It also would be of interest to determine whether blinking is present more commonly in persons before they develop migraine compared to nonmigraineurs, whether a greater lifetime duration of migraine is a risk factor for blinking, and whether blinking is less often present in older previous migraineurs.

My finding is not surprising when one considers that most migraineurs are photosensitive interictally and that only a small percentage of nonmigraineurs are photosensitive. The disproportionately high rate of blinking in response to a photographic flash is consistent with interictal occipital cortical hyperexcitability. This tendency may also be predictive of a diagnosis of migraine.

Randolph W. Evans, MD
Suite 1370, 1200 Binz
Houston, TX 77004
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“Safety” Testing and Herbal Remedies

Danesch and Rittinghausen have provided the most complete account to date of the safety testing of their herbal extract.1 In combination with their previous report,2 the list of toxicity studies now comprises: (1) negative Ames test (4 appropriate strains of Salmonella typhimurium, but no E. coli uvrA2 or similar); (2) acute toxicity (rat) LD_{50} > 2.5 g/kg by mouth and 1 g/kg intraperitoneally; and (3) a 6-month chronic rat study, with no adverse effect level (although the adverse effect at the next highest dose is not stated). In addition, we learn of 187 patients with migraine treated with 100 to 150 mg daily for 3 months in controlled clinical trials. We are told that 90% of the patients rated global tolerability to be “good” or “excellent,” but we are not told why the remaining 10% were less satisfied. Even so, among the 33 treated with active drug in the referenced article, only 2 patients withdrew from the study for reasons unrelated to the study medication.3,4

A further 95 adult and 50 younger (<18 years) migraineurs have been followed for several months according to 4 postmarketing surveillance protocols. Two of these have been in the literature for 7 and 5 years, respectively.5,6 The specified adverse events have included “eructations,” 2 cases of bad smell or bad taste attributed to the product, and 1 case of skin rash.

Lastly, this database includes 93 spontaneous postmarketing reports, of which the large majority (n = 75) is derived from a single country (Germany). The only detail provided concerns a unique case of hepatotoxicity. As a unique case, and in the context of the uncontrolled nature of such reporting, this is insufficient to ascribe a hepatic hazard to this product.

Concern has been expressed previously about the marketing messages used with this product, along with how well patients have been informed as to its preclinical safety testing. Furthermore, the manner in which adverse effects are documented for herbal products, in comparison to synthetic drugs, has been discussed previously, but it is not my intention to repeat those concerns here, unanswered though they remain.7

This latest report is liberally sprinkled with the acronyms of various regulatory authorities. Although these badges of compliance typically assure that the quality of the reported data is very good, this should not distract from a relative assessment of the quantity of data reported. There are 2 aspects to such a relative assessment.

First, how does this product compare with most other herbal products? My own view is that, by this standard, Weber and Weber ought to be congratulated for their efforts to characterize the toxicology of their product. One might dispute a few technical matters, for example, whether a genotoxicology study without an E. coli uvrA2 strain complies with International Conference on Harmonization guidelines. While one can also agree that in an otherwise purely aqueous solution, a concentration of <0.08 parts per million of a chemical with a molecular weight of, say, 1000 D, has a concentration of only about <0.04 nM, it is also true that most regulatory authorities have never accepted chemical purity as evidence of absence of toxicological properties, lest the assay fail to measure an impurity or metabolite that is actually present. Even so, compared with the rest of the herbal industry, this is a much better than average effort.

In comparison with what is needed to get a synthetic drug into clinical trials, let alone approved, however, this database is very small. Without toxicology information from at least 2 species (one nonrodent), clinical trials could not even have begun. Most regulatory authorities also would have required at least 2 further genotoxicology studies (a rodent micronucleus test, and one or the other of a lymphoma forward mutation test or a clastogenesis study); these studies
are widely available and commodity priced. A “segment II” reproductive toxicology study almost always is required if female patients potentially are to receive the synthetic drug. Further specialized tests of cardiovascular safety also might have been required, both in dogs and as part of a careful first-in-man study. A metabolic profile and drug interaction panel (at least in vitro) would have been required. Many of these studies would have required toxicokinetic validation, and at least some basic information on drug metabolism would be required both in animals and in the first-in-man study. This exhaustive assessment actually represents a minimum, especially when subsequent clinical trials are projected to involve oral therapy for many weeks.

With such toxicology in place, the referenced clinical studies would only serve for phase II purposes in a typical drug development program. Clinical databases for new migraine prophylactic agents require that thousands of patients be studied. The rule of thumb is that the adverse event frequency that can be excluded is the reciprocal of one third of the total number of patients studied under appropriate conditions.

One hopes that this provides some perspective that is missing from this latest report. Again, it should be emphasized that few manufacturers would have gone as far as Weber and Weber with an herbal product; but equally, we must understand that “safety” in drug development is a relative assessment (perhaps “tolerability” is a better term for general use), and that neither patients nor investigators should be misled about the scope of herbal product toxicology coverage in comparison with modern standards for synthetic drugs. It is ironic that this should be the case for the treatment of migraine, a disorder where, in many respects, there is greater seamlessness than usual between plant-derived and synthetic drugs.8

Anthony W. Fox, MD
EBD Group
Suite J2, 6120 Paseo Del Norte
Rancho La Costa, CA 92009

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Response From Danesch and Rittinghausen

Any synthetic drug intended for therapeutic use in humans has to undergo extensive preclinical toxicity and pharmacological testing. Even with such testing, however, human toxicity may be revealed only after extensive clinical use, as the recent example of cerivastatin (Baycol, Lipobay) has demonstrated. In Germany, the United Kingdom, and most other European countries, vigorous preclinical testing protocols also are required for new herbs lacking traditional use, where a marketing authorization is intended. This policy is inappropriate for herbal products that have been used traditionally for medicinal purposes over many decades. In fact, drug agencies in many countries have begun to acknowledge that traditional-use therapies cannot be compared to new chemical entities. This notion is reflected in the new European Community Commission Directive 1999/83/EC which states that no pharmacological tests, toxicological tests, or clinical trials are required when so-called “well
established use” has been proven. Well-established use is defined as: (1) a history of medicinal use for not less than 1 decade, (2) treatment of a sufficient number of patients, (3) availability of bibliographic data and information published in official pharmacopoeias and scientific reference textbooks, and (4) coherence of scientific assessments. The special butterbur root extract referred to in our communication complies with the definition of a well-established use herb in Germany. Hence, none of the toxicological assays mentioned by Dr. Fox were required.

Nevertheless, we have begun to provide safety data, and we appreciate the fact that Dr. Fox acknowledges our efforts. Since our manuscript was submitted for publication, an in vitro assessment of the clastogenic activity of the butterbur root extract in cultured human peripheral lymphocytes was done according to Good Laboratory Practice (GLP) (EC and USA) guidelines and various standard international regulations. The mean incidence of chromosomal aberrations without or with metabolic activation by a rat liver postmitochondrial fraction (S9 mix) was within the reference range of the negative control. There is no indication of mutagenic properties of the special butterbur extract with respect to chromosomal or chromatid damage. Mitomycin C and cyclophosphamide as positive controls clearly induced chromosomal damage. These additional results support the safe use of the extract, as does its decade-long record of clinical and traditional use.

Ulrich Danesch, PhD
Reiner Rittinghausen, MD
Weber & Weber GmbH & Co.KG
Herrschinger Str. 33
D-82266 Inning, Germany