EDITORIAL

How to Evaluate Folk Remedy Data for Human Use: Two Approaches

William L. Marcus, PhD, DABT

ARTICLES IN PREVIOUS AND CURRENT ISSUES of the Journal represent a rational attempt to side-step expensive and time-consuming animal testing procedures required by the United States Environmental Protection Agency (USEPA) and by the Food and Drug Administration (FDA) by substituting bacterial tier testing in their place. The goal is to reduce, where possible, the required animal testing if there is also available human exposure information, as explained below.

Tier testing today, by its very nature, implies that it can discern the potential carcinogenicity of a compound by using sequential, well established bacterial testing of one sort or another in the place of long-term animal tests of the same compound(s). Because the testing is sequential and designed to rule in or out the potential carcinogenicity of specific chemical structural moieties, one believes that these tests can extrapolate and aver with some scientific certainty that the compounds tested are or are not potential carcinogens. The idea that tier testing can replace whole animal carcinogenic tests for use by a regulatory agency in the determination of the potential carcinogenicity is misplaced, because bacteria lack a circulatory and nervous system and therefore, a priori, cannot be substituted for mammalian animal tests. Tier testing as was first proposed by the USEPA’s Office of Water was never meant to replace animal testing procedures.

Tier testing was first proposed as a rapid method to develop usable and reliable data to the carcinogenic potential of commercial and industrial chemicals. The procedure was supposed to solve relatively cheaply and extremely rapidly the paucity of available adverse data sets. However, at the initiation of this project, an explicit statement was and always has been included in every official publication: “these procedures cannot take the place of animal testing.” At best, they could be used to prioritize and predict what compounds are most likely to produce carcinogenic responses in whole animal tests if their chemical structure were known and were structurally similar to compounds that had been previously tested in whole animals and in bacterial systems. It is simply not possible to predict toxicological outcomes based on short-term testing. When a compound at very low concentrations (high dilutions) produced death of the test bacterial organisms, another conclusion was drawn: that it may have potential pesticidal applications.

While not explicitly stated, the authors cited imply, based on purely anecdotal data, that the active principles of some plants can be safely administered to people because they have a long history of medicinal uses in India. For instance, the article of Arora et al. in this issue of the Journal discusses *Acacia nilotica* and *Juglans regia*. The bark of *Acacia nilotica* has been used in India for colds, bronchitis, diarrhea, dysentery, “biliousness,” bleeding hemorrhoids, and leukoderma and also serves as a source of polyphenols.¹ The bark of *Juglans regia* has been used as an antihelmintic and for the treatment of ulcers.²
Furthermore, the fruits of *Terminalia chebula* are also used in India for curing a host of ailments, such as hemorrhoids and cirrhosis of the liver with ascites. Also, the fruits of *Terminalia chebula* form one of the components of the “galenical” called Triphala, which was reported as a highly efficacious cardiotonic.³

Based on purely anecdotal data, the use of folk remedies and their successful implementation by Indian physicians who avail themselves of folk remedies may be helpful for their patients. However, anecdotal data do not meet the regulatory requirement of “based on human experience.” The method they chose would not be well received by either the USEPA or by USFDA because tier testing has never been an acceptable substitute for required animal testing. Secondly, purely anecdotal data have always been eschewed by both agencies.

In the article “Evaluation of genotoxicity of medicinal plant extracts by the comet and the Vitotox® test,” the authors demonstrate that the tier testing they performed shows that these materials do not present a carcinogenic risk. Explicit animal testing data on the active principles contained in the extract are not enough to satisfy the requirement. Accurate dose response data in people are needed to meet the “based-on-human-experience” regulation. The authors assert that there is a plethora of anecdotal data on these materials used by people practicing folk medicine in India. To be useful, the data must be centered on the action of the active principle(s) and on enough people in different identifiable cohorts.

There are two approaches that regulatory agencies such as the EPA and the FDA would not object to when it comes to foregoing the usual battery of animal testing. They are titled “on the basis of human experience.” One approach is to use epidemiology data, which by their very nature are based on human exposures. The second approach is to present a complete set of comparative human and animal pharmacologic data, including the metabolites of the active principle. These two sets of experiments need to be performed using drugs that have been given to human patients by folk doctors as well as by traditional medical practitioners in India, in order to demonstrate that the concept “on the basis of human experience” was fulfilled. What is usually not available is the actual dosage used and data on which of the isolates is the active principle of the extracts. Today, it is easier to chemically define the active principle of chemical mixtures and extracts given the major advances in synthetic organic chemical apparatus. Also missing is the set of experiments that define the metabolites that human subjects produce when taking the active principle in question. This too has become much less difficult for the same reasons.

Once the chemical information is developed on commonly administered extracts, one could design a set of studies that side-steps much of the required animal testing. If the human data were available on the toxicity potential posed by chronic exposure, it might be possible to eliminate much of the long-term animal testing step. Similar data would eliminate the need for initial human testing, saving hundreds of thousands of dollars, but, more importantly, would add at least three years to the drug(s) patent usefulness.

An epidemiological approach would suffice if the actual doses were known and acceptable cohorts developed. As in most successful epidemiological studies, there would have to be stratification based on dose, age, and gender. An example would be to determine the following information on drugs that affect hormone levels in women: Do women on this drug experience difficulty in attaining and maintaining pregnancy? What percentage of the drug reaches the developing fetus before the development of a placenta? What happens to the fetus when exposed to the chemical during the first trimester? All the above could be answered if a cohort of women who intend to take this drug during pregnancy were followed to term.

Another approach would be for drugs that do not change hormonal activity. In this case, parallel studies would have to be designed in which the principles of the native drug(s) and the “galenicals” are administered to different cohorts simultaneously and the regression line of the desired effect is compared. If the line does not differ from parallel, then we are indeed testing an active principle.
EDITORIAL

When the epidemiology studies are completed, it should be possible to say that the researchers have developed enough data to obtain a permit for an investigational new drug (IND) and for human testing to begin. Actual human data are far more desirable than animal data when the effects of the compound are known to be beneficial and a history of human use is well documented.

LD₅₀ experiments must be performed on laboratory animals to establish the cause of death from overdose and whether there is a small or large margin of safety. If the material is toxic at some level (as is almost always the case for biologically active compounds), we need to know the level and the actual cause of death. The margin of safety would have to be sufficient that these levels will never be approached under normal clinical conditions.

These are the kinds of human data sets that would accomplish what the authors were attempting. It is possible to side-step and eliminate most—but not all—long-term animal testing with sufficiently high-quality human data. The availability of human data could reduce the time-frame required for approval if all the studies went as planned and the drugs were as safe and efficacious as first thought. In my experience, a set of experiments as complicated as these always has pitfalls. However, a significant advantage with the savings of cost and time can be accomplished. Tier testing was never meant to provide information necessary to allow testing of the compounds as drugs.

Each uniquely biologically active chemical used in folk medicine presents a separate set of problems that need to be addressed. That does not mean that data development must start from scratch. It is just that bacteriological testing of these chemicals cannot be used in place of whole animal tests. Proper design of human cohorts can answer many of the questions that animal testing attempts and with far more useful data.

Compounds known to produce desired therapeutic outcomes are always preferred to compounds thought to have these properties. Successful approaches such as the ones outlined above should encourage researchers to find these native and folk medicines, chemically characterize the active principles, and bring them into the modern armamentarium of therapeutic drugs.

References
