Alchemists and Toxicants

Toxicology has emerged from relative obscurity to a place of prominence in the fields of human and environmental health. No longer is toxicology an esoteric discipline only of interest to and understood by the toxicologist. Chemists, who face potential health effects from materials they work with in laboratories and industrial settings, have become increasingly interested and involved in such studies. Concern has resulted in steps being taken to reduce the chemist’s exposure, such as use of personal protective equipment, installation of ventilated enclosures or fume hoods, as well as the implementation of guidelines for safe handling of chemicals (1).

Animal toxicology studies are fundamental for the formulation of federal, state, and local regulatory agencies’ health and safety guidelines (2). Toxicology studies can be viewed as an exposure of the organism to the test material (administered dose), followed by its absorption and distribution (internal dose), and finally the observation of possible toxic responses. As the appreciation for the significance of toxicology studies grew, it was realized that more standardized tests and procedures were needed. These needs were met by the toxicology community and are exemplified by the specifications for the conduct of toxicology studies developed by the U.S. National Toxicology Program (NTP) (3).

As these refinements have been introduced, the chemist’s input has become increasingly prominent (4). During the planning stages the chemist plays a pivotal role in the toxicity study design by providing information about the test material’s physical state, reactivity, appropriateness or feasibility of the anticipated route of administration, and the potential for the determination of internal dose. Subsequently the chemist’s activities include confirmation of the identity of planned test chemical as well as the identification and quantification of any trace impurities. In addition, since there must be a reliable and reproducible way of exposing animals, the expertise of the chemist is again required. The exposures may be accomplished by mixing the chemical in the animal’s drinking water or diet, or other routes such as intragastric injection, skin paint application, or inhalation. The former two methods require the preparation of solutions or suspensions, while the latter requires the generation of the test chemical in the air. In all cases, the exposures must be fully characterized for accuracy of concentration and homogeneity. Another important area for the chemist during the conduct of the toxicology study is in the determination of the internal dose.

Experience has shown that reliability of the identity of the chemical used in the toxicology study should not be taken for granted (5). In the NTP studies, approximately 1% of the chemicals purchased were misidentified by the supplier, and 8% have had significantly lower purities than claimed. Other results emanating from the chemical evaluations performed by NTP in support of toxicology studies included the determination that the commonly accepted structures for iodinated gelatin and HC Yellow 4 were in error (6,7). Problems with the confirmation of administered dose have also been documented during NTP studies (8). Dose formulations for volatile or reactive chemicals have been addressed with the implementation of microencapsulation technology, and molecular encapsulation is being explored (9,10).

To explore the internal dose theme further, toxic responses to test chemicals are known to be dependent on the exposure route, the kinetic behavior of the chemical, as well as the dosage used in the toxicology study. Therefore, knowledge of internal dose is indispensable for the interpretation of toxicology study results, for the facilitation of interspecies scaling, as well as for risk assessment. By monitoring the blood and/or tissue concentrations of test chemical and/or metabolites versus time after administration of study chemicals by different routes, the bioavailability (rate and extent of chemical availability to the systemic circulation) and kinetic characteristic of test chemicals can be readily obtained. It can also define the so-called linear dose range (increase in dose produces a directly proportional increase in plasma/tissue concentration), clearance (volume of fluid cleared of chemical per unit time), or other related toxicokinetic parameters and can be used to predict the possible bioaccumulation under multiple dose regimes (11,12). All of these values are critical for the development of high-to-low dose and species-to-species extrapolations and for risk assessment.

In summary, the primary goals of any chemistry program in support of toxicology studies should be to better define the study material, characterize the exposure, and determine the internal dose. Attainment of these goals should enhance and strengthen the final results of the animal studies. In the future, the chemist will need to play an even larger role in developing new toxicology tests, elucidating mechanisms of toxicity, and quantifying human exposure. Understanding the mechanisms of toxicity at the molecular level will require even more sophisticated chemistry expertise. Additional biological markers to confirm human exposure will need to be identified. The ultimate use of animal toxicology data is the extrapolation of results from test animal to man. Toxicokinetic data are critical to this extrapolation, which in turn is dependent upon application of appropriate bioanalytical chemistry techniques. The chemist’s vital role in toxicology studies is clear.

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