



Toxicity Testing and the Current Situation in IRAN

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Importance of toxicology

Toxicology is the study of how chemical substances interact with living systems, affecting normal processes, and the use of this information to predict safe exposure levels. The goal of toxicity testing is to insure safety of chemicals (or societally tolerable level of risk) in exposed human populations, although no substance is risk-free. Toxicological testing of new materials, as well as biosafety measurement of existing components, helps us to live safely and to derive benefit from natural and synthetic substances while avoiding toxic substances. Toxicologists are involved in the evaluation of household products, medicines and the effects of incidental and occupational exposure to natural and manufactured substances. Toxicology also assists us to develop the best management in the event of accidental overexposure. One fundamental tenet of the science of toxicology is that all chemicals can be toxic if administered in special doses. This is mentioned as a famous phrase: “The dose makes the poison”(1). During the industrial processes there is a chance some of product contamination due to unwanted materials. Hence, conduction of routine biosafety investigation by most of food and drug agencies is required. Although in Iran progress in the field of toxicology is noticeable, considering the numerous international publications and organization of several domestic and international scientific conferences, as well as the establishment toxicology research centers, we experience difficulties in the field of industrial regulatory toxicology and animal studies. In the clinical section, we have two professional hospitals and few physicians, which comply with the standard procedures of emergency medicine.

Toxicologists conduct basic research, using both whole animals and in vitro methods, to learn how various chemicals and dosages interact with the living systems. Basic research is essential to understand mechanisms underlying the toxic responses and to determine the baselines for physiological processes. Therefore, in the absence of human data, research with experimental animals is the most reliable means of detecting important toxic properties of chemical substances in order to estimate the risks to human and environmental health (2- 4).

Research animals must be used in a responsible manner. The use, care and transportation of animals for training and toxicological testing for the purpose of protecting human and animal health should also comply with domestic and international animal welfare laws. At present, few universities and research centers in Iran use the international animal welfare laws for their animal studies. We believe that the domestic animal laws for research purposes should be mandatory. Care and handling of all animals used for research studies must be directed by veterinarians or other individuals trained and experienced in the proper care, handling and use of the species being maintained or studied. Veterinary care is to be provided in a timely manner, when needed.(5-8). Investigators and other personnel shall be qualified and trained appropriately for conducting procedures on living animals, including training in the proper and humane care and the use of laboratory animals (9-11). There are official protocols for the use of animals in research for example, AAALAC, an organization that has been accrediting programs. For institutions since 1965. AAALAC accreditation signifies the research facilities which are not only meeting the standards required by law, but also have gone the extra step to achieve excellence in animal well-being. Thus, it is required to have a national committee in compliance with

applicable animal welfare laws, guidelines and policies (12-15).

One of the most important difficulties in driving regulatory tests for new materials in our country, on the basis of international protocols, is the budget deficit. Lack of budget and the subsequent need for financial support research staff engaged in the toxicological projects, as well as space and facilities for animal husbandry, remain as the main obstacles in this regard. Few organizations, such as Pasteur and Razi institutes, in Iran could fulfill this criterion.

Animal diets for toxicological research

Finding the optimal laboratory animal diet to sustain growth and longevity and yield reproducible experimental results is of critical importance in toxicological research. Diet is of major concern in toxicological and other research with rodents, since diet composition can affect the activity and metabolism of xenobiotics and alters the outcome and reproducibility of long-term studies. For instance, evaluation of the carcinogenic potential of xenobiotic compounds can differ depending on the diet fed. In general, higher tumor incidences have been reported in rodents fed the AIN-76A or other purified diets, compared with rodents fed natural ingredient diets (1,15). At present, only one animal diet factory exists in Iran, which manufactures pellet food for mice and rats. Nutrient requirements for other laboratory animals are different from mice, causing nutrient deficiency in animals used in long term assays (more than 3 months).

Regulatory toxicology (hazard assessment)

The process of hazard assessment starts with internationally agreed lists of mammalian toxicology studies. This assessment must be conducted based on the type of chemical, for example an agrochemical, to support registration and safe use. These toxicity tests usually cover:

- (1) Acute single high-dose exposures;
- (2) Repeated dose administration (for up to 12 months) for chronic toxicity studies, which are often preceded by daily repeat dose studies of 1 month (subacute) or 3 months (subchronic) duration and usually conducted in rodents and non-rodents;
- (3) Carcinogenicity studies in two rodent species;
- (4) Reproductive toxicology (multigenerational study);
- (5) Developmental toxicology (teratogenicity studies in two species);
- (6) Genetic toxicology studies in vitro and in vivo;
- (7) Additional studies conducted on a case-by-case basis, such as neurotoxicity testing or evaluation for estrogenic and other endocrine activities (2).

Chronic toxicology, carcinogenicity, reproductive or multigenerational studies in our country is unlikely to be performed, due to the deficiency in security of long term animal handling and feeding.

The assessment of biocompatibility or safety of chemicals, which are leachable from medical devices, is another aspect of regulatory toxicology. The word biocompatibility refers to the interaction between a medical device and the tissues and physiological systems of the patient treated with the device. An evaluation of biocompatibility is one part of the overall safety assessment of a device. Biocompatibility of devices is investigated using analytical chemistry, in vitro tests and animal models. While in use, substances may leach off a medical device into the adjacent tissue. Some leachable or extractable compounds are not biologically safe. The primary purpose of biocompatibility assessment of a device is to protect patient safety. Investigation of the adverse effects of various compounds (e. g., metals ion, DEHP, ethylene oxide, bisphenol A, endocrine disruptors) released from medical devices is a requirement of national committees, such as food and drug administration (FDA). Most countries either have national standards for goods, including medical devices, or accept the minimum requirement standards of ISO (16). In Iran few regulations for this purpose have been passed. Thus, a few biocompatibility assessments have been performed. This includes the unintentionally released leachable materials, for instance plasticizers and accelerators from products such as disposable food dishes and tissue engineered medical products. Furthermore, the immunological effects of pesticides

residues should be included (2). In conclusion, the need for new regulations for the purpose of standardization, as well as establishment of an organization for the assessment of such studies is necessary. In long term, this investment could become economically independent from governmental support, because of the financial income coming from the producers.

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