SYMPOSIUM PRESENTATION

Evolution of the Uses of Rats and Mice for Assessing Carcinogenic Risk from Chemicals in Humans

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Abstract

With developments in the philosophy behind animal testing for carcinogenicity and toxicity, with increasing emphasis on Mode of Action analysis, the future usefulness of the 2 year rodent carcinogenesis bioassay is in doubt.

Key Words: Two-year bioassay - carcinogenesis screening - mode of action analysis

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Introduction

For over 40 years, scientists have used 18-24 month rodent carcinogenicity studies (especially by oral and inhalation exposures) to assess carcinogenic potential of chemicals with an ultimate goal of assessing human carcinogenic risk. After intensive study of more than 1500 chemicals over 40 years, carcinogens were found from many chemical classes and rodent targets of carcinogenesis have been seen in numerous tissues. The most common sites of carcinogenesis have been liver, lung, kidney, mammary gland, stomach and the hematopoietic system. Many in vitro assays have been used to offer alternatives to the long term rodent carcinogenesis bioassay.

A combination of these tests and rodent assays have been used for human risk assessment by various individuals and groups especially government regulatory agencies. Also, several short- and medium- term rodent bioassays for carcinogenesis have been developed which offer quicker and cheaper screening methods. With further research on the mechanisms of toxicity and carcinogenesis, a variety of comparative mechanisms have been postulated. Human epidemiology provides evidence of the carcinogenesis of chemicals but the level of sensitivity of such methods is limited. Thus, for many rodent carcinogens, evidence of human carcinogenesis will probably never be proven. Federal and state regulatory agencies of the various nations of the world have their own rules, regulations and laws which govern approval or rejection of the use of chemicals in their societies.

In the USA, many human drugs have been approved for human use despite having been shown to be rodent carcinogens. These drugs are often not genotoxic but have been multi-organ carcinogens. They include many lipid-lowering drugs, and other common prescription drugs. Genotoxic chemicals which are carcinogenic in rodents may be allowed if they are used for treatment of fatal or otherwise incurable diseases such as cancer and HIV. A human risk assessment for each chemical may be performed and a consideration of the use of each results in a final regulatory agency approval or disapproval. Postulated mechanisms of the carcinogenicity of chemicals in target organs of rodents have allowed some regulatory agencies to disregard the occurrence of many tumors in rodent carcinogenesis studies.

Mode of Action analysis can be used for chemicals regulated by the US regulatory agencies. They consider hypothesized mechanisms of carcinogenesis which may not be relevant to human cancer risk assessment including rodent tissue not present in humans (e.g. preputial/ clitoral gland, Zymbal's gland), chronic toxicity leading to cell proliferation and adaptive changes in tissues, inflammation, sensitive rodent tissues such as skin, and the high incidence of rodent tumors. Due to these factors, the future usefulness of the 2 year rodent carcinogenesis bioassay is in doubt if US regulatory bodies continue to allow postulated mechanisms of carcinogenesis to be used for human risk assessment.

References

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