Future strategies for regulatory genotoxicity assessment

G. Repetto[1,*], M.M. Aparicio-Muriana[1], R. Rojas[1], A. del Peso[2], M.R. Repetto[2], R. García Repetto[1,2] and S. Maisanaba[1]

[1] Área de Toxicología, Universidad Pablo de Olavide, Ctra. de Utrera Km 1, 41013 Sevilla, Spain
[2] Instituto Nacional de Toxicología y Ciencias Forenses. Sevilla, Spain
E-mail: grepkuh@upo.es

The present qualitative regulatory framework for genotoxicity assessment was initiated in1983 by the US EPA. It is very inefficient due to the high rate of false positives obtained in the *in vitro* mutagenicity tests. This situation forces to carry out unnecessary animal carcinogenicity assays, of debatable relevance to human safety. Now, it is an adequate moment to consider possible improvements in the process, from easy updates to the classical tests or the selection of suitable battery of tests leading to an absolute new strategy for quantitative risk assessment. The most interesting improvements applied by the OECD and other entities to increase the reproducibility and specificity of the classical mutagenicity tests include the application of good cell culture practices with cells of controlled sources, adequately characterized, and a short number of passages; the consideration of the feeding effect in bacteria due to the presence of amino acids or the false positives due to the ubiquitous flavonoids; the recommended use of p53 and DNA repair competent human cells; the reduction of the maximum concentration assayed to 10 mM or 2000 mg/mL instead of 5000 mg/mL; the control of strong variations of pH and/or osmolarity; or, the use of the comet assay with more relevant modelssuch as human reconstructed skin.

In relation to the strategies, the main battery test should be reduced to increase specificity as the authorities propose, combining the bacterial reverse mutation assay, to detect gene mutations, and the *in vitro* micronucleus test, to detect both structural and numerical chromosome aberrations.

The next generation testing strategy for assessment of genomic damage should provide not only qualitative, but also quantitative information in relation to the relevant mode of action, and be based on high throughput assays by measuring the induction of stress pathways/proteins as endpoints. One approach uses metabolically competent cells or battery of cells with fluorescent or luminescent reporters of genetic or cytotoxic damage. Other approaches employ the gene expression profiles to determine the molecular pathways involved in the response, and the quantitative transcriptomic data to determine the benchmark dose and estimate a point of departure for human health risk assessment.

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