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Follow-up studies to support risk negative – Case studies in pharmaceutical companies

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Registration of pharmaceuticals requires a comprehensive assessment of their genotoxic potential. The usual approach should be to carry out a battery of *in vitro* and *in vivo* tests for genotoxicity, and the following standard test battery is recommended: i) an *in vitro* test for gene mutation in bacteria, ii) an *in vitro* test for chromosomal damage with mammalian cells or an *in vitro* mouse lymphoma tk assay, and iii) an *in vivo* test for chromosomal damage using rodent hematopoietic cells. For compounds giving negative results, the completion of this 3-test battery usually provides a sufficient level of evidence to suggest the absence of genotoxic activity. However, compounds giving positive results in the standard test battery may need to be tested more extensively.

As follow-up genotoxicity studies in addition to the standard battery, several tests for measurement of DNA adducts, DNA strand breaks, DNA repair or recombination, and molecular techniques are useful to study mechanisms of genotoxicity and to help risk assessment. Especially, *in vivo* tests measuring genetic damage in target organs of tumor induction will be also additional genotoxicity testing in relation to the carcinogenicity bioassay. Additionally, from the viewpoint of extrapolation if the genotoxicity is relevant to humans or not, detail information or further studies about metabolism / pharmacokinetics of a drug or the moiety in animals and/or humans will be involved in the interpretation for the risk negative. These follow-up studies can support that the positive result observed in the standard battery is not relevant to human risk.

In this presentation, some case studies in pharmaceutical companies including follow-up strategies to support risk negative in humans, which were surveyed by the Japanese Environmental Mutagen Society / Mammalian Mutagenicity Study Group (JEMS/MMS), are presented.

Risk negativeを支持するためのフォローアップ試験 – 企業の実例
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