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PII: S1383-5718(17)30356-X
DOI: https://doi.org/10.1016/j.mrgentox.2018.03.004
Reference: MUTGEN 402888

To appear in: *Mutation Research*

Received date: 7-11-2017
Revised date: 7-2-2018
Accepted date: 9-3-2018

Please cite this article as: Rola Barcham, Nicolas Orsini, Eric Andres, Alexander Hundt, Anne-Pascale Luzy, Successful proof of concept of a micronucleus genotoxicity assay on reconstructed epidermis exhibiting intrinsic metabolic activity, Mutation Research/Genetic Toxicology and Environmental Mutagenesis https://doi.org/10.1016/j.mrgentox.2018.03.004

TITLE

Successful proof of concept of a micronucleus genotoxicity assay on reconstructed epidermis exhibiting intrinsic metabolic activity.

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HIGHLIGHTS

- We evaluated the performance of a new *in vitro* assay for genotoxicity.
- The Episkin LM™ model was found as suitable for this assay.
- The prediction performances were evaluated for the detection of known genotoxins.
- The ability of Episkin LM™ model to bioactivate progenotoxins was established.

ABSTRACT

We investigated the commercially available Episkin LM™ reconstructed epidermis test system as a potential 3D model for human genotoxicity assessment by cytokinesis-block micronucleus assay to mitigate limitations of the currently accepted micronucleus test.

We established appropriate culture conditions for cytokinesis-block micronucleus assay in maximizing the frequency of binucleated cells by choice of culture medium and calibration of the system exposure to the cytokinesis inhibitor Cytochalasin B, without affecting the basal frequency of micronuclei in the model. We confirmed that the application of the classic solvents had no significant effect on this basal level of micronuclei.

We determined the performance of cytokinesis-block micronucleus assay in Episkin LM™ reconstructed epidermis to predict *in vivo* genotoxins by testing the genotoxicity potential of 17 well known *in vivo* genotoxic, progenotoxic and non-genotoxic reference chemicals over a 48 hours and 72 hours exposure period.

We found that cytokinesis-block micronucleus assays in Episkin™ reconstructed epidermis following the 48 h-topical regimen had a specificity of 60 - 75% and a sensitivity of 83 - 85%, resulting in an overall accuracy of 76 - 82% for genotoxicity assessment in tissues depending on the assessment of the reference chemicals with equivocal genotoxic profiles in the literature.

The positive micronucleus test results obtained without addition of any exogenous metabolic activation system confirmed the ability of Episkin LM™ reconstructed epidermis to intrinsically bioactivate