

Genotoxicity Testing Using the Micronucleus Assay in the Human EpiDerm™ 3D Skin Model

Y.Kaluzhny 1; V.Karetsky1; R.Curren2; M.Aardema 3; P.Hayden 1; T.Hu3; M.Klausner1.

1. MatTek Corporation, Ashland, MA; 2. Institute for In Vitro Science, Inc., Gaithersburg, MD; 3. The Procter & Gamble Co., Cincinnati, OH.

Safety assessment of new products for human use requires genotoxicity testing to ensure their non-carcinogenicity. Current in vitro assays have low specificity resulting in a high rate of false positives that may be due to use of transformed cell lines, non-physiological exposures, and lack of normal metabolism. To help determine the biological relevance of chemicals that are positive in in vitro genotoxicity assays, in vivo assays are conducted. However, starting in 2009, European Union cosmetics manufacturers will not be able to use in vivo genotoxicity tests. To address this problem, more biologically relevant in vitro genotoxicity tests are needed. Since skin has the highest exposure to many cosmetic and personal care products, a skin model will better reflect human exposure and metabolism. EpiDerm forms a 3D tissue that is highly reproducible, contains a skin-like barrier, and possesses biotransformation capabilities including CYP450, GST, and UDP enzymatic activity. The Micronucleus Assay (MNA) utilizing EpiDerm allows topical application of test materials in a similar fashion to actual human contact. Doses are given 24 hours apart in the presence of 3 Mg/ml of Cytochalasin-B in the medium. Cells are harvested from the tissue 24 hours after the last dose. This protocol results in a reproducible population of binucleated cells (49.2% +1-9.5) with a low background % of micronucleated cells (0.08% +/-0.08). We have shown dose-related, statistically significant increases in micronuclei for 3 model genotoxins and for 6 additional rodent skin genotoxins. Also, 4 non-genotoxins were tested at concentrations resulting in <50% cell survival and shown to be negative. Finally, 3 genotoxins that require metabolic activation were positive in the MNA. In conclusion, the MNA that utilizes EpiDerm with inherent metabolic activity is very useful for predicting genotoxicity in a structurally complex tissue of human origin.

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