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Fixate™ Superhold Polymer Toxicology Studies

The toxicology studies summarized below were performed on polymers with chemical compositions representative of Fixate™ Superhold polymer. Therefore, this toxicology data is expected to be predictive of the toxicity of the commercial grades of Fixate Superhold polymer.

Oral Toxicity

The oral toxicity of the test material was evaluated in rats according to OECD Guideline 423; Method B1 of Commission Directive 2004/73/EC. The test material was administered by oral gavage to two groups of three female HanRcc:WIST (SPF) rats at 2000 mg/kg body weight. Animals were subject to daily observations and weekly determination of body weight. Macroscopic examinations were performed after terminal sacrfice on day 15. No mortality occurred. Observations of abnormalities were limited to ruffled fur in one animal. The oral LD50 value was determined to be greater than 2000 mg/kg bodyweight.

Skin Irritation

The skin irritation of the supplied test material was evaluated in rabbits according to OECD Guideline No. 404, 2002; Method B4 of Commission Directive 2004/73/EC. The test material (0.5 ml) was applied to the surgical gauze patch and applied to the intact skin on the backs of three animals. The patch was covered with a semi-occlusive dressing and held in place with surgical tape. Four hours after the application of the test material, the patches were removed, and the skin was flushed with lukewarm tap water. The test sites were evaluated and at 1, 24, 48, and 72 hours, as well as on days 7, 10 and 14 after removal of the patches. The test material produced a primary irritation index score of 2.3, and was classified as a moderate irritant. Based on Commission Directive 2001/59/EC it was concluded that the neat material should be labeled as “Irritating to the Skin” (R38).

The skin irritation of a 50% as supplied test material was evaluated in rabbits according to OECD Guideline No. 404, 2002; Method B4 of Commission Directive 2004/73/EC. The test material (0.5 ml) was applied to the intact skin on the backs of three animals. The patch was covered with a semi-occlusive dressing. Four hours after the application of the test material, the patches were removed, and the test material was gently removed. The test sites were evaluated and at 1, 24, 48, and 72 hours. The test material produced a primary irritation index score of 0.0 out of 8.0, and was classified as a non-irritant.

Eye Irritation

The eye irritation of the supplied test material was evaluated in rabbits according to OECD Guideline No. 405, 2002; Method B5 of Commission Directive 2004/73/EC. The test material (0.1 ml) was placed in the conjuntival sac of the left eye of each of three animals. The right eye served as an untreated control. The eyes were evaluated 1, 24, 48, 72 hours and day 7 following treatment. The test material produced slight to moderate conjunctival irritation which returned to normal in all animals by day 7. The test material produced a maximum mean score of 5 out of 110 and was classified as a mild irritant (Class 4 on a 1 to 8 scale).

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Skin Sensitization

The skin sensitization of the test material was evaluated in the mouse using the Local Lymph Node Assay as indicated in the OECD Guideline No. 429, 2002; Method B.42 of Commission Directive 2004/73/EC. Groups of four mice were treated with the test material at concentrations of 0, 5, 10, or 25 w/v in propylene glycol by daily application to the dorsal surface of each ear for three consecutive days. Five days following the first topical application, all mice were injected with 250 µl ^{3}H-methyl thymidine (^{3}HTdR: 84.47 µCi/ml) via tail vein giving a total dose of 21.1 µCi ^{3}HTdR to each mouse. A single cell suspension of pooled lymph node cells was prepared by gentle mechanical disaggregation through stainless steel gauze (200µm mesh size). After completing washing and centrifuging steps, the precipitates were incubated overnight at 4°C, were re-centrifuged, and measured for ^{3}HTdr incorporation. The stimulation index (SI) for the test substance was determined to be 1.3, 1.5, and 1.1 at 5, 10 and 25%, in propylene glycol respectively. Based on this information it was concluded that the test material is not a skin sensitizer when tested up to the highest applicable concentration of 25% as supplied in propylene glycol.

Mutagenicity

The mutagenic potential of the test material was evaluated in the plate incorporation test (experiment I) and pre-incubation test (experiment II) using the *Salmonella typhimurium* mutation assay using strains TA1535, TA1537, TA98, TA100 and in the *Escherichia coli* mutation assay using strain WP2 uvrA (OECD 471, July 21, 1997; EEC Directive 2000/32/EC, L1362000, Annex 4D dated May 19, 2000). The test was performed in two independent experiments with and without the presence of an induced rat liver S9 mix.

In both independent experiments the test material showed normal background growth up to 5000 µg/plate with and without metabolic activation. There were no substantial increases in revertant colony numbers of any of the five tester strains at any dose level in the presence or absence of metabolic activation (S9 mix).

Based on the results of this study the test material was considered not to be mutagenic in this *Salmonella typhimurium* and *Escherichia coli* reverse mutation assay.