TOX-076
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Fixate™ PLUS Polymer
Toxicology Profile

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

Oral Toxicity
The oral toxicity of the test material was evaluated in rats according to OECD Guideline No. 423, Paris Cedex, 1996; EC Council Directive 67/548/EEC, Annex V, Part B, as last amended by Commission Directive 96/54/EC, Annex IV B, B.1 tris: Official Journal of the European Communities, No. L248, 1996; USEPA Guideline, OPPTS 870.110, June 1996. The test material was administered by oral gavage to three Wistar rats at each sex 2000 mg/kg body weight. Animals were subject to daily observations and weekly determination of body weight. Macroscopic examinations were performed after terminal sacrifice on day 15. No mortality occurred. Observations of abnormalities were limited to hunched posture and chromodacryorrhoea. The oral LD_{50} value was determined to be greater than 2000 mg/kg body weight.

Skin Irritation
The skin irritation of the undiluted test material was evaluated in rabbits according to OECD Guideline No. 404, 1992; Method B4 of Commission Directive 92/69/EEC. The test material (0.5 ml) was applied to the intact skin on the backs of three animals under a semi-occlusive dressing. Four hours after the application of the test material, the patches were removed, and the test material was gently removed from the skin. The test sites were evaluated one hour after removal of the patches and at 24, 48, and 72 hours. The test material produced a primary irritation index score of 1.0 out of 3.0 and was classified as mildly irritating.

Eye Irritation
The eye irritation of the undiluted test material was evaluated in rabbits according to OECD Guideline No. 405, 1987; Method B5 of Commission Directive 92/69/EEC. The test material (0.1 ml) was placed in the conjunctival sac of the one eye of each of three animals. The other eye served as an untreated control. The eyes were evaluated 1, 24, 48, and 72 hours following treatment. The test material produced a maximum mean score of 4 out of 110 and was classified as mildly irritating.

Skin Sensitization
The skin sensitization potential of a number of samples of the test material was evaluated in the mouse using the Local Lymph Node Assay based on the guidelines described in OECD, Section 4, Health Effects, No. 429 (Draft), Paris Cedex, 2000, EC, Council Directive 67/548/EEC, Annex IV C, B.42 (Draft), June 2001 and ICCVAM, NIH publication, No. 99-4494, February 1999. Groups of four mice were treated with the test material at concentrations of 0.5%, 10%, and 25% w/v in propylene glycol formamide (25 µl/ear) 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 25 µl of phosphate buffered saline containing 3H-methyl thymidine via tail vein

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giving a total dose of 20 μCi to each mouse. A single cell suspension of pooled lymph node cells was prepared by mechanical disaggregation through stainless steel gauze (125μm diameter). The cells were washed and centrifuged, precipitated, and re-centrifuged at 4°C, and then were measured for ^{3}HTdr incorporation. Based on the initial results, additional groups of animals were treated with test substance concentrations of 0.5%, 10% (repeat dose), and vehicle alone. A 10% solution of alpha-hexylcinnamic aldehyde in propylene glycol was used as the positive control.

Very slight erythema was noted among the animals. The majority of lymph nodes were enlarged. The largest nodes were seen at 0.05%. No other macroscopic abnormalities of the lymph nodes were noted. The stimulation index (SI) for the test substance was determined to be 2.03, 2.82, 5.65, 1.15, and 2.35 at 0.05, 0.5, 10, 10 (repeat), and 25%, respectively. It was noted that the initial SI at 10% was not confirmed in the repeat of this concentration. Based on this information it was concluded that the test material is not expected to produce an SI value above the criteria for a positive response (test/control ratio > 3). Therefore, the test substance was determined not to cause a sensitization response under the conditions of this test.

Mutagenicity

The mutagenic potential of the test material was evaluated in the *Salmonella typhimurium* mutation assay using strains TA1535, TA1537, TA100, and TA98 and in the *Escherichia coli* mutation assay using strain WP_2uvrA (OECD 471, July 21, 1997; EEC Directive 67/548/EEC, Part B, June 8, 2000). The test was performed in two independent experiments with and without the presence of an induced rat liver S9 liver mix.

In the dose range finding test the test material precipitated on the plates at 5000 μg/plate, the highest concentration tested using TA100 and WP_2uvrA with and without activation. The bacterial background lawn was not reduced at any of the concentrations tested and no decrease in the number of revertants was observed.

In both independent experiments with and without activation the test material precipitated at 5000 μg/plate. The bacterial background lawn was not reduced at any of the concentrations tested and no decrease in the number of revertants was observed. The test material did not induce a dose related, two-fold increase in the number of revertants in any of the strains tested with or without activation. These results were confirmed in the second independent experiment.

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