

A Chronic Toxicity and Carcinogenicity Study in Rats with Elastomer Shell Subcutaneous Implants

SUMMARY AND CONCLUSION

The subcutaneous implantation of LDP reference article or test article in female Fischer 344 rats resulted in an immediate foreign body reaction at the implant sites and subsequent development of significant numbers of palpable masses (primarily fibrosarcomas) in these groups of animals. The foreign body reaction observed in the LDP reference group differed from the group in incidence, speed of onset and in minor histologic features. The LDP reference article elicited a more severe immediate reaction as evidenced by alopecia, scabbing, and ulceration which resulted in the replacement of nearly half of the animals by six weeks. However, the second group of LDP animals (replacement animals) experienced considerably less severe implant site reactions. The immediate response observed in the group was similar to that observed in the LDP reference group, though it was less severe. Ulceration at the implant sites was delayed in the group and involved a limited number of animals.

The presence of pulverized LDP reference article and test article elicited a fibrous encapsulation of the pulverized material with extension of fibrosis into septa penetrating between the fragments of LDP and test article. A high incidence of chronic and granulomatous inflammation and pigmentation (at 12 months) was also observed in the animals. In the group the implant site lesion was similar to that noted in the LDP group with the exception of the higher incidence of mineralization after 12, 18 and 22 months.

Palpable implant site masses (later diagnosed primarily as fibrosarcomas) appeared early in the study (during week 33) in the group. During the second year of the study, palpable masses (primarily fibrosarcomas) were also observed at the implant sites in the LDP reference group. Although the incidence of implant site masses was similar in the test article and LDP reference group after 22 or 24 months, respectively, in the test article group they appeared in higher numbers earlier in the study. The fibrosarcomas metastasized to a variety of organs or tissues in some animals from both of the implanted groups. The appearance of implant site fibrosarcomas in both of these two groups resulted in significantly ($p < 0.01$) reduced overall survival and shortened implant site time-to-tumor when compared to the Sham Control group. When the test article group was compared to the LDP reference group, survival time and implant site time-to-tumor were significantly shorter ($p < 0.01$ and $p < 0.05$, respectively). Time-to-death (time from tumor discovery to death) was significantly ($p < 0.05$) shorter when the test article group was compared to the Sham Control group. No significant differences were noted in time-to-death when the LDP reference or test article groups were compared. When animals with implant site masses were censored, no significant differences were observed in survival among the three groups.

The appearance of implant site sarcoma was not a totally unexpected event, although it was thought that the pulverization of the LDP reference article and test article would reduce if not eliminate the chances for foreign body sarcoma formation while maximizing the surface area presented to the animal. The pulverized LDP and test article were placed in gelatin capsules in order to assure the reasonably accurate delivery of the pulverized, highly electrostatic materials to the animals. With this delivery system the reference and test article could be weighed into the capsules, the capsules closed and sterilized prior to surgery, and placed in the surgically prepared tracts with relative ease.

Other neoplastic and non-neoplastic changes were observed in a variety of organs and tissues in all three groups. The changes observed in the LDP reference and test article groups were of the type commonly observed in Fischer 344 rats of this age. Therefore, no relationship to the implanted materials was apparent.

Under the conditions of this study, the subcutaneous implantation of the reference article, LDP, or the test article, Elastomer Shell, produced no evidence of systemic toxicity as measured by body weight, organ weight (absolute or relative to brain or body weight), hematology, and serum chemistry examinations. Changes attributable to the implantation of LDP and test article were observed at the site of subcutaneous implantation. They consisted of various degrees of inflammation and, later in the study, the appearance of implant site related masses. The initial inflammatory response in the LDP reference article group was more severe than that observed in the test article group. Microscopically the lesion in the LDP reference and test article groups consisted of fibrous septa penetrating between the pulverized LDP and test article fragments and infiltration of chronic and granulomatous inflammation. Mineralization was observed in higher incidence in the implant sites of the test article group animals compared to that observed in the LDP reference group.

Carcinogenicity associated with the test article was limited to the development of implant site related sarcomas, primarily fibrosarcomas, and their subsequent effects. Survival time and time-to-tumor were significantly ($p < 0.01$) reduced in the LDP reference and test article groups compared to the Sham Control and time-to-death was shortened ($p < 0.05$) in the test article group compared to the Sham Control group. Survival time and time-to-tumor were significantly ($p < 0.01$ and $p < 0.05$, respectively) shorter in the test article group compared to the LDP reference group after 22 months of exposure. When the influence of local implant site masses was censored no significant differences in survival time remained when the LDP reference and test article groups were compared to each other or to the Sham Control group.