

A Chronic Toxicity and Carcinogenicity Study in Rats with Gel Subcutaneous Implants

SUMMARY AND CONCLUSION

The subcutaneous implantation of LDP reference article or GEL [REDACTED] 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 elicited by the implanted LDP reference article was more severe as evidenced by alopecia, eschar, ulceration and the replacement of nearly half of the animals by week six in this group due to ulceration of the skin over the implant. However, the second group of LDP animals (replacement animals) experienced considerably less severe implant site reactions. The immediate response to the gel implant was mild.

The presence of pulverized LDP reference article elicited a fibrous encapsulation of the pulverized material with extension of fibrosis into septa penetrating between the fragments of LDP. A high incidence of chronic and granulomatous inflammation with occasional pigment (12 months) and mineralization (after 18 months) was also observed in these animals. In the GEL [REDACTED] group, a delicate thin fibrous capsule formed around the implanted gel. Occasionally, chronic inflammation was observed in or about the fibrous capsule.

During the second year of the study, palpable masses (primarily fibrosarcomas) were observed at the implant sites in the LDP reference and GEL [REDACTED] groups. The incidence of fibrosarcoma in the LDP reference group (65/111) was higher than that noted in the GEL [REDACTED] group (34/120). The fibrosarcomas metastasized to a variety of organs and tissues in some animals from both groups. The appearance of implant site fibrosarcomas resulted in significantly decreased survival and time-to-tumor in both implanted groups (LDP and GEL [REDACTED]) compared to the Sham Control group. Overall survival and time-to-tumor in the GEL [REDACTED] group was significantly ($p < 0.05$ and $p < 0.01$ respectively) longer compared to the LDP reference group. Time from tumor discovery to death was significantly ($p < 0.05$) shorter in the GEL [REDACTED] group when compared to the LDP reference group. When the palpable implant site masses were censored, survival in the LDP reference and GEL [REDACTED] groups was comparable to the Sham Control group.

Overall survival and time-to-tumor in the GEL [REDACTED] group were significantly longer than were observed in the LDP reference group and are likely related to the differences in physical properties (i.e. pulverized solid versus a gel). The significantly shorter time from tumor discovery to death noted in the GEL P/N [REDACTED] group compared to the LDP reference group probably occurred as a result of the older age (longer survival) of GEL [REDACTED] group animals.

The appearance of implant site sarcomas was not a totally unexpected event, although it was thought that the pulverization of the LDP reference article would reduce, if not eliminate, the chances for foreign body sarcoma formation while maximizing the surface area presented to the animal.

Other neoplastic and non-neoplastic changes were observed in all three groups of animals. The changes observed in the LDP reference and GEL P/N [REDACTED] 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, GEL P/N [REDACTED] produced no evidence of systemic toxicity as measured by body weight, hematology, serum chemistry examinations, and organ weight (absolute or relative to body weight or brain weight) evaluations. Changes attributable to the implantation of LDP and GEL P/N [REDACTED] 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 GEL [REDACTED] group.

Microscopically the lesion in the LDP reference article group consisted of fibrous septa penetrating the pulverized LDP reference article, chronic and granulomatous inflammation and traces of mineralization. In contrast, the lesion in the GEL [REDACTED] group animals was characterized by a thin fibrous capsule surrounding, but not penetrating the implanted gel and containing occasional incidences of chronic inflammation. Carcinogenicity was limited to the development of implant site related sarcomas, primarily fibrosarcomas, and their subsequent effects. Survival time, time-to-tumor, and time-to-death after tumor discovery was significantly reduced in both the LDP and GEL [REDACTED] groups when compared to the Sham Control group. When compared to the LDP reference article, survival time and time-to-tumor were significantly longer in the GEL P/N [REDACTED] group. Time-to-death after tumor discovery was significantly shorter in the GEL [REDACTED] group compared to the LDP reference group. Survival in the GEL [REDACTED] group was comparable to the Sham Control group when the influence of palpable implant site masses was removed.

REFERENCES

- ¹ Brischoff, F. and Bryson, G.: Carcinogenesis through solid state surfaces.: *Progr. Exp. Tumor Res.* 5:85-133 (1964).
- ² Oppenheimer, B.S., Oppenheimer, E.T. and Stout, A.P.: Sarcomas induced in rats by implanting cellophane. *Proc. Soc. Exp. Biol. Med.* 67:33-34 (1948).
- ³ Oppenheimer, B.S., Oppenheimer, E.T., Stout, A.P. and Danishefsky, I.: Malignant tumors resulting from embedding plastics in rodents. *Science* 118: 305-306 (1953).
- ⁴ Oppenheimer, B.S., Oppenheimer, E.T., Stout, A.P., Danishefsky, I. and Eirlich, F.R.: Malignant tumors and high polymers. 118: 783-784 (1953).
- ⁵ Oppenheimer, B.S., Oppenheimer, E.T., Danishefsky, I., Stout, A.P. and Eirlich, F.R.: Further studies of polymers as carcinogenic agents in animals. *Cancer Res.* 15: 333-340 (1955).
- ⁶ Oppenheimer, B.S., Oppenheimer, E.T., Danishefsky, I. and Stout, A.P.: Carcinogenic effect of metals in rodents. *Cancer Res.* 16: 439-441 (1956).
- ⁷ Oppenheimer, B.S., Oppenheimer, E.T., Stout, A.P., Danishefsky, I. and Willhite, M.: Studies of the mechanism of carcinogenesis by plastic films. *Acta Un. Int. Cancr.* 15: 659-662 (1959).
- ⁸ Oppenheimer, B.S., Oppenheimer, E.T., Stout, A.P., Willhite, M. and Danishefsky, I.: The latent period in carcinogenesis by plastics in rats and its relation to the precancerous stage. *Cancer. Philadelphia* 11: 204-215 (1958).
- ⁹ Brand, K.G., Buoen, L.C., Johnson, K.H., and Brand, I.: Etiological factors, stages, and role of the foreign body in foreign body tumorigenesis: a review. *Cancer Res.* 35: 279-286 (1975).
- ¹⁰ Brand, K.G., Exploration of implant-associated carcinogenesis in animals. *Biomaterials in Reconstructive Surgery*, St. Louis, C.V. Mosby Co. 1983, pp. 27-35.
- ¹¹ Brand, K.G.: Solid state carcinogenesis. *Brandbury Report # 25: Nongenotoxic mechanisms in carcinogenesis.* pp. 205-213 (1987).
- ¹² Woodward, S.C.: How to relate observations of foreign-body oncogenesis in experimental animals to human health risk. *Biomaterials in Reconstructive Surgery*, St. Louis, C.V. Mosby Co., 1983, pp. 17-20.