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Review of Draft Final Report of Project #305-001

Entitled:

Embryo/Fetal Toxicity and Teratogenic Potential

of Saytex 111 Administered Orally by Gavage to CRL:COBS, CD, (SD), BR

Presumed Pregnant Rats Dated April 15, 1985

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by

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E. Marshall Johnson, Ph.D.

Professor and Chairman, Department of Anatomy

Director, Daniel Baugh Institute

Jefferson Medical College of

Thomas Jefferson University

1020 Locust Street

Philadelphia, PA 19107

E. Marshall Johnson 10/21/85

Methods

This is a report of a well-executed guideline-compliant developmental toxicity (Segment II) evaluation of Saytex 111 in rats. The test compound was administered once daily by oral intubation (in corn oil) to rats on days 6-15 of presumed gestation. Dosage was at levels 0, 2.5, 10.0 and 25.0 mg/kg/day with the dose volume held constant at 5 ml/kg/day but adjusted each day based on maternal body weight. On gestation day 20 the females were killed by carbon monoxide asphyxiation. The uteri were excised and the fetuses were removed. Half were processed for soft tissue and the remainder for alizarin red staining of ossified skeleton.

The females were individually housed after having been bred naturally to single males. Throughout the experiment they were supported in a room controlled at 74° ± 4°F and between 35 and 56 percent relative humidity. The air was changed approximately 12 times per hour and consisted of 100 percent fresh air passed through 99.97% Hepa-filters. They were fed Ralston certified rodent chow and provided reverse osmosis-prepared water ad libitum.

Results

There was no increase in clinical signs due to the treatment with the test compound, and maternal weight change during treatment was unaffected. Beginning about day 16 there was a decrement of anticipated maternal weight gain in the high dose group which could be attributed directly to the increased resorptions that occurred in these animals. At laparotomy there were 25, 24, 24, and 22 females with live fetuses in the control 2.5, 10.0 and 25 mg/kg/day dose groups, respectively. There were no gross externally evident malformations or variations in any of the

groups which could be related to the test compound. In both the mid- and high-dose groups, there were litters containing one and three pups, respectively, with slightly dilated lateral cerebral ventricles. In the high-dose animals there were three litters containing six fetuses with enlarged hearts and several instances of statistically significantly elevated numbers of skeletal variations and/or abnormalities. These effects included the scapula, femur, tibia, fibula, as well as various intramembranous and intracartilagenous bones of skull. Delayed ossification was also observed in the vertebral column, ribs and pelvis in the high-dose group.

Summary

This is an excellently executed study which does not, itself, show an adverse effect on the dams unrelated to fetal resorptions but reports a pilot study wherein a dosage of 100 mg/kg/day clearly resulted in a decrement of maternal body weight gain. Adverse developmental effects were evident in the high-dose group. These were seen as statistically significantly reduced fetal body weight, delayed skeletal maturation, and possibly by dilated lateral cerebral ventricles and cardiac enlargement. These last two are of questionable biological significance and could represent biologic variation. The reduction in fetal body weight and skeletal immaturity and perhaps even limb defects in the high-dose are considered as compound-related. The 10 mg/kg/day group shows some instances of non-statistically significant elevations above the control level which could be part of a dose response relationship. This is evident for the incomplete ossification of the innominate, sphenoid and possibly calvarium. Fetal body weight was not significantly reduced at the 10 mg/kg/day dosage level although it tended to be somewhat smaller than either the

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control or the 2.5 mg/kg/day group. Clearly the low-dose is a fetal no-effect level, but in my opinion, the findings in the 10 mg/kg/day animals are of marginal significance and I would consider this a developmental no-effect level for all practical purposes.

The interesting aspect of this test compound is that it produced adverse signs in the conceptus at a dosage level that did not cause overt signs of maternal toxicity. Determination of safe exposure to their test chemical is best considered on the basis of this developmental effects-NOE of 10 mg/kg/day.