MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Charles J. Kokoski, Ph.D.
Chief, Food Additives Evaluation Branch, HFF-185

DATE: September 11, 1978

FROM : Thomas F.X. Collins, Ph.D. Thomas F.X. Collins
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SUBJECT: Aspartame (SC-18862). Review of four studies submitted by G.D. Searle as entries to Food Additive Master File 134, in response to your memo of September 1, 1978.

1. E-79. SC-18862: Segment II, an evaluation of the teratogenic potential in the rabbit. Final report. Hazleton Laboratories, Inc., Vienna, Virginia, October 8, 1974.

Procedure. New Zealand white rabbits were given a 5% or 15% aqueous suspension of aspartame in 1% aqueous Tween-80 by oral intubation twice per day from day 6 through day 18 of gestation. The dosage given was 0.75 g/kg/day for the low dose and 2.0 g/kg/day for the high dose. The control group received a 1% aqueous solution of Tween-80 by oral intubation twice daily during the same days of gestation in a volume equal to that received by the highest dose level. The study was done in three replicates (sub-groups A, B, C). The number of animals per subgroup ranged from 10 to 12 for the controls, from 11 to 14 for the low level, and 28 to 38 for the high level. Control females in each group were pair fed on a g/kg basis with the appropriate number of group-3 does from the corresponding subgroup which consumed the least amount of the diet on the preceding day (same day of gestation). To accomplish pair feeding, the control females in each subgroup were inseminated 24 hours following insemination of animals assigned the the corresponding high level group. Pair feeding began on day 6 and continued until sacrifice at day 29. During treatment, the animals were fasted 8-9 hours (1.5-2 hours preceding the first daily dose and ending after completion of the second dose).

Results. Mortality rate was slightly increased at both dose levels but this was not related to dose. Conception rates showed a dose-related decrease. Both experimental groups gained weight during the period of treatment while the controls actually lost weight. The pre-treatment food consumption rates were similar for the control and treatment groups. During treatment, the treated groups consumed significantly more food than the controls. Following treatment, the controls consumed slightly more food than during the treatment period, while the treated groups consumed slightly less, but still the treated groups consumed significantly more food than the controls.

There appeared to be a slight increase in pre-implantation loss at the high dose level. There appeared to be a decrease in the mean number

of live fetuses and an increase in the mean number of resorption sites at the high dose level. Statistics were only done on the combined data. If statistics were done on the subgroups, significant effects on these parameters might be noted. There was no increase in the number of does with implantation scars, resorption sites, or dead fetuses.

Mean fetal weight was significantly increased at the low dose level (0.75 g/kg) but was not affected at the high level. There appeared to be no effect on fetal length.

At the high dose level, there was an increase in the number of fetuses with abnormalities and an increase in the number of litters affected. No abnormalities were observed in the control animals (19 litters). At the low dose level, 1 of 198 fetuses (24 litters) showed gastroschisis with associated rotation of hindlimbs, rotation of the eye, and other anomalies. At the high dose level, 7 of 343 fetuses (6 litters out of 45) showed major and minor anomalies consisting in part of: bi-clefted lip, cleft palate, fused mandible, short maxillary bones, fusion and misalignment of caudal vertebrae, reduced ossification of thoracic and caudal vertebrae and phalanges, hydrocephalus, missing ribs, and ectrodactyly.

Problems. 1. The exact mechanism of the pair-feeding schedule is not clear.
2. Eighteen fetuses at the high level were too small to be processed, hence the evaluation of these fetuses is not available.

Conclusion. There were deleterious effects at the high dose level, 2.0 g/kg, but no effects at the low level, 0.75 g/kg. Rigorous pair feeding was certainly a factor.

2. E-83. SC-18862 Placebo: An evaluation of embryotoxic and teratogenic potential of specially prepared pelleted diet in the rabbit. Searle Laboratories, October 1974.

Procedure. This study was done to test the diet used in a previous segment II rabbit study conducted at Searle and Hazleton Laboratories. A commercially available diet from the same manufacturer served as the control. Sixty New Zealand white female rabbits approximately 9 months old were given one of the following diets: commercial control (10 animals), Searle control (25 animals), and Hazleton control (25 animals). The animals had a mean body weight of 3.8 kg. Searle and Hazleton diets were offered ad libitum to the appropriate groups of animals from the morning of gestation day 6 to the morning of gestation day 19. Commercial diet was given prior to and subsequent to this period. The animals were sacrificed near term (day 28) and the uterine contents examined. The diets were analyzed for moisture content, aflatoxins, aerobic bacteria, yeasts, and molds.