31R0089

USDA ANNUAL REPORT-

REPORTING PERIOD: OCTOBER 1, 1998 THRU SEPTEMBER 30, 1999

FACILITY REGISTRATION NUMBER: 31-R-0089

Category E.- Dogs/Rabbits:

Pain and/or distress for which no anesthetic, analgesic or tranquilizing drug(s) were used:

The use of analgesics or nonsteroidal anti-inflammatory agents are neither scientifically acceptable nor is their use acceptable to the governing agencies involved.

One of 22 dogs on a dose range-finding study is believed to have experienced pain and/or distress. The purpose of the study was to evaluate the lethality and short term toxicity of the test articles and to establish dosages on a longer-term subchronic study. The study was conducted in compliance with the U.S. FDA (Food and Drug Administration) Good Laboratory Practice Regulations, 21 CFR Part 58. The clinical observations for this dog were intermittent and continual monitoring was therefore necessary.

One of 72 rabbits in a dose range-finding developmental toxicity study is believed to have experienced distress. The purpose of the study was to determine dose levels for a definitive developmental toxicity study. The study was conducted in accordance with the U.S. EPA Good Laboratory Practice Regulations, 40 CFR Parts 160 and 792. The onset of this animal's clinical signs was very sudden.

Two of 110 rabbits in a prenatal developmental toxicity study are believed to have experienced pain and/or distress. The purpose of the study was to was to determine the potential of the test article to induce development toxicity after maternal exposure during the critical period of organogenesis, to characterize maternal toxicity at the exposure levels tested and to determine a NOEL for maternal toxicity and development toxicity. The study was conducted in accordance with the United States Environmental Protection Agency (EPA) Health Effects Test Guidelines OPPTS 870.3700, Prenatal Developmental Toxicity Study, August 1998. The clinical observations of these two animals were intermittent and continued observation was necessary to elucidate a potential pattern of symptoms.

One of 108 rabbits in a study on embryo/fetal development is believed to have experienced pain and/or distress. The purpose of the study was to was to determine the potential of the test article to induce development toxicity after maternal exposure during the critical period of organogenesis, to characterize maternal toxicity at the exposure levels tested and to determine a NOEL for maternal toxicity and development toxicity. The study was conducted in accordance with the International Conference on Harmonization (ICH) Tripartite Guideline on Detection of Toxicity to Reproduction for Medicinal Products, Federal Register, September 22, 1999, Section 4.1.3. The study was also conducted in accordance with the U.S. FDA Good Laboratory Practice Standards (21 CFR Part 58). The onset of the clinical observations was sudden.

Two of 45 rabbits in a dose range-finding developmental study were believed to have experienced pain and/or distress. The onset of this animals' clinical signs was very sudden and timely intervention could not be accomplished. The purpose of the study was to determine dose levels for a definitive developmental toxicity study. The study was conducted in accordance with the U.S. EPA Good Laboratory Practice Regulations, 40 CFR Parts 160 and 792.

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FACILITY REGISTRATION NUMBER: 31-R-0089
Category E.- Dogs/Rabbits (continued):
Pain and/or distress for which no anesthetic, analgesic or tranquilizing drug(s) were used:

Two of 44 rabbits in a tolerability and toxicokinetic study were believed to have experienced pain and/or distress. The purpose of the study was to assess the toxicity following repeated dosing in order to determine dose levels for a dose range-finding embryo/fetal development study. The study was conducted in accordance with the U.S. EPA Good Laboratory Practice Regulations, 40 CFR Parts 160 and 792.

One of 170 rabbits in a prenatal developmental toxicity study was believed to have experienced pain and/or distress. The purpose of the study was to was to determine the potential of the test article to induce development toxicity after maternal exposure during the critical period of organogenesis, to characterize maternal toxicity at the exposure levels tested and to determine a NOEL for maternal toxicity and development toxicity. The study was conducted in accordance with The EPA Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Pesticide Assessment Guidelines (Subdivision F; series 83-3), the EPA Toxic Substances Control Act (TSCA) Health Effects Test Guidelines, 40 CFR 798.4900, the OECD (Organization for Economic Cooperation and Development) Guidelines for Testing of Chemicals, Health Effects Test Guidelines, Section 414, adopted May 12, 1981, the EPA Health Effects Test Guidelines OPPTS 870.3700, Prenatal Developmental Toxicity Study, August 1998, and the Japanese Agricultural Chemicals Laws and Regulations Testing Guidelines for Toxicology Studies (59 NohSan No. 4200) published by the Society of Agricultural Chemical Industry, issued January 28, 1985, under the auspices of MAFF (Ministry of Agriculture, Forestry and Fisheries). The study was also conducted in compliance with the U.S. EPA, 40 CFR Part 160, the OECD, [C(97) 186/Final], and the Japanese MAFF Good Laboratory Practice Regulations, 59 NohSan No. 3850, August 10, 1984.

REPORTABLE EXCEPTIONS TO ANIMAL WELFARE ACT-
The Attending Veterinarian exempted one male dog on a subchronic toxicity study for one day's exercise period (10/28/98) due to its favoring of the right hindlimb. The Veterinarian rechecked the animal after this exempted day and from then on was returned to the normal exercise and socialization regimen for this study.

The 38 dogs on a chronic toxicity study were exempted from exercise and socialization during the week of December 14, 1998 due the collection of clinical pathology and ECG parameters on December 14, 1998 and subsequent study termination on December 15 & December 16, 1998.

One male dog on a subchronic toxicity study was exempted, by the Attending Veterinarian, from group exercise and socialization for one week due to left rear limb lameness. This dog was afforded individual exercise periods for 15 minutes to one ½ hour on the regular exercise schedule. This dog was rechecked by the Attending Veterinarian and cleared for group exercise and socialization on December 29, 1999.

On January 3, 1999 the animals (48/28/44) on three studies (2 chronic and 1 subchronic studies) for the same client were exempted from exercise and socialization period due to inclement weather which caused a shortage of personnel to perform these duties. It was opted that due to the personnel shortage it was important to provide the animal care