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ICIA5504

Developmental Study OPPTS 870.3700 (§83-3(b))

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DATA EVALUATION RECORD

STUDY TYPE: Prenatal Rangefinding and Developmental Studies -
Rabbit; OPPTS 870.3700 [§83-3b]

DP BARCODE: D218319
P.C. CODE: 128810

SUBMISSION CODE: S489692
TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): ICIA5504

SYNONYMS: Azoxystrobin

CITATIONS: Moxon, M.E. 1995. ICIA5504: Dose Range Finding Study
in the Rabbit. Zeneca Central Toxicology Laboratory.
Report No. CTL/P/4608 May 26, 1995. MRID 44058702.
Unpublished.

Moxon, M.E. 1995. ICIA5504: Embryotoxicity Study in
the Rabbit. Zeneca Central Toxicology Laboratory.
Report No. CTL/P/4607 July 8, 1995. MRID 44058703.
Unpublished.

Moxon, M.E. 1995. ICIA5504: Second Dose Range
Finding Study in the Rabbit. Zeneca Central
Toxicology Laboratory. Report No. CTL/P/4791 Oct.
26, 1995. MRID 44058705. Unpublished.

Moxon, M.E. 1995. ICIA5504: Second Dose Range
Finding Study in the Pregnant Rabbit. Zeneca Central
Toxicology Laboratory. Report No. CTL/P/4786 Oct.
26, 1995. MRID 44073202. Unpublished.

Moxon, M.E. 1995. Evaluation of the Suitability of
Different Vehicles for Use in Developmental Toxicity
Studies in the Rabbit. Zeneca Central Toxicology
Laboratory. Project ID CTL/M217 Nov. 10, 1995. MRID
44073201. Unpublished.

SPONSOR: Zeneca Inc., Wilmington, DE

EXECUTIVE SUMMARY:

The studies in the rabbit were not necessarily conducted
according to guidelines, but were supporting, fact-finding
studies performed in connection with other guideline
developmental toxicity studies in the rabbit. These data show
that corn oil is not an innocuous vehicle, but can be toxic to

235

rabbit dams at volumes of 2 ml/kg and above, and can enhance the toxicity of ICIA5504 at dose volumes of 2 ml/kg and above. These data support the Submitter's conclusion that the toxicity seen at 50 mg/kg in the 1994 rabbit developmental toxicity study (MRID 43678143) may be due to high volumes of corn oil vehicle (2 ml/kg).

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. SUMMARIES

- A. In a dose range finding study in the rabbit (MRID 44058702) two female New Zealand white rabbits (animals #1 and #2) were dosed by gavage with 200 mg/kg ICIA5504 in corn oil (Kraft Wesson - Y00790/004) at a concentration of 1 ml/kg for eight consecutive days. The dose was then increased to 400 mg/kg/d and administered for eight consecutive days (2 days at 1 ml/kg and 6 days at 2 ml/kg). The dose level was increased again to 800 mg/kg/d (4 mg/kg) and administered for three consecutive days. Two fresh animals (#3 and #4) were then treated with ICIA5504 at 800 mg/kg/d for three consecutive days.

Animals #1 and #2 (200 mg/kg/d) produced few or no feces during the greater part of the study, and both animals were notably thin by day 19. Animals #3 and #4 (800 mg/kg/d) showed severe diarrhea, and on day 3 #4 was cold, subdued and hunched. Animals #1 and #2 showed weight loss (-10% and -5.0%, respectively) after treatment at 200 mg/kg/d, continued weight loss after dosing at 400 mg/kg/d (-1.4% and -5.0%, respectively) and dosing at 800 mg/kg/d (-7.3% and -4%, respectively). Animals #3 and #4 lost weight (-11% and -14%, respectively) after dosing at 800 mg/kg/d. Food consumption showed a transient decrease at 200 mg/kg/d in both animals, a sustained decrease by the 8th day of dosing at 400 mg/kg/d, and animals #1 - #4 stopped eating completely at 800 mg/kg/d.

The author concluded that the highest dose level to be used in an embryotoxicity study should be greater than 400 mg/kg/d and less than 800 mg/kg/d. This study was not designed to establish an NOEL or LOEL.

- B. In an embryotoxicity study in the rabbit (MRID 44058703) ICIA5504 was administered in corn oil (Kraft Wesson - Y00790/004 than Mazola Y00790/002) (3.0 ml/kg) to 10 pregnant New Zealand white rabbits/group at 0, 200, 400 or 600 mg/kg/d during gestation days (gd) 7 - 19.

The study was terminated early, on gd 22 or 23 instead of gd 30, due to high toxicity in all groups, including controls. Weight loss and lack of food consumption were seen in nearly all animals in the treatment groups, and in 50% of controls. Three control animals, eight each in the 200 and 400 mg/kg/d groups and seven in the 600 mg/kg/d group were found dead or killed in moribund condition.

The author observed that these results are uninterpretable in terms of the original design of the study. It was also evident that while a dose-response relationship could not be established, the presence of ICIA5504 did increase the degree of toxicity observed. The author concluded that all dose levels given in this study are above the maximally tolerated dose in the rabbit. **The LOEL is therefore 200 mg/kg/d, and the NOEL has not been established.**

- C. In a dose range finding study in the rabbit (MRID 44058705) two female New Zealand white rabbits (animals #1 and #2) were dosed by gavage with 50 mg/kg ICIA5504 in corn oil (Kraft Wesson - Y00790/004) at a concentration of 1 ml/kg for four consecutive days. The dose was then increased to 100 mg/kg/d and administered for four consecutive days. The dose level was increased again to 400 mg/kg/d and administered for six consecutive days. Another two female rabbits (#3 and #4) were treated with ICIA5504 as just described, except that the vehicle was used at a concentration of 2 ml/kg. Two additional animals (#5 and #6) were treated with ICIA5504 at 600 mg/kg/d in 1 ml/kg or corn oil.

There were no changes in clinical condition, body weight or food consumption observed at any dose level in the animals #1 and #2 which received corn oil at 1 ml/kg. In the next group which received corn oil at 2 ml/kg, animal #3 showed no adverse changes food consumption, but animal #4 showed reduced food consumption (36% less than #3). Body weight gains over the 22-day study period in #3 and #4 were -1.1% and -7.2% respectively, compared with +6.3% and +4.8% in animals #1 and #2. In the third group (600 mg/kg/d), both animals showed transient diarrhea early in the treatment period, along with transient decreased food intake and body weight gain. Over the 15-day study period, body weight gains for #5 and #6 were -9.0% and +0.8%, respectively.

The author concluded that the effects of ICIA5504 were enhanced by the use of 2 ml/kg corn oil compared with 1 ml/kg, and that the highest dose to be recommended in 1

ml/kg corn oil is greater than 400 mg/kg/d and less than 600 mg/kg/d. **This study was not designed to establish a NOEL or LOEL.**

- D. In a dose range finding study in the pregnant rabbit (MRID 44073202) ICIA5504 was administered to groups of New Zealand white pregnant rabbits (8/group) at 0, 100, 250 or 500 mg/kg/d in 1 ml/kg corn oil (Kraft Wesson - Y00790/004) on gd 8 - 20. Secondly, additional groups were dosed as just described, except that the 2 ml/kg corn oil was used, and 500 mg/kg/d was not administered. Thirdly, another group of rabbits was sham-dosed. All rabbits were killed on gd 30 and their uteri examined for live fetuses and intra-uterine deaths. The fetuses were weighed and examined for external abnormalities.

The sham-dosed animals showed no adverse effects on food consumption, body weight gain or clinical signs. At 100 mg/kg/d there was no significant differences in toxicity in either group. At 250 and 500 mg/kg/d the 1 ml/kg corn oil group exhibited the established profile of toxicity, decreased body weight gain and decreased food consumption, that was seen in the studies described earlier. The effects increased with dose, but were tolerated by the animals with full recovery during the post-dosing period. However, at 250 mg/kg/d the 2 ml/kg corn oil group caused severe effects on food consumption and body weight gain, such that the animals were all killed for humane reasons prior to the end of the study. No adverse effects were observed on the number, growth or survival of the concepti in any group.

The author concluded that corn oil as a vehicle at 2 ml/kg elicits maternal toxicity in the rabbit and so enhances the effects of ICIA5504, and that 500 mg/kg/d should be the highest dose level used with 1 ml/kg corn oil vehicle in a rabbit developmental toxicity study. **This study was not designed to determine a LOEL and NOEL.**

- E. In a suitability study (MRID 44073201) an evaluation was made of different vehicles for use in developmental toxicity studies in the rabbit. Groups of 10 pregnant New Zealand white rabbits were dosed with 2 ml/kg or 5 ml/kg (3 or 4 for some vehicles due to excessive toxicity) of 0.5% hydroxypropylmethylcellulose in 0.1% w/v Tween 80 [0.5% HPMC], polyethylene glycol 300 [PEG 300], polyethylene glycol 400 [PEG 400], 0.5 w/v gum xanthan in 0.1% Tween 80 [0.5% Xanthan] and corn oil. The dosing period was gd 8 - 20. On gd 30 animals were killed and their uteri examined for live fetuses and intra-uterine

deaths. The fetuses were weighed, examined for external and visceral abnormalities, sexed, eviscerated and stained for skeletal examination.

Administration of 0.5% HPMC or 0.5% Xanthan at 2 or 5 ml/kg had no significant effect on dams. Administration of PEG 300, PEG 400 or corn oil at dose volumes greater than 2 ml/kg were not tolerated by the rabbits, and the scheduled number of daily doses could not be given. At 2 ml/kg these three vehicles caused diarrhea, decreased body weight gain and decreased food consumption, and decreased survival. Effects on the fetuses were not thoroughly investigated or reported.

The author concluded that PEG 300, PEG 400 and corn oil are toxic to the pregnant rabbit at dose volumes of 2 ml/kg or more, and that 0.5% HPMC and 0.5% Xanthan are candidate vehicles at 2 ml/kg since they had no adverse effects on the dams.