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March 15, 1999

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Attention: TSCA Section 8(e) Coordinator
Office of Environmental Protection Agency
401 M Street SW
Washington, DC 20460

Company Sanitized

Subject: TSCA Section 8(e) Submission
CASRN Confidential []
Carboxylic acid ester []

Dear Sir or Madam:

The following report is herewith submitted pursuant to TSCA Section 8(e) compliance requirements:

[]: Reproductive Toxicology Studies
Study No. []
Preliminary Study of Effects on Reproductive Performance in CD Rats by Dietary Administration – Draft Provisional Interim Study Report – dated 24 February 1999, 5 March 1999 and 9 March 99
[]

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We wish to maintain the identity of our company, the chemical identity, the trade name of the product tested, the study number, the identity of the testing laboratory and the identity of the submitter as Confidential Business Information. Therefore, we have provided both a Confidential Version and Public Version of this submission. **Confidential Business Information is enclosed in brackets [] or circled and is usually in bold print.**

We have unaudited draft provisional interim study reports of a preliminary (dose-range finding) reproductive performance toxicity study in the CD rat by dietary administration on our product []. This product (test substance) is a [] carboxylic acid ester [].

The unaudited results contained in these draft provisional interim study reports may meet the criteria in EPA's TSCA Section 8(e) Reporting Guide (June 1991). Because we wish to be conservative in our approach to this regulation, we are submitting this interim information as reportable under TSCA Section 8(e).

The objective of this study was to assess the influence of continuous dietary administration of the test substance [] on the reproductive performance of CD rats (CrI:(IGS)CD®BR) in order to establish suitable dosages for a two-generation reproductive

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performance study to be conducted according to test guidelines OPPTS 870.3800 (1998) and OECD 416 (Draft of September 1998).

A synopsis of the study to date is given on Attachment 1.

Given that:

1. This is an ongoing dose range-finding study.

It is important when evaluating the significance of findings in a preliminary study of reproductive performance to remember that the principal aim of the study is to establish suitable dosages for further investigation of reproductive toxicity. This study is not designed to provide sufficient detailed information to allow a full and comprehensive assessment and evaluation of reproductive performance or reproductive toxicity. Assessments made too definitely at this stage may be misleading.

2. This is an unaudited draft provisional interim study report – not an audited and peer reviewed final report.

The study is ongoing and the data collected to this point in time has not been fully analyzed. In addition, the study has not been taken to its planned conclusion when the selected F₁ animals are 6 weeks of age or reach sexual maturity. Microscopic examination of selected tissues is also not yet completed. This additional data may have some bearing on the interpretation of the data that has been analyzed to date.

3. The observations can be described and possibly explained as follows:

- a) A clear sex difference in paternal response to treatment was established.

Eleven treated females receiving 25000, 15000 or 2500 ppm were killed for reasons of animal welfare compared with no males. In addition some females exhibited signs of what appeared to be agonal convulsive-like behavior, no such behavior was observed in the males of the group.

This sex difference may reflect a treatment-related exacerbation of sensitivity of the females during periods of severe physiological stress associated with parturition, or the demands of supporting offspring during lactation.

- b) Mortality of the dams, litters and post-natal pups was significantly in excess of controls.

The maximum tolerated dose (MTD) for this type of study was clearly exceeded; the usual regulatory limit dose is 10000ppm. There were zero mortalities in non-pregnant female CD rats exposed to the substance via the diet at similar dose levels for 13 weeks ([]). Significant changes in clinical signs, mortality and other measured parameters did not appear until very late gestation / very early lactation. Again, it is likely that the increased mortality is a treatment-related exacerbation of sensitivity of the females during periods of severe physiological stress associated with parturition, or the demands of supporting offspring during lactation. The increased post-natal pup mortality is likely an extension of the excess MTD maternal stress and is Supported by the low mean bodyweight of the pups that survive to weaning and selection.

- c) The episodes of irregular muscular contraction (convulsive-like behavior) in certain 25000 ppm dose group dams is again indicative of severe toxicity to the dams. This

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ATTACHMENT 1

Carboxylic acid ester []: Reproductive Toxicology Studies
Preliminary Study of Effects on Reproductive Performance in CD Rats by Dietary Administration
– Draft Provisional Interim Study Reports – dated 24 February, 5 March and 9 March 1999
[] Study No. []

Study Synopsis and Adverse Findings

Species : Rat (Charles River CD – CrI: (IGS)CD®BR)
Number of Animals : 10 per group (1 control + 4 treated groups)
Age of Animals : 9-10 weeks old at start of treatment
Route : Dietary, constant concentration (ppm)
Dosages : 0 (control), 2500, 7500, 15000 and 25000 ppm
Treatment : Continuous - 15 days prior to pairing through mating, gestation, lactation and weaning till 6 weeks of age and/or sexual mature.
Study Status : Selected F1 animals continuing treatment until 6 weeks of age or sexual maturity.
Period Reports Cover : 15 days prior to pairing until necropsy of F₀ animals and unselected F₁ animals at Day 28 of lactation.

Findings

F₀ Males Possible adverse effects of treatment on:

Bodyweight gain in all treatment groups - Bodyweight gain was significantly below the control, but there was no clear concentration relationship.

F₀ Females Adverse effect of treatment on:

Clinical signs and mortality at 25000, 15000 and 2500 ppm - Serious clinical signs, severe debilitation including agonal irregular muscular contractions (convulsion-like) behavior in the 25000 ppm group resulted in 4 humane kills. Clinical signs and severe debilitation also resulted in 1 humane kill in the 15000 ppm group. In addition, 6 animals (2 each at 25000, 15000 and 2500 ppm) were humanely killed after their litters were found not cared for or dead.

The high mortality rate at 25000 ppm obviously grossly exceeded the Maximum Tolerated Dose for females during parturition and lactation. We therefore decided to humanely sacrifice all remaining animals and offspring in the 25000 ppm group on Day 21 of lactation and not to use this dose level of this substance in any single or multi-generation reproductive performance study.

Offspring (F₁) Adverse effects of treatment on:

Litter mortality at 25000, 15000 and 2500 ppm – total litter deaths in these dose groups was significantly higher than the control with 6, 3 and 2 litters respectively found dead or humanely killed. There were no total litter losses in the 7500 ppm dose group. This specific strain of rat has a history of post gestation death (random total litter loss) during lactation (see attached [] - [] Position Statement). There are indications that two of the litter mortalities at 25000 ppm and the two litter mortalities at 2500 ppm are due to this post gestation death syndrome in this rat strain. These indications are no maternal spleen/kidney problems, but mammary tissue pale and inactive at necropsy, pups normal, but not cared for during one or more days during the first three days post-partum, no milk in stomach of pups at necropsy and total litter loss in first 3 days of lactation. Therefore it is considered that 4 litter losses at 25000 ppm and 3 litter losses at 15000 ppm are likely to be treatment related.

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Post natal pup mortality elevated at 25000 and 15000 ppm – pup mortality in these dose groups was significantly higher than the controls.

Low mean bodyweights – Male and female offspring bodyweights remained lower than controls to Day 28 of lactation for the 15000 and 7500 ppm dose groups, approximately 10% and 7% respectively. While for the 25000 ppm dose group, mean bodyweights to Day 21 of lactation were approximately 50% lower than the controls.

Conclusions

: The 25000 ppm dose and 15000 ppm dose are unsuitable for a single or multi-generation reproductive performance study due to high mortality of female parents as well as male and female offspring. A decision on the suitability of the 7500 ppm dose is dependent upon the findings of work that has not yet been completed.

The results to date are not totally unexpected, given that the normal regulatory limit dose for reproductive performance studies is usually 10000 ppm. While almost all previous studies with this strain of rat at this laboratory indicated that a dietary dose of up to 25000 ppm would not result in significant mortalities in nonpregnant rats, there was no information on the effect of these doses through late gestation, parturition and lactation thru weaning. In addition it was known that at doses up to 10000 ppm, no biologically significant effects would be seen in non-pregnant rats of this strain. Work thus far may indicate that with doses of the test substance above approximately 10000 ppm, the significant added physiological stresses of parturition and lactation are more than the already physiologically stressed system of the female rat can take.