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April 13, 2000

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RE: Final Report 418-008 - Combined Oral (Gavage) Fertility, Developmental and Perinatal/Postnatal Reproduction Toxicity of PFOS in Rats
Sponsor's Study Number: 6295.9

Dear Dr. Case:

Enclosed is one copy of the final report Amendment 1 to the above-referenced report.

If you have any questions, please do not hesitate to contact me.

Sincerely,

Raymond C. York, Ph.D, DABT
Associated Director of Research
and Study Director

RGY:kgp
Attach.

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REPORT AMENDMENT 1
13 APRIL 2000

PROTOCOL 418-008
SPONSOR'S STUDY NUMBER: 6295.9

COMBINED ORAL (GAVAGE) FERTILITY, DEVELOPMENTAL AND PERINATAL/POSTNATAL REPRODUCTION TOXICITY STUDY OF PFOS IN RATS

FINAL REPORT

1. Page I-9, paragraph 4 has been revised to:

   Pregnancy occurred in 22 (95.6%), 21 (84.0%) and 24 (96.0) of the 23, 25 and 25 female rats assigned to cohabitation in the 0 (Vehicle), 0.1 and 0.4 mg/kg/day dosage groups, respectively. All pregnant dams delivered litters. The gestation index was comparable across the three dosage groups. ***Viability and growth of the second generation offspring (F2 pups) to weaning were also unaffected by the highest dosage tested, 0.4 mg/kg/day. There were no toxicologically important differences from the control group values.*** No clinical or necropsy observations in the F2 generation pups were attributable to dosages of the test article as high as 0.4 mg/kg/day.

2. Page I-10, paragraph 4 has been revised to:

   The F1 generation reproductive NOEL is greater than a dosage of 0.4 mg/kg/day; no effects on mating or fertility occurred. The NOEL for viability and growth in the F2 generation offspring is ***also 0.4*** mg/kg/day. ***There were no toxicologically important effects on pup survival or growth at the highest dosage tested, 0.4 mg/kg/day.***

3. Page V-8, paragraph 3 has been revised to:

   The viability of the second generation offspring (F2 pups) was unaffected at the highest dosage tested, 0.4 mg/kg/day. Small increases in the number of dams with stillborn pups and in the number of pup deaths after DL 2 in the 0.4 mg/kg/day dosage group were not toxicologically important because: 1) the values were not significantly different from the control group values; 2) the average for live litter sizes delivered and surviving to DL 21 were greater than or comparable to the control group values; and 3) neither the viability or lactation indices for the 0.4 mg/kg/day dosage group remarkably differed from the control group values.

4. V-8, paragraph 4 has been revised to:

Pup body weights of the second generation offspring (F2 pups) were unaffected at the highest dosage tested, 0.4 mg/kg/day. Small reductions in pup body weights in the 0.1 and 0.4 mg/kg/day dosage groups were not toxicologically important because: 1) the small differences between the pup body weights for the control and 0.1 mg/kg/day dosage groups were not statistically significant and were associated with the larger live litter sizes of the 0.1 mg/kg/day dosage group on DLs 1 through 4, as compared with the control group values, and the random selection of pups for continued observations on DL 4; 2) the small reductions in pup body weights in the 0.4 mg/kg/day dosage group were associated with a minimally larger live litter size at birth (DL 1) and on DL 4 preculling, as compared with the control group values, and the random selection of pups for continued observation on DL 4; the statistically significant reductions ($p \leq 0.05$ and $p \leq 0.01$, respectively) present on DLs 7 and 14, as compared to the control group values, were transient and disappeared by DL 21.

5. Page V-9: Revisions to paragraph 4 on page V-8 caused it to extend onto page V-9.

These revisions were made to clarify the interpretation of the observations reported and the NOEL for the second generation offspring (F2 generation).

13-APR-00

Raymond G. York, Ph.D., DABT Date
Associate Director of Research
and Study Director

13 Apr 00

Nancy J. Gongliewski Date
Quality Assurance Manager

feed consumption values were reduced during lactation in the 0.4 mg/kg/day dosage group.

Dosages of the test article as high as 0.4 mg/kg/day did not affect the average day of vaginal patency in the F1 generation female rats. There were no biologically important differences in the values for learning, short-term retention, long-term retention or response inhibition in the F1 generation female rats, as evaluated by performance in a passive avoidance or watermaze performance paradigm.

Dosages of the test article as high as 0.4 mg/kg/day did not affect any mating and fertility parameters evaluated in the F1 generation female rats.

All necropsy observations in the F1 generation female rats were considered unrelated to the test article.

Pregnancy occurred in 22 (95.6%), 21 (84.0%) and 24 (96.0) of the 23, 25 and 25 female rats assigned to cohabitation in the 0 (Vehicle), 0.1 and 0.4 mg/kg/day dosage groups, respectively. All pregnant dams delivered litters. The gestation index was comparable across the three dosage groups. Viability and growth of the second generation offspring (F2 pups) to weaning were also unaffected by the highest dosage tested, 0.4 mg/kg/day. There were no toxicologically important differences from the control group values. No clinical or necropsy observations in the F2 generation pups were attributable to dosages of the test article as high as 0.4 mg/kg/day

C. Conclusions

On the basis of these data, the Fo generation maternal and paternal no-observable-effect-level (NOEL) of PFOS is 0.1 mg/kg/day (0.4 mg/kg/day and higher dosages caused reductions in body weight gain and reduced feed consumption values).

The Fo generation reproductive NOEL is greater than 3.2 mg/kg/day; no effects on mating, fertility or estrous cycling occurred. The NOEL for viability and growth in the F1 generation offspring is 0.4 mg/kg/day (1.6 mg/kg/day and higher dosages caused preimplantation loss and reductions in litter size, pup viability, growth and survival).

The F1 generation maternal and paternal NOEL of PFOS is 0.1 mg/kg/day (0.4 mg/kg/day dosage caused reductions in body weight gain and reduced feed consumption values).

The F1 generation reproductive NOEL is greater than a dosage of 0.4 mg/kg/day; no effects on mating or fertility occurred. The NOEL for viability and growth in the F2 generation offspring is also 0.4 mg/kg/day. There were no toxicologically important effects on pup survival or growth at the highest dosage tested, 0.4 mg/kg/day.

13 Apr 00

Mildred S. Christian, Ph.D., Fellow, ATS Date
Executive Director of Research

for

Alan M. Hoberman, Ph.D., DABT Date
Director of Research

13-APR-00

Raymond G. York, P.D., DABT Date
Associate Director of Research and Study Director

B.8. Necropsy Observations (Summary - Table E18; Individual Data - Table E34)

All necropsy observations in the F1 generation female rats were considered unrelated to the test article because: 1) the observations occurred in rats in the control group; and 2) the observation commonly occurs in this strain of rat. These observations included rough and/or pitted cortex of the kidneys with calculi in the kidney and/or urinary bladder of two control group rats. One of these rats also had a tan granular material in the renal cortex and thickened walls of the urinary bladder. Necropsy observations for the 0.4 mg/kg/day dosage group dam that died as the result of an intubation error were described previously.

B.9. Natural Delivery and Litter Observations (Summaries - Tables E19 and E20; Individual Data - Tables E35 through E38)

Pregnancy occurred in 22 (95.6%), 21 (84.0%) and 24 (96.0%) of the 23, 25 and 25 female rats assigned to cohabitation in the 0 (Vehicle), 0.1 and 0.4 mg/kg/day dosage groups, respectively. All pregnant dams delivered litters. The gestation index (the percentage of pregnant rats with live offspring) was comparable across the three dosage groups.

The viability of the second generation offspring (F2 pups) was unaffected at the highest dosage tested, 0.4 mg/kg/day. Small increases in the number of dams with stillborn pups and in the number of pup deaths after DL 2 in the 0.4 mg/kg/day dosage group were not toxicologically important because: 1) the values were not significantly different from the control group values; 2) the average for live litter sizes delivered and surviving to DL 21 were greater than or comparable to the control group values; and 3) neither the viability or lactation indices for the 0.4 mg/kg/day dosage group remarkably differed from the control group values.

Pup body weights of the second generation offspring (F2 pups) were unaffected at the highest dosage tested, 0.4 mg/kg/day. Small reductions in pup body weights in the 0.1 and 0.4 mg/kg/day dosage groups were not toxicologically important because: 1) the small differences between the pup body weights for the control and 0.1 mg/kg/day dosage groups were not statistically significant and were associated with the larger live litter sizes of the 0.1 mg/kg/day dosage group on DLs1 through 4, as compared with the control group values, and the random selection of pups for continued observations on DL 4; 2) the small reductions in pup body weights in the 0.4 mg/kg/day dosage group were associated with a minimally larger live litter size at birth (DL 1) and on DL 4 preculling, as compared with the control group values, and the random selection of pups for continued observation on DL 4; the statistically significant reductions

($p \leq 0.05$ and $p \leq 0.01$, respectively) present on DLs 7 and 14, as compared to the control group values, were transient and disappeared by DL 21.

Administration of the test article at dosages as high as 0.4 mg/kg/day did not adversely affect any other parameter evaluated at natural delivery or during the 21-day lactation period (duration of gestation, averages for implantations and live litter sizes, numbers of dams with all pups dying during lactation, viability and lactation indices, surviving pups per litter and pup sex ratios).

B.10. Clinical Observations from Birth to Day 21 Postpartum and Necropsy Observations (Summaries - Tables E21 and E22; Individual Data - Tables E39 and E40)

No clinical or necropsy observations were attributable to dosages of the test article as high as 0.4 mg/kg/day because: 1) the incidences were not dosage-dependent; and/or 2) the observation occurred in only one or two pups. These clinical observations included one control group pup that was not nesting or nursing, had decreased motor activity and was cold to the touch, one pup in each of the control and 0.4 mg/kg/day dosage groups that had a missing tip of tail and one 0.4 mg/kg/day dosage group pup that had an umbilical hernia.

No milk in stomach occurred in 2, 4 and 4 pups that were found dead in the three respective dosage groups. One control group pup had hydrocephaly and one 0.1 mg/kg/day dosage group pup had a raised tan area on the median and left lateral lobes of the liver at necropsy on DL 21.