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OFFICE OF
 PREVENTION, PESTICIDES AND
 TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Phorate (PC Code: 057201) FQPA uncertainty factor;
 Preliminary assessment of additional data submission
 DP Barcode: D240930

FROM: Susan Makris
 Toxicology Branch 1, HED (7509C)

Susan Makris 12/4/97

THROUGH: Y. Mike Ioannou
 Toxicology Branch 1, HED (7509C);

Y. Mike Ioannou 12/5/97

TO: Mike Metzger
 Reregistration Branch 2, HED (7509C)

cc: Chris Olinger (7509C)
 Jess Rowland (7509C)

INTRODUCTION

A prenatal toxicity study in rats (MRID 44422301) and a two-generation reproduction study in rats (MRID 44422302) were submitted by the Registrant for review in support of the reregistration of phorate. At the request of Reregistration Branch 1, the study reports were reviewed in an expeditious but cursory manner in order to assess the issue of whether or not the data might affect recent peer review decisions made at the Hazard ID SARC meeting of September 25, 1997.

EXECUTIVE SUMMARIES

The following preliminary Executive Summaries describe the study methodologies and findings.

Prenatal developmental toxicity study in rats (§83-3):

Citation: Lochry, E.A. (1990) An oral developmental toxicity (embryo-fetal toxicity/teratogenicity) definitive study with AC 35024 in rats. Argus Research Laboratories, Inc., Horsham, PA. Study No. 101-112, October 23, 1990. MRID No. 44422301. Unpublished.



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Preliminary Executive Summary:

In a prenatal developmental toxicity study, AC 35024 (92.1% phorate) was administered by gavage to pregnant female Crl:CD®BR (Sprague-Dawley) rats (24-25/group) on days 6-15 of gestation at dose levels of 0, 0.1, 0.2, 0.3, and 0.4 mg/kg/day. Corn oil was used as the vehicle, and the dosing volume was 5 ml/kg. The rats were observed for signs of toxicity; body weight and food consumption values were recorded. On day 20 of gestation, the rats were killed and necropsied; gravid uterine weights were recorded. The uteri were examined, implantation sites were counted and characterized, and the numbers of corpora lutea were determined. The fetuses were counted, removed, weighed, sexed, and examined for external anomalies. They were then processed for visceral and skeletal evaluation. Cholinesterase activity was not measured for either dams or fetuses.

At the 0.4 mg/kg/day dose level, six females died after five to ten doses of test substance; these deaths were preceded by observations associated with test substance administration, including clinical observations, decreased body weight gains and/or body weight loss, decreased food consumption, and necropsy lesions. Treatment-related clinical observations at this dose level included tremors, excess salivation, decreased motor activity, impaired righting reflex, hunched posture, labored breathing, chromodacryorrhea, chromorhinorrhea, red substance around the nose, red or tan oral discharge, urine-stained abdominal fur, and red vaginal discharge. At necropsy, enlarged adrenal glands were observed. Significant maternal body weight loss, decreases in mean body weight gain for the period of treatment, reductions in mean body weight on days 12-20 of gestation, and decreases in feed consumption for the entire dosing period were noted.

Maternal NOEL = 0.3 mg/kg/day

Maternal LOEL = 0.4 mg/kg/day, based upon increased incidences of treatment-related clinical observations, including signs of cholinergic toxicity; increased incidence of mortality; decreased body weight, body weight gain, and food consumption; and enlarged adrenal glands.

At the 0.4 mg/kg/day dose level, fetal body weights were significantly decreased and there were significant increases in the fetal and/or litter incidences of variations in skeletal ossification (generally delays in ossification of the sternum and pelvis).

Developmental NOEL = 0.3 mg/kg/day

Developmental LOEL = 0.4 mg/kg/day, based upon decreased fetal body weights and increased incidences of skeletal variations (delayed ossification of the sternum and pelvis)

Two-generation reproduction study in rats (§83-4):

Citation: Schroeder, R.E. (1991) A two-generation (two litters) reproduction study with AC 35024 to rats. Bio/dynamics, Inc., East Millstone, NJ. Study No. 88-33540,

September 23, 1991. MRID No. 44422302. Unpublished.

Preliminary Executive Summary:

In a two-generation reproduction study in Sprague-Dawley derived rats (at least 25/sex/group), 92.1% phorate (AC 35024) was administered at dietary levels of 0, 1, 2, 4, or 6 ppm (corrected for purity; equivalent to 0.086, 0.171, 0.347, or 0.523 mg/kg/day for males and 0.101, 0.197, 0.401, or 0.622 mg/kg/day for females) over two consecutive generations of two litters each. After a pre-mating treatment interval (at least 60-days for the P generation animals and 10 days for the F1 generation animals), during which clinical observation, body weight, and food consumption data were collected, the rats were mated 1:1. A second mating in each generation was conducted after the weaning of the first litters. The dams were monitored throughout the gestation and lactation periods. Offspring from the resulting litters were examined; pups were weighed, and survival was monitored until weaning and sacrifice. Ophthalmoscopic examination were conducted for P females and F1 animals prior to sacrifice. Plasma, erythrocyte, and brain cholinesterase activity was measured in 10 F1 rats/sex/dose at necropsy. Gross and histopathological evaluations were performed on all adults, with particular emphasis on the reproductive organs, the pituitary gland, and the eyes; F2b offspring (1/sex/litter) were necropsied at weaning.

At the 4 ppm (0.347/0.401 mg/kg/day for M/F) dietary treatment level, tremors were observed in several parental females from each generation, weight loss was observed in both litters of both generations on lactation days 0-21, and plasma and brain cholinesterase levels were reduced for F1 females. (Slight reductions in female plasma and brain cholinesterase levels at 2 ppm were not statistically significant, not observed in males, and not considered to be biologically significant.)

At 6 ppm (0.523/0.622 mg/kg/day for M/F), increased F1 mortality, tremors in P females and F1 animals, reduced pre-mating body weight for P females and F1 animals, reduced pre-mating weight gain for P females, reduced gestation and lactation weights for both P and F1 litters, decreased plasma, erythrocyte, and brain cholinesterase activity were observed. Ocular disease was noted in the F1 animals at this treatment level; however, these lesions were attributed to ocular infections that occurred at an early age and were not judged to be related to treatment.

Parental systemic NOEL = 2 ppm (0.171 mg/kg/day for males, 0.101 mg/kg/day for females)

Parental systemic LOEL = 4 ppm (0.347 mg/kg/day for males, 0.401 mg/kg/day for females), based upon

At 4 ppm (0.347/0.401 mg/kg/day for M/F), pup weights (F1a, F1b, and F2a) were reduced on postnatal days 14 and 21 of lactation and F2a pup survival indices were decreased for postnatal days 0-4 and 4-21.

At 6 ppm (0.523/0.622 mg/kg/day for M/F), reduced litter size at birth was observed in the F2a and F2b litters, and there were reduced pup and litter survival indices and reduced pup weights in all litters of both generations.

Offspring NOEL = 2 ppm (0.171 mg/kg/day for males, 0.101 mg/kg/day for females)

Offspring LOEL = 4 ppm (0.347 mg/kg/day for males, 0.401 mg/kg/day for females), based upon reduced day 14 and 21 pup weights (F1a, F1b, and F2a) and decreased F2a pup survival indices (days 0-4 and 4-21).

DISCUSSION/CONCLUSIONS:

Adequacy of studies: Following a preliminary review, both submitted studies appeared to be adequate for the evaluation of the endpoints measured, in accordance with standard guideline protocols (§83-3 and §83-4).

Indications of susceptibility to infants and children: The data from the recently-submitted studies do not provide any evidence of additional susceptibility to the offspring of rats when treated pre- and/or postnatally with phorate. Toxicity to the offspring occurred only in the presence of maternal/parental toxicity. In the prenatal developmental study in rats, the developmental NOEL was equivalent to the maternal NOEL, and in the two-generation reproduction study, the NOEL for effects on the offspring was equivalent to the parental systemic NOEL.

Previous recommendations of the HazardID SARC: On September 25, 1997, following a review of the available data base, a 10-fold uncertainty factor for FQPA considerations was retained for phorate, upon the recommendations of the HazardID SARC. This was based upon identified data gaps, but was not based upon any demonstrated increase in susceptibility to the offspring following pre- and/or postnatal exposure to phorate. The following data gaps were cited:

1. The data package contained no acute or subchronic neurotoxicity studies in rats, including data on cholinesterase inhibition, functional observation battery results, and histopathology of perfused tissues of the central and peripheral nervous system following single or repeated doses of phorate.
2. The multigeneration reproduction study in rats contained in the data package was not deemed adequate to support reregistration of phorate; this did not allow an adequate assessment of the potential for sensitivity to infants and children.
3. Since phorate is considered to be a potent cholinesterase inhibitor, the Committee recommended that a developmental neurotoxicity study be conducted as confirmatory data; it was suggested that this study could be combined with a multigeneration reproduction study.

Possible effects on the conclusions of the HazardID SARC (9/25/97):

Data gaps:

Since an adequate and acceptable prenatal developmental toxicity study in rats was previously received by the Agency and reviewed by HED staff, the study recently submitted by the Registrant (MRID 44332201), which was conducted at similar but slightly high dose levels than the previous study, is confirmatory in nature.

The two-generation reproduction study (MRID 4433202) appears as if it will satisfy the requirement for a multigeneration reproduction study in rats in support of the reregistration of phorate. If this study is determined to be Acceptable, following full HED review, it will fulfill the data gap for a two-generation reproduction study in rats.

However, a developmental neurotoxicity study remains outstanding, and the effect of phorate on functional development following pre- and/or postnatal exposure to phorate is unknown.

Endpoints for risk assessment:

The acute and chronic risk assessment endpoints for phorate were based on plasma cholinesterase inhibition in dogs, with a NOEL of 0.05 mg/kg/day and a LOEL of 0.25 mg/kg/day. Neither of the two submitted studies provide a lower NOEL for appropriate acute or chronic endpoints. (Cholinesterase inhibition, the most sensitive endpoint of toxicity for this chemical was not measured in either study.)

FQPA uncertainty factor for infants and children:

The profile of phorate now consists of the following considerations: 1) there is no demonstrated susceptibility to offspring following pre- and/or postnatal exposure to phorate, 2) a complete database exists for the standard assessment of developmental and reproductive toxicity (i.e., prenatal developmental toxicity studies in rodent and nonrodent species and a two-generation reproduction study in rats), 3) an acute delayed neurotoxicity study in hens was found to be negative for organophosphate-induced delayed neurotoxicity (OPIDN), and 4) data gaps consist of the acute and subchronic neurotoxicity studies and the developmental neurotoxicity study in rats.

In assessing the history of recent FQPA decisions on organophosphorus chemicals, it was noted that for several OP chemicals with similar profiles, 10-fold uncertainty factor had been reduced to 3-fold. These include coumaphos, terbuphos, and phostebupirim, for which no sensitivity to offspring was noted, no evidence of OPIDN was demonstrated, and neither the acute nor subchronic neurotoxicity studies in rats were available so the need for a developmental neurotoxicity study could not be fully assessed.

RECOMMENDATIONS: It is recommended that the two-generation reproduction study be evaluated immediately, with subsequent resubmission to the HazardID SARC for reconsideration of the FQPA uncertainty factor for phorate.