UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

TXR NO. 0052140

DATE: **October 6, 2003**

This report contains HIARC conclusions on the reevaluation of the dermal absorption value to be used in risk assessment considering new data and supercedes the previous report, TXR No. 0051596.

MEMORANDUM

SUBJECT: **THIACLOPRID - 2nd Report** of the Hazard Identification Assessment Review Committee.

FROM: Cathy Eiden
Acting Branch Chief
Reregistration Branch III
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: David Soderberg, Risk Assessor
Reregistration Branch III
Health Effects Division (7509C)

PC Code: 014019

On June 19, 2003, HED's Hazard Assessment Review Committee (HIARC) evaluated a new dermal penetration study (MRID Nos.: 45846701 and 45846702) in monkeys to determine the dermal absorption factor for risk assessments. The HIARC determined a dermal absorption value of 5% is considered appropriate for use in dermal exposure risk assessments for thiacloprid formulated as YRC SC-480 (as opposed to the 30% value previously selected from comparison of LOAELs in oral and dermal studies in rats).

Committee Members Concurring

HIARC members were asked via E-mail to comment/concur with a proposal submitted by Donna Davis to reevaluate the dermal absorption value. The consensus of the committee was to adopt the proposed change, which is presented in Section II.5 (Dermal Absorption) of this report.

Members concurring with the proposed changes were: Jess Rowland, William Dykstra, William Burnam, PV Shah, Elizabeth Mendez, Jonathan Chen, Pamela Hurley, and Ayaad Assaad

Members not commenting were: John Liccione and Susan Makris.

Data evaluation prepared by: Donna Davis, RRB3

INTRODUCTION

On December 19, 2002, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for thiacloprid with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to thiacloprid was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996 according to the 2002 OPP 10X Guidance Document.

ELECTRONIC CONCURRENCE -Bren

I. FQPA HAZARD CONSIDERATIONS

1. Adequacy of the Toxicity Data Base

The HIARC concluded that the toxicology database for thiacloprid is complete.

There are acceptable acute and subchronic neurotoxicity studies..

A developmental neurotoxicity study is available and is currently classified as Unacceptable/Guideline pending receipt and review of additional analysis of the low and mid dose groups for certain morphological parameters.

2. Evidence of Neurotoxicity

The HIARC concluded that there is a concern for neurotoxicity resulting from exposure to thiacloprid based mainly on the fact that thiacloprid is a chemical that is known to affect nicotinyl cholinergic receptors.

Acute Neurotoxicity

EXECUTIVE SUMMARY: In an acute neurotoxicity study (1997, MRID 44927703), groups of fasted, nine-week-old Fischer 344 rats (12/sex) were given a single oral dose of technical YRC 2894 (approximately 97% a.i., batch # 290894) in 0.5% methyl cellulose-0.4% Tween 80 in deionized water at doses of 20, 50, or 100 mg/kg bw and observed for 14 days. Functional observational battery [FOB] and motor activity testing was performed in 12 animals/sex/group pretreatment, at 4 hours post-dosing (the time of peak effect), and at days 7 and 14 post-treatment. Because a NOAEL for decreases in motor activity was not attained in female rats in this study, a second (supplemental) neurotoxicity study (1998, MRID 44927704) was performed. Doses in the supplemental study were 0, 2.5, or 10 mg/kg bw. Actual doses based on analytical results in the two studies were 0, 3.1, 11, 22, 53, and 109 mg/kg. Abbreviated FOB and motor activity tests were conducted in the supplemental study (Day 0, females only). At study termination, six animals/sex/group from the main study were euthanized and perfused *in situ* for neuropathological examination. Only the control and high-dose groups were subjected to histopathological evaluation of brain and peripheral nervous system.

There were no mortalities. A transient decrease in body weight was observed in males in the 100 mg/kg dose group. There was no affect of treatment on gross pathology, brain weights, or incidences of microscopic lesions of the brain, spinal cord, or peripheral nervous system.

The only clinical sign considered treatment-related in the lower dose groups occurred in the 50 mg/kg group and involved dilated pupils in 1 of 12 female rats. Clinical signs consisting of tremors, decreased activity, ataxia, dilated pupils, cool-to-touch body, urine stained fur, and partially closed eyelids were observed in the majority of male and female rats that received 100 mg/kg. Most of the above signs were observed only on the day of treatment, and all signs had resolved by day 5.

During the FOB, in addition to the clinical signs at higher doses, treatment-related signs of slight tremors and ptosis in males in the 20 mg/kg dose group (3/12 and 1/12, respectively) and slight incoordination of the righting reflex in 1 of 12 females in the 20 mg/kg dose group were observed on the day of treatment.

There was no effect of treatment on total motor or locomotor activity of male rats in the main study. However, subsession data indicated significantly reduced activity for early subsessions in the 100 mg/kg group. For females in the main study, total motor activity was significantly reduced at doses of 50 and 100 mg/kg ($p<0.05$) and total locomotor activity was significantly reduced at doses of 20, 50, and 100 mg/kg ($p<0.05$). Locomotor subsession data for males and females in the 100 mg/kg group indicated that rats did not move from where they were placed in the maze. In the supplemental study, non-significant reductions in total motor and total locomotor activity of 21 and 27%, respectively, in the 10 mg/kg group (females only) were considered treatment related and biologically significant. There were no effects of treatment in any dose group at the 7- and 14-day observation times. **The LOAEL in females was 11 mg/kg bw (based on reductions in motor and locomotor activity), with a NOAEL of 3.1 mg/kg bw. The LOAEL in males was 22 mg/kg bw (based on FOB observations of slight tremors and ptosis of the eyelids on the day of treatment), with a NOAEL of 11 mg/kg bw.**

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for an acute neurotoxicity study in rats (870.6200a; OECD 424).

Subchronic Neurotoxicity

EXECUTIVE SUMMARY: In a subchronic neurotoxicity study (1997, MRID 44927645) YRC 2894 Technical (Thiacloprid; 96.6-97.5% a.i., batch #290894) was administered to 12 Fischer 344 CDF(F-344)/BR rats/sex/dose at dietary concentrations of 0, 50, 400, or 1600 ppm (equivalent to 0, 2.94, 24.2, or 101 mg/kg bw/day for males and 0, 3.41, 27.9, or 115 mg/kg bw/day for females) for 13 weeks. All animals were subjected to ophthalmological examinations prior to treatment and at termination. Neurobehavioral assessment (functional observational battery and motor activity testing) was performed in 12 animals/sex/group prior to treatment and during weeks 4, 8, and 13 of the study. At study termination, 6 animals/sex/group were euthanized and perfused *in situ* for neuropathological examination and all control and high-dose animals were subjected to histopathological evaluation of brain and peripheral nervous

system tissues.

There were no treatment-related deaths or clinical signs. At 1600 ppm, body weight gain was decreased during the first week (83% for males and 62% for females) and for the last month of the study (22% for males and 19% for females), with absolute body weights decreased on day 7 (12% for males; $p<0.05$). Mean food consumption was decreased for both sexes during the first week (63 and 66% for males and females, respectively; $p<0.05$) and remained decreased for males during weeks 2-4 (85-88%; $p<0.05$). There were no treatment related effects on ophthalmology, brain weight or gross and histologic pathology or neuropathology, and on motor/locomotor activity. The only treatment-related FOB finding was decreased hindlimb grip strength in high-dose males during week 13 (21%s; $p<0.05$). **The LOAEL for is 1600 ppm (101 and 115 mg/kg bw/day for males and females, respectively), based on decreased body weight gains and food consumption in both sexes and decreased hindlimb grip strength in males. The NOAEL is 400 ppm (24.2 and 27.9 mg/kg bw/day for males and females, respectively).**

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for a subchronic neurotoxicity study in rats (OPPTS 870.6200b; [§82-7]; no OECD guideline).

Developmental Neurotoxicity Study

In a developmental neurotoxicity study (MRID 45516601) YRC 2894 (Thiacloprid; 99.2% a.i., 898013001) was administered to 25 female Crl:CD®(SD)IGS BR VAF/Plus® rats per dose in the diet at dose levels of 0, 50, 300, or 500 ppm (0, 4.4, 25.6, and 40.8 mg/kg/day during gestation; 0, 8.2, 49.4, and 82.8 mg/kg/day during lactation) from gestation day (GD) 0 through lactation day (LD) 22. The day that litter delivery was completed was designated postnatal day (PND) 1 (or LD 1). Body weight and food consumption data were recorded for dams. Detailed clinical observations, including assessments of autonomic function, were conducted daily during gestation and on LD 1, 5, 8, 14, and 22. Dams were killed and necropsied on LD 22. On PND 5, litters were standardized to yield 5 males and 5 females (as closely as possible), and 10 randomly selected pups/sex/group were subjected to detailed clinical examination outside the home cage. On PND 12, pups were randomly assigned to each of the following four subsets: 1) fixed brain weights and/or neuropathological evaluation on PND 12 (10/sex/group); 2) passive avoidance testing (on PND 23-25 and 30-32) and water maze testing (on PND 59-63 and 66-70) (20/sex/group); 3) motor activity testing (on PND 14, 18, 22, and 58-60) and auditory startle habituation (on PND 23 and 59-61) (20/sex/group); 4) detailed clinical exam outside the home cage on PND 12 and weekly during the postweaning period (20/sex/group), fixed brain weights and neuropathological evaluation on PND 68-79 (10/sex/group). In addition, the pups from subsets 2-4 were observed for the age of attainment of balanopreputial separation or vaginal patency (60/sex/group).

There were no treatment-related effects on maternal survival, clinical or functional observations, reproductive function, or gross pathology at any dietary level. Treatment-related decreases (p 0.05) in maternal body weight gain were observed in the 300 and 500 ppm dams during GDs 0-6 (31-56%), and in the 500 ppm dams during LDs 1-4 (67%). Treatment-related decreases in food consumption (p 0.01) were also noted in the 300 and 500 ppm dams during GDs 0-6

(16-30%) and in the 500 ppm dams during LD 4-7 (11%). Significant decreases (p 0.01) in relative food consumption on GD 0-6 at 300 (14%) and 500 ppm (27%) support the conclusion that the effects on body weight gain in early gestation were not solely related to palatability. **The maternal LOAEL is 300 ppm (25.6 mg/kg/day), based on decreased body weight gain and food consumption during early gestation (GD 0-6). The maternal NOAEL is 50 ppm (4.4 mg/kg/day).**

Offspring survival, assessments of autonomic function, watermaze, brain weights, and qualitative histopathology were unaffected by treatment. Suggestive effects on motor activity and auditory startle were seen in the 300 and 500 ppm groups. Increased incidences (p 0.01) of malaligned incisors and chromodacryorrhea were observed at postpartum week 10 in 500 ppm offspring. These findings were considered to be treatment-related, perhaps a latent expression of a developmental anomaly. In the 300 and 500 ppm offspring, preweaning body weights were decreased (p 0.01) on PNDs 8-22 (5-15%). In addition, postweaning body weights were decreased (p 0.01) in these animals (4-15%). Sexual maturation was delayed (p 0.05) in the 300 and 500 ppm male pups (48.2 days each treated vs. 46.7 days controls), and in the 500 ppm female pups (34.7 days treated vs. 33.4 days controls).

Passive avoidance testing revealed significant increases in Trial 2 latency during the first testing session in 300 and 500 ppm females (p 0.05 and p 0.01, respectively) in weanling offspring. Also at these doses, examination of the individual data indicated slower responses, and an adverse effect on retention of behaviors learned in Session 1.

At histopathological evaluation, in the 500 ppm males, the size of the corpus striatum (4%) and corpus callosum (14%) were decreased (p 0.05) from controls on PND 12. At study termination, the corpus striatum (4%) and dentate gyrus (5%) were smaller (p 0.05) than controls. A definitive NOAEL was not established for these findings. **The offspring LOAEL is tentatively set at 300 ppm (25.6 mg/kg/day), based on decreased preweaning and postweaning body weights in both sexes and delayed sexual maturation in the males, and altered performance in passive avoidance testing. The tentative offspring NOAEL is 50 ppm (4.4 mg/kg/day).**

This study is classified **unacceptable/guideline** and does not satisfy the guideline requirement for a developmental neurotoxicity study in rats (OPPTS 870.6300, §83-6); OECD 426 (draft). This study can be upgraded following the submission of acceptable morphometric histopathology data to establish a definitive NOAEL for alterations in brain development, procedural information for functional observation assessments, and adequate positive control data.

3. Developmental Toxicity Study Conclusions

Rat Developmental Toxicity Study

EXECUTIVE SUMMARY: In a developmental toxicity study (1997, MRID 44927741), YRC 2894 (thiacloprid; Lot/batch # 290894; 97.0-97.3% a.i.) was administered in 0.5% carboxymethylcellulose via gavage, in a dosing volume of 10 mL/kg, to 28 female Wistar

rats/group, at dose levels of 0, 2, 10, or 50 mg/kg/day, on gestation days (GDs) 6 through 19. All surviving dams were sacrificed on GD 20 and their fetuses were removed by cesarean section and examined.

Maternal Toxicity. At 10 mg/kg, body weight gains were decreased p 0.05) only for the first day of treatment, and water consumption and fecal output were marginally reduced. In the 50 mg/kg dams, decreases (p 0.05) were observed in body weights beginning on GD 7 (decr. 5-11%) and in daily body weight gains during GDs 6-7, 7-8, 8-9, 14-15, and 17-18. Furthermore, body weight gains were decreased (p 0.01) for the overall (GD 6-19) treatment interval (decr. 46%) and for the overall (GD 0-20) study when the weight of the gravid uterus was included (decr. 32%) or excluded (decr. 52%). Gravid uterine weights were decreased by 20% (p 0.01). Food consumption was decreased 9-64% (p 0.01) during the treatment period. Clinical signs revealed decreased water consumption and fecal output immediately following initiation of treatment and increased water consumption and urination during the second half of gestation. One 50 mg/kg dam had complete resorption of its litter. The number of late resorptions was increased (p 0.01) at 50 mg/kg (83) compared to controls (25). Likewise, the number of late resorptions per dam was increased at this dose (2.8) compared to controls (0.9) and historical controls (0.3-1.3). Consequently, post-implantation loss was higher in this group (23.9%) compared to controls (7.2%) and historical controls (4.3-12.6%). **The maternal LOAEL is 50 mg/kg/day based on decreased body weights, body weight gains, food consumption, increased urination, and changes in water consumption. The maternal NOAEL is 10 mg/kg/day.**

Developmental Toxicity. At 50 mg/kg, increased fetal (p 0.05) and litter (not significant) incidences of bilateral dysplasia of the humerus, radius, and scapulae (a malformation) and asymmetrical sternebrae and wavy ribs (variations) were observed. Increases (not significant) in fetal and litter incidences of dilatation of the renal pelvis(es) exceeded the range of historical controls at 50 mg/kg. Skeletal retardation was observed, characterized by incomplete ossification/unossifcation of the phalanges, metacarpals, sternebrae, parietal bone, interparietal bone, supraoccipital bone, fontanelle, and cervical, thoracic, and caudal vertebral bodies and/or arches. These skeletal retardations were associated with decreases in fetal weights of 11-14% (p 0.01) compared to concurrent controls. Decreased pup weight (2.8%, p 0.05) was also evident at 10 mg/kg/day. **The developmental toxicity LOAEL is 50 mg/kg based on increased resorptions (complete and late), skeletal retardations, variations (wavy ribs and asymmetrical sternebrae), and malformations (dysplastic humerus, radius, and scapulae) and on decreased fetal weights. The developmental toxicity NOAEL is 10 mg/kg/day.** The slight decrease in fetal weight at 10 mg/kg/day was not included as a toxic response.

This study is classified **acceptable/guideline** (OPPTS 870.3700a; OECD 414) and satisfies the requirements for a developmental study in the rat.

Rabbit Developmental Toxicity Study

EXECUTIVE SUMMARY: In a developmental toxicity study (1996, MRID 44939201), YRC 2894 (thiacloprid; Lot/batch # 290894; 97.3% a.i.) was administered in 0.5% carboxymethyl-

cellulose via gavage, in a dosing volume of 5 mL/kg, to 24 female Himalayan CHBB:HM rabbits/group, at dose levels of 0, 2, 10, or 45 mg/kg/day, on gestation days (GDs) 6 through 28. All surviving does were sacrificed on GD 29 and their fetuses were removed by cesarean and examined.

Maternal Toxicity. At 10 and 45 mg/kg, maternal rabbits exhibited decreased water consumption and, consequently, decreased and discolored (light yellow) urination. Maternal food consumption was decreased (p 0.01) during the first week of treatment (GDs 6-11) at 10 mg/kg (28%) and throughout treatment at 45 mg/kg (21-76%). Consequently, does at 10 and 45 mg/kg had reduced fecal output. Body weights were decreased (5-9%; p 0.05) in the 45 mg/kg does beginning on GD 15. Body weight gains were decreased at 10 mg/kg during GDs 6-11 (p 0.05) and at 45 mg/kg during GDs 6-11, for the overall (GDs 6-28) treatment interval, and for the overall (GD 0-29) study. Placental weights were decreased (p 0.01) at 45 mg/kg (14%). The percent of male fetuses was decreased (p 0.01) at 45 mg/kg (35.5% compared to controls 51.4%) and was also lower than the historical control range (41.4-61.3%).

Two females in the 45 mg/kg group aborted on GDs 24 and 28. The percent of rabbits aborting at 45 mg/kg (8.3%) fell within the range of historical controls (0.0-13.3%). Similarly, three females in the 45 mg/kg group experienced total resorption of their litters. The percent of does with implantations resulting in complete resorption at 45 mg/kg (13.6%) fell just within the upper end of the range of historical controls (0.0-15.4%). The number of early resorptions was increased (p 0.01) at 45 mg/kg (8) compared to controls (0). However, the group mean number of early resorptions per doe (0.4) fell within the range of historical controls (0.0-1.2). Although the incidences of complete resorption and early resorption at 45 mg/kg fell within the historical control ranges, an effect of treatment cannot be ruled out. **The maternal LOAEL is 10 mg/kg/day based on decreased body weight gains, food consumption, and fecal output. The maternal NOAEL is 2 mg/kg/day.**

Fetal weights were decreased (p 0.01) in the 10 mg/kg females (7%) and 45 mg/kg males and females (21-22%). Other indications of developmental toxicity were noted at 45 mg/kg including increased (p 0.01) incidences of incomplete ossification and/or unossification were observed in numerous bones, including phalanges of the forelimb and hindlimb, metacarpals, calcaneus, cervical and caudal vertebrae, and hyoid body. Increased fetal (p 0.01) and litter (not significant) incidences of bilateral presence of the 8th caudal vertebral arch and the 15th caudal vertebral body were observed. The decreased fetal weights and skeletal retardations were considered treatment-related, although possibly secondary to maternal effects. An increased (not significant) incidence of supernumerary (13th) ribs was observed (3.5% fetal; 15.8% litter). This variation was not observed in concurrent controls or historical controls; thus, it is considered treatment-related. **The developmental toxicity LOAEL is 10 mg/kg based on decreased fetal weights. The developmental toxicity NOAEL is 2 mg/kg/day.**

This study is classified **acceptable/guideline** (OPPTS 870.3700b; OECD 414) and satisfies the requirements for a developmental study in the rabbit.

4. Reproductive Toxicity Study Conclusions

EXECUTIVE SUMMARY. In a two-generation reproduction toxicity study (1995 and 1997, MRIDs 44927702 and 44927638), YRC 2894 (Thiacloprid; 96.7-97.5% a.i.; Lot/batch #290894) was administered to Sprague Dawley rats (30/sex/dose) at nominal dietary dose levels of 0, 50, 300, or 600 ppm (equivalent to 0/0, 3.5/4.2, 21/26, and 41/51 mg/kg bw/day for males/females). The P animals were dosed for approximately 10 weeks prior to mating to produce the F_1 litters. After weaning, F_1 animals (30/sex/dose) were selected to and were dosed for approximately 10 weeks prior to mating to produce the F_2 litters.

Systemic effects. Parental P1 body weights were decreased at 300 ppm on GD 0 and at 600 ppm during the last three weeks of premating and throughout most of gestation and lactation. In the 600 ppm F_1 animals, body weights were decreased in the males throughout the study and in the females throughout premating, gestation, and lactation. In the 300 ppm F_1 males, food consumption was increased during weeks 8 and 10. Food consumption was increased during premating in the F_1 males during weeks 2-12 (except week 11) and in the F_1 females during weeks 2, 5, and 8-10. Absolute and relative (to body weight) **liver weights** were increased in the 300 ppm males and 600 ppm males and females in the P generation. In the F_1 generation parents, absolute and relative liver weights were increased in the 300 and 600 ppm females. In the F_1 males, relative liver weights were increased at 600 ppm. **Hepatocytomegaly** was increased in incidence and severity (minimal to slight) in the 300 and 600 ppm males and females in the P and F_1 generations. Dose-dependent increases (not significant) in the incidence and severity (minimal to moderate) of necrosis were observed in the liver in the P females. Absolute and relative (to body weight) **thyroid weights** were increased in the 300 ppm females and 600 ppm males and females in the P generation. In the F_1 generation parents, relative thyroid weights were increased in the 300 ppm males and 600 ppm males and females. In both generations, incidences of **thyroid follicular cell hypertrophy** were increased in the 300 ppm females and 600 ppm males and females. Average severity (minimal to slight) of follicular cell hypertrophy was dose-dependently increased in the F_1 generation. **The LOAEL for parental systemic toxicity is 300 ppm (21 mg/kg/day) based on increased liver and thyroid weights and on hepatocytomegaly, liver necrosis, and thyroid follicular cell hypertrophy. The NOAEL is 50 ppm (3.5 mg/kg/day).**

Reproductive performance. Estrous cycle length and periodicity, reproductive performance (mating index, fertility index, and gestation length), pup clinical signs, sex ratio, implantation sites, birth index, and lactation index were unaffected by treatment. In the P generation, four dams at 300 ppm and three dams at 600 ppm were found dead or sacrificed on GD 23-24 because of **dystocia**. Paleness and stained/wet centrum were associated with dystocia in these animals. Dystocia was not noted in the F1 parental group. **The LOAEL for reproductive performance is 300 ppm (26 mg/kg/day) based on dystocia. The NOAEL for reproductive performance is 50 ppm (4.2 mg/kg/day).**

Developmental toxicity. At 300 ppm, **pup weights** were decreased after PND 14 in the F_1 females and in the F_2 males and females. Pup weights were decreased in the 600 ppm F_1 and F_2 litters after PND 7; the magnitude of the decrease was more pronounced as lactation proceeded.

The number of stillborn pups was increased in all treated F_1 groups (2, 16, 13, and 16 in the 0, 50, 300, and 600 ppm groups, respectively) but there was no dose response. The **live birth index** was decreased (not significant) at 600 ppm in the F_1 and F_2 generations. In the F_1 generation pups, the **viability index** (days 0-4) was decreased (not significant) at 600 ppm. **The LOAEL for offspring toxicity is 300 ppm based on decreased pup weight during lactation. The NOAEL is 50 ppm.**

The study is **acceptable/guideline** and satisfies the requirements for a two-generation reproduction study (OPPTS 870.3800; OECD 416) in the rat.

5. Additional Information from Literature Sources

Since thiacloprid is a new chemical, there were few reports in the open literature regarding its toxicity. One study (Tembisa et al, Toxicol. Appl. Pharmacol. 177:77-83, 2001) discusses the analgesic and toxic effects in mice of thiacloprid and other related chemicals and presents data on their interaction with ACHE receptors.

6. Pre-and/or Postnatal Toxicity

A. Determination of Susceptibility

The HIARC concluded that there is no increase in qualitative or quantitative susceptibility demonstrated in the rat developmental neurotoxicity, rabbit developmental or rat reproduction studies. However, there was noted a *qualitative* increase in susceptibility in the rat developmental toxicity study as indicated by increases in resorptions, increases in skeletal variations and retardations and malformations and decreases in fetal body weight that occurred at the same dose showing a decrease in maternal body weight.

B. Degree of Concern Analysis and Residual Uncertainties

The HIARC concluded that there is a *low* degree of concern for the qualitative increase in susceptibility noted in the rat developmental toxicity study because there is a well characterized dose response with a clear NOAEL and LOAEL, the fetal effects were noted in the presence of maternal toxicity, and the doses selected for overall risk assessments would address the concerns seen in this study. Therefor, there are no residual uncertainties for pre- and/or postnatal toxicity following exposure to thiacloprid.

C. Special FQPA Safety Factor(s):

The HIARC concluded that the Special FQPA Safety Factor should be 1x because there are no and/or low concerns and no residual uncertainties with regard to pre- and/or postnatal toxicity.

The Special FQPA Safety Factor recommended by the HIARC **assumes** that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

7. Recommendation for a Developmental Neurotoxicity Study

A developmental neurotoxicity study (2001, MRID 45516601) has already been conducted and reviewed. It is presently classified as Unacceptable/Guideline pending receipt and review of morphological assessment for the low and mid dose groups.

In accordance with the 2002 OPP 10x guidance document, the HIARC determined that a Database Uncertainty Factor (UF_{DB}) of 3x is required for the lack of morphometric assessments for the low- and mid-dose group animals in the developmental neurotoxicity study (DNT). A 3x (as opposed to a 10x) was judged to be adequate because the dose selected for overall risk assessments is already based on the most sensitive end points for acute (i.e., clinical signs indicative of neurotoxicity) and chronic (i.e. liver and thyroid effects) dietary and non-dietary exposure scenarios, and the available data indicate that the full characterization of brain morphometrics from the DNT study would not be expected to lower the dose used for risk assessments by more than 3-fold. Therefore, a UF_{DB} of 3x will be applied to the acute and chronic RfDs as well as short- and intermediate-term oral and short-, intermediate- and long-term dermal and inhalation residential exposure scenarios.

II. HAZARD IDENTIFICATION

1. Acute Reference Dose (aRfD) - All populations.

Study Selected: Rat Acute Neurotoxicity Screen Study. § 870.6200.

MRID No.: 44927703 and 44927704.

EXECUTIVE SUMMARY. In an acute neurotoxicity study (1997, MRID 44927703), groups of fasted, nine-week-old Fischer 344 rats (12/sex) were given a single oral dose of technical YRC 2894 (approximately 97% a.i., batch # 290894) in 0.5% methyl cellulose-0.4% Tween 80 in deionized water at doses of 20, 50, or 100 mg/kg bw and observed for 14 days. Functional observational battery [FOB] and motor activity testing was performed in 12 animals/sex/group pretreatment, at 4 hours post-dosing (the time of peak effect), and at days 7 and 14 post-treatment. Because a NOAEL for decreases in motor activity was not attained in female rats in this study, a second (supplemental) neurotoxicity study (1998, MRID 44927704) was performed. Doses in the supplemental study were 0, 2.5, or 10 mg/kg bw. Actual doses based on analytical results in the two studies were 0, 3.1, 11, 22, 53, and 109 mg/kg. Abbreviated FOB and motor activity tests were conducted in the supplemental study (Day 0, females only). At study termination, six animals/sex/group from the main study were euthanized and perfused *in situ* for neuropathological examination. Only the control and high-dose groups were subjected to histopathological evaluation of brain and peripheral nervous system.

There were no mortalities. A transient decrease in body weight was observed in males in the 100 mg/kg dose group. There was no affect of treatment on gross pathology, brain weights, or incidences of microscopic lesions of the brain, spinal cord, or peripheral nervous system.

The only clinical sign considered treatment-related in the lower dose groups occurred in the 50 mg/kg group and involved dilated pupils in 1 of 12 female rats. Clinical signs consisting of tremors, decreased activity, ataxia, dilated pupils, cool-to-touch body, urine stained fur, and partially closed eyelids were observed in the majority of male and female rats that received 100 mg/kg. Most of the above signs were observed only on the day of treatment, and all signs had resolved by day 5.

During the FOB, in addition to the clinical signs at higher doses, treatment-related signs of slight tremors and ptosis in males in the 20 mg/kg dose group (3/12 and 1/12, respectively) and slight incoordination of the righting reflex in 1 of 12 females in the 20 mg/kg dose group were observed on the day of treatment.

There was no effect of treatment on total motor or locomotor activity of male rats in the main study. However, subsession data indicated significantly reduced activity for early subsessions in the 100 mg/kg group. For females in the main study, total motor activity was significantly reduced at doses of 50 and 100 mg/kg ($p<0.05$) and total locomotor activity was significantly reduced at doses of 20, 50, and 100 mg/kg ($p<0.05$). Locomotor subsession data for males and females in the 100 mg/kg group indicated that rats did not move from where they were placed in the maze. In the supplemental study, non-significant reductions in total motor and total locomotor activity of 21 and 27%, respectively, in the 10 mg/kg group (females only) were considered treatment related and biologically significant. There were no effects of treatment in any dose group at the 7- and 14-day observation times. **The LOAEL in females was 11 mg/kg bw (based on reductions in motor and locomotor activity), with a NOAEL of 3.1 mg/kg bw. The LOAEL in males was 22 mg/kg bw (based on FOB observations of slight tremors and ptosis of the eyelids on the day of treatment), with a NOAEL of 11 mg/kg bw.**

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for an acute neurotoxicity study in rats (870.6200a; OECD 424).

Dose and Endpoint for Establishing aRfD: NOAEL = 3.1 mg/kg based on reduced motor activity at the LOAEL of 11 mg/kg in females.

Uncertainty Factor (UF): 300 based on 10 X for interspecies and 10 X for intraspecies variation and an additional 3X data base uncertainty factor for the lack of morphometric measures in the developmental neurotoxicity study. Additional morphologic measurements are requested for the low- and mid-dose groups.

Acute RfD (All Populations) = $\frac{3.1 \text{ mg/kg (NOAEL)}}{300 \text{ (UF)}}$ = **0.01 mg/kg**

Comments about Study/Endpoint/Uncertainty Factor: The effects were seen after a single oral dose and thus is appropriate for this risk assessment. This dose and endpoint was selected over the rabbit developmental toxicity study with a NOAEL and LOAEL of 2 and 10 mg/kg/day because there is no indication that either the maternal or developmental toxicity resulted from a single dose of thiacloprid. The developmental effects in the rat study were seen at a much higher

dose (50 mg/kg/day), the developmental NOAEL was 10 mg/kg/day.

3. Chronic Reference Dose (cRfD)

Study Selected: Chronic Feeding/oncogenicity study in rats. § 870.4300.

MRID No.: 44927712

EXECUTIVE SUMMARY: In a combined chronic toxicity/carcinogenicity study (1998, MRID 44927712), YRC 2894 (thiacloprid, 96.8-97.2% a.i., batch # 290894) was administered to groups of 60/sex Wistar Hsd Cpd:WU rats at dietary levels of 0, 25, 50, 500, or 1000 ppm (0, 1.2, 2.5, 25.2, and 51.7 mg/kg/day, respectively, for males and 0, 1.6, 3.3, 33.5, and 69.1 mg/kg/day, respectively, for females) for up to 2 years. Groups of 10/sex per dose were sacrificed at 12 months for interim evaluations. Thyroid hormones were evaluated at the same time as serum chemistry parameters, and liver homogenates were prepared from 10 rats/sex/dose at 0 and 25 ppm and 5 rats/sex/dose at 50, 500, and 1000 ppm for evaluation of phase I and phase II enzymes at 54 weeks.

No treatment-related effects occurred on clinical signs of toxicity, mortality rates, hematologic, clinical chemistry, urinalysis parameters, or serum thyroid hormone levels at any dose. The 500-ppm female group weighed 4-15% less than controls during most of the study, gained 16% less weight, consumed 8% less food, and had an overall food efficiency value 9% less. Male rats in the 1000-ppm group weighed 12% ($p<0.01$) less than controls during weeks 1 and 2 and 4-11% ($p<0.01$ or <0.05) for most time points thereafter, gained 43% less weight during week 1, gained 12% less over the entire study, and consumed 20% less food during week 1 and a similar amount averaged over the entire study. Overall food efficiency was reduced by only 9%. Females in the 1000-ppm group weighed 5-21% ($p<0.01$ or <0.05) less during the study, gained 20% less weight, consumed 8% less food, and had an overall food efficiency value 12% less. The only treatment-related finding reported during the ophthalmoscopic examination was an increased incidence of cortical lens abnormalities (waterclefts and opacity) in females receiving the 1000-ppm diet.

Phase I enzymes, ethoxycoumarin deethylase (ECOD), aldrin epoxidase (ALD), and epoxide hydrolase (EH) (females only), and phase II enzymes, glutathione-S-transferase (GS-T) and UDP-glucuronyl transferase (GLU-T), in liver homogenates were significantly increased at 500 ppm. ECOD and ALD in males and EH in females also were increased at 50 ppm. EH was significantly increased in males only at 1000 ppm. No effect was observed on 7-ethoxyresorufin deethylase (EROD).

Treatment-related lesions at 50 ppm and above included hepatocellular cytoplasmic change (eosinophilic cytoplasm with basophilic strands), hepatocyte centrilobular hypertrophy, and thyroid follicular epithelial hypertrophy in males and retinal atrophy in females. Treatment-related lesions occurring only at concentrations 500 ppm included skeletal muscle atrophy and lens degeneration in females; colloid alteration and pigment in the thyroid of males and females; and sciatic nerve degeneration and cholesterol clefts in the pituitary of males. The following treatment-related lesions occurred only at 1000 ppm: hepatocellular vacuolation in males; and sciatic nerve degeneration, cholesterol clefts in the spinal cord, thyroid follicular epithelial

hyperplasia, sinus histiocytosis in the mesenteric lymph nodes, and skeletal muscle degeneration and mononuclear infiltration in females. The only treatment-related organ weight change was increased absolute (19% in males, $p < 0.01$) and relative (31% in males and 16% in females, $p < 0.01$) liver weight in 1000-ppm males at study termination. Relative brain weight was increased for males (9%, $p < 0.01$ at 1000 ppm)and females (9% at 500 ppm $p < 0.05$ and 17% at 1000 ppm $p < 0.01$). Increased incidences of liver lesions were also observed at 500 ppm in male and females sacrificed after 1 year.
The LOAEL is 50 ppm (2.5 in males and 3.3 in females mg/kg/day) based on liver toxicity (hepatocellular hypertrophy and cytoplasmic change and increased enzyme activity), thyroid follicular epithelial hypertrophy in males and oculotoxicity (retinal atrophy) in females. The corresponding NOAEL is 25 ppm (1.2 in males and 1.6 in females mg/kg/day).

The incidence of **thyroid follicular cell adenomas** was 0%, 0%, 2%, 10% ($p<0.05$), and 16% ($p<0.01$) in males at 0, 25, 50, 500 and 1000 ppm, respectively. The incidence of **uterine adenocarcinomas** was 12%, 6%, 6%, 28% ($p<0.05$), and 36% ($p<0.01$). One female rat each at 50 and 500 ppm and two rats at 1000 ppm also had uterine adenomas compared with none of the controls. Dosing was considered adequate based on microscopic lesions at 50 ppm in both sexes and decreased body weight and weight gain in males at 1000 ppm and females at 500 and 1000 ppm.

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirements for a chronic toxicity/carcinogenicity study in rats [OPPTS 870.4300; OECD 453].

Dose and Endpoint for Establishing cRfD: NOAEL = 1.2 mg/kg/day based on hepatic hypertrophy, cellular change and thyroid hypertrophy in males and retinal effects in females at the LOAEL of 2.5 mg/kg/day in males and 3.3 mg/kg/day in females.

Uncertainty Factor(s): 300 consisting of 10 X for interspecies and 10 X for intraspecies variability and an additional 3X data base uncertainty factor for the lack of morphometric measures in the developmental neurotoxicity study. Additional morphologic measurements are requested for the low- and mid-dose groups.

Chronic RfD = $\frac{\text{1.2 mg/kg/day (NOAEL)}}{\text{300 (UF)}}$ = 0.004 **mg/kg/day**

Comments about Study/Endpoint/Uncertainty Factor: This dose/endpoint/study is appropriate for chronic dietary risk assessment. The rat thyroid tumors in males and *possibly* also the rat uterine tumors and mouse ovary tumors are considered to be associated with increased hepatic enzyme activity due to thiacloprid. At the LOAEL of 2.5 mg/kg/day there is increased incidence of hepatic hypertrophy and cytoplasmic change and thyroid follicular epithelial change in males. These are considered to be potentially related to changes in circulating hormone levels. There were also noted effects in the retina of females that may reflect an acceleration of the aging process.It should be noted that the results of the subchronic study indicated a slight increase (14%, $p < 0.05$) in T3 at 25 ppm at 3 weeks but this not evident after 12 weeks. This dose is supported by comparable NOAELs in the multi generation reproduction study (NOAEL of 3.5

mg/kg/day) and the rat developmental neurotoxicity study (NOAEL of 4.4 mg/kg/day).

4. Incidental Oral Exposure: Short term (1-30 days) and Intermediate term (1-6 Months)

Study Selected: Rat Chronic feeding carcinogenicity § 870.4300

MRID No.: 44927712

Executive Summary: Refer to chronic dietary section above.

Dose and Endpoint for Risk Assessment: NOAEL of 1.2 mg/kg/day based on hepatic hypertrophy, cellular change and thyroid hypertrophy in males at the LOAEL of 2.5 mg/kg/day in males.

Comments about Study/Endpoint/Margins of Exposure: This dose/endpoint is appropriate for the population (infants and children) and duration (short and intermediate) of concern. It was determined that the selection of the chronic study is appropriate for these durations since the endpoints of concern is based on induction of the liver hypertrophy and cytoplasmic change, thyroid hypertrophy and induction of the enzymes, UDP-Glu-T and aromatase. These enzymes can *potentially* alter the thyroid and estrogen hormone levels which are important in the developing human child for which this exposure grouping is designed to protect. Special studies (MRID 45307403, 44927734 and 44927735) indicate that induction of hepatic enzymes can occur following only about four weeks of dosing or less. The selection of this dose level is supported by the rabbit developmental toxicity study having a maternal NOAEL and LOAEL of 2 and 10 mg/kg/day.

5. Dermal Absorption

Dermal Absorption Factor: 5% at 8 hours.

This 5% value is based on a study conducted in monkeys with 40.4% liquid formulation YRC-2894 SC 480. This value can also be used for other thiacloprid liquid formulations that are shown to be similar to SC 480 and for aqueous dilutions of most thiacloprid formulations. The 5% dermal absorption factor would likely overestimate the risk for granular formulations to mixers and loaders due to the nature of the granular material. However, until the registrant provides dermal absorption data with granular formulations that would support a lower value, the 5% value can be used for risk assessment purposes.

Executive Summary. In a dermal penetration study (2002, MRIDs 45846701 and 45846702), radiolabeled YRC 2894 in SC 480 (formulated thiacloprid, Lot numbers 1417/1 and 1417/3, radiochemical and chemical purity > 97.8%, radiolabel located at the 4 and 5 thiazolidine positions) was applied to the shaved backs of male rhesus monkeys. The five monkeys reported in MRID 45846701 received 5.53 $\mu g/cm^2$ of the radiolabeled material while the one monkey reported in MRID 45846702 received 9.25 $\mu g/cm^2$. All dermal exposures were for 8 hours. To simulate 100% absorption, one male monkey received an IV bolus dose of 234 µg radiolabeled material.

No clinical signs of toxicity were observed. Recovery ranged from 96.8 to 99.5% following dermal application and 92.4% following IV administration. Dermal absorption, implied by the detection of radiolabel in the urine, feces, cage debris/rinse/wipes, and the chair urine pan/screen rinse and wipes was ~3.2% in MRID 45846701 and ~1.6% in MRID 45846702. Following an intravenous dose ~67% of the radioactivity was recovered in the urine and only ~5% in the feces with the rest in the debris and cage wash indicated that the urinary route was the primary route of elimination. The IV study also demonstrated that most elimination occurring within 8 hours of treatment and >85% of the radiolabel that was eliminated occurred within 48 hours of treatment. **A dermal absorption factor of 5% is supported for thiacloprid formulated as SC 480 based on a mean of 3.15%±1.32% for recovery attributed to absorption.**

This study is classified as **Acceptable/NonGuideline** and does not satisfy the guideline requirements for a dermal penetration study (870.7600) which require rats as the test species. However, the study meets its stated objectives and defines the dermal absorption of thiacloprid (YRC 2894 SC 480) formulation.

6. Dermal Exposure: *All* Durations

Study Selected: Rat chronic feeding/carcinogenicity. § 870.4300

MRID No.: 44927712

Executive Summary: refer to the Chronic Dietary Section above.

Dose and Endpoint for Risk Assessment: NOAEL of 1.2 mg/kg/day based on hepatic hypertrophy, cellular change and thyroid hypertrophy in males at the LOAEL of 2.5 mg/kg/day in males.

Comments about Study/Endpoint/Margins of Exposure: This selected endpoint is considered appropriate for all dermal exposure since the endpoints of concern is based on induction of the liver hypertrophy and cytoplasmic change, thyroid hypertrophy and induction of the enzymes, UDP-Glu-T and aromatase. These enzymes can *potentially* alter the thyroid and estrogen hormone levels which are important in the developing human child for which this exposure grouping is designed to protect. Special studies (MRID 45307403, 44927734 and 44927735) indicate that induction of hepatic enzymes can occur following only about four weeks of dosing or less. Since an oral dose was selected, 5% dermal absorption factor should be used in route-to-route extrapolation. The rat 28 day dermal toxicity study was not selected because no NOAEL was established, there was a low power (only 5 rats/sex were treated per dose; guideline requires 10 rats/sex) and because no hormonal measurements were conducted.

7. Inhalation Exposure: *All* Durations.

Study Selected: Subchronic 28-day- inhalation - rats Series 870.3465

EXECUTIVE SUMMARY. In a subacute inhalation toxicity study (1998, MRID 44927715

and 1995, MRID 44927636), YRC 2894 (thiacloprid; 96.8-97.2% a.i., Batch No. 290894) was administered to 10 Wistar rats/sex/concentration by dynamic nose-only exposure at target concentrations of 0, 2, 20, or 200/100 mg/m^3 (achieved mean analytical dosages of 0, 2, 18.2, and 143.4 mg/m^3) for 6 hours per day, 5 days/week for a total of 28 days (20 exposures). The achieved MAD was ~ 2.9 μmeters. The high dose animals were exposed to 200 mg/m^3 for study Days 0-7, then exposed to 100 mg/m^3 for Days 8-28 due to marked respiratory distress and decreased body weight gain observed at the initial concentration.

There were no treatment-related effects on mortality, urinalysis, body weights, and ophthalmoscopic, neurologic, and macroscopic changes. Rectal temperature was decreased while exposed to 200 mg/m^3 but was normal when the dose was reduced.

The only findings observed at 20 mg/m^3 were an increase in the liver enzyme, aminopyrine-N-demethylase (N-DEM) and minimal to slight hepatocyte hypertrophy in the males (5/10). These observations were also noted at a greater incidence in the 200/100 mg/m^3 males and females. At 200/100 mg/m^3, a slight to moderate piloerection and slight to severe bradypnea were observed throughout treatment in both males and females. Liver enzymatic activity of p-nitroanisole-O-demethylase (O-DEM) and cytochrome P450 (P450) were increased (p 0.01) in both sexes. Absolute and relative (to body and brain) liver weights were elevated (p 0.01) in females, while relative (to body) liver weights were elevated (p 0.01) in males. Minimal single cell necrosis and fat deposition in the liver were observed in the controls and treated animals; a minor increase in the incidence of these findings was observed in the liver of both sexes at 200/100 mg/m^3 (3-5/10 treated vs 1-3/10 controls). Findings in the thyroid at 200/100 mg/m^3 included slight hypertrophy of the thyroidal epithelium in males (2/10 treated vs 0/10 controls), and statistically insignificant increases in absolute and relative thyroid weights in males and females (incr. 28-40%) and in triiodothyronine (T3) and thyroxine (T4) in the females (incr. 12-26%). **The LOAEL is 20 mg/m^3 (achieved mean analytical dose of 18.2 mg/m^3), based on liver effects (hypertrophy and increased N-DEM). The NOAEL is 2 mg/m^3.** Note: The liver hypertrophy and increase in N-DEM are considered a LOAEL because these same increases are thought to be related to increases in UDP-Glu-T and aromatase which can affect circulating hormones in response to thiacloprid treatment.

This study is classified as **acceptable/non-guideline**. The guideline study calls for 90 days of exposure and this study was for 28 days only. Otherwise it is closely consistent with the guidelines.

Dose/Endpoint for Risk Assessment: NOAEL of 2 mg/m^3 (0.542 mg/kg/day) based on liver effects at the LOAEL of 18.2 mg/m^3 (4.93 mg/kg/day).

Comments about Study/Margins of Exposure: The NOAEL of 2 mg/m^3 is based on the occurrence of liver hypertrophy and increased N-DEM at 18.2 mg/m^3. These conditions are related to the expected effects of thiacloprid in the rat liver that were seen in the rat oral and dermal studies. They are believed to be related to increased activity of UDP-Glu-T and aromatase, enzymes that can lead to alterations in hormone levels (i.e thyroid and estrogens).

The atmospheric dose of 2 mg/m^3 (0.002 mg/L) is converted to an estimated daily intake of 0.542 mg/kg/day based on a respiratory volume of 8.46 L/hr for the Wistar strain rat and assumes the

rat weights 0.187 kilograms. The daily intake value of 0.542 mg/kg/day is less than the NOAEL of 1.2 mg/kg/day based on the rat chronic feeding study. Thus, the subchronic inhalation study rather than the rat chronic feeding study is considered to provide a more appropriate endpoint for all inhalation exposures to thiacloprid.

8. Margins of Exposure

Summary of target Margins of Exposure (MOEs) for risk assessment.

Route / Duration	Short-Term (1-30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure			
Dermal	100	100	100
Inhalation	100	100	100
Residential (Non-Dietary) Exposure			
Oral	300	300	NA
Dermal	300	300	300
Inhalation	300	300	300

For **occupational** exposure risk assessments, a **MOE of 100** is adequate. This is based on the conventional 100 which includes 10X for intra-species extrapolation and inter-species variation.

For **residential** exposure (oral, dermal and inhalation) risk assessments, a **MOE of 300** is required and includes the conventional 100 plus an additional 3x database factor for the lack of morphological measurements in the low- and mid-dose groups in the developmental neurotoxicity study.

9. Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. For short and intermediate term aggregate exposure risk assessments, the oral and dermal (oral equivalent) and inhalation can be aggregated because of common toxicity endpoints (hepatotoxicity). For long term dermal and inhalation aggregate exposure risk assessment, these routes can be combined because of the common toxicity endpoint (hepatotoxicity).

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Chronic/ Carcinogenicity Study in Rat

In a combined chronic toxicity/carcinogenicity study (1998, MRID 44927712), YRC 2894 (thiacloprid, 96.8-97.2% a.i., batch # 290894) was administered to groups of 60/sex Wistar Hsd Cpd:WU rats at dietary levels of 0, 25, 50, 500, or 1000 ppm (0, 1.2, 2.5, 25.2, and 51.7 mg/kg/day, respectively, for males and 0, 1.6, 3.3, 33.5, and 69.1 mg/kg/day, respectively, for females) for up to 2 years. Groups of 10/sex per dose were sacrificed at 12 months for interim evaluations. Thyroid hormones were evaluated at the same time as serum chemistry parameters, and liver homogenates were prepared from 10 rats/sex/dose at 0 and 25 ppm and 5 rats/sex/dose at 50, 500, and 1000 ppm for evaluation of phase I and phase II enzymes at 54 weeks.

No treatment-related effects occurred on clinical signs of toxicity, mortality rates, hematologic, clinical chemistry, urinalysis parameters, or serum thyroid hormone levels at any dose. The 500-ppm female group weighed 4-15% less than controls during most of the study, gained 16% less weight, consumed 8% less food, and had an overall food efficiency value 9% less. Male rats in the 1000-ppm group weighed 12% ($p<0.01$) less than controls during weeks 1 and 2 and 4-11% ($p<0.01$ or <0.05) for most time points thereafter, gained 43% less weight during week 1, gained 12% less over the entire study, and consumed 20% less food during week 1 and a similar amount averaged over the entire study. Overall food efficiency was reduced by only 9%. Females in the 1000-ppm group weighed 5-21% ($p<0.01$ or <0.05) less during the study, gained 20% less weight, consumed 8% less food, and had an overall food efficiency value 12% less. The only treatment-related finding reported during the ophthalmoscopic examination was an increased incidence of cortical lens abnormalities (waterclefts and opacity) in females receiving the 1000-ppm diet.

Phase I enzymes, ethoxycoumarin deethylase (ECOD), aldrin epoxidase (ALD), and epoxide hydrolase (EH) (females only), and phase II enzymes, glutathione-S-transferase (GS-T) and UDP-glucuronyl transferase (GLU-T), in liver homogenates were significantly increased at 500 ppm. ECOD and ALD in males and EH in females also were increased at 50 ppm. EH was significantly increased in males only at 1000 ppm. No effect was observed on 7-ethoxyresorufin deethylase (EROD).

Treatment-related lesions at 50 ppm and above included hepatocellular cytoplasmic change (eosinophilic cytoplasm with basophilic strands), hepatocyte centrilobular hypertrophy, and thyroid follicular epithelial hypertrophy in males and retinal atrophy in females. Treatment-related lesions occurring only at concentrations 500 ppm included skeletal muscle atrophy and lens degeneration in females; colloid alteration and pigment in the thyroid of males and females; and sciatic nerve degeneration and cholesterol clefts in the pituitary of males. The following treatment-related lesions occurred only at 1000 ppm: hepatocellular vacuolation in males; and sciatic nerve degeneration, cholesterol clefts in the spinal cord, thyroid follicular epithelial hyperplasia, sinus histiocytosis in the mesenteric lymph nodes, and skeletal muscle degeneration and mononuclear infiltration in females. The only treatment-related organ weight change was

increased absolute (19% in males, $p < 0.01$) and relative (31% in males and 16% in females, $p < 0.01$) liver weight in 1000-ppm males at study termination. Relative brain weight was increased for males (9%, $p < 0.01$ at 1000 ppm)and females (9% at 500 ppm $p < 0.05$ and 17% at 1000 ppm $p < 0.01$). Increased incidences of liver lesions were also observed at 500 ppm in male and females sacrificed after 1 year.

The LOAEL is 50 ppm (2.5 in males and 3.3 in females mg/kg/day) based on liver toxicity (hepatocellular hypertrophy and cytoplasmic change and increased enzyme activity), thyroid follicular epithelial hypertrophy in males and oculotoxicity (retinal atrophy) in females. The corresponding NOAEL is 25 ppm (1.2 in males and 1.6 in females g/kg/day).

Discussion of Tumor Data

The incidence of **thyroid follicular cell adenomas** was 0%, 0%, 2%, 10% ($p<0.05$), and 16% ($p<0.01$) in males at 0, 25, 50, 500 and 1000 ppm, respectively. The incidence of **uterine adenocarcinomas** was 12%, 6%, 6%, 28% ($p<0.05$), and 36% ($p<0.01$). One female rat each at 50 and 500 ppm and two rats at 1000 ppm also had uterine adenomas compared with none of the controls. Dosing was considered adequate based on microscopic lesions at 50 ppm in both sexes and decreased body weight and weight gain in males at 1000 ppm and females at 500 and 1000 ppm.

Extensive mechanism data have been presented for both the thyroid tumors and the uterine in rats. The Mechanisms SARC has determined that there are insufficient data at this time to correlate an association between the uterine tumors and increases in hepatic aromatase. The issue of a relationship between increase thyroid hormone metabolism by the liver and consequent induction of thyroid tumors will be further evaluated by the HED CARC.

Adequacy of the Dose Levels Tested

On The CARC determined that the highest dose (1000 ppm) to be adequate, but not excessive, for carcinogenicity assessment. This was based on the following effects, which were not considered to be severely adverse: 1) an overall decrease in body weight gain of 20% in females and 12% in males at 1000 ppm, and 16% in females at 500 ppm; 2) no treatment-related effects on mortality; 3) increased absolute/relative liver weight (19/31%) in males at 1000 ppm, increases in several hepatic enzymes at 50 ppm, hepatic hypertrophy and cytoplasmic change at 50 ppm, and eventual vacuolation at the highest test dose; 4) thyroid hypertrophy, cellular alteration and pigment formation in both sexes and indications of acceleration of ocular degeneration in females. In addition, tumors (thyroid and uterus) were also seen at the next to highest dose of 500 ppm.

2. Carcinogenicity Study in Mice

MRID No. 44927710 and 44927711

Executive Summary: In a 24-month carcinogenicity study (1998, MRID 44927710 and MRID 44927711) YRC 2894 (96.8-97.2% a.i., batch # 290894) was administered to a total of 60 SPF-bred B6C3F_1 mice/sex/dose in the diet at concentrations of 0, 30, 1250, or 2500 (equivalent to 0, 5.7, 234.1, or 546.4 mg/kg bw/day for males and 0, 10.9, 475.3, or 872.5 mg/kg bw/day for females). Ten mice/sex/dose were examined after 12 months of treatment.

There were no treatment-related effects on mortality or clinical signs. **Body weight** gain of males at 2500 ppm was decreased by 14% after 24 months of treatment and food consumption was increased by 21%. **Food efficiency** was decreased by 22% in high-dose males. Body weight and food consumption were not affected significantly in males in the lower dose groups or in females in any dose group. **Total leucocyte count** was increased in males at weeks 53, 79, and 104 in the 1250 ppm (by 31, 46, and 12%, respectively) and 2500 ppm groups (by 64, 37, and 38%, respectively). In females, the leucocyte count was increased at week 53 in the 1250 ppm group (by 27%) and at week 79 (by 38%), but not at week 104. Absolute and relative (to body) **liver weights** were increased in males by 25% and 32%, respectively, at 2500 ppm after 12 months of treatment, and relative liver weight was increased by 8% at 1250 ppm and 17% ($p<0.01$) at 2500 ppm. At the 24-month sacrifice, only the liver-to-body-weight ratio was increased in males (by 17%). Absolute and relative liver weights were increased in females by 33% and 32%, respectively, after 12 months at 2500 ppm and by 29% and 22% after 24 months compared to the control (all $p<0.01$). Mean relative liver weight in females was increased by 9% ($p<0.05$) after 24 months at 1250 ppm. Incidences of **hepatocellular hypertrophy, vacuolization, and fatty changes**, graded slight to minimal, were increased in males at 2500 ppm after 12 months and in both sexes after 24 months compared to controls. Incidences of hepatocellular necrosis were increased in males in the 1250 ppm group (12%, $p<0.05$) and in the 2500 ppm group (62%, $p<0.01$) and in females in the 2500 ppm group (50%, $p<0.05$) after 24 months compared to the control groups (incidences of 10% in males in the control group and 30% in females in the control group). Incidences of **hepatocellular degeneration** were increased in males at 1250 ppm (10%, $p<0.05$) and at 2500 ppm (32%, $p<0.01$) after 24 months compared to the controls (2%). Hepatocellular degeneration was not seen in treated females. Increased incidences and severity of **vacuolation in the mesenteric and mandibular lymph nodes** were seen at 1250 ppm and 2500 ppm in both sexes. Incidences of hemorrhage in the mesenteric lymph nodes were also increased at 1250 ppm and 2500 ppm in both sexes compared to the controls. Decreased incidences of proximal tubule vacuoles were seen in The **kidneys** of males after 12 months at 2500 ppm (80%) compared to the control (0%, $p<0.01$), but not at 24 months. The incidence and severity of **adrenal X-zone vacuolization** in females was increased after 12 months at 2500 ppm (80%) and after 24 months at 1250 ppm (96%) and 2500 ppm (100%) compared to the controls (12 months, 20%; 24 months, 67%, $p<0.01$). The numbers of females with **increased eosinophilic luteinized cells in the ovaries** were increased at 1250 ppm (10%, NS) and at 2500 ppm (17%, $p<0.01$) compared to the control (6%). **The LOAEL is 1250**

ppm for males (234.1 mg/kg/day) and females (475.3 mg/kg/day) based on liver toxicity and microscopic lymph node changes in both sexes and increased X-zone vacuolization of the adrenal glands in female mice. The NOAEL is 30 ppm for males (5.7 mg/kg/day) and females (10.9 mg/kg/day).

There were statistically significant increases in the incidences of **benign ovarian luteomas** and a significant positive trend for ovarian luteomas (control, 0%; 30 ppm, 2%; 1250 ppm, 10%; 2500 ppm, 11%, $p<0.05$). One malignant luteoma was found in the high-dose group compared to none in the control or other dose groups.

This is **Acceptable/Guideline** and satisfies guideline requirements for a carcinogenicity study [OPPTS 870.4200b; OECD 451] in mice.

Discussion of Tumor Data Thiacloprid was determined to result in increases in ovary luteomas in the mid and high dose groups. Thus, thiacloprid is considered carcinogenic in the mouse. Studies have been submitted to explain a mechanism based on increased hepatic enzymes including aromatase and consequential hormonal imbalance that results in constant stimulation of the ovary to cause these tumors. This mechanism was evaluated by the Mechanisms SARC and it was determined that there are insufficient data at this time to support a possible correlation between increased hepatic aromatase and the ovary tumors. The significance of the ovary tumors will be further evaluated by the CARC.

Adequacy of the Dose Levels Tested.

In mice, dosing at the highest dose (2500 ppm) was considered by the CARC to be adequate, but not excessive, for carcinogenicity assessment . This was based on the following effects, none of which were considered to be severely adverse: 1) no treatment-related effects on survival; 2) a 14% decrease in body weight gain for males; body weight was not affected in females; 3) increases in relative liver weight and hypertrophy (severity was slight to minimal), as well as enzymes (possibly including aromatase) and eventual hepatic fatty change and necrosis (severity was slight to minimal) in both sexes; male mice had centrilobular hepatocellular degeneration at 1250 and 2500 ppm (severity was slight to minimal); 4) increases in vacuolation and atrophy of the X-zone of the adrenal in females and there was an increase in "eosinophilic luteinized cells" in the ovary to indicate possible disruption of the endocrine systems.

3. Classification of Carcinogenic Potential

On January 29, 2003, the *Cancer Assessment Review Committee* (CARC) of the Health Effects Division (HED) of the Office of Pesticide Programs (OPP) met to evaluate the carcinogenic potential of thiacloprid. In accordance with the EPA *Draft Guidelines for Carcinogen Risk Assessment* (July 1999), the CARC classified thiacloprid into the category **"Likely to be Carcinogenic to Humans"**. The Committee further recommended that a linear low-dose extrapolation approach for the quantification of human cancer risk be applied to the experimental animal tumor data and that quantifications of risk be estimated for male rat thyroid, rat uterine, and mouse ovarian tumors for thiacloprid. The data did not support a mode of action.

IV. MUTAGENICITY

The HIARC concluded that there is not a concern for mutagenicity resulting from exposure to thiacloprid. A summary of the mutagenicity/genetic toxicity data base with thiacloprid is presented in the following table.

Study	Results
Bacterial systems (*Salmonella and Escherichia)* mammalian activation gene mutation assay. Nihon Bayer (Japan), Study # 95A011, August 21, 1995. MRID #44927643.	Neither in the presence or absence of the S9 mix were there indications of increased revertants at concentrations up to and including 5000 µg/plate.
Bacterial systems (*Salmonella and Escherichia)* mammalian activation gene mutation assay. Bayer AG, Study # T4049371, February 13, 1995. MRID #45307401.	No evidence of increased revertants at dose levels up to and including 5000 µg/plate in presence or absence of S9.
Bacterial systems (*Salmonella and Escherichia)* mammalian activation gene mutation assay. Bayer AG, Study # T5054097, December 9, 1994. MRID #45307402.	No evidence of increased revertants at dose levels up to and including 5000 µg/plate in presence or absence of S9.
Bacterial systems (*Salmonella and Escherichia)* mammalian activation gene mutation assay. Bayer AG, Study # T 1053977 October 31, 1995. MRID #45307402.	*Study with metabolite KKO 2254.* No evidence of increased revertants at dose levels up to and including 5000 µg/plate in presence or absence of S9.
Bacterial systems (*Salmonella and Escherichia)* mammalian activation gene mutation assay. Bayer AG, Study # T 8053974, October 26, 1995. MRID #45307406.	*Study with metabolite WAK 6999.* No evidence of increased revertants at dose levels up to and including 5000 µg/plate in presence or absence of S9.
Bacterial DNA damage/repair in *Bacillus subtilis.* Nihon Bayer (Japan), Study # 97220, No date provided. MRID No.: 45344001.	No growth inhibition (differential zones) observed up to 6660 µg/disc in presence or absence of S9 mix.
Mammalian cells in culture gene mutation assay in V79 (CHO). Bayer AG, Study # T7054080, June 11, 1996. MRID # 44927739.	No evidence of increases in mutant frequency at dose levels up to and including 500 µg/mL in the presence or absence of S9 mix.
In vivo mammalian cytogenetic- micronucleus assay in mice. Bayer AG, Study # T0059051, November 23, 1995. MRID # 44927641.	No indication of clastogenic effect in bone marrow following a dose of 60 mg/kg.
In vitro mammalian chromosome aberration in Chinese hamster V79 cells. Bayer AG, Study No.: T5054079, November 23, 1995. MRID # 44927642.	No increases in number of aberrant metaphases at dose levels up to and including 750 µg/mL in the presence or absence of S9.
Unscheduled DNA synthesis in rat primary hepatocytes. Bayer AG, Study #T8054081, September 10, 1996. MRID # 44927738.	No evidence of unscheduled DNA repair at dose levels up to and including 500 µg/mL.

V. HAZARD CHARACTERIZATION

Acute Toxicity. Technical grade thiacloprid has an oral LD_{50} of between 700 and 1000 mg/kg in male and 300 and 500 mg/kg in female rats indicating that it is moderately toxic (Toxicity category II). The acute dermal (LD_{50} > 2000 mg/kg and inhalation LC_{50} > 0.481 mg/L) render thiacloprid as Toxicity Category III. Ocular and dermal irritation studies allowed classification into Toxicity Category IV. The dermal sensitization study did not demonstrate sensitization but the study is classified as unacceptable until resolution of certain problems.

Rat Studies. Subchronic studies in rats indicated liver effects including hypertrophy and cytoplasmic change and increased enzyme activity and body weight decreases. Subsequent special studies determined that the hepatic UDP-Glu- transferase and aromatase (in females) were increased. Thyroid hyperplasia was also evident. There is some question regarding whether or not aromatase was actually specifically increased or if the apparent increase is an artifact of the assay. However, until demonstrated otherwise, HED is assuming that thiacloprid can potentially increase hepatic aromatase. The chronic studies in rats indicated hepatocellular hypertrophy and cytoplasmic changes and increases in the activity of several hepatic enzymes as well as thyroid follicular cell hypertrophy and other changes in the thyroid. Other age related effects included retinal atrophy, lens degeneration, and sciatic nerve degenerative changes indicated that thiacloprid may accelerate age related degeneration. Thiacloprid was demonstrated to be associated with increases in thyroid tumors in males and ovary tumors in rats. The increase in UDP-Glu-T with associated increase in the metabolism of thyroid hormones T3 and T4 with resulting stimulation of the thyroid to produce thyroid hyperplasia was responsible for the induction of the thyroid tumors. Similarly it has been proposed that the induction of aromatase with changes in estrogen balance results in uterine tumors. The latter hypothesis requires further verification.

Mouse studies. Thiacloprid was demonstrated to affect the liver as indicated by increases in weight, hypertrophy, fatty vacuolation and degeneration and to have an unusual finding of increased hypertrophy and vacuolation of the adrenal X zone. Thiacloprid was demonstrated to induce ovary luteomas in mice as well as non-neoplastic conditions including "eosinophilic luteinized cells"in the ovary. In the subchronic study there were also treatment related increases in ovary "activated interstitial glands" and there was an effect of thiacloprid on the degree of advanced corpora lutea with higher doses being less severe. Both the effects in the adrenal gland X-zone and the ovary (including tumors and the non-neoplastic conditions) were attributed to increased hepatic aromatase but more definite verification is required for this relationship.

Dog Studies. Toxicity in the dog demonstrated that the liver was affected as indicated by increased activity of certain enzymes such as epoxide hydrolase, glutathione transferase, GS-transferase, N-demethylase and O-demethylase in two separate studies. The enzyme changes were accompanied by decreases in T4 and possibly an increase in thyroxine binding capacity. Prostate weight was also increased. The dog subchronic feeding study indicated several possible effects in the testis, prostate, epididymides, uterus and vagina that could not be verified in the dog chronic feeding study possibly because the dogs were more mature when examined in the chronic study. Overall the dog is considered to be less sensitive than the rat. Spleen weight data indicated lower values for all dosed groups but there was no associated histopathological finding and there were no changes in the blood elements to support a conclusion that there was an effect of thiacloprid on this organ.

Subchronic Dermal Toxicity. A 28-day dermal toxicity study indicated toxicity at 100 mg/kg/day in males that consisted of moderate centrilobular hypertrophy and cytoplasmic changes at higher doses there were effects liver weight and increases in thyroid follicular epithelium pathology. This study is considered limited since only 5 rats per sex were used.

Subchronic Inhalation Toxicity. A four week inhalation toxicity study demonstrated a NOAEL and LOAEL of 2 and 18.2 mg/m^3 based on hepatic hypertrophy and increase in N-demethylase. At higher doses (100 to 200 mg/m^3) there was piloerection and bradypnea in both sexes and hypertrophy of the thyroid epithelium in males and increases in thyroid weight in both sexes and increases in T3 and T4 in females as well as further increases in hepatic enzymes aminopyrine-N-demethylase (N-DEM) and hepatocyte hypertrophy.

Neurotoxicity testing. There are acute, subchronic and developmental neurotoxicity studies with thiacloprid. The acute study demonstrated neurotoxicity as indicated by decreased motor activity and at higher doses there were signs of dilated pupils, tremors, decreased activity, ataxia, cool-to-touch body, urine stain fur and partially closed eyelids. The subchronic neurotoxicity study demonstrated only one indication of possible neurotoxicity being a decrease in hindlimb grip strength. The developmental neurotoxicity study is currently classified as Unacceptable/Guideline because additional morphological measurements are needed for the low and mid dose groups in order to determine a NOAEL for apparent decreased brain measurements.

Developmental Toxicity. The rat and rabbit developmental toxicity studies indicated that for both species, developmental toxicity was at the same dose as maternal toxicity. Thus, there was no *quantitative* increase in susceptibility. The rabbit developmental toxicity demonstrated a NOAEL and LOAEL of 2 and 10 mg/kg/day based on decreased body weight gains and food consumption and fecal output. Developmental toxicity indicated only decreased fetal weights. The rat developmental toxicity study demonstrated a NOAEL and LOAEL of 10 and 50 mg/kg/day based on decreased body weight and food consumption and increased urination and changes in water consumption. There were also increased resorptions. Developmental toxicity was evident by there being increases in variations (wavy ribs and asymmetric sternebrae), and malformations (dysplastic humerus, radius and scapulae) and decreased fetal weight. Overall, because of the several effects seen at the LOAEL for developmental toxicity, it was determined that the rat study demonstrates a *qualitative* increase in susceptibility.

Reproduction Study. The rat multigeneration reproduction study indicated liver and thyroid weight effects and hepatocytomegaly and thyroid follicular hypertrophy as well as dystocia in the parental groups. Offspring toxicity occurred at the same dose based on decreased pup weight during lactation. Special studies were conducted to attempt to demonstrate a mechanism for dystocia but no direct effects of thiacloprid were found on the female reproductive system that would indicate a mechanism for the dystocia. The possibility that hormonal imbalance due to induction of hepatic enzymes upsets the birthing signals remains a possibility.

Mutagenicity/Genetic Toxicity. The mutagenicity studies with thiacloprid and its metabolites did not indicate a pattern of positive responses such that there is a mutagenicity/genetic toxicity concern for thiacloprid..

Metabolism. The metabolism and pharmacokinetics studies demonstrated that thiacloprid is rapidly absorbed (maximum plasma concentration within 1 to 4 hours depending on the dose), retention in tissues was unremarkable (i.e. no evidence of bioaccumulation) and the pathways of degradation (hyroxylation, opening of the thiazolidine ring, formation of an oxazole ring, oxidation and methylation and oxidative cleavage of the methylene bridge and conjugation of some of the metabolites.

Dermal Absorption. A dermal absorption factor of 5% was determined based on the results of a dermal absorption study with monkeys with the 40.4% liquid formulation SC-480. This 5% value can also be used for other liquid thiacloprid formulations that can be shown to be similar to SC-480 and for aqueous dilutions of most thiacloprid formulations. The 5% dermal absorption factor would likely overestimate the risk for granular formulations to mixers and loaders but to the nature of the granular material. However, the 5% value can be used for risk assessment purposes until the registrant provides dermal absorption data with granular formulations that would support a lower value.

VI. DATA GAPS / REQUIREMENTS

There are no data gaps for guideline studies at this time.

VII. ACUTE TOXICITY

Acute Toxicity of Thiacloprid

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral	4497730	LD_{50} between 100 and 140 mg/kg for males and 140 and 200 mg/kg for females	II
81-1	Acute Oral	44927644	621 mg/kg - males 396 mg/kg - females	II
81-2	Acute Dermal	44927731	LD_{50} > 2000 mg/kg	III
81-3	Acute Inhalation	44927732	LC_{50} > 0.481 mg/L	III
81-4	Primary Eye Irritation	44927635	Ocular irritation resolving in 24 hours.	IV
81-5	Primary Skin Irritation	44927635	Very slight erythema resolving in 72 hours.	IV
81-6	Dermal Sensitization	44927733	Did not indicate sensitization but study is unacceptable at this time (a)	

Refer to DP Barcode D287034. Test material YRC 2894 (97.2% ai for the inhalation study and 97.3% for all other studies). Summary table provided by Tracy Keigwin, RD, December 31, 2002.
(a) As per e-mail message from Tracy Keigwin to David Soderberg, the dermal sensitization study is now acceptable and there was no evidence of dermal sensitization.

VIII. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

Summary of Toxicological Dose and Endpoints for Thiacloprid

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (all population groups)	NOAEL = **3.1** mg/kg UF = **300** **Acute RfD = 0.01** mg/kg.	FQPA SF = **1** **aPAD** = acute RfD / FQPA SF = **0.01** mg/kg	Acute Neurotoxicity - rats LOAEL = 11 mg/kg/day based on decreased motor activity in females.
Chronic Dietary (All populations)	NOAEL= **1.2** mg/kg/day UF = **300** **Chronic RfD = 0.004** mg/kg/day	FQPA SF = **1** **cPAD** = chronic RfD / FQPA SF = **0.004** mg/kg/day	Chronic feeding in rats. LOAEL = 2.5 mg/kg/day based on hepatic hypertrophy and cytoplasmic change and thyroid hypertrophy and retinal degeneration.
Incidental Oral - Short and Intermediate term	NOAEL= **1.2** mg/kg/day	**Residential** LOC for MOE = **300**[a] **Occupational** = N/A	Chronic feeding in rats. LOAEL = 2.5 mg/kg/day based on hepatic hypertrophy and cytoplasmic change and thyroid hypertrophy.
Dermal- *All* Durations.	Oral NOAEL= **1.2** mg/kg/day (dermal absorption rate = 5%) (a)	**Residential** LOC for MOE = **300**[a] **Occupational** LOC for MOE= **100**	Chronic feeding in rats. LOAEL = 2.5 mg/kg/day based on hepatic hypertrophy and cytoplasmic change and thyroid hypertrophy.
Inhalation - *All* Durations.	Inhalation NOAEL = **0.542** mg/kg/day (converted)	**Residential** LOC for MOE = **300**[a] **Occupational** LOC for MOE = **100**	28 day inhalation study in rats. LOAEL = 4.93 mg/kg/day based on liver hypertrophy increased N-DEM.

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable.

a; The 5% dermal absorption factor should be used in route-to-route extrapolation.

NOTE: The Special FQPA Safety Factor recommended by the HIARC **assumes** that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

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R086534

Chemical:	**?3-?(6-Chloro-3-pyridinyl)methylU-2-thia**
PC Code:	**014019**
HED File Code	**13000 Tox Reviews**
Memo Date:	**10/06/2003**
File ID:	**TX0052140**
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