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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: ***Trifloxystrobin***- Report of the Hazard Identification Assessment Review Committee

FROM: William B. Greear, MPH William B. Greear 5/26/99
Registration Action Branch 3
Health Effects Division (7509C)

THROUGH: Pauline Wagner, Chairman Pauline Wagner
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

And

Jess Rowland, Co-Chairman
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TO: Mary Rust
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On May 11, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base on trifloxystrobin, established Reference Doses (RfDs) and selected the toxicological endpoints for occupational/residential exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to trifloxystrobin as required by the Food Quality Protection Act of 1996. The Committee's conclusions are presented in this report.

Committee Members in Attendance

Members present were David Anderson, William Burnam, Virginia Dobozy, Karen Hamenick, Pam Hurley, Mike Ioannou, Tina Levine, Sue Makris, Nancy McCarroll, Nicole Paquette, Kathleen Raffaele, Jess Rowland, P.V. Shah and Pauline Wagner

Other HED members present:

Report Preparation: William B. Greear 5/26/95
William B. Greear, M.P.H., D.A.B.T.
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Report Presentation: Stephen C. Dapson 5/27/94
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I. INTRODUCTION

On May 11, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of trifloxystrobin and selected doses and endpoints for acute and chronic dietary, as well as occupational and residential exposure risk assessments, and addressed the sensitivity of infants and children from exposure to trifloxystrobin as required by the Food Quality Protection Act (FQPA) of 1996. The application of the 10x factor for potential enhanced sensitivity of infants and children from exposure to trifloxystrobin will be determined by the FQPA Safety Factor Committee (FQPA SFC). The HIARC's conclusions are presented below.

II. HAZARD IDENTIFICATION

A1. Acute Reference Dose (Acute RfD) **Females (13 +years)**

Study Selected: Developmental Toxicity - Rabbit §83-3b

MRID No.: 44496709

Executive Summary: In a developmental study (MRID# 44496709), 5 groups of 19 THOMAE RUSSIAN, Chbb:HM Rabbits from Dr. K. Thomae GmbH (Chemisch-Pharmazeutische Fabrik, 7950 Biberach, Germany) received CGA 279202 Technical (Trifloxystrobin; Purity: 96.4%; Batch No.: P.405009) in a 0.5% w/w aqueous solution of sodium carboxymethylcellulose at either 0, 10, 50, 250 or 500 mg/kg/day by oral gavage from gestation days 7 through 19, inclusive. Maternal observations and measurements included daily mortality, cage-side observations, body weights and food consumption determined on days 4, 7, 12, 16, 20, 24 and 29 post coitum. The maternal animals were sacrificed on gestation day 29 and subject to a gross necropsy, the uterine contents were examined and the fetuses were examined for external, visceral or skeletal anomalies by standard techniques.

Maternal toxicity manifested as decreased body weight gains at 50, 250 and 500 mg/kg/day during the dosing period (gestation days 7-19, statistically significant at the 2 higher doses, $p<0.01$), post dosing period (gestation days 7-29) and the entire gestation period (gestation days 0-29). However, there was a rebound in body weight gain in the 250 and 500 mg/kg/day dose groups for the post dosing period (gestation days 19-29). There was reduced food consumption in the 50 mg/kg/day dose groups and above during the dosing period, for the dosing plus post dosing period and for the entire gestation period with a rebound in food consumption noted during the post dosing period. There was reduced food efficiency noted during the same time periods for the 50 mg/kg/day dose groups and above. **The Maternal Toxicity NOAEL was 10 mg/kg/day and the Maternal Toxicity LOAEL was 50 mg/kg/day based on reduced body weights, body weight gains, food consumption and food efficiency.**

Developmental toxicity was observed as a very marginal increase in fetal and litter incidence of fused sternebrae #3 and 4 at the 500 mg/kg/day dose group, no other observations were noted. **The Developmental Toxicity NOAEL was 250 mg/kg/day and the Developmental Toxicity LOAEL was 500 mg/kg/day based on a marginal increased incidence of skeletal anomalies.**

This study is classified as Acceptable-Guideline and satisfies the requirement (OPPTS 870.3700, OPP §83-3b) for a developmental toxicity study in rabbits.

Dose and Endpoint for Risk Assessment: Developmental NOAEL 250 mg/kg/day based on increase in fetal incidence of fused sternebrae #3 and 4 at 500 mg/kg/day (LOAEL).

Comments about Study/Endpoint: The developmental effects are presumed to occur after a single expsoure (dose). Since this in an *in utero* effect, it is applicable only to the population subgroup Females 13+.

Uncertainty Factor (UF): 100 (includes 10x for inter-species extrapolation and 10x for intra-species variation).

$$\textbf{Acute RfD} = \frac{\text{250 mg/kg/day (NOAEL)}}{\text{100 (UF)}} = \textbf{2.5 mg/kg/day}$$

This risk assessment is required.

A.2. Acute Reference Dose (Acute RfD) General Population including Infants and Children.

It was determined that there was no endpoint appropriate in any study that could be used to determine the acute RfD for the general population.

B. Chronic RfD

Study Selected:	Chronic Toxicity - Dog	§83-1b
MRID No.:	44496704	

Executive Summary: In a chronic toxicity study (MRID # 44496704), 4 beagle dogs/sex/group were treated orally with 0, 2, 5, 50 or 200 mg/kg/day of CGA-279202 Technical (purity: 96.4%) in gelatin capsules for 12 months. No mortality resulted from the treatment. Animals in the 200 mg/kg/day group suffered from an increased frequency and severity of diarrhea and vomiting. Dark discoloration of the hair, skin of the paws, thorax and abdomen was noted in animals in the 50 and 200 mg/kg/day treatment groups.

Food consumption was significantly reduced ($p<0.05$) in the high dose female group for weeks 2 and 3. However, treatment did not affect the mean body weight values. Although some hematological parameters for the treated animals were statistically different from those of the control animals, none of the parameters demonstrated a significant treatment effect. Mean serum albumin levels were reduced for the males in the 50 ($p<0.05$) and 200 mg/kg groups ($p<0.01$) for the three sampling times (weeks 13, 26, and 52). The albumin level for the females was not affected. Total bilirubin was reduced at weeks 13 and 26 for the 200 mg/kg males ($p<0.05$) and at all three sampling times for the 200 mg/kg females (13 and 52 weeks, $p<0.05$, 26 weeks, $p<0.01$). Triglycerides were increased for the 200 mg/kg males at 13 and 52 weeks ($p<0.01$) and for the 200 mg/kg females at 13 ($p<0.05$) and 26 weeks ($p<0.01$). Mean serum alkaline phosphatase activities were increased for the 200 mg/kg males at all sampling times ($p<0.01$) and for the 50 mg/kg males at 26 ($p<0.05$) and 52 weeks ($p<0.01$). Serum alkaline phosphatase activities for the 200 mg/kg females were increased at week 52 ($p<0.05$). There were no treatment-related effects upon the urinalysis parameters.

At the necropsy, the mean absolute liver and testes weights were increased for the 50 ($p<0.05$) and 200 mg/kg males ($p<0.01$). The mean relative liver weight was increased for the 200 mg/kg male group ($p<0.01$). The mean relative testes weights were increased for the 50 ($p<0.05$) and 200 mg/kg groups ($p<0.01$). The mean relative liver weight was increased for the 200 mg/kg females ($p<0.01$). An increased number of animals exhibited hepatocellular hypertrophy in the 50 mg/kg females (3/4) and the 200 mg/kg males (3/4) and females (4/4), compared to the control group (1/4 males, 0/4 females). Likewise, bone marrow hypocellularity was noted for a greater number of animals in the 200 mg/kg group (males: 3 vs. 1 for the controls, females: 4 vs. 2 for the controls).

The LOAEL is 50 mg/kg/day, based on The NOAEL is 5 mg/kg/day.

This chronic toxicity study in the dog is Acceptable-Guideline, and satisfies the requirement for a chronic oral study (83-1b) in dogs.

Dose and Endpoint for Establishing RfD: NOAEL = 5 mg/kg/day based on increased incidence of clinical signs, increased mean liver weight, and hepatocellular hypertrophy. The LOAEL is 50 mg/kg/day.

Uncertainty Factor(s): 100 (includes 10x for inter-species extrapolation and 10x for intra-species variation).

$$\textbf{Chronic RfD} = \frac{\text{5 mg/kg/day (NOAEL)}}{\text{100 (UF)}} = \textbf{0.05 mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factor(s): The lowest NOAEL in the most sensitive species following chronic exposure. Also, the toxic effects observed (liver effects and/or body weight decreases) in dogs were also seen in rats in the chronic toxicity and the multigeneration reproducitons study.

This risk assessment is required.

C. Occupational/Residential Exposure

1. Dermal Absorption

Dermal Absorption Factor: No dermal absorption studies are available. However, the LOAEL of 337 mg/kg/day observed in the 28-day range-finding study in rats (MRID 44496643) can be compared to the LOAEL of 1000 mg/kg/day observed in the 28-day dermal toxicity study in rats (MRID 44496704) to yield a calculated dermal absorption factor of approximately 33 %. Both of the LOELs were based on increases in liver weight.

1. Short-Term Dermal (1-7 days)

Study Selected: 28-day Dermal Toxicity Study - Rat §82-2

MRID No.: 4496703

Executive Summary: In a 28-Day Repeated Dermal Toxicity Study in the Rat (MRID # 44496703, CGA 279202 Technical (trifloxystrobin, 96.4% a.i), mixed with ionized water in 0.5% (w/w)carboxymethylcellulose and aqueous polysorbate 80, was applied to the clipped skin of 5 Tif:RAIf (SPF) hybrids of RII/1 x RII/1 rats/sex/dose at concentrations of 0,10,100,1000 mg/kg/day. The test article was applied for 6 hours/day, 5 days/week (4 ml/kg-BW) for a total of 4 weeks using an occlusive dressing.

All animals survived the treatment. There were no compound related effects in mortality, clinical signs, body weight, food consumption, hematology, clinical chemistry, or gross and histologic pathology. Both absolute and relative weights of the liver and kidneys increased by 17 and 15%, respectively, in males of group 4 (1000 mg/kg).

The LOAEL (systemic) is 1000 mg/kg/day in males, based on increases in mean absolute and relative liver and kidneys weights. The NOAEL (systemic) is 100 mg/kg/day.

The NOAEL (dermal) for both sexes is 1000 mg/kg/day, based on absence of treatment-related dermal irritations in both sexes.

This 28-Day Repeated Dermal Toxicity Study in the Rat is classified Acceptable-Guideline, and satisfies the requirement for a 28-day dermal study (82-2) in rats.

Dose and Endpoint for Risk Assessment: Dermal NOAEL = 100 mg/kg/day based on the increase in liver and kidney wts at 1000 mg/kg/day

Comments about Study/Endpoint:Study Selected: This study was selected since the exposure route (dermal) and duration of the study are appropriate for this route (dermal) and exposure period of concern (1-7 days).

This risk assessment is required.

2. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: 28-day Dermal Toxicity Study - Rat §82-2

MRID No.: 4496703

Executive Summary: see 28-Day Dermal - Rat in Section II.1.

Dose and Endpoint for Risk Assessment: Dermal NOAEL = 100 mg/kg/day based on the increase in liver and kidney wts at 1000 mg/kg/day

Comments about Study/Endpoint:Study This study was selected since the exposure route (dermal) and duration of the study are appropriate for this route (dermal) and exposure period of concern.

This risk assessment is required.

3. Long-Term Dermal (Several Months to Life-Time)

Study Selected: Chronic Toxicity - Dog §83-1b

MRID No.: 44496704

Executive Summary: see Chronic Toxicity Study in Dogs in Section II.B.

Dose and Endpoint for Risk Assessment: NOAEL = 5 mg/kg/day based on increased incidence of clinical signs, increased mean liver weight, and hepatocellular hypertrophy. The LOAEL is 50 mg/kg/day.

Comments about Study/Endpoint/Uncertainty Factor(s): This dose/endpoint/ study was used for establishing the chronic RfD. Since an oral value was selected the 33% dermal absorption factor should be used for route-to-route extrapolation.

This risk assessment is required.

4. Inhalation Exposure (Any Time Period)

Only an acute inhalation LC_{50} (4.65 mg/L) study was available in the database Therefore, the HIARC selected the oral values for inhalation exposure risk assessments. Since an oral dose is used, risk assessment should follow the route-to-route extrapolation as below:

The inhalation exposure component (i.e. μ a.i./day) using 100 % absorption rate (default value) and application rate should be converted to an **equivalent oral dose** (mg/kg/day). This oral equivalent dose should then be compared with the following NOAELs to calculate the Margin of Exposure for the respective exposure scenarios:

For Short-Term and Intermediate-Term:	250mg/kg/day
For Long-Term	5 mg/kg/day

The inhalaiton and dermal MOEs can NOT be combined since a dermal NOAEL was selected for Short and Intermediate term exposure scenarios.

This risk assessment is required.

D. Recommendation for Aggregate Exposure Risk Assessments

There are no residential uses at this time. Therefore, aggregate exposure risk assessment will be limited to food + water.

For **acute** aggregate exposure risk assessment, combine the high end exposure values from food + water and compare it to the acute RfD.

E. Margins of Exposures for Occupational/Residential Exposure Risk Assessments

A MOE of 100 is adequate for occupational exposure risk assessments. The MOE for residential exposure will be determined during risk characterization by the FQPA Safety Committee.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Carcinogenicity Study in Rats

Executive Summary

In a chronic toxicity/carcinogenicity study (MRID 44496711) CGA-279202 technical, 96.2%) was administered to 70 Tif: RalF (SPF)rats/sex/group in the diet at dose levels of 0, 50, 250 750 or 1500 ppm (M: 0, 1.95, 9.81, 29.7 or 62.2 mg/kg/day; F: 0, 2.22, 11.37, 34.5 or 72.8 mg/kg/day) for 2 years. Additionally, groups of 10 rats/sex/group were fed the same diets for 53 weeks and then sacrificed. Observations for clinical signs of toxicity, body weight, food consumption, ophthalmology, hematology, clinical chemistry, organ weights, gross necropsy and histopathology were determined.

There were no compound related effects in mortality, ophthalmology, hematology, clinical chemistry, urinalysis, organ weights, or gross and histologic (including tumors) pathology. Towards the end of the study, diarrhea was observed in several males in the 1500 ppm group. Body weights were decreased in males in the in the 750 ppm (5.2% at 51 weeks) and 1500 ppm (16.3% at 51 weeks) groups. Body weights were also decreased in females in the 750 ppm (10.8% at 51 weeks) and in the 1500 ppm (26.2% at 51 weeks) groups. Body weight gain was decreased in males by 5% (750 ppm) and 13% (1500 ppm) and in females by 10% (750 ppm) and 19% (1500 ppm) after 12 weeks. Food consumption was decreased in females in the 1500 ppm group (7.9% from week 1-103). **The LOEL is 750 ppm (M: 29.7 mg/kg/day; F: 34.5 mg/kg/day), based on decreased body weights and body weight gain. The NOEL is 250 ppm (M: 9.81 mg/kg/day; F: 11.37 mg/kg/day).**

MRID No.: 44496711

Discussion of Tumor Data **There was no evidence of carcinogenicity**

Adequacy of the Dose Levels Tested The adequacy of the dosing is indicated by the decrease in body weight of males (16.3% at 51 weeks) and females (26.2% at 51 weeks) and a decrease in body weight gain of 13% in males in the 1500 ppm group and 19% in females in the 1500 ppm group after 12 weeks. Food consumption was decreased 7.9% in females at 1500 ppm..

2. Carcinogenicity Study in Mice

Executive Summary

In a carcinogenicity toxicity study (MRID 44496705), CGA-279202 (96.2%, Batch No. P.405009 was administered to 70 Tif: MAGf (SPF) mice/sex/dose in the diet at dose levels of 0, 30, 300, 1000 or 2000 ppm (M:0, 3.90, 39.4, 131.1 or 274 mg/kg/day; F: 0,

3.51, 35.7, 124.1 or 246 mg/kg/day) for 18 months. Additional groups of 10 mice/sex were fed the test diets for a period of 52 weeks and then sacrificed. Observations for clinical signs of toxicity, mortality, hematology, organ weights, gross necropsy and histopathology were made.

There were no compound related effects on mortality or clinical signs of toxicity. Body weights were decreased for females in the 300 ppm (10% at 43 weeks), 1000 ppm (7% at 43 weeks) and 2000 ppm (11% at 43 weeks). Body weight gain was decreased in females in the 300 ppm (21% at 43 weeks), 1000 ppm (16% at 43 weeks) and 2000 ppm (20% at 43 weeks). Mean liver weights were increased in males in the 2000 ppm group at 39 weeks (49%) and 79 weeks (22%), and in females in the 2000 ppm group (5%) at 79 weeks. Mean relative liver weights were increased in males in the 2000 ppm group at 39 weeks (27%) and 79 weeks (25%), and in females in the 2000 ppm group at 39 weeks (14%) and 79 weeks (12%). There was an increase in fatty change in the liver of male mice at 2000 ppm (48/60; control 41/60). Single cell necrosis of the liver was increased in males in the 1000 ppm (17/60; control 7/60) and 2000 ppm (26/60) groups and in females in the 2000 ppm group (17/60; control 7/60). Necrosis of the liver was also increased in females in the 2000 ppm group (10/60; control 3/60). Hepatocellular hypertrophy was increased in females in the 1000 ppm (15/60; control 9/60) and 2000 ppm (26/60) groups. Chronic reactive hyperplasia of the mesenteric lymph node was increased in females in the 1000 ppm (17/47; control 9/44) and 2000 ppm (17/47) groups. There was an increase in systemic malignant lymphoma with statistical significance (trend test) in the bone marrow, kidneys, and lacrimal gland in males in the 2000 ppm group and in the ovaries and salivary gland of females in the 2000 ppm group. The LOAEL is 300 ppm (35.7 mg/kg/day) in females based on decreases in body weight and body weight gain. The NOAEL is 30 ppm (3.51 mg/kg/day).

[The LOAEL in males is 1000 ppm (131.1 mg/kg/day) based on liver pathology. The NOAEL is 300 ppm (39.4 mg/kg/day)].

MRID No.44496705

Discussion of Tumor Data: There was an increase in systemic malignant lymphoma with statistical significance (trend test) in the bone marrow, kidneys, and lacrimal gland in males in the 2000 ppm group and in the ovaries and salivary gland of females in the 2000 ppm group.

Adequacy of the Dose Levels Tested: The adequacy of the dosing is indicated by the decrease in body weight of females (11% at 43 weeks) in the 2000 ppm group and in liver pathology in both sexes at 2000 ppm.

3. Classification of Carcinogenic Potential

The classification of trifloxystrobin was made by an ad hoc subcommittee of the Cancer Assessment Review Committee on May 27, 1999, that trifloxystrobin would be classified as a "Not Likely Human Carcinogen".

IV. MUTAGENICITY

Nine acceptable studies on trifloxystrobin were available for review; summaries of these studies follow:

MUTAGENICITY SUMMARY FOR TRIFLOXYSTROBIN

Eight acceptable genetic toxicology studies were available for review. The results from these studies indicate that trifloxystrobin, Z and E-isomers of trifloxystrobin, and two metabolites were not mutagenic in *Salmonella typhimurium* or *Escherichia coli*. There was, however, a positive, dose-related increase in mutation in Chinese hamster V79 lung fibroblasts at 100-250 µg/mL in the presence of S9 activation. There was no evidence of clastogenicity *in* vitro or clastogenicity and/or aneuploidy *in vivo*. Similarly, trifloxystrobin did not induce unscheduled DNA synthesis (UDS) in primary rat hepatocytes. No relevant data were found in the open literature.

The acceptable studies satisfy the 1991 mutagenicity guideline requirements. Under the OPP testing scheme, the positive data from the *in vitro* gene mutation assay triggers the need for an assay to determine interaction with the mammalian gonad. However, the HIARC concluded that since there was no evidence of an adverse effect on germinal cells from the entire toxicology database, which included a two-year reproductive toxicity and two developmental toxicity tests, an assay to evaluate interaction with gonadal DNA was not warranted. Summaries of the acceptable studies are presented below:

Gene Mutations

1) Gene Mutation: S. typhimurium and E. Coli (MRID 44496712) - In a reverse gene mutation assay in bacteria (MRID 44496712), mutant cultures of Salmonella typhimurium strains TA 98,TA100, TA102, TA1535, TA1537 and Escherichia coli strain WP2 uvrA were treated for 48 hours at 37 degrees C with trifloxystrobin technical (purity 96.4%) at concentrations in triplicate ranging from 312.5 to 5000 µg/plate with and without mammalian metabolic activation in an initial experiment, and from 61.73 to 5000 µg/plate with/without activation in a confirmatory (independent) experiment. The mammalian metabolic activation system was prepared from Aroclor 1254-induced rat liver S9 fraction, supplemented with NADP(H)-generating co-factors. Strain-specific mutagens were used as positive controls in both experiments. Whereas precipitation of

test material was observed at the two highest doses in both assays, none of the tested concentrations of the test article with or without metabolic activation were toxic, or increased the incidence of revertants compared to the vehicle control (DMSO), in contrast to the positive responses of all mutagen-treated controls.

2) Gene Mutation: S. typhimurium and E. Coli (MRID 44496715) - In a reverse gene mutation assay in bacteria (MRID 44496715) triplicate cultures of the mutant strains of mutation assay Salmonella typhimurium (TA98, T100, TA102, TA1535, TA1537) and Escherichia coli WP2 urvA were exposed for 48 hours to CGA 357261 technical (Z,E-isomer of trifloxystrobin, 99%) dissolved in dimethylsulfoxide in two trials at concentrations ranging from 312.5 to 5000 μg/plate in the presence and absence of the post-mitochondrial supernatant (S9 fraction) from Aroclor 1254-stimulated male rat liver (supplemented by NADP(H) generating cofactors, as an exogenous mammalian metabolic activation. In addition to vehicle (DMSO) controls, other cultures were treated to strain-specific mutagens. After the 48-hour incubation, colonies of revertant cells from test cultures were counted and compared to vehicle control counts; nonstatistical analysis criteria (1.5X or 2X fold) were used to define a positive response. In neither trial was an increase in revertant colonies observed at any concentration of any of the six bacterial strains treated up to the limit dose, 5000 μg/plate, with/without activation, accompanied by normal background growth in all strains at all concentrations.

3) Gene Mutation: S. typhimurium and E. Coli (MRID 44496716) - In a reverse gene mutation assay in bacteria (MRID No. 4496716), triplicate cultures of Salmonella typhimurium strains TA98, TA100, TA102, TA1535, TA1537 and Escherichia coli strain WP2 *uvr*A were exposed in two trials to CGA-373466 (99%) in acetonitrile at five concentrations ranging from 312.5 to 5000 μg/plate in the presence and absence of a metabolic activation system consisting of the post-mitochondrial (S9) fraction of Arochlor 1254-induced male rat liver. In addition to solvent controls, additional cultures were treated with strain-specific mutagens as positive controls. After 48 hours incubation at 37 degrees C, the frequency of revertant colonies in test cultures was compared to solvent controls. Nonstatistical analysis criteria (1.5X or 2X fold) were used to define a positive response. In no strain at any concentration of test article was an increase over negative controls in the incidence of revertant colonies observed, in contrast to the strong positives found in all mutagen-treated cultures.

4) Gene Mutation: S. typhimurium and E. Coli (MRID 44496717) - In a reverse gene mutation assay in bacteria (MRID 44496717), triplicate cultures of Salmonella typhimurium strains TA98, TA100, TA102, TA1535, TA1537 and Escherichia coli strain WP2 *uvr*A were exposed in two trials to test article in dimethylsulfoxide (DMSO) for 48 hours at five concentrations ranging from 312.5 to 5000 μg/plate in the presence and absence of the post-mitochondrial supernatant (S9 fraction) from Arochor 1254-induced male rat liver. In addition to vehicle (DMSO) controls, additional cultures were treated with strain-specific mutagens as positive controls. Following the two days incubation, the frequencies of revertant colonies in test cultures were compared to DMSO controls.

using the criterion of multiplicity (1.5 to 2.0 x-fold) to define a positive response for the test article. In none of the treated cultures at any concentration was an increase in revertant colonies over negative controls observed, in contrast to the strong positives in all mutagen treated cultures.

5) Gene Mutation: Chinese Hamster V79 (MRID 44496713) - In a mammalian cell forward gene mutation assay (MRID 44496713), duplicate cultures of V79 Chinese hamster lung cells were exposed in three independent trials to Trifloxystrobin technical (96.4%) dissolved in dimethylsulfoxide (DMSO) for five hours at concentrations ranging from 11.11 to 833.5 μg/mL in cultures activated by post-mitochondrial supernatant (S9 fraction) from Aroclor 1254-induced rat liver (supplemented with NADP(H)-generating co-factors), or for 21 hours at test concentrations ranging from 0.14 to 833.5 μg/mL in the absence of such activation. In addition to vehicle (DMSO) controls, additional cultures of V79 cells were exposed to the mutagens dimethylnitrosamine (1.0 μL/mL DMN, active only under metobolic activation) and ethylmethanesulfonate (0.3 μL/mL EMS, active directly without such activation) as positive controls. Following subculturing for 5 to 7 days (expression period) to accumulate any mutations, detection of gene mutation colonies was quantified by comparing 6-thioguanine (6-TG)-resistant colonies in test and vehicle control cultures. A test article concentration of 833.5 μg/mL was the highest that could be applied to cell cultures, because of severe solubility limitations; precipitation of test substance was also visible at concentrations as low as 150 μg/mL with activation, and 50 μg/mL without. In the first trial, severe (>90%) cytotoxicity was observed at the highest test concentration with/without S9 activation, precluding any analysis of mutation; lesser degrees of cytotoxicity (25-50%) were found at lower concentrations in activated cultures of trial-1 (at 277.8 μg/mL), trial-2(at 300 μg/mL) and trial-3 (at 250 μg/mL). Varying degrees of cytotoxicity were also observed in nonactivated cultures: 50% at 92.6 μg/mL in trial-1; 30% at 100 μg/mL in trial-2, and approximately the same at 150 μg/mL in trial-3. No cytotoxicity was found in activated cultures treated at concentrations less than 150 μg/mL, nor in nonactivated cultures exposed to less than 50 μg/mL. Statistically significant increases in mutant frequency were recorded in activated cultures of trial-1 at 277.8 μg/mL but not at the next lower (nontoxic) concentration (92.6 ug/mL), nor at any nontoxic concentration (11, 33, or 100 μg/mL) below the lethal 300 μg/mL of trial-2. All activated cultures of trial-3, both toxic (200, 250 μg/mL) and nontoxic (100, 150 μg/mL) concentrations provided statistically significant increases in mutant frequencies and the vehicle control frequency was within historical range (0-100 x 10^6). **We conclude that this series of experiments with V79 cells demonstrates a relevant increase in mutant frequencies, though at dose levels of cytotoxicity.** Among nonactivated cultures, consistently significant increased mutation was evident at 92.6 μg/mL in trial-1 and 100 μg/mL in trial-2 (both moderately toxic doses), but nonsignificant in trial-3 at nontoxic (50, 75, or 100 μg/mL) or toxic (150 μg/mL) concentrations. The test article, however, is considered to be equivocal in this part of study since lower absolute number of mutant colonies at 92.6 μg/mL in trial 1 was observed when comprared with negative control (14.4 vs 17.0). Compared to these varied results with the test compound, both positive controls registered strongly positive results

in all trials.

Chromosome Aberrations

6) Structural Chromosomal Aberration: Micronucleus-Mouse (MRID 44496714) - In an in vivo micronucleus assay (MRID No. 44496714), groups of Tif: MAGF/SPF (Sprague Dawley-derived) mice (5M:5F per group) were administered 20 mL/kg volumes of trifloxystrobin (96.4% active ingredient) in 0.5 % aqueous carboxymethyl cellulose (CMC) by oral gavage at single doses of 1250, 2500 or 5000 mg/kg. In addition to vehicle (CMC) control groups of 5M:5F, a group of 5 M and 5 F was given the mutagen, cyclophosphamide (CPA, 64 mg/kg) in a single oral dose. An additional 3M and 3F were also given 5000 mg/kg test article, to serve as reserves in the event of premature deaths at the high dose. High dose animals and vehicle controls were sacrificed (by CO_2 gas) 16, 24 and 48 hours after dosing; all other groups only at 24 hours. At sacrifice, femoral bone marrow was removed from each animal and prepared by conventional cytological (smear) procedures onto coded microscope slides. Polychromatic erythrocytes (1000 PCE per slide) were scored for the presence of micronuclei (MNPCE), and the ratio of PCE to normochromatic erythrocytes (NCE) among the 1000 cells counted was also determined for each slide. Differences between test and vehicle controls were calculated by Chi-Square ($F=1$; $p < 0.05$). At no dose or sampling time was a statistically significant increase over CMC controls in MNPCE found in animals treated with trifloxystrobin, and no signs of either clinical or cytotoxicity recorded. By contrast, slides from CPA-treated animals showed a large increase in MNPCE compared to negative controls, again with no reported clinical or recorded (cyto-)toxicity.

7) Structural Chromosomal Aberration: Cytogenetics-Chinese Hamster (MRID 44496718) - In an *in vitro* mammalian cytogenetic assay (MRID 44496718), duplicate cultures of Chinese hamster ovary (CHO, clone K1) cells were exposed to trifloxystrobin in dimethylsulfoxide (DMSO) in three separate experiments at concentrations ranging from 0.049 to 3.125 μg/mL without mammalian metabolic activation, and from 12.5 to 200 μg/mL in the presence of activation provided by the post-mitochondrial supernatant (S9 fraction) of Arochlor 1254-induced male rat liver. Higher concentrations of test article could not be applied due to severe cytotoxicity. Non-activated cultures of trials-1 (0.781-3.125 μg/mL) and -2 (0.049-0.195 μg/mL), were treated for 18 hours before harvesting, whereas those of trial-3 (also 0.49-0.195 μg/mL were treated for 42 hours; activated cultures of all trials were exposed for only 3 hours, followed by a 15-hour recovery in fresh non-test article medium for trials-1 (initially exposed to 12.5-50 μg/mL) and -2 (25-100 μg/mL), and 39 hours for trial-3 (12.5-50 μg/mL). In addition to vehicle controls, additional cultures were exposed to the clastogens mitomycin-C (MC, 0.2 μg/mL) and cyclophosphamide (CPA, 20 μg/mL), to serve as positive controls for, respectively, the non-activated and activated test series. Two hours prior to harvest (18 or 42 hours), all cultures were treated with Colcemid (to arrest cells in metaphase), followed by conventional cytological procedures for microscope slide preparation. Two hundred metaphases on coded slides from two cultures per dose (100 per replicate) were scored

for the standard array of structural chromatid and chromosome aberrations as well as numerical (genomic) changes (metaphase with greater than 21 centromeres), such as polyploidy and reduplication figures. The incidences of aberrations were subjected to Chi-Square analysis. The highest concentrations selected for cytogenetic analysis were cytotoxic (20-50% relative viability compared to vehicle controls) as determined by mitotic indices. At none of the concentrations in trials-1 and -2 were significant increases over DMSO controls in chromosome aberrations observed, under either activation on non-activation conditions. In trial-3, a statistically significant ($p<0.01$) increase (3.5% of cells with aberrations) was calculated in activated cultures exposed at the HDT, 50 μg/mL; however, this value is not considered biologically relevant since it is compared to a rather low concurrent negative control value (0.5%, whereas aberration incidences of 1.5% to 4.5% were registered in trials-1 and -2), and is also within the laboratory's historical solvent control data base. Hence under the experimental conditions of these repeat trials, there was no evidence of clastogenicity in CHO cells treated up to cytotoxic concentrations.

Other Mutagenic Mechanisms

8) DNA Repair-Rat Hepatocyte (MRID 44496719) - In an unscheduled DNA synthesis assay (MRID 44496719), triplicate primary rat hepatocyte cultures were exposed for 16-18 hours in two independent trials to trifloxystrobin technical (96.4% a.i.) in dimethylsulfoxide at concentrations ranging from 0.39 to 50.0 ug/mL. In addition to solvent (DMSO) controls, additional cultures were treated with 2-acetaminofluorene (2-AAF, 45 uM), to serve as positive control. Following treatment, all cultures were exposed to tritiated thymidine, and prepared by standard autoradiographic procedures for the determination of silver grain counts, a measure of unscheduled DNA repair synthesis. Trifloxystrobin was tested up to cytotoxic concentrations. In contrast to the positive control, which induced the appropriate response, there was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures (nuclear silver grain counts), was induced.

V. FQPA CONSIDERATIONS:

1. Acute Neurotoxicity:

Trifloxystrobin (purity 96.4%, Batch No. P.405009) was administered to Tif: RAlf Sprague-Dawley rats (10/sex/dose) by gavage, at single doses of 0 or 2000 mg/kg/day. Body weights and food consumption were recorded at pretest, day 1, and twice weekly thereafter. Clinical signs were recorded daily. Neurobehavioral assessment (functional observation battery and motor activity) was performed pretest, day one at time of peak effect (approximately 6 hours post-dosing), and on days 8 and 15. At study termination. all surviving animals were sacrificed by in situ perfusion; histopathological examination of nervous system tissue was conducted on 5 animals/sex/group.

One male from the treated group was sacrificed in extremis on day 2 of the study. This death was not considered treatment-related. No treatment-related effects were seen on body weight, weight gain, food consumption, clinical signs, functional observation battery performance or histopathological examination, or on motor-activity testing in males. For treated females, there was a slight decrease in several measured motor-activity parameters. Interpretation of this decrease was confounded by study deficiencies: data from only 6 females/sex/group were reported for this time period, and no positive control data were submitted.

Due to study deficiencies, a LOAEL and NOAEL could not be determined for this study.

This study is classified as UNACCEPTABLE (GUIDELINE) and does not satisfy the requirement for a series 81-7 acute neurotoxicity study in rats. The study may be upgradable upon submission of requested information (additional procedural information for FOB and motor activity testing, analytical data presented as concentration of active ingredient, the referenced range-finding study, and further information regarding missing motor activity data for females). However, the lack of a NOEL for decreased motor activity in females may preclude upgrading the study.

There are no subchronic neurotoxicity screening batteries in rats that have been submitted to date.

2. Developmental Toxicity:

In a developmental study (MRID# 44496708) groups of 24 Tif: RAI f (SPF), hybrids of RII/1 x RII/2 albino rats from Animal Production, WST-455, CIBA-GEIGY Ltd., 4332 Stein, Switzerland received CGA-279202 Technical (Trifloxystrobin; Purity: 96.4%; Batch No.: P.405009) in a 0.5% w/w aqueous solution of sodium carboxymethylcellulose at either 0, 10, 100 or 1000 mg/kg/day by oral gavage from gestation days 6 through 15, inclusive. Maternal observations and measurements included daily mortality, cage-side observations, body weights and food consumption determined on days 6, 11, 16 and 21 post coitum. The maternal animals were sacrificed on gestation day 21 and subject to a gross necropsy, the uterine contents were examined and the fetuses were examined for external, visceral or skeletal anomalies by standard techniques.

Maternal toxicity was seen as reduced body weights in the 1000 mg/kg/day group on gestation days 16 and 21. There were also decreased body weight gains in the 1000 mg/kg/day group during the dosing period ($p<0.01$; gestation days 6-16), the dosing period plus post dosing period (gestation days 6-21), the entire gestation period (days 0-21) and in the 100 and 1000 mg/kg/day groups for the corrected body weight gain for the dosing period plus post dosing period ($p<0.05$ for 100 mg/kg/day and $p<0.01$ for the 1000 mg/kg/day groups). There was increased body weight gains in the 100 mg/kg/day and 1000 mg/kg/day groups in the postdosing period (gestation days 16-21) an indication of a

rebound effect. There was reduced food consumption in the 100 mg/kg/day and 1000 mg/kg/day groups during the dosing period ($p<0.05$ for the 100 mg/kg/day and $p<0.01$ for the 1000 mg/kg/day groups). No biologically relevant effects were noted in food efficiency data. **The Maternal Toxicity NOAEL was 10 mg/kg/day and the Maternal Toxicity LOAEL was 100 mg/kg/day based on reduced body weight gains and food consumption.**

No developmental toxicity was observed at dose levels tested. **The Developmental Toxicity NOAEL is equal to or greater than 1000 mg/kg/day and the Developmental Toxicity LOAEL is greater than 1000 mg/kg/day.**

This study is classified as Acceptable-Guideline and satisfies the requirements (OPPTS 870.3700, OPP §83-3a) for a teratology study in rats.

The developmental study in rabbits (MRID# 44496709) is discussed in detail in Section II. Hazard Identification, Acute Dietary. **The Maternal Toxicity NOAEL was 10 mg/kg/day and the Maternal Toxicity LOAEL was 50 mg/kg/day based on reduced body weights, body weight gains, food consumption and food efficiency. . The Developmental Toxicity NOAEL was 250 mg/kg/day and the Developmental Toxicity LOAEL was 500 mg/kg/day based on a marginal increased incidence of skeletal anomalies.**

3. Reproductive Toxicity

In a multigeneration reproduction study (MRID# 44496710), groups of Tif: RAI f (SPF) (hybrids of RII/1 x RII/2) rats (30 per sex, per dose) from Animal Production, WST-455 of CIBA-GEIGY Limited, received 0, 50, 750 or 1500 ppm CGA 279202 Technical (Trifloxystrobin; Purity: 96.4%; Batch No.: P.405009) in the diet for two successive generations (2 litters in the first generation) [Mean intakes for the 50, 750 and 1500 ppm dose groups in mg/kg/day were 3.8 for males and 4.1 for females, 55.3 for males and 58.0 for females, and 110.6 for males and 123.1 for females, respectively, in the F0 generation; from 4.2 for males and 4.4 for females, 65.5 for males and 67.0 for females and 143.0 for males and 146.0 for females, respectively, in the F1 generation]. Maternal and paternal recordings and measurements included daily clinical observations, weekly body weights (individual pup weights on days 0, 4, 7, 14, and 21 postpartum), weekly feed consumption, mating, gestation and delivery parameters (number of viable and stillborn pups on day 0 postpartum; external sex of viable pups), pup survival and physical and behavioral developmental landmarks (righting reflex and eye opening), and gross necropsy (macroscopic pathological examination) and histopathological observations in organs of parental animals showing gross pathological changes, as well as representative organs from all control and high dose F0 and F1 animals.

Systemic toxicity to the parental animals included in the F0 male high dose group, statistically significant reductions from control in body weights (90% of control, $p<0.01$),

body weight gains (76-89% of control, $p<0.01$ for days 1-134) and food consumption (87-93% of control, $p<0.01$) and in the F1 male mid high dose group as statistically significant reductions from control in body weights (70-93% of control, $p<0.01$) and there were reductions in the mid and high dose for body weight gains (92-96% of control) and food consumption (80-98% of control). No significant clinical signs of toxicity were noted in F0 or F1 males.

Systemic toxicity to the maternal animals during the premating period was noted in the F0 female high dose group as statistically significant reductions from control in body weights (91-96% of control, $p<0.01$). There were also reduced body weight gains in the mid and high dose groups, for the 1-68 day period (83% of control, $p<0.01$, other time periods 81-91% of control). The F1 female mid and high dose groups had statistically significant reductions from control in body weights (71-91% of control, $p<0.01$). Body weight gains were also slightly reduced for the mid and high dose groups ($p<0.05$ for overall mid dose group). Food consumption was statistically significantly reduced in the mid and high dose groups (except for the last 2 weeks, 79-93% of control, $p< 0.01$).

Systemic toxicity to the maternal animals during the gestation period was noted in the F0 female mid and high dose groups as statistically significant reductions from control in body weights (88-95% of control, $p<0.05$-0.01) (both gestation periods). Body weight gains were slightly reduced in the mid and high dose groups for the 1st gestation period and were more affected in the 2nd gestation period (89-90% of control, $p<0.01$ for the high dose). Food consumption was reduced in the high dose group for the 2nd gestation period (91-95% of control, $p<0.05$-0.01). The F1 female mid and high dose groups had statistically significant reductions from control in body weights (83-92% of control, $p<0.01$). Body weight gains for the mid and high dose groups were also reduced (81-98% of control; for the 0-21 day period, $p<0.05$-0.01). Food consumption for the mid and high dose groups was reduced (86-99% of control, $p<0.05$-0.01).

Systemic toxicity to the maternal animals during the lactation period was noted in the F0 female high dose group as statistically significant reductions from control in body weights (87-93% of control, $p< 0.05$-0.01) (both lactation periods). Food consumption values were reduced in the high dose group. The F1 female mid and high dose groups had statistically significant reductions from control in body weights (82-95% of control, $p<0.01$) for the lactation period. Food consumption values were slightly affected in the in the high dose group (85-90% of control).

Other systemic toxicity to the parental animals included a minimal to moderate hypertrophy of centrilobular hepatocytes in F0 animals of both sexes in the 1500 ppm dose group (males,10/30 and females, 5/30) and in F1 animals of both sexes in the 750 (males, 14/30 and females, 7/30) and 1500 ppm (males, 24/30 and females, 9/30) dose groups. There was also a slightly increased incidences of a minimal pigmentation of renal tubules in 750 ppm F0 males (7/30) and F0 animals of both sexes in the 1500 ppm dose group (males, 3/30 and females, 4/30). There were also decreased incidences of splenic

hemosiderosis in F0 and F1 animals both sexes of the 750 (F0 males, 12/30 and F0 females 15/30; F1 males, 5/30 and F1 females, 17/30) and 1500 ppm dose groups (F0 males, 9/30 and F0 females, 8/30; F1 males, 2/30 and F1 females, 14/30). There were no treatment related findings in the reproductive system of animals of either sex. **The Parental (Paternal/Maternal) Systemic Toxicity NOAEL was 50 ppm (3.8-4.2 mg/kg/day for males and 4.1-4.4 mg/kg/day for females) and the Parental (Paternal/Maternal) Systemic Toxicity LOAEL was 750 ppm (55.3-65.5 mg/kg/day for males and 58.0-67.0 mg/kg/day for females) based on reduced body weights, body weight gains, reduced food consumption and liver, renal and spleen histopathological observations.**

Systemic/developmental toxicity was noted as decreased F1a, F1b and F2 pup body weights in the mid and high dose pups at lactation days 7, 14 and 21. There was a slight increase in time to eye opening in the high dose group in both F1a, F1b and F2 litters. **The Offspring Systemic/Developmental Toxicity NOAEL was 50 ppm (3.8-4.2 mg/kg/day for males and 4.1-4.4 mg/kg/day for females) and the Offspring Systemic/Developmental Toxicity LOAEL was 750 ppm (55.3-65.5 mg/kg/day for males and 58.0-67.0 mg/kg/day for females) based on decreased pup body weights during lactation.**

No effects were noted on reproductive parameters. **The Reproductive Toxicity NOAEL is equal to or greater than 1500 ppm and the Reproductive Toxicity LOAEL is greater than 1500 ppm.**

This study is classified as Acceptable-Guideline and satisfies the requirements (OPPTS 870.3800, OPP §83-4) for a multigeneration reproduction study in rats.

4. Determination of Susceptibility

The data provided no indication of increased susceptibility in rats or rabbits from *in utero* and/or post natal exposure to trifloxystrobin. In the prenatal developmental toxicity study in rats, the NOAEL for developmental toxicity was higher than the maternal NOAEL. In the developmental toxicity study in rabbits, developmental toxicity was seen in the presence of maternal toxicity at the highest dose level. In the two-generation reproduction study in rats, efects in the offspring were observed only at or above treatment levels that resulted in evidence of parental toxicity.

5. Recommendation for a Developmental Neurotoxicity Study

The Committee determined that, based on a weight-of-the-evidence review of the available data, a developmental neurotoxicity study with trifloxystrobin in rats was not required.

i. Evidence that suggest requiring a developmental neurotoxicity study:

None

ii. Evidence that do not support a need for a developmental neurotoxicity study:

No evidence of neuropathology was seen in the acute and subchronic toxicity studies. Neither brain weight nor histopathology (nonperfused) of the nervous system were affected by treatment in the subchronic or chronic toxicity studies.

No evidence of functional abnormalities were seen in the rat and rabbit developmental toxicity or the two-generation reproduction studies.

6. Determination of the FQPA Safety Factor:

The application of an FQPA factor for the protection of infants and children from exposure to trifloxystrobin as required by FQPA, will be determined during risk characterization by the FQPA Safety Factor Committee. However, based on hazard assessment alone, the HIARC recommends to the FQPA Safety Factor Committee that the additional 10x factor should be removed because:

(i) The data provided no indication of increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure.

(ii) No evidence of developmental anomalies, including abnormalities in the development of fetal nervous system, was observed in the pre-and/or postnatal studies.

(iii) The toxicology data base is complete, except for the acute neurotoxicity study in rats.

VI. DATA GAPS

1. Acute Neurotoxicity - Rat

VII. HAZARD CHARACTERIZATION

The database is incomplete in that an acute neurotoxicity study in the rat is a data gap. Trifloxystrobin is Toxicity III-IV for acute toxicity. However, trifloxystrobin is a strong dermal sensitizer. Trifloxystrobin is positive for mutagenicity in Chinese Hamster V79 cells, albeit at cytotoxic dose levels. However, trifloxystrobin is negative in the remaining mutagenicity studies. Developmental NOAELs and LOAELs for both rats and rabbits occurred at either the same dose levels or were above the NOAELs and LOAELs for maternal toxicity. The NOAEL for offspring effects in the 2-generation rats reproduction study occurred at a dose level equivalent to the NOAEL for parental findings. Based on these data, there was no increased susceptibility demonstrated under FQPA for infants and children. Trifloxystrobin was carcinogenic in mice following dietary administration to Tif: MAGf (SPF) mice for 18 months, producing malignant lymphoma. Trifloxystrobin was negative for carcinogenicity in rats in a 2-year study at dose levels up to 1500 ppm (62.2 mg/kg/day). . There is a high degree of confidence in the studies upon which the acute and chronic RfDs are based. The study from which an acute RfD (females 13+) was derived was a developmental toxicity study in rabbits. It is considered to be appropriate for an acute risk assessment by the HIARC because the skeletal anomalies seen at the LOAEL are presumed to occur after a single dose. An appropriate endpoint could not be determined for the risk assessment for the general population acute RfD. The study selected for the chronic RfD was a chronic toxicity study in dogs. This study exposed a common strain of laboratory dog (beagle) to a wide range of doses of trifloxystrobin. The dose selected upon which to base the RfD was 5 mg/kg/day (NOAEL).

VIII. ACUTE TOXICITY

Acute Toxicity of Trifloxystrobin

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral	44496622 44496623	LD_{50} > 5 g/kg	IV
81-2	Acute Dermal	444496626 44496627	LD_{50} > 2 g/kg	IV
81-3	Acute Inhalation	44496630	LC_{50} > 4.65 mg/L	IV
81-4	Primary Eye Irritation	44496632	mild irritant	III
81-5	Primary Skin Irritation	44496635	mild irritant	IV
81-6	Dermal Sensitization	44496637 44496638	strong sensitizer	N/A

IX. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary Females 13+	NOAEL= 250 UF = 100	Increased fetal skeletal anomalies	Developmental Toxicity-Rabbit
	Acute RfD = 2.5 mg/kg		
Chronic Dietary	NOAEL =5 UF = 100	Increased incidence of clinical signs, increased mean liver weight, and hepatocellular hypertrophy	Chronic Toxicity - Dog
		Chronic RfD = 0.05 mg/kg/day	
Short-Term (Dermal)	Dermal NOAEL= 100	Increases in liver and kidney weights	28-Day Dermal Toxicity Study in Rats
Intermediate-Term (Dermal)	Dermal NOAEL = 100	Increases in liver and kidney weights	28-Day Dermal Toxicity Study in Rats
Long-Term (Dermal) [a]	Oral NOAEL = 5	Increased incidence of clinical signs, increased mean liver weight, and hepatocellular hypertrophy	Chronic Toxicity - Dog
Short-Term (Inhalation)	Oral NOAEL = 250	Increased fetal skeletal anomalies	Developmental Toxicity-Rabbit
Intermediate and Long-Term (Inhalation) [b]	Oral NOAEL = 5	Increased incidence of clinical signs, increased mean liver weight, and hepatocellular hypertrophy	Chronic Toxicity - Dog

a= Since an oral NOAEL was selected, a dermal absorption factor of 33 % should be used for route-to-route extrapolation

b= Since an oral NOAEL was selected, inhalation absorption factor 100 % should be used for route-to-route extrapolation.