3-3-98

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DATE: **March 3, 1998**

MEMORANDUM

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

FROM: Jess Rowland
Executive Secretary,
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

THROUGH: K. Clark Swentzel, Chairman,
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
and
Mike Metzger, Co-Chairman
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Rick Loranger, Branch Senior Scientist
Registration Action Branch 2
Health Effects Division (7509C)

PC Code: 128997

On February 17, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of Tebuconazole and re-assessed the existing Reference Dose (RfD) and the toxicological endpoints selected for acute dietary as well as occupational and residential exposure risk assessments. HIARC also addressed the potential enhanced sensitivity to infants and children as required by the Food Quality Protection Act (FQPA) of 1996. The Committee's conclusions are presented in this report.

Committee Members in Attendance

Members present were Karl Baetcke, William Burnam, Robert Fricke, Karen Hamernik, Susan Makris, Mike Metzger, Melba Morrow, John Redden, Jess Rowland (Executive Secretary) and Clark Swentzel (Chairman). Data was presented by Ed Budd of Registration Action Branch 2.

Data Presentation: _____

Ed Budd, M.S.
Toxicologist

Report Preparation: _____

Jess Rowland, M.S.
Executive Secretary

I. INTRODUCTION

On April 4, 1996, the Health Effects Division's RfD/Peer Review Committee established a Reference Dose (RfD) of 0.03 mg/kg/day based on a NOEL of 3 mg/kg/day and an Uncertainty Factor of 100 for inter-species extrapolation and intra-species variability (Memorandum: G. Ghali, HED to C. Welch, RD, dated June 27, 1996).

On May 7, 1996, the Health Effects Division's Toxicology Endpoint Selection (TES) Committee selected the doses and endpoints for acute dietary as well as occupational and residential exposure risk assessments (TES Document dated June 6, 1996).

On February 17, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) re-assessed the existing RfD and the toxicology endpoints selected for acute dietary as well as occupational and residential exposure risk assessments pursuant to the Food Quality Protection Act (FQPA) of 1996. The need for the application of the FQPA safety factor to ensure for the protection of infants and children to Tebuconazole, as required by FQPA, will determined during risk characterization.

This report the supersedes the previous RfD and TES Committee reports.

II. HAZARD IDENTIFICATION

A.1. Acute Dietary **Females 13+**

Study Selected: Developmental Toxicity - Mice §83-3

MRID. Nos. 40821501

Executive Summary: In a study conducted in 1988, pregnant NMRI mice received oral (gavage) administration of Tebuconazole (93.6%) in aqueous 0.5% Cremophor EL at dose levels of 0, 10, 30 and 100 mg/kg/day during gestation days 6 through 15, inclusive. Dams were sacrificed on day 18 of gestation. No overt signs of maternal toxicity were observed in this study. An additional study was conducted to examine further the maternal toxicity at dose levels tested in the aforementioned study (also MRID 40821501). In that study pregnant mice received oral doses of Tebuconazole at doses of 0, 10, 20, 30 or 100 mg/kg/day. Maternal toxicity manifested as statistically significant decreases in hematocrit and mean corpuscular volume (at 20-100 mg/kg/day) and increased hepatic triglycerides, pale lobular liver and increased severity of hepatic vacuolization and lipidosis (at 100 mg/kg/day). For maternal toxicity, the NOEL was 10 mg/kg/day and the LOEL was 20 mg/kg/day, based on reductions in hematocrit and mean corpuscular volume. No developmental toxicity was observed at 10 mg/kg/day. There was a dose-dependent and statistically significant increase in the number of runts per litter (fetuses weighing less than 1.3 g) at 30 mg/kg/day (0.91) and 100 mg/kg/day (1.20)

compared to controls (0.21). Other developmental effects observed at 100 mg/kg/day were increased placental weights, increased numbers of resorptions/dam (not statistically significant) and increased numbers of malformed fetuses/litter. The malformations were primarily in the skull, brain and spinal column. For developmental toxicity, the NOEL was 10 mg/kg/day and the LOEL was 30 mg/kg/day, based on increased number of runts.

Dose and Endpoint for Risk Assessment: Developmental NOEL=10 mg/kg/day based on an increase in the number of runts (weight <1.3 g) at 30 mg/kg/day (LOEL).

Comments about Study and Endpoint: The developmental NOEL/LOEL established in the 1988 study was also supported by the similar developmental NOEL/LOEL established in a 1995 study conducted in the same strain (NMRI) of mice (MRID No. 43776202). In the latter study, the developmental toxicity NOEL was 10 mg/kg/day and the LOEL was 30 mg/kg/day based on marginal increases in postimplantation loss, marginal increases in the incidence of abnormal external fetal findings, and marginal retardation of skeletal development. For maternal toxicity, however, the NOEL was 3 mg/kg/day which was lower than that established (10 mg/kg/day) in the 1988 study. The Committee, however, did not select the lower NOEL because the maternal effects (hepatic enzyme induction and hepatic vacuolization) observed were not considered to be the result of a single exposure (dose) and thus not suitable for the exposure period of concern.

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

$$\textbf{Acute RfD} = \frac{\text{10 mg/kg/day (NOEL)}}{\text{100 (UF)}} = \textbf{0.1 mg/kg/day}$$

This risk assessment is required.

A.2 **Acute Dietary** **General Population including Infants and Children**

There were no toxicological effects applicable to these subpopulaitons and attributable to a single exposure (dose) observed in oral toxicity studies including the developmental toxicity studies in mice, rats and rabbits. Therefore, a dose and endpoint were not identified and an acute dietary risk assessment is not required for these subpopulations.

B. Chronic Dietary [Reference Dose (RfD)]

The RfD established in 1996 was re-assessed by this Committee pursuant to the FQPA and is discussed below:

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

MRID No. 42030601 & 42537201

Executive Summary: In a chronic toxicity study, groups of beagle dogs (4/sex/dose) were fed diets containing Tebuconazole (96%) at dose levels of 0, 100 or 150 ppm (equivalent to 0, 2.96, or 4.39 mg/kg/day for males and 0, 2.94 or 4.45 mg/kg/day for females, respectively) for 52 weeks. Histopathology revealed the adrenal glands to be the target organ for Tebuconazole-induced toxicity. Hypertrophy of adrenal zona fasciculata cells was seen in 4/4 males and 4/4 females at 150 ppm compared to 0/4 males and 1/4 females in the controls. Male dogs at 150 ppm also exhibited fatty changes in the zona glomerulosa (3/4) and lipid hyperplasia in the cortex (2/4) compared to controls (1/4 for both lesions). Female dogs at 150 ppm also exhibited fatty changes (2/4) compared to controls (1/4). For chronic toxicity, the NOEL was 100 ppm (2.96 mg/kg/day in males and 2.94 mg/kg/day in females) and the LOEL was 150 ppm (4.39 mg/kg/day in males and 4.45 mg/kg/day in females) based on histopathological lesions in the adrenal glands.

Dose/Endpoint for establishing the RfD: NOEL=2.94 mg/kg/day based on histopathological lesions of the adrenal glands at 4.39 mg/kg/day (LOEL).

Comments about Study and Endpoint: The HIARC re-affirmed the dose and endpoints selected by the RfD/Peer Review Committee in 1996 which was a revision of the previous RfD (0.01 mg/kg/day) established in 1991.

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

$$\textbf{Chronic RfD} = \frac{\text{2.94 mg/kg/day (NOEL)}}{\text{100 (UF)}} = \textbf{0.03 mg/kg/day}$$

This risk assessment is required

C. Occupational/Residential Exposure

1. Dermal Absorption

Dermal Absorption Factor: Not Applicable since dermal risk assessments are not required.

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

Study Selected: None

MRID No. None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not Applicable

Comments about Study and Endpoint: This risk assessment is not required since no systemic toxicity was observed in a 21-day dermal toxicity study in rabbits as well as dermal developmental toxicity studies in mice and rats. These studies are discussed below:

In a 21-day dermal toxicity study with New Zealand white rabbits, no dermal or systemic toxicity was seen following 15 repeated dermal applications of Tebuconazole (97.1%) at 0, 50, 250 or 1000 mg/kg/day, 6 hours/day, 5 days/week over a three week period. For dermal and systemic toxicity, the NOEL was ≥1000 mg/kg/day (MRID No. 40700937).

In a dermal developmental toxicity study with pregnant NMRI mice, no maternal or developmental toxicity was seen following dermal applications of Tebuconazole (98.1%) in aqueous 4% carboxy methylcellulose at 0, 100, 300 or 1000 mg/kg/day, 6 hours/day during gestation days 6 through 15. For maternal and developmental toxicity, the NOEL was ≥ 1000 mg/kg/day (MRID No. 42010301).

In a dermal developmental toxicity study with pregnant Wistar rats, no maternal or developmental toxicity was seen following dermal applications of Tebuconazole in 1% aqueous Cremaphor EL at 0, 100, 300 or 1000 mg/kg/day, 6 hours/day during gestation days 6 through 15. For maternal and developmental toxicity, the NOEL was ≥ 1000 mg/kg/day (MRID No. 41450801).

This risk assessment is **NOT** required.

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

Study Selected: None

MRID No. None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not Applicable

Comments about Study and Endpoint: This risk assessment is not required since

no systemic toxicity was seen in a 21-day dermal toxicity study in rabbits as well as dermal developmental toxicity studies in mice and rats. See Short-Term.

This risk assessment is **NOT** required.

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

Study Selected: None

MRID No. None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not Applicable

Comments about Study and Endpoint: Based on the use pattern, no long-term dermal exposure is expected to occur.

This risk assessment is **NOT** required.

5. Inhalation Exposure (Any-Time period)

Study Selected: 21-Day Inhalation Toxicity -Rat §82-4

MRID No. 40700938

Executive Summary: In a subchronic inhalation toxicity study, Tebuconazole (96.2% a.i.) was administered to 10 Wistar rats/sex/dose by head/nose only exposure at analytical concentrations of 0 (control air), 0 (control vehicle: 1:1 polyethylene glycol E40/ethanol), 1.2, 10.6, or 155.8 mg/m^3/day [0, 0, 0.0012, 0.0106, or 0.1558 mg/l] for 15 daily 6-hour exposures over 3 weeks. At 1.2 or 10.6 mg/m^3, there were no toxic signs or any effects on in-life parameters, on organ weights, or on gross or histologic findings. Exposure at 155.8 mg/m^3 caused piloerection. At the highest expsoure level, there was also a moderate induction of liver O-demethylase and a statistically significant induction of liver N-demethylase in both sexes. There were no effects of toxicological importance on clinical laboratory parameters or organ weights nor was there an increase in histological lesions. This study defined a LOEL of 155.8 mg/m^3/day [0.1558 mg/L/day] based on clinical signs and induction of liver microsomal enzymes. The NOEL was 10.6 mg/m^3/day [0.0106 mg/L/day].

Dose and Endpoint for Risk Assessment: NOEL=10.6 mg/m^3/day [0.0106 mg/L/day]. Based on piloerection and induction of liver microsomal enzymes at 155.8 mg//m^3/day (LOEL).

Comments about Study and Endpoint: This dose should be used for Short, Intermediate and Long-Term inhalation exposure risk assessments.

This risk assessment is required.

III. FQPA CONSIDERATIONS

1. Neurotoxicity Data

No acute or subchronic neurotoxicity studies on Tebuconazole are available. In a complete battery of subchronic and chronic studies and a reproduction study, as required for a food-use chemical, there were no indications of treatment-related effects on the central or peripheral nervous system of mice, rats, or rabbits. No changes in clinical signs, brain weights, gross necropsy results or histopathological results suggested any part of the nervous system as a target organ.

However, in the developmental toxicity studies, there was evidence of alterations to the development of the fetal nervous system in mice (increased malformations of the brain and spinal column, and exencephaly, MRID Nos. 40821501 & 43776202), in rats (anophthalmia, MRID No. 40700943) and in rabbits (neural tubule defects characterized as meningocoele and spina bifida, and hydrocephalus, MRID Nos 43776201 & 40700945). HIARC observed that effects on the nervous system of fetuses occurred only at doses of 100 mg/kg/day or higher--i.e., at doses at least 10-fold higher than the developmental toxicity NOEL (10 mg/kg/day) to be used for the assessment of acute dietary risk.

2. Determination of Susceptibility

On the basis of the NOELs and LOELs, the data provided no indication of increased susceptibility of mice, rats or rabbits to *in utero* and/or postnatal exposure to Tebuconazole. In the prenatal developmental toxicity studies in mice, rats and rabbits, the NOELs for developmental toxicity were comparable or higher than the NOEL for maternal toxicity. In all three species, maternal toxicity was minimal at the LOEL and did not increase substantially in severity at higher doses. Eventhough the maternal and developmental LOELs were the same in each study, there was more concern for the developmental effects at each LOEL. Additionally, the developmental effects were quite severe (including frank malformations) at higher doses in mice (100 mg/kg/day), rats (120 mg/kg/day) and rabbits (100 m g/kg/day). In the two-generation reproduction study, NOELs/LOELs were the same for offspring and parental systemic toxicity.

(i) Developmental Toxicity:

(a) Mice

The **oral** prenatal developmental toxicity study conducted in 1988 in NMRI mice is discussed in Section II.A.Acute Dietary. For maternal toxicity, the NOEL was 10 mg/kg/day and the LOEL was 20 mg/kg/day based on reductions in hematocrit and mean corpuscular volume. For developmental toxicity, the NOEL was 10 mg/kg/day and the LOEL was 30 mg/kg/day, based on an increased number of runts. There was a dose-dependent and statistically significant increase in the mean number of runts per litter (fetuses weighing less than 1.3 g) at 30 mg/kg/day (0.91) and 100 mg/kg/day (1.20) compared to controls (0.21). At 100 mg/kg/day , the following additional effects were also observed: increased placental weights, increased numbers of resorptions/dam (not statistically significant) and increased number of malformed fetuses/litter. The malformations were primarily in the skull, brain and spinal column. Malformations in the skull seen in 7 fetuses of 6 litters were characterized as cleft palate, micrognathia, and partial dysplasia of the parietal bone. Malformations of the neural tube seen in 5 fetuses of 4 litters manifested as enlarged brain ventricles, asymmetry of vertebral bodies, dysplasia of the spinal column and abnormal flexion of the spinal column (MRID No 40821501).

In an **oral** developmental toxicity study conducted in 1995, pregnant NMRI mice received Tebuconazole by gavage at dose levels of 0, 10, 30 or 100 mg/kg/day during gestation days 6 through 15, inclusive. Dams were sacrificed on day 18 of gestation. In a concurrent group of mice, with an identical treatment regimen, blood was collected on gestation day 16 for hematology and clinical chemistry evaluations and for liver biochemical investigations. In addition, selected tissues were weighed and examined histopathologically. In a further study, Tebuconazole was administered by gavage to pregnant mice on days 6-15 of gestation at dose levels of 0, 1 or 3 mg/kg/day and the dams were sacrificed on day 18 of gestation. Based on the results from all three studies, for maternal toxicity, the NOEL was 3 mg/kg/day and the LOEL was 10 mg/kg/day, based on hepatic enzyme induction (increased P-450 and N-demethylase activity) and on higher average degrees of vacuolization in liver cells (based on the examination of only 5 animals for each parameter). The NOEL/LOEL for maternal toxicity in the 1995 study was lower than that established in the 1988 study. For developmental toxicity, the NOEL was 10 mg/kg/day and the LOEL was 30 mg/kg/day, based on marginal increases in postimplantation loss, marginal increases in the incidence of abnormal external fetal findings, and marginal retardation of skeletal development (MRID 43776202).

In a **dermal** developmental toxicity study, pregnant NMRI mice received repeated dermal applications of Tebuconazole in aqueous 4% carboxymethylcellulose at dose levels of 0, 100, 300, or 1000 mg/kg/day during gestations days 6 through 15, inclusive. The test material was applied to shaved skin for 6 hours/day. Dams were sacrificed on day 18 of

gestation. Since no overt maternal toxicity was observed in this study, a second study, employing the same treatment regimen was conducted and additional maternal toxicity parameters were examined. In the second study, liver microsomal enzyme activities were increased, the incidence and severity of fatty changes in the liver were increased, and increases were observed in the activities of AST (GOT) and ALT (GPT) in plasma. Nevertheless, the maternal toxicity observed in this study was considered to be equivocal. No treatment-related developmental toxicity was observed in this study. For maternal and developmental toxicity the NOEL was 1000 mg/kg/day (HDT) and the LOEL was ≥1000 mg/kg/day (MRID 42010301).

(b) Rats

In an **oral** developmental toxicity study, Tebuconazole in aqueous 0.5% Cremophor EL was administered by gavage to pregnant Wistar rats on gestation days 6 through 15, inclusive, at dose levels of 0, 30, 60 or 120 mg/kg/day. Dams were sacrificed on day 21 of gestation. Slight maternal toxicity, as evidenced by increased absolute liver weights and liver/body weight ratios, was observed in the mid and high dose groups. At the high dose, slightly decreased body weights and food consumption were also noted. In the mid and high dose groups, increased skeletal variations (delayed ossification of several bones) and increased numbers of animals with supernumerary ribs were observed. At the high dose, the following was also noted: increased early and late resorptions, decreased live fetuses/dam, decreased fetal weights, and frank malformations in two fetuses (missing tail, agnatha, microtomia and anophthalmia). For maternal toxicity, the NOEL was 30 mg/kg/day and the LOEL was 60 mg/kg/day, based on increased absolute liver weights and relative liver/body weight ratios. For developmental toxicity, the NOEL was 30 mg/kg/day and the LOEL was 60 mg/kg/day, based on delayed ossification of several bones and increased numbers of fetuses with supernumerary ribs (MRID 40700943).

In a **dermal** developmental toxicity study, Tebuconazole in aqueous 1% Cremophor EL was administered dermally to pregnant Wistar rats on gestation days 6 through 15, inclusive, at dose levels of 0, 100, 300, or 1000 mg/kg/day. The test material was applied to shaved skin for 6 hours/day. Dams were sacrificed on day 20 of gestation. No evidence of maternal toxicity or developmental toxicity was observed at any dose level. It was noted that higher dose levels could have been used as indicated by the absence of maternal toxicity. For maternal and developmental toxicity, the NOEL was 1000 mg/kg/day (HDT) and the LOEL was >1000 mg/kg/day (MRID 41450801).

c Rabbits

In an **oral** developmental toxicity study, pregnant Chinchilla rabbits received Tebuconazole in aqueous 0.5% Cremophor EL by gavage at dose levels of 0, 10, 30 or 100 mg/kg/day during gestation days 6 through 18, inclusive. Dams were sacrificed on day 28 of gestation. Slightly decreased body weight gains and decreased food

consumption were noted during the dosing period in high dose does. The following developmental toxicity was observed at the highest dose tested (100 mg/kg/day): post-implantation loss (as evidenced by increased fetal resorptions and decreased numbers of live fetuses/dam), frank malformations (peromelia, malrotation of hindlimbs, palatoschisis, agenesis of claws of the hindpaw), hydrocephalus, and delayed ossification of bones. For maternal toxicity, the NOEL was 30 mg/kg/day and the LOEL was 100 mg/kg/day, based on decreased body weight gain and decreased food consumption during dosing. For developmental toxicity, the NOEL was 30 mg/kg/day and the LOEL was 100 mg/kg/day, based on post-implantation loss, frank malformations, hydrocephalus and delayed ossification. (MRID 40700945)

In another **oral** developmental toxicity study, Tebuconazole was administered by gavage to pregnant Chinchilla rabbits on gestation days 6 through 18, inclusive, at dose levels of 0, 10, 30 or 100 mg/kg/day. Dams were sacrificed on day 28 of gestation. In a concurrent group of rabbits, with an identical treatment regimen, blood was collected on gestation days 6, 12 and 19 from 5 rabbits/group for hematology and clinical chemistry evaluations. The does were sacrificed on day 19 of gestation and tissue samples were collected for liver biochemical investigations. In addition, selected tissues were weighed and examined histopathologically. In the main study, decreased body weights and decreased food consumption for gestation days 6-11 were noted in does at the high dose (100 mg/kg/day). In the concurrent study, single cell necrosis in the liver (minimal severity) was observed in all treated does (5 animals/group) at all dose levels (compared to 1/5 in the control group). In addition, focal necrosis in the liver was noted in one dam at the mid dose level. At the high dose (100 mg/kg/day), the following developmental toxicity was observed: increased post-implantation loss, slightly decreased fetal body weights, delayed or incomplete ossification sites and increased numbers of fetuses with abnormalities (including runts, hemidiaphragm, limb abnormalities and neural tube defects e.g., meningocoele and spina bifida). Based on a consideration of data from both studies, for maternal toxicity, the NOEL was <10 mg/kg/day (LDT) and the LOEL was 10 mg/kg/day, based on increased incidence of single cell necrosis (minimal severity) in liver cells. For developmental toxicity, the NOEL was 30 mg/kg/day and the LOEL was 100 mg/kg/day, based on increased post-implantation loss, decreased fetal body weights, delayed ossification of bones and increased percent of fetuses with abnormalities. The maternal toxicity NOEL and LOEL in this study were lower than in the earlier rabbit study (MRID 43776201).

(ii) Reproductive Toxicity

In a 2-generation reproduction study in rats, Tebuconazole was administered in the diet to male and female Wistar rats at dose levels of 0, 100, 300 or 1000 ppm (equivalent to 0, 5, 15 and 50 mg/kg/day) for 2 consecutive generations. Parental (systemic) toxicity was observed primarily at the high dose (50 mg/kg/day) as loss of hair (females only), decreased body weights, decreased food consumption, increased severity of spleen

hemosiderosis (females only), and decreased liver and kidney weights. Reproductive (pup) toxicity was observed at the high dose (50 mg/kg/day) as statistically significant decreased pup body weights in all litter groups (F_{1a}, F_{1b}, F_{2a}, F_{2b}) from birth through weeks 3-4. For parental (systemic) toxicity, the NOEL was 300 ppm (15 mg/kg/day) and the LOEL was 1000 ppm (50 mg/kg/day), based on loss of hair, depressed body weights, decreased food consumption, increased severity of spleen hemosiderosis and decreased liver and kidney weights. For offspring toxicity, the NOEL was 300 ppm (15 mg/kg/day) and the LOEL was 1000 ppm (50 mg/kg/day), based on decreased pup body weights from birth through weeks 3-4 in all litter groups. (MRID 40700946).

3. Recommendation for a Developmental Neurotoxicity Study

The Committee determined that a postnatal developmental neurotoxicity study in rats is **required** based on the following weight-of-the-evidence considerations:

- In the developmental toxicity studies, there was evidence of alterations to the development of the fetal nervous system in mice (increased malformations of the brain and spinal column, and exencephaly, MRID Nos. 40821501 & 43776202), in rats (anophthalmia, MRID No. 40700943) and in rabbits (neural tubule defects characterized as meningocoele and spina bifida, and hydrocephalus, MRID Nos 43776201 & 40700945). HIARC observed that effects on the nervous system of fetuses occurred only at doses of 100 mg/kg/day or higher--i.e., at doses at least 10-fold higher than the developmental toxicity NOEL (10 mg/kg/day) to be used for the assessment of acute dietary risk.

- Concern for Structure Activity Relationship. Tebuconazole is structurally related to Triadimefon (Bayleton), Triademenol(Baytan), Bitertanol (Baycor), Uniconazole (Prunit), Propiconazole(Tilt), Etaconazole (Vanguard), Azaconazole, Hexaconazole (Anvil) and Cyproconazole (SAN 619F). All of these compounds, except Etaconazole and Hexaconazole, have shown a developmental toxicity LOEL below the maternal toxicity LOEL in rats and/or rabbits.

4. Determination of the FQPA Factor:

The application of an FQPA safety factor to ensure the protection of infants and children from exposure to Tebuconazole, as required by FQPA, will determined during risk characterization.

IV. DATA GAPS

The toxicology data base is adequate as defined for a food-use chemical in 40 CFR Part 158.. The HIARC, however, has determined that a post natal developmental neurotoxicity study in rats (§83-6) is required.

VII 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+)	Developmental NOEL=10	Increased incidences of runts.	Developmental- Rat
	Acute RfD = 0.1 mg/kg/day		
Chronic Dietary	NOEL=3	Histopathological lesions of the adrenal glands in both sexes.	Chronic Toxicity - Dog
		Chronic RfD = 0.03 mg/kg/day	
Short-Term (Dermal)	Not Applicable	None; no systemic toxicity was seen at the Limit-Dose (1000 mg/kg/day) in the 21-day dermal toxicity study in rabbits or in dermal developmental toxicity studies in mice and rats.	
Intermediate-Term (Dermal)	Not Applicable	None; no systemic toxicity was seen at the Limit-Dose (1000 mg/kg/day) in the 21-day dermal toxicity study in rabbits or in dermal developmental toxicity studies in mice and rats.	
Long-Term (Dermal)	Not Applicable	Based on the use pattern, long-term dermal exposure is not anticipated.	
Inhalation (Any Time Period)	NOEL= 10.6 mg/m^3/day	Piloerection and induction of liver microsomal enzymes	21-day Inhalation Toxicity - Rat