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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: April 20, 1999

SUBJECT: PP#0E03853. Hexaconazole (ANVIL 25 SC; ANVIL 25EC/OL)) in or on Imported **Bananas. HED Risk Assessment**. DP Barcode: D252487. PC Code: 128925. Submission #: S544138. Case #: 194111

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The Health Effects Division (HED) of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The Registration Division (RD) of OPP has requested that HED evaluate toxicology and residue chemistry data and conduct dietary, occupational, residential and aggregate risk assessments, as needed, to estimate the risk to human health that will result from the use of hexaconazole in/on import bananas.

A summary of the findings and an assessment of human risk resulting from the proposed use of hexaconazole is provided in this document. The hazard assessment was provided by Albin Kocialski, Ph.D. of Registration Action Branch 1 (RAB1) and the residue chemistry data review and dietary risk assessment by Susie Chun of RAB1. There are currently no permanent existing tolerances for hexaconazole in the U.S. There are currently no products registered for hexaconazole. This action is for a tolerance on imported bananas only. No water or occupational exposure assessment is required.

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1.0 EXECUTIVE SUMMARY

HED is conducting a risk assessment for hexaconazole [(alpha-butyl-alpha-(2,4-dichloro-phenyl)-1H-1,2,4-triazole-1-ethanol)] in support of the establishment of permanent tolerances on imported bananas. A time-limited tolerance, that expired 3/31/99 (40 CFR § 180.488), was established to support the import use. HED has evaluated toxicology and residue data for hexaconazole submitted by Zeneca Corporation. **The data are adequate to support the establishment of a permanent tolerance on bananas.**

Hexaconazole is systemic triazole fungicide controlling black and yellow sigatoka diseases of bananas. It is used foliarly on bananas. For the purposes of this action only, emulsifiable concentrate formulations are being supported. Hexaconazole is formulated as ANVIL 25 EC/OL, a emulsifiable concentrate containing 250 g/L w/v a.i and as ANVIL 25 SC, a emulsifiable concentrate containing 350 g/L w/v a.i. English translations of the labels were provided. There are no proposed or existing residential uses for this product. The single maximum application rate for ANVIL 25 SC is 140 g a.i./ha (0.12 lb. a.i./A) using aerial equipment application. Hexaconazole can be applied a maximum 10 times per year for a total maximum application rate of 1400 g a.i./ha (1.2 lbs. a.i./A) with a time interval of 14 to 21 days between each application and a 0-day preharvest interval (PHI). The single maximum application rate for ANVIL 25 EC/OL is 100 g a.i./ha (0.09 lb. a.i./A) using either ground or aerial equipment application. It can be applied a maximum of 8 times in any 12 month period for a total maximum application rate of 800 g a.i./ha (0.72 lb. a.i./A) per year with a time interval of 15-21 days between each application and 0-day PHI..

There are no proposed or existing residential uses for hexaconazole. The proposed use is limited to import bananas only. Therefore, no water or occupational exposure assessment was required.

Hazard Assessment

The toxicological data base for hexaconazole is adequate to support an import tolerance.

On December 8, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of hexaconazole, reconfirmed the Reference Dose (RfD), addressed the potential enhanced sensitivity to infants and children as required by the Food Quality Protection Act (FQPA) of 1996, and selected the toxicological endpoints for acute dietary as well as occupational exposure risk assessments (there are no residential uses at this time for hexaconazole). The FQPA Safety Factor Committee (SFC) met on January 25, 1999 and addressed the potential enhanced sensitivity to infants and children as required by FQPA and recommended retaining a 10x FQPA Safety Factor for the acute dietary risk assessment only.

Hexaconazole possesses low acute toxicity by all routes of exposure [categories 3/4] with some evidence of sensitization in females. It is slightly to moderately irritating to the eye and non-irritating to the skin. Subchronic and chronic studies in mice, rats and dogs indicate that the liver is the primary target organ as generally seen by increased liver enzyme levels, liver cell hypertrophy, and fatty infiltration of the liver across species. Decreased body weight gain was also seen across species. Developmental studies in rats and rabbits showed increased

susceptibility to offspring with effects occurring at doses below maternal effects. Delayed ossification of the 7th cervical transverse process and a numerical increase in the 14th rib of rats as well as a decrease in fetal body weight in rabbit offspring were noted. A two generation reproduction study in rats revealed decreased body weight gains, deceased litter size and decreased pup survival as well as some liver effects in offspring which occurred at the same doses that induced parental toxicity. Oncogenicity in the form of benign Leydig cell tumors was noted in the rat study which resulted in a C classification **(likely to be a human carcinogen)** with a Q_1* designation assigned by the Cancer Peer Review Committee (CPRC). The most recent revision of the Q_1* occurred on the November 18, 1998 using the body weight ¾ in lieu of the body weight ⅔ interspecies scaling factor. The Maximum Tolerated Dose (MTD) was deemed not reached in the mouse study by the CPRC, which cautioned that the results of this study should be viewed conservatively.

Dose Response Assessment

An acute reference dose (RfD) of 0.025 mg/kg/day was established for the subpopulation group, females 13+ only, based on a no observable adverse effect level (NOAEL) of 2.5 mg/kg/day from a developmental study in the rat. Effects at the next higher dose level of 25 mg/kg/day were an increase in the delayed ossification of the 7th cervical transverse process and the presence of the extra 14th rib. Effects were dose responsive and statistically significant. These effects are presumed to occur after a single exposure *in utero* and therefore, are considered to be appropriate for this risk assessment.

The FQPA SFC recommended that the 10x FQPA safety factor be applied only to subpopulation group females 13+ for the determination of acute dietary risk because the effects occur only during *in utero* exposure and are not post natal effects. **The acute population adjusted dose (PAD) is 0.0025 mg/kg/day for the subpopulation group females 13+ only and includes the additional 10x FQPA safety factor.**

An acute dose and endpoint were not selected for the general population group (including infants and children) because there were no effects observed in oral toxicology studies, including maternal toxicity in the developmental toxicity studies in rats and rabbits, that are attributable to a single exposure [dose].

The chronic RfD of 0.02 mg/kg/day was determined on the basis of a 1 year oral gavage study in dogs. Fatty infiltration of the liver and an increase in liver weights occurred at the lowest observable adverse effect level (LOAEL) of 10 mg/kg/day. This RfD was originally established at an RfD meeting in August of 1993 and re-confirmed by the HIARC on December 8, 1998 (Memo, A. Kocialski and B. Tarplee, 1/21/99). A FQPA safety factor was not applied for chronic dietary risk assessment because: 1) the NOAEL used in deriving the RfD was based on liver effects in the chronic dog study; 2) the developmental effects on which the FQPA factor is based were seen in pregnant animals of a different species (rats, and rabbits); and 3) the developmental effects are considered to be "acute" effects. Therefore, the chronic PAD and the RfD are the same.

At the June 27, 1990 meeting the HED Cancer Peer Review Committee (CPRC) classified hexaconazole as a Group C (likely) carcinogen based on benign Leydig cell tumors in the male

rats. The HIARC concurred with the previous classification. A revised Q_1^* was calculated using the body weight ¾ interspecies scaling factor (Memo, L. Brunsman, 11/18/98). This resulted in a revised potency factor of 1.6×10^{-2} $(mg/kg/day)^{-1}$.

Occupational Exposure Assessment

The use of bananas is for import use only. There are currently no proposed or registered domestic uses for hexaconazole. Therefore, no occupation exposure assessment is required. If domestic uses are added in the future, an occupational exposure assessment will have to be completed.

Dietary/Aggregate Risk Estimates

There are no proposed or existing residential uses for hexaconazole. The proposed use is limited to import bananas only. **The aggregate exposure risk is limited to dietary exposure only**. If new uses are added in the future, the Agency will reassess the impact of these uses, which may result in the necessity of residential and water exposure assessments.

For all dietary analyses, the anticipated residue levels based on the field trials on banana pulp were used. The use of banana pulp residue levels provides a more realistic dietary exposure as individuals do not usually eat the banana peel. Due to the Metabolism Committee decision concerning hexaconazole (Memo, S. Willett, 6/19/95), the residue levels of the diol metabolites were also included in the dietary exposure analysis. The diol metabolites are expected to be of comparable toxicity to the parent compound. HED will require residue data on these metabolites for bananas, as well as future food uses.

The dietary exposure analyses for hexaconazole is a conservative but more realistic estimate of dietary exposure with the use of the pulp residue values and 100 percent of the commodities assumed to be treated. The residue level value of 0.56 ppm, which was the highest residue level for pulp (hexaconazole-0.17 ppm + diol metabolites- 0.39 ppm), was used in the acute dietary analysis. The residue level value of 0.11 ppm , which was the average from the field trials for pulp (hexaconazole- 0.03ppm + diol metabolites- 0.08 ppm), was used in the chronic dietary analysis.

Acute Dietary

The acute dietary exposure analysis for the population subgroup females 13+ was performed using the highest pulp residue level (parent + diol metabolites) and 100 percent crop treated. The FQPA Safety Factor of 10x was retained for the acute dietary analysis only for the population subgroup females 13+. The acute population adjusted dose (aPAD) used in the acute dietary analysis was **0.0025 mg/kg/day**.

The percent aPAD is below HED's level of concern at the 95th percentile exposure for the females 13+ subgroup. The highest % aPAD at the 95th percentile of exposure was 47% for the subgroup, females 13+ (pregnant, not nursing). Therefore, the acute dietary risk associated with the proposed use of hexaconazole on bananas is below the Agency's level of concern.

Chronic Dietary

The FQPA Safety Factor was removed (i.e., reduced to 1x) for chronic dietary exposure. Therefore the chronic PAD (cPAD) and the chronic RfD are the same . For chronic dietary risk, HED's level of concern is greater than 100% chronic PAD. All chronic (non -cancer) % cPADs for all subgroups were ≤ 1%. The results of the chronic dietary exposure analysis indicate that the chronic dietary risk associated with the proposed use of hexaconazole is below the Agency's level of concern.

Cancer Dietary

The Agency generally considers 1 x 10^{-6} as negligible risk (i.e, less than 1 in 1 million) for cancer. The results of this analysis indicate that the cancer dietary risk of 5.3 x 10^{-7} associated with the proposed use of hexaconazole is below the Agency's level of concern.

Recommendation for Tolerances

Adequate residue chemistry and toxicology data have been submitted to support the establishment of the following permanent tolerance for residues of hexaconazole expressed as parent only:

Bananas . . . . . 0.7 ppm

Note: The tolerance should be footnoted in the 40 CFR to note clearly that there are no U.S. registrations for this use.

To provide for the re-evaluation of the anticipated residues, the Agency will require under Section 408(b)(2)(E) that additional residue data be submitted within five years.

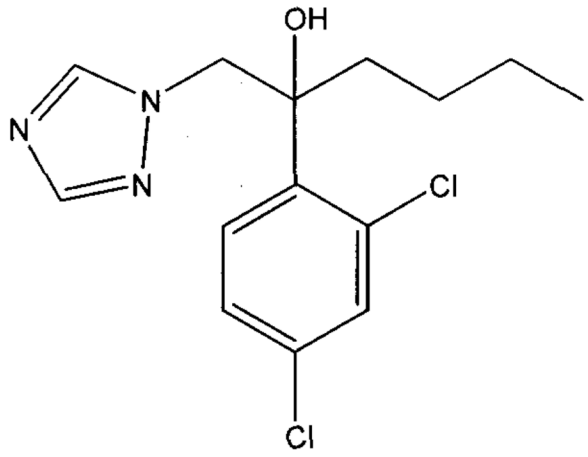
2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

2.1. Identification of Active Ingredients

Chemical Name:	(alpha-butyl-alpha-(2,4-dichloro-phenyl)-1H-1,2,4-triazole-1-ethanol)
Common Name:	Hexaconazole
PC Code Number:	128925
CAS Registry No.:	79983-71-4
Empirical Formula:	$C_{17}H_{17}Cl_2N_3O$
Molecular Weight:	314.21
Vapor Pressure (PAI):	3 x 10^{-9} Pa (@10°C) 2 x 10^{-8} Pa (@ 20°C) 9 x 10^{-8} Pa (@ 30°C)

Solubility (ppm , @ 20°C):	water	18
	methanol	246
	acetone	164
	dichloromethane	336
	toluene	59
	ethylacetate	120
	hexane	<1
Octanol/Water Partition Coefficient:	log 3.9 (PAI) (@ 20°C)	
Dissociation Constant:	pKa = 2.3 @ 25°C	

2.2. Structural Formula (Hexaconazole)



2.3. Physical and Chemical Properties

Product chemistry data for hexaconazole were reviewed (Memos, R. Lozada, 1/26/90; S. Willett, 2/19/91; J. Morales, D181190, 5/3/93; M. Flood, D194643, 9/1/94; S. Willett, D205627, 3/30/95; S. Willett, D220052, 12/11/95) and deemed adequate to fulfill the requirements for a Section 3 permanent tolerance request. Though additional inert information was requested, HED noted that this was under the purview of RD as there is no U.S. registration for this chemical (Memo, S. Willett, D220052, 12/11/95). No additional product chemistry data are required for the purposes of this permanent tolerance request.

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

Hexaconazole possesses a low order acute toxicity by the oral, dermal and inhalation routes of exposure [categories 3/4]. It is slightly to moderately irritating to the eye and non-irritating to the skin. Hexaconazole tested positive in animal studies for skin sensitization.

Subchronic and chronic dietary feeding studies in mice, rats and dogs indicate that the liver is the primary target organ as generally seen by increased enzyme levels, liver cell hypertrophy, and fatty infiltration of the liver across species. Decreased body weight gain

was also seen across species.

Groups of male and female mice fed dietary doses ranging from 3.75 mg/kg/day to 225 mg/kg/day for 29 days manifested group mean body weight decreases of 17% [M] and 14%[F] at the lowest observed adverse effect level (LOAEL) of 15 mg/kg/day concurrent with hepatotoxicity. The no observed adverse effect level (NOAEL) was 3.75 mg/kg/day. Male and female mice fed hexaconazole for a period of 2 years at doses ranging from 0.57 to 29.6 mg/kg/day showed body weight gain decreases and decreased food efficiency at the LOAEL of 23.5 mg/kg/day [M] and 29.6 mg/kg/day [F]. Increased liver weight and an increase in hepatocellular hypertrophy as well as an increase in centrilobular fatty infiltration of the liver in both sexes was also reported at the high dose. However, the high dose tested [HDT] was not considered to be the maximum tolerated dose for the purpose of carcinogenicity testing. Therefore the negative finding for carcinogenicity in the mouse should be viewed with caution [CPRC memo , 6/27/90].

Male and female rats were given dietary levels of compound in feed for a period of either 90 days or two years at doses ranging from 2.5 to 250 mg/kg/day for 90 days or 2 years at doses ranging from 0.47 mg/kg/day to 61 mg/kg/day. Body weight gains in the 90 day study were statistically significantly decreased at 250 mg/kg/day in both sexes at this high dose. The LOAEL of 25 mg/kg/day for both sexes was based on slight fatty changes in the liver of males and cortical parenchymal vacuolation for the adrenal gland in both sexes. The NOAEL was 2.5 mg/kg/day. In a three dose chronic dietary rat feeding study males and females received either 0, 10, 100 or 1000 ppm of compound in the diet. The NOAEL was 4.7 and 6.1 mg/kg/day for males and females respectively. The LOAEL was 47 [M] and 61mg/kg/day [F] based on decreased body weight gains in females of 7% and fatty changes in the centrilobular region of the liver of males as well as increased incidence of cortical vacuolation of the adrenal gland and tubular atrophy of the testes in males which was considered to be an acceleration of natural occurring lesions. Effects at the HDT LOAEL were essentially an extension of the effects at the lower doses. There was a dose responsive positive trend in the number of benign Leydig cell tumors in the testes and a significant pair wise comparison between the HDT and the controls. These tumors were considered uncommon in the test strain and occurred at an accelerated rate.

Dogs in a 90 day study given hexaconazole by capsule at doses of 0, 5, 25 or 125 mg/kg/day [reduced to 50 mg/kg/day with the addition of a new group and the termination of the original group at 125 mg/kg/day as a result of extreme toxicity] manifested increases in alkaline phosphatase and SGPT and decreases in cholesterol and triglycerides as well as fatty infiltration of the liver at the LOAEL of 25 mg/kg/day. The NOAEL was 5 mg/kg/day. Liver organ weight increases on a relative and absolute basis were increased at the HDT accompanied by pallor and enlargement of the liver and an accumulation of lipid. Male and female dogs in a 12 month oral gavage study given either 0, 2, 10 or 50 mg/kg/day of hexaconazole showed fatty infiltration of the liver in males and an increase in the liver weights of females at the LOAEL of 10 mg/kg/day. The NOAEL was 2 mg/kg/day. Albumin, total protein, calcium, cholesterol, and triglyceride were decreased at 50 mg/kg/day at all time periods. Females showed an increase in SGPT and a decrease in plasma urea at the HDT. Alkaline phosphatase was also increased in both sexes at the HDT. Liver and kidney weight were increased at the high dose. Fatty infiltration of the

liver was seen at the high dose in all dogs.

In a two-generation reproduction study animals were fed either 0, 1, 5, or 50 mg/kg/day of test compound. There were no treatment related effects on reproductive performance of either sex for the F_0 or the F_1 generations. The parental NOAEL was 1 mg/kg/day. The parental systemic LOAEL was determined to be 5 mg/kg/day based on liver pathology [fatty infiltration] which was considered to be minimal. At 50 mg/kg/day, liver weight was increased accompanied with fatty changes in the liver. There was also an increased incidence of cytoplasmic vacuolation of the adrenal cortex in both sexes. The NOAEL for offspring was 5 mg/kg/day. The LOAEL for offspring was 50 mg/kg/day based on decreased body weight gain in pups, decreased litter size and decreased pup survival. Liver weights were increased and fatty infiltration was also observed.

In a rat developmental study, pregnant females were gavaged with either 0, 2.5, 25, or 250 mg/kg/day of hexaconazole. The parental NOAEL was 25 mg/kg/day and the LOAEL was 250 mg/kg/day based on decreased body weight gain and decreased food consumption. The developmental NOAEL was 2.5 mg/kg/day and the developmental LOAEL was 25 mg/kg/day based on delayed ossification of the 7th cervical transverse process and the presence of the extra 14th rib. At 250 mg/kg/day there was a statistically significant increase in late uterine deaths.

In a rabbit developmental study, animals tested at doses of 0, 25, 50 and 100 mg/kg/day also showed increased susceptibility to the effects of compound. The maternal NOAEL was 50 mg/kg/day and the LOAEL for maternal effects was 100 mg/kg/day based on a decreased body weight gain. The developmental NOAEL was 25 mg/kg/day and the developmental LOAEL was 50 mg/kg/day based on a decrease in mean fetal body weight.

Hexaconazole was the only triazole in this class of chemicals that produces Leydig cell tumors in male rats but not liver tumors in mice as do the majority of other triazoles in this chemical class. However, it was determined by the CPRC that hexaconazole was not tested at the maximum tolerated dose [MTD] in mice. Therefore, as stated in the HED CPRC document of June 27, 1990, the results in mice should be viewed with caution.

Hexaconazole is not considered to be a mutagen with the currently available database.

Hexaconazole administered dermally to rats over a period of 21 days for six hours a day at dose levels of 0, 100, 300 and 1000 mg/kg/day induced no systemic toxicity and was not irritating to the skin. The LOAEL was concluded to be greater than 1000 mg/kg/day the highest dose tested [HDT].

The overall quality of the toxicology data base is good. Confidence in the hazard and dose response is also good. There are no data toxicology data gaps.

Table 1. Acute Toxicity of Hexaconazole Technical.

Guideline No.	Study Type	MRID #s	Results	Toxicity Category
81-1	Acute Oral[1]	00160491	LD_{50} = 2189 mg/kg	3
81-2	Acute Dermal[2]	00160491	$LD_{50} \geq$ 2000 mg/kg	3
81-3	Acute Inhalation[3]	40742901	$LD_{50} \geq$ 5.9 mg/L	4
81-4	Primary Eye Irritation[4]	00160792	slight/moderate irritation to irrigated/non-irrigated eyes	3
81-5	Primary Skin Irritation[5]	00160492	non-irritating	4
81-6	Dermal Sensitization[6]	00160493	moderately positive to females	NA

[1,2,4,5,6] tested with 92.3% technical
[3] tested with 90.0% technical

Note: dermal sensitization studies with formulated products of 5%SG [MRID 00160496]; 10%WG [MRID 41052308]; and 5.62 %[unknown formulation] [MRID 00160669], resulted in negative, mild positive findings in females, and negative findings respectively.

All technical and formulated products are categorized as either 3 or 4 for any individual acute study.

Table 2. Subchronic and Chronic Toxicity Profile of Hexaconazole technical

Study Type	MRID #s	Results
21-Day Dermal Toxicity-Rat	40944807	NOAEL > 1000 mg/kg/day LOAEL > 1000 mg/kg/day
Subchronic 29 Day Feeding-Mouse	41142801	NOAEL = 3.75 mg/kg/day LOAEL = 15 mg/kg/day
Subchronic 90 day Feeding Rats	40944805 40944806	NOAEL = 2.5 mg/kg/day LOAEL = 25 mg/kg/day
Subchronic 90 day Gavage Dog	40944806	NOAEL = 5 mg/kg/day LOAEL = 25 mg/kg/day
Chronic Feeding Oncogenicity - Mouse	40944809	NOAEL = 4.66 mg/kg/day LOAEL = 23.5 mg/kg/day
Chronic Toxicity Carcinogenicity Rat Feeding	40944808 41084702	NOAEL = 4.7 mg/kg/day LOAEL = 47 mg/kg/day
Chronic One Year Dog Gavage	40944810 41084704 42006401	NOAEL = 2 mg/kg/day LOAEL = 10 mg/kg/day
Developmental Toxicity-Rat	40944811	Parental Systemic NOAEL = 25 mg/kg/day LOAEL = 250 mg/kg/day Offspring NOAEL = 2.5 mg/kg/day LOAEL = 25 mg/kg/day

Study Type	MRID #s	Results
Developmental Toxicity-Rabbit	42016301	Parental Systemic NOAEL = 50 mg/kg/day LOAEL = 100 mg/kg/day Offspring NOAEL = 25 mg/kg/day LOAEL = 50 mg/kg/day
Reproductive Toxicity Two-Generation Rat	40944813	Parental Systemic NOAEL = 1 mg/kg/day LOAEL = 5 mg/kg/day [minimal effects] Offspring NOAEL = 5 mg/kg/day LOAEL = 50 mg/kg/day
Gene Mutation - *Salmonella* Ames Assay	40944814 42006401	Non-mutagenic (±) activation
Micro nucleus Assay Mice	40948815	Non-mutagenic
In Vitro Cytogenetics Human Lymphocytes Cells	40944818	Non-mutagenic
Unscheduled DNA Synthesis in Primary Rat Hepatocytes	40944817	Non-mutagenic
Metabolism-Rat	40944819 40944822 40944823	Hexaconazole is readily absorbed and excreted in both urine and feces in both males and females. Metabolites underwent extensive glucuronidation, biliary excretion, and enterohepatic recirculating. Radio labeled hexaconazole concentrated in liver, kidney and adrenal at 24 hours. About 94-98% of the radio labeled material was excreted in 7 days by both sexes with males excreting 77% in three days and females excreting 88-95% in three days. Males excreted 41% in urine and 52% in feces compared to females 64% and 29% in urine and feces, respectively. The majority of the metabolites were oxidation products of the n-butyl chain [hexaconazole acid, 5- hydroxy-hexaconazole, 5-keto hexaconazole and an unspecified hydroxy-keto-hexaconazole]. Preferential elimination of hexaconazole was seen in the urine of females as 5-hydroxy-hexaconazole.

3.2 FQPA Considerations

There are no exposure or toxicity data gaps in the consideration of the FQPA safety factor. The FQPA SFC recommended that the 10x FQPA safety factor be applied only to subpopulation group females 13+ for the determination of acute dietary risk because the effects occur only during *in utero* exposure and are not post natal effects. Hexaconazole is structurally related to Triadimefon (Bayleton), Triademenol (Baytan), Bitertanol (Baycor), Uniconazole (Prunit), Propiconazole (Tilt), Etaconazole (Vanguard), Azaconazole, Tebuconazole, and Cyproconazole (SAN 619F). All of these compounds, except Etaconazole, have shown a developmental toxicity LOAEL below the maternal toxicity LOAEL in rats and/or rabbits.

The FQPA safety factor will not be applied for chronic dietary risk assessment because: 1) the NOAEL used in deriving the RfD is based on liver effects from the chronic dog study; 2) the developmental effects on which the FQPA factor is based were seen in pregnant animals of a different species (rats, and rabbits); and 3) the developmental effects are considered to be "acute" effects, and not a result of chronic exposure.

The available data indicated evidence of increased susceptibility of rat and rabbit fetuses to the *in utero* exposure of hexaconazole in developmental studies. In both the rat and rabbit developmental toxicity studies, developmental effects occurred at dose levels lower than those causing maternal toxicity; in rats developmental toxicity was manifested as delayed ossification and an extra 14th rib; and in rabbits, decreased fetal weights occurred at doses below maternally toxic levels.

In the two generation reproduction study, no increased susceptibility was observed. Effects in the offspring occurred only at or above treatment levels which resulted in evidence of parental toxicity

It was also determined that a developmental neurotoxicity study in rats is not required for hexaconazole because: 1) hexaconazole is not structurally related to a neurotoxic agent; 2) there is no evidence in the acute, subchronic, or chronic studies that indicate that hexaconazole induces neurotoxic effects; and 3) the developmental and reproductive studies do not indicate that the chemical is neurotoxic. Developmental effects occurred at dose levels that were below maternally toxic levels for both rat and rabbit but were not associated with neurotoxicity (Memo, A. Kocialski and B. Tarplee, 1/21/99).

3.3 Other FQPA Considerations

3.3.1. Cumulative Risk

EPA does not have, at this time, available data to determine whether hexaconazole has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of this tolerance action, therefore, EPA has not assumed that hexaconazole has a common mechanism of toxicity with other substances.

On this basis, the petitioner must submit, upon EPA's request and according to a schedule determined by the Agency, such information as the Agency directs to be submitted in order to evaluate issues related to whether hexaconazole share(s) a common mechanism of toxicity with any other substance and, if so, whether any tolerances for hexaconazole need to be modified or revoked.

3.3.2. Endocrine Disruption

EPA is required to develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect..." The Agency is currently working with interested stakeholders,

including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed 3 years from the passage of FQPA (August 3, 1999) to implement this program. At that time, EPA may require further testing of hexaconazole for endocrine effects.

3.3 Dose Response Assessment

An acute reference dose (RfD) of 0.025 mg/kg/day was established for the subpopulation group, females 13+ only, based on a NOAEL of 2.5 mg/kg/day from a developmental study in the rat. Effects at the next higher dose level of 25 mg/kg/day were an increase in the delayed ossification of the 7th cervical transverse process and the presence of the extra 14th rib. Effects were dose responsive and statistically significant. These effects are presumed to occur after a single exposure *in utero* and therefore are considered to be appropriate for this risk assessment. The **acute population adjusted dose (aPAD) is 0.0025 mg/kg/day and includes the additional 10x FQPA safety factor.** An acute dose and endpoint were not selected for the general population group (including infants and children) because there were no effects observed in oral toxicology studies including maternal toxicity in the developmental toxicity studies in rats and rabbits that are attributable to a single exposure [dose].

The chronic RfD of 0.02 mg/kg/day was determined on the basis of a 1 year oral gavage study in dogs. The NOAEL in this study was 2 mg/kg /day. Fatty infiltration of the liver and an increase in liver weights occurred at the LOAEL of 10 mg/kg/day. This RfD was originally established at an RfD meeting in August of 1993 and re-confirmed by the HIARC on December 8, 1998 (Memo, A. Kocialski and B. Tarplee, 1/21/99). A FQPA safety factor was not applied for chronic dietary risk assessment because: 1) the NOAEL used in deriving the RfD was based on liver effects in the chronic dog study; 2) the developmental effects on which the FQPA factor is based were seen in pregnant animals of a different species (rats, and rabbits); and 3) the developmental effects are considered to be "acute" effects. Therefore, the chronic PAD and the RfD are the same.

The World Health Organization [WHO] reviewed this chemical in 1990 and established an RfD of 0.005 mg/kg/day.

Hexaconazole causes Leydig Cell tumors in male rats and no tumors in mice. It is the only triazole of this fungicide class that causes Leydig Cell tumors which were statistically significant by pair wise and trend analysis. Other triazole fungicides have been known to produce liver tumors in mice. The absence of tumors in mice should, however, be viewed with caution because as stated earlier, the MTD was not attained and therefore the negative results of the study are suspect. The current Q_1^* value based on the Leydig Cell tumors for hexaconazole using the body weight ¾ inter species scaling in lieu of the body weight ⅔ inter species scaling factor is 1.6×10^{-2} $(mg/kg/day)^{-1}$ (Memo, L. Brunsman, 11/18/98).The CPRC also indicated that these tumors appeared at a dose level below that which would be considered an adequate level to determine an overall evaluation of the carcinogenic potential of this chemical. Other methods for the calculation of risk as supported by the available data could be considered at a later date pending a change in the

current policy and mode of action data for this chemical.

No short-, intermediate-, or long-term dermal or aggregate exposure risk assessments are required as this is an import tolerance only for bananas.

Table 3. Summary of Toxicological Dose and Endpoints for Hexaconazole Use in Human Risk Assessment

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary - Females 13+	NOAEL= 2.5 UF = 100 FQPA SF = 10	increase in the occurrence of the 14th rib on a litter basis and a partially ossified 7th cervical transverse process	developmental rat
	Acute RfD = 0.025 mg/kg/day **Acute PAD** = 0.0025 mg/kg/day		
Chronic (non-cancer) Dietary	NOAEL = 2 UF = 100 FQPA SF = 1	fatty infiltration of the liver and increased liver weights	one year dog [oral gavage]
	Chronic RfD = 0.02 mg/kg/day **Chronic PAD** = 0.02 mg/kg/day		
Chronic (cancer) Dietary	**Group C - (likely human carcinogen) - Q_1* = 1.6 x 10^{-2} (mg/kg/day)$^{-1}$** in human equivalents (converted from animals to humans by use of the $BW^{3/4}$'s scaling factor)		
Short-, Intermediate, and Long-Term (Dermal)	NOAEL= na	na	na
Short-, Intermediate, and Long-Term (Inhalation)	NOAEL= na	na	na

na = not applicable

4.0 EXPOSURE ASSESSMENT

4.1 Summary of Registered/Proposed Uses

Hexaconazole is systemic triazole fungicide controlling black and yellow sigatoka diseases of bananas. It is used foliarly on bananas. Hexaconazole is formulated as ANVIL 25 EC/OL, a emulsifiable concentrate containing 250 g/L w/v a.i and as ANVIL 25 SC, a emulsifiable concentrate containing 350 g/L w/v a.i. English translations of the labels were provided. There are no proposed or existing residential uses for this product.

The single maximum application rate for ANVIL 25 SC is 140 g a.i./ha (0.12 lb. a.i./A) using aerial application with a 0-day preharvest interval (PHI) . Hexaconazole can be

applied a maximum 10 times per year for a total maximum application rate of 1400 g a.i./ha (1.2 lbs. a.i./A) with a time interval of 14 to 21 days between each application.

The single maximum application rate for ANVIL 25 EC/OL is 100 g a.i./ha (0.09 lb. a.i./A) using either ground or aerial application with a 0-day PHI. It can be applied a maximum of 8 times in any 12 month period for a total maximum application rate of 800 g a.i./ha (0.72 lb. a.i./A) per year with a time interval of 15-21 days between each application.

4.2 Dietary Exposure

4.2.1 Food Exposure

4.2.1.a. Nature of the Residue

Plants: The nature of the residue in plants is understood. Plant metabolism studies were conducted on grapes, apples, and wheat and found acceptable (Memos, S. Willett, 2/19/91; J. Morales, D181190, 5/3/93; M. Flood, D194643, 9/1/94; S. Willet, 5/15/95). As the nature of the residue is understood in these crops, no additional metabolism studies for bananas were required. The data indicate that the major terminal residues in plants will be parent hexaconazole, its diol metabolites [(±)-5-(2,4-dichlorophenyl)-6-(1H-1,2,4-triazol-1-yl)hexan-2,6-diol, (±)-5-(2,4-dichlorophenyl)-5-hydroxy-6-(1H-1,2,4-triazol-1-yl)hexanoic acid, (±)-2-(2,4-dichlorophenyl)-1-(1H-1,2,4-triazol-1-yl)hexan-2,5-diol, and (±)-2-(2,4-dichlorophenyl)-1-(1H-1,2,4-triazol-1-yl)hexan-2,4-diol, free and conjugated] resulting from oxidation of the alkyl side chain of hexaconazole, and its triazole metabolites [1H-1,2,4-triazole, (RS)-3-(1H-1,2,4-triazol-1-yl) alanine (aka triazole alanine), (1H-1,2,4-triazole-1-yl) acetic acid (aka triazole acetic acid)], resulting from the cleavage of the triazolyl moiety of the parent compound.

The predominant residues in apples and grapes are hexaconazole and its diol metabolites. The metabolism in wheat apparently differs in that while hexaconazole and its diol metabolites were the major terminal residues in straw and chaff, the major terminal residues in grain were the triazole degradation products. Any residues in banana flesh will result from extensive translocation through leaves, stalk and skin.

Animals: Because there are no animal feed items associated with this petition, data depicting the nature of hexaconazole residues in animal commodities are not required. For any future petition in which there is a potential for transfer of residues to animals (meat, milk, poultry, eggs, etc.), animal metabolism studies will be required.

The HED Metabolism Committee met on June 1, 1995 to discuss the toxicological significance of potential hexaconazole metabolites. It was decided that parent hexaconazole is the only terminal residue that needs to be included in the tolerance expression for bananas, which is the only food use pending at this time. The diol metabolites are expected to be of comparable toxicity to the parent compound and

will be included in risk assessments. HED will require residue data on these metabolites for bananas, as well as future food uses. If monitoring data for the parent need to be used in the future for dietary risk assessments, then diol residues may be estimated based on their ratio to parent hexaconazole. The triazole metabolites will not be regulated or included in risk assessments since they are of low toxicity and are not likely to be present at detectable levels in bananas (Memo, S. Willett, 6/19/95).

4.2.1.b. Residue Analytical Methods

Plants: The petitioner has proposed "Agrochemical Residue Analytical Method 108/1 for Residues of Hexaconazole in Crops" as the analytical enforcement method. Samples of homogenized whole bananas are weighed into a round bottom flask (fortification occurs at this step). The sample is extracted by refluxing with methanolic sodium hydroxide for one hour. Aqueous sodium chloride is then added, and the hexaconazole is partitioned from the methanol/aqueous solution into dichloromethane. The extracts in dichloromethane are cleaned up using silica adsorption micro-columns. Parent hexaconazole is then determined using capillary column GLC/NP or GLC/EC.

HED concluded that Method 108/1 is adequate for enforcement purposes. An independent laboratory validation (ILV) of the method has been submitted and a satisfactory petition method validation (PMV) by ACL was completed (Memo, S. Willett, D220052, 12/11/95).

4.2.1.c. Multi-Residue Method

The results of multiresidue testing of hexaconazole was forwarded to FDA. Hexaconazole is included in a method in PAM I, Section 302.

4.2.1.d. Crop Field Trials

A total of 18 field trials were submitted and reviewed (Memos, S. Willett, 2/19/91; S. Chun, D246865, 12/14/98). The residue levels of hexaconazole (parent only) in whole unbagged bananas from all trials ranged from < 0.01 (LOQ) - 0.64 ppm. The residue levels of hexaconazole in unbagged banana pulp from all field trials ranged from < 0.01 ppm (LOQ) - 0.17 ppm. The residue levels of the diol metabolites in whole unbagged bananas from all trials ranged from < 0.03 (LOQ) - 1.6 ppm. The residue levels of the diol metabolites in unbagged banana pulp from all field trials ranged from < 0.03 ppm (LOQ) - 0.39 ppm. The submitted data indicate that residues of hexaconazole in whole bananas will exceed the existing time-limited tolerance level of 0.1 ppm for bananas. The appropriate tolerance level is 0.7 ppm for bananas. A revised Section F was submitted amending the tolerance to 0.7 ppm for bananas (Memo, S. Chun, D253279, 3/2/99).

4.2.1.e. Processed Food/Feed

There are no processed commodities associated with bananas; therefore, no tolerances for processed commodities are required.

4.2.1.f. Meat, Milk, Poultry, Eggs

There are no animal feed items associated with bananas; therefore, no tolerances for meat, milk, poultry, and eggs are required. For any future petition in which there is a potential for transfer of residues to animals (meat, milk, poultry, eggs, etc.), animal metabolism studies will be required.

4.2.1.g. Anticipated Residues

Anticipated residues were calculated from field trial data. The residue levels from banana pulp for parent and diol metabolites were used (Memo, S. Chun, D246865, 12/14/98). The residue level value of 0.56 ppm, which was the highest residue level for pulp (hexaconazole-0.17 ppm + diol metabolites- 0.39 ppm), was used in the acute dietary analysis. The residue level value of 0.11 ppm , which was the average from the field trials for pulp (hexaconazole- 0.03ppm + diol metabolites- 0.08 ppm), was used in the chronic dietary analysis.

To provide for the re-evaluation of the anticipated residues, the Agency will require under Section 408(b)(2)(E) that additional residue data be submitted within five years.

4.2.1.h. Confined Accumulation in Rotational Crops - Not Required

4.2.1.i. Codex Harmonization

There is neither a Codex proposal, nor Canadian or Mexican limits for residues of **hexaconazole** in bananas. Therefore, a compatibility issue is not relevant to the proposed tolerance.

4.2.2. Dietary Exposure and Risk Analysis

A dietary exposure analysis using the Dietary Exposure Evaluation Model (DEEM™) was completed (Memo, S. Chun, D252486, 2/19/99) for acute, chronic (non-cancer), and cancer dietary exposure. The DEEM™ analysis evaluated the individual food consumption as reported by respondents in the USDA 1989-91 Continuing Surveys for Food Intake by Individuals (CSFII) and accumulated exposure to the chemical for each commodity. The complete analysis is attached (Attachment 3).

For all dietary analyses, the residue values (hexaconazole + diol metabolites) from the field trials on banana pulp were used. The use of banana pulp residue levels provides a more realistic dietary exposure as individuals do not usually eat the banana peel. Due to the Metabolism Committee's decision concerning hexaconazole (Memo, S. Willett, 6/19/95),

the diol metabolites residue levels were also included in the dietary exposure analysis.

Acute Dietary Exposure and Risk

The acute dietary exposure analysis for hexaconazole is a conservative but more realistic estimate of dietary exposure with the use of the pulp residue values. The acute dietary exposure analysis for the population subgroup females 13+ was performed using the highest pulp residue (parent + diol metabolite) levels and 100 percent crop treated (CT). The FQPA Safety Factor of 10x was retained for the acute dietary analysis only. The aPAD used in the acute dietary analysis was **0.0025 mg/kg/day**. Table 5 summarizes the acute dietary exposure.

Table 5. Summary of Acute Dietary Exposure and Risk for Hexaconazole at 95th Percentile of Exposure

Population Subgroup	Exposure (mg/kg/day)	% Population Adjusted Dose (PAD)
Females (13+, preg., not nursing)	0.001181	47.2
Females (13+, nursing)	0.001136	45.4
Females (13-19 yrs., not preg., not nursing)	0.000892	35.7
Females (10+ years, not preg., not nursing)	0.001030	41.2
Females (13-50 years)	0.000954	38.1

The percent acute population adjusted doses (PADs) were below HED's level of concern at the 95th percentile of exposure for the females 13+ subgroup. The highest % aPAD at the 95th percentile of exposure was 47% for the subgroup, females 13+ (pregnant, not nursing). Therefore, the acute dietary risk associated with the proposed use of hexaconazole on bananas is below the Agency's level of concern.

Chronic and Cancer Dietary Exposure and Risk

The chronic (non-cancer) and cancer DEEM™ analyses used mean consumption (3 day average). Average pulp residues from field trials and 100% CT information were used. Table 6 summarizes the chronic dietary exposure and includes the U.S. general population and other subgroups. The other subgroups included are all infant and children subgroups and the highest dietary exposures for the respective adult population subgroups (i.e., females and the other general population subgroup higher than U.S. population)..

Table 6. Summary of Chronic (non-cancer) Dietary Exposure and Risk for Hexaconazole

Population Subgroup	Exposure (mg/kg/day)	%RfD
U.S. Population (48 states)	0.000033	< 1
Non-hispanic other than black or white	0.000050	< 1
All infants (< 1 year)	0.000167	< 1
Nursing infants (< 1 year)	0.000077	< 1
Non-nursing infants (< 1 year)	0.000205	1.0
Children (1-6 years old)	0.000091	< 1
Children (7-12 years old)	0.000037	< 1
Females (13+/nursing)	0.000035	< 1

The FQPA Safety Factor was removed (equivalent to a factor of 1x) for chronic exposures. Therefore the chronic PAD and the chronic RfD are identical . For chronic dietary risk, HED's level of concern is greater than 100% cPAD. All chronic (non -cancer) %PADs for all subgroups were ≤ 1%. The results of the chronic dietary analysis indicate that the chronic dietary risk associated with the existing and proposed uses of hexaconazole is below the Agency's level of concern (< 100% PAD).

Cancer Dietary Risk:

The Agency generally considers 1 x 10^{-6} as negligible risk (i.e, less than 1 in 1 million) for cancer. The results of this analysis indicate that the cancer dietary risk of 5.3 x 10^{-7} associated with the proposed use of hexaconazole is below the Agency's level of concern.

Subgroup	Exposure (mg/kg/day)	Lifetime Risk[1]
U.S. Population (48 states)	0.000033	5.3 x 10^{-7}

[1] $Lifetime\ Risk = 70\text{-}year\ Lifetime\ Exposure\ (mg/kg/day) \times Q_1^*$

$= (0.000033\ mg/kg/day) \times (1.6 \times 10^{-2}\ (mg/kg/day)^{-1})$

4.2.3 Water

The use on bananas is an import use only. There are currently no registered or proposed uses for hexaconazole in the U.S. Therefore, a drinking water exposure assessment from the Environmental Fate and Effects Division (EFED) is not necessary. If domestic uses are added in the future, OPP will reassess the potential impacts of hexaconazole on drinking water as a part of the aggregate risk assessment process.

4.3 Occupational Exposure

The use of bananas is for import use only. There are currently no proposed or registered domestic uses for hexaconazole. Therefore, no occupation exposure assessment is required. If domestic uses are added in the future, an occupational exposure assessment will have to be completed.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

There are no proposed or existing residential uses for hexaconazole. The proposed use is limited to import bananas only. Therefore, no residential or water assessments are required. The aggregate exposure risk assessment is limited to dietary only. Details concerning the information used in deriving the dietary exposure estimates and conclusions are in Section 4.2.2.

To reiterate the conclusions from the dietary analysis: acute, chronic, and cancer risks do not exceed the Agency's level of concern for hexaconazole with the proposed use. If new uses are added in the future, the Agency will reassess the impact of these uses, which may result in the necessity of residential and water exposure assessments.

6.0 DATA GAPS

6.1. Chemistry - None
6.2 Toxicology - None

7.0 REFERENCES

All documents are available electronically unless stated otherwise.

DP Barcode(s): None
Subject: HEXACONAZOLE - Report of the Hazard Identification Assessment Review Committee [HIARC]
From: Albin Kocialski, Ph.D, Pharmacologist and Brenda Tarplee
To: George Kramer, Ph.D.
Dated: 1/21/99
MRID(s): NA

DP Barcode(s): None
Subject: HEXACONAZOLE - Report of the FQPA Safety Factor Committee.
From: Brenda Tarplee
To: George Kramer, Ph.D.
Dated: 2/5/99
MRID(s): NA

DP Barcode(s): None
Subject: REVISED Hexaconazole Quantitative Risk Assessment(Q_1^*) Based On Wistar Rat Dietary Study With $^3/_4$'s Interspecies Scaling Factor
From: Lori Brunsman, Statistician
To: Albin Kocialski, Pharmacologist

Dated: 11/18/98
MRID(s): NA

(No Accompanying Memo Located)
DP Barcode(s): None
Subject: DER 7, 8, or 9; Toxicity Profile
From: NA
To: NA
Dated: 11/13/98
MRID(s): 40944805-11, 40944813, 41084702, 41084704, 41142801, 42006401, 42016301

DP Barcode(s): None
Subject: Dose Response Assessment of the carcinogenic Effects of Hexaconazole at Low Doses Using the Linearized Multistage Model for Extrapolating the Experimental Data Points
From: Jack Quest
To: Reto Engler
Dated: 6/27/90 *(Not available electronically)*
MRID(s): NA

DP Barcode(s): None
Subject: Hexaconazole: RfD/Peer Review Report
From: George Z. Ghali, Ph.D.
To: Susan Lewis
Dated: 11/10/93
MRID(s): NA

(No Accompanying Memo Located)
DP Barcode(s): N/A
Subject: Twenty-Nine (29) Day Feeding Study in Mice, DER 13
Reviewed by: Elizabeth A. Doyle, Ph.D.
Dated: 2/8/90 *(Not available electronically)*
MRID(s): 41142801

(No Accompanying Memo Located)
DP Barcode(s): N/A
Subject: Chronic Feeding Oncogenicity Study in Mice, DER 6
Reviewed by: William L. McLellan, Ph.D.
Dated: 3/30/90 *(Not available electronically)*
MRID(s): 40944808

(No Accompanying Memo Located)
DP Barcode(s): N/A
Subject: Ninety-Day Feeding Study in Rate, DER 10
Reviewed by: Elizabeth A. Doyle, Ph.D.
Dated: 3/20/90 *(Not available electronically)*
MRID(s): 40944805

(No Accompanying Memo Located)
DP Barcode(s): N/A
Subject: Two-Year Feeding/Oncogenicity Study in Rats, DER 1

Reviewed by: Elizabeth A. Doyle, Ph.D.
Dated: 3/20/90 *(Not available electronically)*
MRID(s): 41084702

No Accompanying Memo Located)
DP Barcode(s): N/A
Subject: Ninety-Day Oral Gavage Study in Dogs, DER 11
Reviewed by: Elizabeth A. Doyle, Ph.D.
Dated: 1/29/90 *(Not available electronically)*
MRID(s): 40944806

DP Barcode(s): D172819 and D173462
Subject: Hexaconazole - Petitions for Registration of Two Formulations for Non-food/feed Use ; One-Year Oral Gavage Dog Study, DER 2
From: Elizabeth A. Doyle, Ph.D.
To: Sidney Jackson
Dated: 3/29/93 *(Not available electronically)*
MRID(s): 40944810, 41084704, 42006401

No Accompanying Memo Located)
DP Barcode(s): N/A
Subject: Two Generation Reproduction Study in Rats, DER 3
Reviewed by: Elizabeth A. Doyle, Ph.D.
Dated: 2/9/90 *(Not available electronically)*
MRID(s): 40944813

No Accompanying Memo Located)
DP Barcode(s): N/A
Subject: Developmental Toxicity Study in Rats, DER 4
Reviewed by: Elizabeth A. Doyle, Ph.D.
Dated: *(Not available electronically)*
MRID(s): 40944811

DP Barcode(s): None
Subject: Developmental Toxicity Study in Rabbits, DER 5
From: Susan L. Makris, M.S.
To: Susan Lewis/Sidney Jackson
Dated: 2/12/93 *(Not available electronically)*
MRID(s): 42016301

No Accompanying Memo Located)
DP Barcode(s): N/A
Subject: Teratology (Developmental Toxicity) Study in Rabbits
Reviewed by: Susan L. Makris, M.S.
Dated: 3/24/92 *(Not available electronically)*
MRID(s): 42016301

No Accompanying Memo Located)
DP Barcode(s): N/A
Subject: Teratology-Developmental Toxicity in Rabbits
Reviewed by: Elizabeth A. Doyle, Ph.D.
Dated: 3/22/90 *(Not available electronically)*

MRID(s): 40944812

No Accompanying Memo Located)
DP Barcode(s): N/A
Subject: Embryotoxicity - Rabbit
Reviewed by: Elizabeth A. Doyle, Ph.D.
Dated: 3/22/90 (*Not available electronically)*
MRID(s): 41084706, 41384702

No Accompanying Memo Located)
DP Barcode(s): N/A
Subject: Maximum Tolerated Dose -Rabbit
Reviewed by: Elizabeth A. Doyle, Ph.D.
Dated: 3/7/90 (*Not available electronically)*
MRID(s): 41084705

No Accompanying Memo Located)
DP Barcode(s): N/A
Subject: Twenty-one (21) Day Dermal Toxicity Study, DER 12
Reviewed by: Elizabeth A. Doyle, Ph.D.
Dated: 1/5/90 (*Not available electronically)*
MRID(s): 40944807

DP Barcode(s): None
Subject: PP# 0E3853. Import Tolerance for Hexaconazole on Bananas (First Food Use). Review of Residue Chemistry Data and Analytical Methodology.
From: Stephanie H. Willett, Chemist
To: Susan Lewis/Sidney Jackson
Dated: 2/19/91 (*Not available electronically)*
MRID(s): 41419600, 41419618

DP Barcode(s): D181190
Subject: PP#0E3853. Import Tolerance for Hexaconazole on Bananas (First Food Use). Amendment in response to review of 2/19/92.
From: José J. Morales, Chemist
To: Susan Lewis/Sidney Jackson and Albin Kocialski
Dated: 5/3/93
MRID(s): 42416700-02

DP Barcode(s): D194643
Subject: PP#0E3853. Hexaconazole. Banana Import Tolerance Petition. Zeneca Ag Products' Response to CBTS Review of 5/3/93. Response to 1/26/90 Product Chemistry Review.
From: Michael T. Flood, Ph.D., Chemist
To: S. Robbins
Dated: 9/1/94
MRID(s): 42891801-06

DP Barcode(s): D205627
Subject: PP No. 0E3853. Hexaconazole on Imported Bananas. Petition Amendment dated 7/7/94.

From: Stephanie H. Willett, Chemist
To: Connie Welch/Sidney Jackson and Jane Smith/Steve Robbins
Dated: 3/30/95
MRID(s): 43298400 -07

DP Barcode(s): None
Subject: PP No. 0E3853. Hexaconazole on Imported Bananas. Petition Method Validation Request.
From: Stephanie H. Willett, Chemist
To: Donald A. Marlow
Dated: 4/24/95
MRID(s): 42891805, 41419610

DP Barcode(s): None
Subject: PP No. 0E3853. Hexaconazole on Imported Bananas. Issues to be Presented at the 6/9/95 HED Metabolism Committee Meeting.
From: Stephanie H. Willett, Chemist
To: HED Metabolism Committee
Dated: 5/15/95
MRID(s): NA

DP Barcode(s): None
Subject: Metabolism of Hexaconazole in Plants. Minutes of the 6/1/95 HED Metabolism Committee Meeting
From: Stephanie H. Willett, Chemist
To: The Metabolism Committee
Dated: 6/16/95
MRID(s): NA

DP Barcode(s): D217133
Subject: PP No. 0E3853. Hexaconazole on Imported Bananas. Review of EPA Petition Method Validation Results.
From: Stephanie H. Willett, Chemist
To: Connie Welch/Sidney Jackson
Dated: 9/7/95
MRID(s): NA

DP Barcode(s): D220052
Subject: PP No. 0E3853. Hexaconazole on Imported Bananas. Revised Analytical Methodology.
From: Stephanie H. Willett, Chemist
To: Connie Welch/Sidney Jackson
Dated: 12/11/95
MRID(s): 43792300, 43792301

DP Barcode(s): None
Subject: Enforcement Method to FDA
From: Stephanie H. Willett, Chemist
To: Marion Clower, FDA
Dated: 3/21/96MRID(s): NA

013324

DP Barcode(s):	D246865
Subject:	PP#0E03853. Hexaconazole in or on Imported Bananas. Amendment of 5/7/97.
From:	Susie Chun, Chemist
To:	Terri Stowe/Mary Waller
Dated:	12/14/98
MRID(s):	44558000 -01

DP Barcode(s):	D253279
Subject:	PP#0E03853. Hexaconazole in or on Imported Bananas. Amendment of 2/10/99.
From:	Susie Chun, Chemist
To:	Terri Stowe/Mary Waller
Dated:	3/2/99
MRID(s):	NA

DP Barcode(s):	D25486
Subject:	Hexaconazole - Dietary Exposure Analysis for Hexaconazole in/on Bananas (PP # 0E03853).
From/To:	Susie Chun, Chemist
Dated:	2/19/99
MRID(s):	NA

Attachment 1: FQPA Safety Factor Committee Report
Attachment 2: Hazard Identification Assessment Review Committee Report
Attachment 3: Dietary Exposure Analyses
Attachment 4: Codex Form

cc (with attachments): PP#0E3853, S. Chun (RAB1), A. Kocialski (RAB1)
RDI: Chemists (3/18/99); Team (3/17/99), M. Morrow (3/23/99); RARC (4/15/99)
S. Chun:806R:CM#2:(703) 305-2249: 7509C:RAB1

ATTACHMENT 1 - FQPA Safety Factor Committee Report (*Available Electronically*)

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

013168

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

05-FEB-1999

MEMORANDUM

SUBJECT: *HEXACONAZOLE* - Report of the FQPA Safety Factor Committee.

FROM: Brenda Tarplee, Executive Secretary
FQPA Safety Factor Committee
Health Effects Division (7509C)

THROUGH: Ed Zager, Chairman
FQPA Safety Factor Committee
Health Effects Division (7509C)

TO: George Kramer, Branch Senior Scientist
Registration Action Branch 1
Health Effects Division (7509C)

PC Code: 128925

The Health Effects Division (HED) FQPA Safety Factor Committee met on January 25, 1999 to evaluate the hazard and exposure data for hexaconazole and recommended that the FQPA Safety Factor (as required by Food Quality Protection Act of August 3, 1996) be retained (10x) in assessing the risk posed by this chemical.

I. HAZARD ASSESSMENT

1. Determination of Susceptibility

The Hazard Identification Assessment Review Committee (HIARC) determined that the available Agency Guideline studies indicate evidence of increased susceptibility of rat and rabbit fetuses to the *in utero* exposure of hexaconazole in developmental studies. In both the rat and rabbit developmental toxicity studies, developmental effects occurred at dose levels lower than those causing maternal toxicity: in rats developmental toxicity was manifested as delayed ossification and an extra 14th rib; and in rabbits, decreased fetal weights occurred at doses below maternally toxic levels.

In the two generation reproduction study, no increased susceptibility was observed, effects in the offspring occurred only at or above treatment levels which resulted in evidence of parental toxicity (*Memorandum:* A. Kocialski to G. Kramer dated January 21, 1999.)

2. Adequacy of Toxicity Database

The HIARC determined that a developmental neurotoxicity study in rats is **not required** for hexaconazole because: 1) hexaconazole is not structurally related to a neurotoxic agent; 2) there was is no evidence in the acute, subchronic, or chronic studies that indicate that hexaconazole induces neurotoxic effects; and 3) the developmental and reproductive studies do not indicate that the chemical is neurotoxic. Developmental effects occurred at dose levels that were below maternally toxic levels for both rat and rabbit but were not associated with neurotoxicity (*Memorandum:* A. Kocialski to G. Kramer dated January 21, 1999).

II. EXPOSURE ASSESSMENT AND RISK CHARACTERIZATION

1. Dietary (Food) Exposure Considerations

Hexaconazole is a fungicide proposed for permanent registration on imported bananas. A time-limited tolerance for bananas is established at 0.1 ppm and expires 3/31/99 (40 CFR 180.488). There are currently no established domestic tolerances for hexaconazole.

The HED Metabolism Assessment Review Committee (MARC) has determined that hexaconazole should be regulated in terms of the parent compound only (tolerance expression), however, dietary risk assessments for hexaconazole should include the parent compound plus diol metabolites.

Currently, there are no percent crop treated information or monitoring data available for hexaconazole. However, adequate field trial data have been submitted and reviewed.

The HED Dietary Exposure Evaluation Model (DEEM) will be used to assess the risk from acute and chronic dietary exposure to residues of hexaconazole in food. These analyses will likely be unrefined (Tier 1), assuming that all bananas contain residues of hexaconazole at the level of tolerance, which would exaggerate the dietary exposure estimates.

2. Dietary (Drinking Water) Exposure Considerations

A drinking water exposure assessment was not performed for hexaconazole at this time since there are no domestic uses for this pesticide and therefore, no potential exists for ground and/or surface water contamination.

3. Residential Exposure Considerations

There are currently no registered residential uses of hexaconazole.

III. SAFETY FACTOR RECOMMENDATION AND RATIONALE

1. FQPA Safety Factor Recommendation

The Committee recommended that the **FQPA safety factor** for protection of infants and children (as required by FQPA) be **retained.**

2. Rationale for Retaining the FQPA Safety Factor

The FQPA Safety Factor Committee recommended that the **FQPA safety factor** be **retained** because increased susceptibility was demonstrated in two species:

- In the developmental (*in utero*) toxicity study in rats, developmental toxicity (manifested as delayed ossification and an extra 14th rib) occurred at doses below maternally toxic levels.
- And in the developmental (*in utero*) toxicity study in rabbits, developmental toxicity (manifested as decreased fetal weights) occurred at doses below maternally toxic levels.

3. Population Subgroups for Application of the Safety Factor

The Committee determined that the10x FQPA safety factor is applicable for the following population subgroups:

Acute Dietary Assessment: The FQPA Safety Factor will be applied for acute dietary risk assessment for **Females 13 + only** because the effects occur only during *in utero* exposure and are not postnatal effects. Thus, it is not appropriate to apply this safety factor to the acute dietary risk assessment of the general population including infants and children.

Chronic Dietary Risk Assessment: The FQPA safety factor will not be applied for chronic dietary risk assessment because: 1) the NOEL used in deriving the RfD is based on liver effects in the chronic dog study; 2) the developmental effects on which the FQPA factor is based were seen in pregnant animals of a different species (rats, and rabbits); and 3) the developmental effects are considered to be "acute" effects.

013168

FQPA Safety Factor Committee Meeting
25JAN1999
Chemical: HEXACONAZOLE

Name	Division/Branch
Ray Kent	HED/CRB2, RAB4
Susan Chun	HED/RAB1
Tom Kocialski	HED/RAB1
Dana Vogel	HED/RAB1
Ed Budd	HED/RAB2
DIRK YOUNG	EFED/IV
Susan Makris	HED/TOX1
Jean Holmes	EFED/ERB1
Anthony Monk	SRRD
	HED
	HED/SAB

ATTACHMENT 2 - Hazard Identification Assessment Review Committee Report (*Available Electronically*)

Helicid

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

013076

DATE: January 21, 1998

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: ***HEXACONAZOLE*** - Report of the Hazard Identification Assessment Review Committee [HIARC]

FROM: Albin B. Kocialski Ph.D. ABK 1/27/99
Registration Action Branch 1
Health Effects Division (7509C)
and
Brenda Tarplee, Executive Secretary
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

THROUGH: Mike Ioannou Ph.D., Co-Chairman, 1/27/99
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
and
Pauline Wagner Ph.D., Co-Chairman 1/27/99
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: George Kramer Ph.D.,
Registration Action Branch 1
Health Effects Division (7509C)

PC Code: 128925

On December **8, 1998**, the Health Effects Division's Hazard Identification Assessment Review Committee evaluated the toxicology data base of **hexaconazole,** re-assessed the Reference Dose (RfD) established in 1993 and selected the toxicological endpoints for acute dietary as well as occupational exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to hexaconazole 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: Mike Ioannou, Pauline Wagner, David Anderson, Bill Burnam, Pam Hurley, Tina Levine, Nicole Paquette, Jess Rowland, P.V. Shah, Kathleen Raffaele, Virginia Dobozy, and Brenda Tarplee. Member(s) in absentia: Karen Hamernik, Sue Makris, and Nancy McCarroll. Data were presented by Albin B. Kocialski of Registration Action Branch 1.

In attendance were Suzie Chun, Dana Vogel, George Kramer who attended the meeting to discuss exposure.

Data Presentation:
and
Report Presentation

Albin B. Kocialski
Toxicologist

Report Concurrence:

Brenda Tarplee
Executive Secretary

I. INTRODUCTION

II. HAZARD IDENTIFICATION

A. Acute Dietary Reference Dose (RfD) Subpopulation of females 13+

Study Selected: Developmental Toxicity Rat §Guideline 83-3a

MRID No.: 40944811

Executive Summary: Ninety-six pregnant female Alpk:AP [Wistar-derived] rats were divided into four groups of 24 animals each and given either 0, 2.5, 25, or 250 mg/kg of hexaconazole by gavage on days 7-16 of pregnancy and sacrificed on day 22 of gestation. Clinical signs were not remarkable. Body weight gains and food consumption in animals receiving 250 mg/kg day were statistically significantly decreased. Maternal gross pathology was not remarkable. Statistically significant increases in late uterine deaths at 250 mg/kg were noted as well a statistically significant decrease [$p<0.01$] in the body weight data of litters. No trend related developmental toxicity was observed in the external examination of fetuses or the visceral examination of fetuses at any dose level. Skeletal developmental defects were seen at all dose levels in the form of extra ribs [14th rib] and were dose responsive. Increased delayed ossification of the 7th cervical transverse process was also recorded at the low and the mid dose in the absence of maternally toxic effects. The maternal LOAEL was 250 mg/kg based on a reduced body weight gain [-11%;$p<0.01$] and a reduction in food consumption. The maternal NOAEL is 25 mg/kg. The developmental NOAEL is 2.5 mg/kg based on delayed ossification of the 7th cervical transverse process and the presence of the extra 14th rib at the LOEL of 25 mg/kg/d.

Dose and Endpoint Proposed for Consideration: NOAEL = 2.5 mg/kg/d based on delayed ossification and the presence of the extra 14th rib at 25.0 mg/kg/d The delayed ossification and the presence of the extra 14th rib at 2.5 mg/kg/d were not considered to be biologically significant on a litter basis. [RfD Peer Review Document of 11/10/93 and comments by David Anderson at the HIARC meeting].

Uncertainty Factor(s) Proposed for Consideration: 100 based on inter [10] and intra [10] species variation.

Comments about Study/Endpoint/Uncertainty Factor(s): The increases in delayed ossification and the presence of the extra 14th rib are presumed to occur after a single exposure and therefore are considered to be appropriate for this risk assessment since these are *in utero* effects. This dose and endpoint are applicable only to this subpopulation group.

Uncertainty Factor (UF): 100

$$\text{Acute RfD} = \frac{2.5 \text{ mg/kg}}{(100)} = 0.025\text{mg/kg}$$

This Risk Assessment is required.

A2. Acute Dietary Reference Dose (RfD) : General population including infants and children.

Study Selected :None

MRID No.: None

Executive Summary : None

Dose and Endpoint for Risk Assessment: A dose and endpoint were not selected for this population group because there were no effects observed in oral toxicology studies including maternal toxicity in the developmental toxicity studies in rats and rabbits that are attributable to a single exposure [dose].

Acute RfD: None for this population subgroup.

B. Chronic RfD

Study Selected: One Year Dog [oral gavage study] §Guideline #: 83-1a

MRID No.: 40944810; 41084704; 42006401

Executive Summary: Thirty-two male and female beagle dogs were divided into four groups of 4 males and 4 females per group and given either 0, 2; 10 or 50 mg/kg of hexaconazole by gavage [gelatin capsule] on a daily basis for a period of one year. Daily observations revealed no treatment related effects. There were no treatment related deaths or changes in body weight gains for either sex. Females showed no consistent treatment related effects in food efficiency whereas males showed some decrease at all dose levels that were not biologically or statistically significant. Ophthalmological examination revealed no untoward effects. Platelet count was statistically significantly increased in both males and females at 50 mg/kg. Clinical chemistry values in males and females were decreased at all sampling times for albumin, total protein, calcium, cholesterol and triglyceride at 50 mg/kg. Females but not males showed an increase in SGPT and a decrease in plasma urea at all time periods and alkaline phosphatase was increased in both sexes at all time periods at the high dose. Alkaline phosphatase was also increased in females and males at 10 mg/kg. Examination of urinalysis values was not remarkable. Liver weights were increased [$p<0.01$] at 50 mg/kg for both sexes and in females at 10

mg/kg [$p<0.01$] . Liver weights were increased in males but values were not statistically significant at 10 mg/kg. Kidney weights were increased at 50 mg/kg in both males and females and the increase was statistically significant. Gross pathology revealed liver effects at 50 mg/kg in both sexes as pallor and an accentuation of the lobular pattern of the liver. Microscopic examination showed a diffuse fatty infiltration of the liver in all dogs at 50 mg/kg and a focal fatty infiltration of the liver in 3 of 4 males at 10 mg/kg. **The LOAEL is 10 mg/kg/day based on fatty infiltration of the liver in males and increased liver weights in females with the NOAEL being 2 mg/kg/day.**

Dose and Endpoint for Establishing RfD: NOAEL = 2.0 mg/kg/d based on fatty infiltration in the liver of males and increased liver weights in females at 10.0 mg/kg/d.

Uncertainty Factor(s): 100

$$\textbf{Chronic RfD} = \frac{\text{2.0 mg/kg/day}}{(100)} = \textbf{0.02 mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factor: The RfD was originally established at the RfD meeting of August 5, 1993. The UF utilized was 100 [10 for intra and 10 for inter species variation]. The HIARC re-affirmed the chronic RfD. It is pointed out here for the purpose of clarification that the one-year dog study with an NOAEL of 2.0 mg/kg/d was selected over the 2-generation rat reproduction study which had the lower NOAEL of 1.0 mg/kg/d. The RfD Committee indicated in the RfD Peer Review Document of August 5, 1993 that the effects that were observed at 5.0 mg/kg/d in the reproduction study, which was the LOAEL, were minimal thus allowing the NOAEL for chronic effects to be established on the basis of the dog study.

This risk assessment is required.

C. Occupational/Residential Exposure

1. Dermal Absorption

Type of Study Proposed: None

MRID No.: None.

Executive Summary: None

Comments about Study /Endpoint: This registration action is an import tolerance only. Therefore this study is not required.

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

Type of Study Proposed: None

MRID No.: None

Executive Summary: None

Dose and Endpoint Proposed for Consideration: None

Comments about Study/Endpoint: This registration action is an import tolerance only. Therefore this risk assessment is not required.

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

Type of Study Proposed: None

MRID No.: None

Executive Summary: None

Dose and Endpoint Proposed for Consideration: None

Comments about Study/Endpoint: This registration action is an import tolerance only. Therefore this risk assessment is not required.

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

MRID No.: None

Executive Summary:None

Dose and Endpoint Proposed for Consideration:None

Comments about Study/Endpoint: This registration action is an import tolerance only. Therefore this risk assessment is not required.

5. Inhalation Exposure (Any Time period).

Type of Study Proposed: None

MRID No.: None

Executive Summary: None

Dose and Endpoint Proposed for Consideration: None

Comments about Study/Endpoint: None

Risk Assessment for Inhalation Exposure Required: This registration action is an import tolerance only. Therefore this risk assessment is not required.

D. Recommendation for Aggregate (Food, Water and Dermal) Exposure Risk Assessments

This is an import tolerance. For acute aggregate exposure risk assessment, combine the high end exposure values from food and compare it to the acute RfD for females 13+. An acute RfD is not established for the general population including infants and children.

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

No occupational/residential risk assessments are required.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No: 41084702

Executive Summary: Two hundred and fifty-six male and female Alpk:APfSD [Wistar-derived] rats 5 weeks old, in good health and weighing between 81 and 155 grams were divided into four groups of 52 [main study] and 12 [interim sacrifice] males and females per group. Groups received either 10, 100, 1000 ppm hexaconazole in the diet for two years or twelve months. Control group received diet without the test compound. Observations and clinical chemistry were taken at predetermined intervals and animals were sacrificed as scheduled. There were no overt clinical signs. Mortality was comparable to controls with the exception of high dose females where survival was better than controls. Food consumption and body weight gains were statistically significantly decreased in males and females at 1000 ppm [$p<0.01$]. Body weight gains were also decreased in females at 100 ppm but generally were not statistically significant until week 96 [$p<0.05$: -7%]. Body weight gains were comparable to controls at 10 ppm in both sexes and at 100 ppm in males. Food efficiency was comparable for all groups. Males sacrificed at week 52 showed an apparent dose related decrease in platelet count from the HDT [$838x10^9$ /l] to the LDT [$736x10^9$/]. No other hematological effects were noted. Clinical chemistry values were not remarkable although variability in values was reported for SGOT, SGPT, cholesterol and triglyceride values. Hepatic amino-N-demethylase [APDM] was statistically significantly increased in males at 100 and 1000 ppm and in females at 1000 ppm. Urinalysis showed no treatment related effects. Kidney weights at the interim sacrifice were increased in females at 100 and 1000 ppm with statistical

significance at HDT. Increases were not observed at terminal sacrifice [this increase may reflect a transient change as this effect was observed in two other studies]. Kidney effects were not noted in males. Liver weight was statistically increased in males and females at 1000 ppm at 24 months. Gross pathology in males and females showed changes in liver at the interim and terminal sacrifice at 1000 ppm and was seen as swollen and /or enlarged lobes, an accentuated lobular pattern and pale spots. Microscopic examination revealed fatty changes in the centrilobular region in 100 ppm males and 1000 ppm males and females. Hepatocellular hypertrophy was observed in high dose males only. Males in the 100 ppm and 1000 ppm dose groups exhibited and increased incidence of cortical vacuolation of the adrenal gland and tubular atrophy of the testes which was seen as an acceleration of naturally occurring lesions. There was a dose related positive trend [<0.01] in benign Leydig cell tumors in the testes and a significant pair wise comparison [p<0.05] between the HDT and the controls. The incidence at 100 and 1000 ppm was also outside the historical control range for this type of tumor in this strain of rat. These tumors were also considered uncommon in this strain of rat and also occurred at an accelerated rate. The CPRC [CPRC memo of 9/26/90 from E.Doyle and G. Ghali to Susan Lewis of Registration Division] classified this chemical as a Cq with a Q* of 2.3 x 10^{-2} **The LOAEL was 1000 ppm [47 and 61 mg/kg/d in males and females respectively] in both sexes based on decreased body weight gain in females of 7% [p<0.05] and fatty changes in the centrilobular region of the liver of males as well as increased incidence of cortical vacuolation of the adrenal gland and tubular atrophy of the testes which was seen as an acceleration of naturally occurring lesions. The NOAEL was 100 ppm in both males and females [4.7 and 6.1 mg/kg/d in males and females respectively]. RfD Committee Report of 11/10/93.**

Discussion of Tumor Data: There was a dose related positive trend [<0.01] in benign Leydig cell tumors in the testes and a significant pair wise comparison [p<0.05] between the HDT and the controls. The incidence at 100 and 1000 ppm was also outside the historical control range for this type of tumor in this strain of rat. These tumors were also considered uncommon in this strain of rat and also occurred at an accelerated rate. The CPRC [memo of 9/26/90] classified this chemical as a Cq with a Q* of 2.3 x 10^{-2} The treatment did not alter the spontaneous tumor profile in the female rat. [Note: a revised potency factor was calculated on 11/18/98 using the 3/4 interspecies scaling factor resulting in a new q-star value of 1.6 x 10^{-2}. See paragraph on the Classification of Carcinogenic potential which follows below].

Adequacy of the Dose Levels Tested: Based on the absence of significant systemic toxic signs, the Cancer Peer Review Committee concluded that the high dose tested might not have been adequate for carcinogenicity testing and that the animals could have tolerated higher doses.

2. Carcinogenicity Study in Mice

MRID No.: 40944805

Executive Summary: Two hundred male and two hundred female CD-1/AlpK mice were divided into four groups of 50 male and 50 females per sex per dose group and fed diets

of either 0, 5, 40, or 200 ppm hexaconazole for a period of two years [equivalent to 0.66, 5.3 or 26.3 mg/kg/d]. There were no overt signs of toxicity or increased mortality. Mean weight gains were decreased in males at 200 ppm and were 6% and 11% lower than the control gain at weeks 12 and 78; food efficiency was slightly but significantly [$p<0.05$] decreased. Weight gains and food efficiency for females were comparable to control values although food consumption was slightly decreased. No treatment related effects were noted for hematology. Liver was the target organ. The absolute mean liver weights and the liver to body weight ratio were increased [$p<0.01$] in males and females receiving 200 ppm hexaconazole in the diet [30% in males and 18% in females]. There was an increased incidence of centrilobular infiltration and hypertrophy in males and females at 200 ppm with the severity slightly higher in males than females. No effects were noted in the liver at lower doses. There were no reported effects at other organ sites. The treatment did not generally alter the spontaneous tumor profile for this strain of mice under the test conditions. There was however some indication of liver cell tumor increase. The CPRC concluded that based on the absence of significant toxic signs and the knowledge available on this class of compounds, the highest dose did not approach an acceptable level for the determination of the carcinogenic potential for this chemical. Therefore the negative finding in this study should be viewed with caution. **The LOAEL was determined to be 200 ppm [equal to 23.5 and 29.6 mg/kg/d for males and females respectively] based on decreased body weight gains and food efficiency in males and increased liver weight, hypertrophy and centrilobular fatty infiltration of the liver in males and females . The NOAEL was 40 ppm [equal to 4.66 and 5.94 mg/kg/d for males and females respectively].**

Discussion of Tumor Data: Treatment did not generally alter the spontaneous tumor profile for this strain of mice under the test conditions. There was however some indication of liver cell tumor increase.

Adequacy of the Dose Levels Tested: The CPRC concluded however that based on the absence of significant toxic signs and the knowledge available on this class of compounds that the highest dose did not approach an acceptable level for the determination of the carcinogenic potential for this chemical. Therefore the negative finding in this mouse study should be viewed with caution.

3. Classification of Carcinogenic Potential

At the June 27, 1990 meeting the HED Cancer Peer Review Committee classified hexaconazole as Group C carcinogen based on benign Leydig cell tumors in the male rats. The HIARC concurred with the previous classification. **On November 18, 1998 a revised Q-star was calculated using the 3/4 interspecies scaling factor [refer to memo of L. Brunsman, Science Analysis Branch to Albin B. Kocialski of Registration Action Branch 1 dated November 18, 1998] . This resulted in a revised potency factor of 1.6×10^{-2}.**

IV. MUTAGENICITY

The available data indicates that hexaconazole is not mutagenic.

V. FQPA CONSIDERATIONS

The data base for hexaconazole is adequate for FQPA considerations.

1.Neurotoxicity: Acute delayed neurotoxicity study in hen and acute and subchronic neurotoxicity studies for this chemical is not required as this chemical is not a cholinesterase inhibitor and there is no evidence in the available data base that hexaconazole possess neurotoxic properties. It is not structurally related to known neurotoxic compounds.

2a.Developmental Toxicity - Rat: Ninety-six pregnant female Alpk:AP [Wistar-derived] rats were divided into four groups of 24 animals each and given either 0, 2.5, 25, or 250 mg/kg of hexaconazole by gavage on days 7-16 of pregnancy and sacrificed on day 22 of gestation. Clinical signs were not remarkable. Body weight gains and food consumption in animals receiving 250 mg/kg/day were statistically significantly decreased. Maternal gross pathology was not remarkable. Statistically significant increases in late uterine deaths at 250 mg/kg were noted as well a statistically significant decrease [$p<0.01$] in the body weight data of litters. No trend related developmental toxicity was observed in the external examination of fetuses or the visceral examination of fetuses at any dose level. Skeletal developmental defects were seen at all dose levels in the form of extra ribs [14th] and was dose responsive. Increased delayed ossification was also recorded at the low and the mid dose in the absence of maternally toxic effects.

The maternal LOAEL was 250 mg/kg/d based on a reduced body weight gain [-11%;$p<0.01$] and a reduction in food consumption. The maternal NOAEL is 25 mg/kg/d. The developmental NOAEL is 2.5 mg/kg/d based on delayed ossification of the 7th cervical transverse process and the presence of the extra 14th rib at the LOEL of 25.0 mg/kg/d. [RfD Peer Review of 11/10/93 and comments of David Anderson at the HIARC meeting of 12/8/98].

2b. Developmental Toxicity - Rabbit: Seventy-two pregnant New Zealand White rabbits were divided into four groups of 18 animals each and given either 0, 25, 50, and 100 mg/kg of hexaconazole by gavage on days 7-16 of pregnancy and sacrificed on day 30 of gestation. Maternal toxicity was evidenced at 100 mg/kg by reduced body weight gain, supported by a slight decrease in food consumption and followed by subsequent recovery [immediate increased weight gain after cessation of dosing]. Decreased mean body weight and food consumption values in the low and mid dose level groups were not considered to be treatment related due to the lack of evidence of recovery. Examination of

of all other maternal parameters indicated no treatment related effects. Developmental effects were noted as decreased mean fetal body weights at 50 and 100 mg/kg.

The LOAEL for maternal effects was 100 mg/kg/d based on a decreased maternal body weight gain and the NOAEL was 50 mg/kg. The LOAEL for developmental effects was 50 mg/kg/d based on decreased [$p<0.05$-$p<0.01$] mean fetal body weight and the NOAEL was 25 mg/kg/d.

3.Reproductive Toxicity: Sixty male and 120 female Alpk:APfSD [Wistar-derived] rats comprising the F_0 generation were divided into four groups of 15 males and 30 females per group and fed either 0, 20, 100 or 1000 ppm [0, 1, 5, or 50 mg/kg/d] of hexaconazole on a daily basis for two generations. No treatment related mortality or clinical observations were reported. Body weight gains [-4.5%] for F_0 females were less than control [$p<0.01$] only at 1000 ppm. Males also had a body weight gain decrease of -5.7% at 1000 ppm but the decrease was not statistically significant. However, these body weight gain decreases were attributed to a decreased palatability at the high dose as food consumption was decreased at this level.

F_1 males and females showed no treatment related effects with respect to body weight gain at 20 and 100 ppm during the pre-mating period. However males and females at the 1000 ppm level had body weights which were initially lower than control group weights [-11% for males and -7.7% for females] at the beginning of the pre-mating period with the differences reduced to -6% and -5% for males and females respectively by the beginning of the mating period. No treatment related effects were noted in females for any treatment group during pregnancies.

There was no treatment related effect on the reproductive performance of either sex for the F_0 or the F_1 generation.

Liver weight for the 1000 ppm dose group males and females of the F_0 and the F_1 generation were increased [$p<0.01$]. Gross pathology indicated no treatment related effects for males or females at 20 and 100 ppm for the F_0 and F_1 parental generation. However, both males and females at 1000 ppm had enlarged livers with some pallor and an accentuation of the lobular pattern. Microscopic examination of these same livers indicated a dose- related fatty change in both sexes at 100 and 1000 ppm. The high dose males and females also had an increased incidence of cytoplasmic vacuolation of the adrenal cortex.

There were no readily apparent treatment related effects regarding the viability or clinical signs of the offspring. Body weight gain was decreased significantly at 1000 ppm in the F_1a litter of males and females as was mean litter size [day 29]. Decreased viability [$p<0.05$] was also noted at 1000 ppm [HDT] in the F_{2a} generation. Offspring showed increased liver weights [$p<0.01$] at 1000 ppm. Gross pathology was seen at 1000 ppm in

the liver as a pallor and an accentuated reticular pattern which was similar to the parents. Histopathology of the high dose animals revealed fatty changes similar to parental rats at 1000 ppm.

The LOAEL for offspring was 1000 ppm [50 mg/kg/d] based on a decrease in body weight gain in pups decreased litter size and a decreased pup survival. The NOAEL was 100 ppm [5 mg/kg/d] . The LOAEL for parental toxicity was 100 ppm [5 mg/kg/d] based on liver pathology [fatty infiltration of the liver] in both sexes with NOAEL being 20 ppm [1 mg/kg/d].

4. Open Literature: There was no additional information obtained from the literature.

5.Determination of Susceptibility: The available data indicate that there is adequate evidence of increased susceptibility of rat and rabbit fetuses to the *in utero* exposure of hexaconazole in developmental studies.

In the two generation reproduction study effects in the offspring were only observed at or above treatment levels which resulted in evidence of parental toxicity.

6.Recommendation for a Developmental Neurotoxicity Study: There is currently no available evidence supporting the argument for a developmental neurotoxicity study:

Hexaconazole is not structurally related to a neurotoxic agent.

There was is no evidence in the acute, subchronic and chronic studies that hexaconazole induces neurotoxic effects.

Developmental and reproductive studies do not indicate that the chemical is neurotoxic.

Developmental effects occurred at dose levels that were below maternally toxic levels for both rat and rabbit but were not associated with neurotoxicity. Rats manifested delayed ossification and an extra 14th rib and rabbits showed decreased fetal weights at doses below maternally toxic levels but no neurotoxicity. Effects on offspring in reproductive studies were not associated with neurotoxicity and occurred only at dose levels above maternally toxic doses.

7.Determination of the FQPA Safety Factor: The final application and determination an FQPA factor for the protection of infants and children from exposure to hexaconazole as required by FQPA, will be determined by the FQPA Safety Factor Committee. However, based solely on the toxicity data base, the HIARC recommended that the 10x safety factor be retained.

VI. HAZARD CHARACTERIZATION

Hexaconazole possesses low acute toxicity by all routes of exposure [categories 3/4] with some evidence of sensitization in females. Subchronic and chronic studies in mice, rats and dogs indicate that the liver is the primary target organ as generally seen by increased liver enzyme levels, liver cell hypertrophy, and fatty infiltration of the liver across species. Decreased body weight gain was also seen across species. Developmental studies in rats and rabbits showed increased susceptibility to offspring with effects occurring at doses below maternal effects. Delayed ossification of the 7th cervical transverse process and a numerical increase in the 14th rib of rats as well as a decrease in fetal body weight in rabbit offspring were noted. A two generation reproduction study in rats revealed decreased body weight gains, deceased litter size and decreased pup survival as well as some liver effects in offspring which occurred at the same doses as for those for parents . Oncogenicity in the form of benign Leydig cell tumors was noted in the rat study which resulted in a C classification with a q-star designation by the Cancer Peer Review Committee. The most recent revision of the q-star occurred on the 18th of November 1998 using the 3/4s in lieu of the 2/3s interspecies scaling factor. The MTD was deemed not reached in the mouse study by the CPRC and cautioned that the results of this study should be viewed conservatively.

VII. DATA GAPS: None

VIII. ACUTE TOXICITY

Acute Toxicity of Hexaconazole

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral[1]	00160491	LD_{50} = 2189 mg/kg	3
81-2	Acute Dermal[2]	00160491	LD_{50} = >2000 mg/kg	3
81-3	Acute Inhalation[3]	40742901	LC_{50} = >5.9 mg/L	4
81-4	Primary Eye Irritation[4]	00160492	slight/moderate irritation to irrigated/non-irrigated eyes	3
81-5	Primary Skin Irritation[5]	00160492	non-irritating	4
81-6	Dermal Sensitization[6]	00160493	moderately positive to females	na

1,2,4,5,6 tested with 92.3% technical

3 tested with 90.0% technical

note: dermal sensitization studies with formulated products of 5%SG [MRID 00160496]; 10%WG [MRID 41052308]; and 5.62 %[unknown formulation] [MRID 00160669], resulted in negative, mild positive findings in males, and negative findings respectively. All technical and formulated products are categorized as either 3 or 4 for any individual acute study.

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	NOEL= 2.5 UF = 100	increase in the occurrence of the 14th rib on a litter basis and a partially ossified 7th cervical transverse process	developmental rat
	Acute RfD = 0.025 mg/kg/d		0.0025
Chronic Dietary	NOEL = 2.0 UF = 100	fatty infiltration of the liver and increased liver weights	one year dog [oral gavage]
	Chronic RfD = 0.02 mg/kg/d		0.02
Short-Term (Dermal)	NOEL= na	na	na
Intermediate-Term (Dermal)	NOEL= na	na	na
Long-Term (Dermal)	NOEL= na	na	na
Short Term (Inhalation)	NOEL= na	na	na
Intermediate Term (Inhalation)	NOEL= na	na	na
Long Term (Inhalation)	NOEL= na	na	na

HED Hazard Identification Assessment Review Committee Meeting

Chemical: HEXACONAZOLE (Terbufos Dermal Studies - piggyback)
08DEC1998

HIARC Members	Signature
David Anderson	
William Burnam	
Virginia Dobozy	
Karen Hamernik	
Pamela Hurley	
Mike Ioannou, Co-Chair	
Tina Levine (RD)	
Susan Makris	
Nancy McCarroll	
Nicole Paquette	
Kathleen Raffaele	
Jess Rowland	
PV Shah	
Pauline Wagner, Co-Chair	
Brenda Tarplee, Exec. Sec.	

Presenter / Branch / Division	Signature
Albin Kowalski	
Paul CHIN	

Other Team Members (O/RE reviewer, etc.)	Signature
William J. Hazel	

Other Attendees / Branch / Division	Signature
ALAN C. LEVY RAB-2 HED	
Whang Phang	

013076

Hazard Identification Assessment Review Committee (HIARC)

Meeting Agenda for

December 8, 1998

9:00AM	Terbufos	Presented by B. Chin (RRB1) **Tentatively scheduled** for review of two new dermal studies.
9:45AM	Hexaconazole	Presented by A. Kocialski (RAB1)
11:45AM	Committee announcements and recap issues to share with Branch Staff.	
12:00PM	Adjourn	

ATTACHMENT 3 - Dietary Exposure Analyses (*Available Electronically*)

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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: February 19, 1999

SUBJECT: Hexaconazole - Dietary Exposure Analysis for Hexaconazole in/on Bananas (PP # 0E03853). Chemical#: 128925. DP Barcode: D252486. Case #: 194111. Submission #: S544138.

FROM/TO: Susie Chun, Chemist
Registration Action Branch 1
Health Effects Division

THROUGH: Melba Morrow, D.V.M., Branch Senior Scientist
Registration Action Branch 1
Health Effects Division

Action Requested

Provide an estimate of the dietary exposure and associated risk for hexaconazole resulting from an existing time-limited tolerance for import bananas (0E3853). HED has concluded that the appropriate tolerance level for bananas should be 0.7 ppm (Memo, D246865, S. Chun, 12/14/98).

Note: An existing time-limited tolerance for bananas expires 3/31/99.

Toxicological Endpoints

On December 8, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of hexaconazole, reassessed the Reference Dose (RfD) established in 1993 and selected the toxicological endpoints for acute dietary as well as occupational exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to hexaconazole as required by the Food Quality Protection Act (FQPA) of 1996.

The doses and toxicological endpoints selected for various exposure scenarios are summarized in Table 1.

Table 1. Summary of Toxicological Endpoints for Hexaconazole Use in Human Risk Assessment

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOAEL= 2.5 UF = 100	increase in the occurrence of the 14th rib on a litter basis and a partially ossified 7th cervical transverse process	developmental rat
	Acute RfD = 0.025 mg/kg/day		
Chronic Dietary	NOAEL = 2.0 UF = 100	fatty infiltration of the liver and increased liver weights	one year dog [oral gavage]
	Chronic RfD = 0.02 mg/kg/day		

Cancer

On June 27, 1990, the Carcinogenicity Peer Review Committee recommended that a quantitative risk assessment for hexaconazole be estimated for benign Leydig cell tumors in male rats. A quantitative risk assessment (Dose Response Assessment of the Carcinogenic Effects of hexaconazole at Low Doses Using the Linearized Multistage Model for Extrapolating the Experimental Data Points, R. Engler, 6/27/90) was prepared using the $^{2}/_{3}$'s scaling factor. This revised quantitative risk assessment reflects the Division change from use of the $^{2}/_{3}$'s to the $^{3}/_{4}$'s scaling factor in 1994. The unit risk, Q_1^* (mg/kg/day)$^{-1}$, of hexaconazole based upon male rat benign Leydig cell tumor rates is **1.60 x 10^{-2}** in human equivalents (converted from animals to humans by use of the $^{3}/_{4}$'s scaling factor - Tox_Risk program, Version 3.5, K. Crump, 1994). The dose levels used from the 2-year dietary study were 0, 10, 100, and 1000 ppm of Hexaconazole. The corresponding tumor rates for the male rat benign Leydig cell tumors were 2/61, 2/61, 4/61, and 8/61, respectively (Memo, L. Brunsman, 11/18/98).

FQPA Recommendation

The HIARC recommended that the 10x safety factor be retained (Memo, A. Kocialski, 1/21/99). The FQPA Safety Factor Committee (SFC) met on January 25, 1999 and recommended that the FQPA safety factor of 10x for protection of infants and children (as required by FQPA) be retained.

The FQPA SFC recommended that the **FQPA safety factor** of 10x be **retained** because increased susceptibility was demonstrated in two species:

- In the developmental (*in utero*) toxicity study in rats, developmental toxicity (manifested as delayed ossification and an extra 14th rib) occurred at doses below maternally toxic levels.

- And in the developmental (*in utero*) toxicity study in rabbits, developmental toxicity (manifested as decreased fetal weights) occurred at doses below maternally toxic

levels.

The SFC determined that the 10x factor should be applied only to populations subgroup females 13+ in acute dietary risk assessments (Memo, B. Tarplee, 2/5/99). This will result in an acute population adjusted dose (PAD) of 0.0025 mg/kg/day. For chronic dietary risk assessment, the 10x factor was reduced to 1x.

Residue Information

A time-limited tolerance for hexaconazole (parent only) residues in bananas is published in 40 CFR §180.3488.

The HED Metabolism Assessment Review Committee (MARC) met on June 1, 1995 to discuss the toxicological significance of potential hexaconazole metabolites. The MARC decided that parent hexaconazole is the only terminal residue that needs to be included in the tolerance expression for bananas, which is the only food use pending at this time. The diol metabolites are expected to be of comparable toxicity to the parent compound and will be included in risk assessments (Memo, S. Willett, 6/19/95).

For all dietary analyses, the residue values (hexaconazole and diol metabolites) from the field trials on banana pulp were used. The use of banana pulp residue levels provides a more realistic estimate of dietary exposure as individuals do not usually eat the banana peel.

In the case of the acute dietary analysis, the highest banana pulp field trial residue values for the parent and diol metabolites (Memo, S. Chun, D246865, 12/14/98) and 100 percent crop treated (%CT) were used. For the chronic and cancer analyses, the average field trial banana pulp residue levels based on field trial data (Memo, S. Chun, D246865, 12/14/98) and 100 % CT information were used.

A dietary analysis for chronic and cancer with the Dietary Risk Evaluation System (DRES) system was previously completed (Memo, D. Miller, 10/31/95).

Results

The Dietary Exposure Evaluation Model (DEEM™) analysis evaluated the individual food consumption as reported by respondents in the USDA 1989-91 Nationwide Continuing Surveys for Food Intake by Individuals (CSFII) and accumulated exposure to the chemical for each commodity. Summaries of the residue information used in the acute and chronic and cancer dietary exposure analyses are attached (Attachments 1 and 3).

Acute Dietary Exposure Analysis

The acute dietary exposure analysis estimates the distribution of single-day exposures for the U.S. population and certain subgroups and accumulates exposure to the chemical for each commodity. Each analysis assumes uniform distribution of hexaconazole (and its diol metabolites) for the commodities on which hexaconazole is used.

The acute dietary exposure analysis for the population subgroup females 13+ was performed using the highest pulp residue level (parent + diol metabolites) and 100 percent crop treated (Attachments 2). The FQPA Safety Factor of 10x was retained for the acute dietary analysis only and for the population subgroup females 13+. The population adjusted dose (PAD) used in the acute dietary analysis was **0.0025 mg/kg/day**.

Dietary exposures and associated acute risk at the 95th percentile are shown in Table 1 for the population subgroup females 13+.

Table 1. - Acute Dietary Exposure Results

Subgroups	Exposure (mg/kg/day)	% acute PAD
Females (13+, preg., not nursing)	0.001181	47.2
Females (13+, nursing)	0.001136	45.4
Females (13-19 yrs., not preg., not nursing)	0.000892	35.7
Females (10+ years, not preg., not nursing)	0.001030	41.2
Females (13-50 years)	0.000954	38.1

Chronic Dietary Analysis

The chronic DEEM™ dietary exposure analysis used mean consumption (3 day average). The average pulp residue level (parent + diol metabolites) from field trials and 100% CT information were used

The FQPA Safety Factor was reduced to 1x. Therefore the chronic PAD and the chronic RfD are the same . For chronic dietary risk, HED's level of concern is 100% RfD. Dietary exposures for the U.S. general population and other subgroups are presented in Table 2. The other subgroups included in Table 2 represent the highest dietary exposures for their respective subgroups (i.e., children, females, and the other general population subgroup higher than U.S. population).

Table 2. - Chronic Dietary Exposure Results

Subgroups	Exposure (mg/kg/day)	% RfD
U.S. Population (48 states)	0.000033	< 1
Non-hispanic other than black or white	0.000050	< 1
Non-nursing infants (< 1 year old)	0.000205	1.0
Females (13+/nursing)	0.000035	< 1

The complete chronic dietary exposure analysis is attached (Attachment 4).

Cancer Dietary Analysis

The average pulp residue level (parent + diol metabolites) from field trials and 100% CT information were used to calculate the upper bound lifetime cancer risk for dietary exposure to hexaconazole (and diol metabolites). The cancer DEEM™ analysis used mean consumption and gave the following results:

Subgroups	Exposure (mg/kg/day)	Lifetime Cancer Risk
U.S. Population (48 states)	0.000033	5.3×10^{-7}

A summary of the cancer dietary exposure analysis is attached (Attachment 6).

Conclusions

The acute analysis for hexaconazole is a conservative but more realistic estimate of dietary exposure with the use of the pulp residue values and 100 percent of the commodities assumed to be treated. The percent acute PADs were below HED's level of concern at the 95th percentile for the females 13+ subgroup. The results of this analysis indicate that the acute dietary risk associated with the proposed use of hexaconazole on bananas is below the Agency's level of concern.

The chronic and cancer analyses for hexaconazole also estimated dietary exposure using field trial data for the pulp and 100 % CT information. All chronic (non -cancer) % RfDs for all subgroups were ≤ 1%. The results of the chronic analysis indicate that the chronic dietary risk associated with the existing and proposed uses of hexaconazole is below the Agency's level of concern (< 100% RfD).

The Agency considers 1×10^{-6} as negligible risk (i.e, less than 1 in 1 million) for cancer. The results of this analysis indicate that the cancer dietary risk of 5.3×10^{-7} associated with the proposed use of hexaconazole is below the Agency's level of concern.

Attachment 1: Residue File -Acute
Attachment 2: Acute DEEM™ analysis - U.S. Population (S. Chun, 2/2/99)
Attachment 3: Residue File - Chronic and Cancer
Attachment 4: Chronic DEEM™ analysis (S. Chun, 2/2/99)
Attachment 5: Cancer DEEM™ analysis (S. Chun, 2/2/99)

cc: S. Chun (RAB1); M. Sahafeyan (CEB1), PP# 0E3853
RDI: Dietary Exposure SAC [C. Swartz (2/18/99), D. Hrdy 2/18/99)]
S. Chun:806R:CM#2:(703)305-2249:7509C:RAB1

Attachment 1: Residue Information - Acute

FILENAME: C:\deem89\resdata\128925a.R91

CHEMICAL NAME: Hexaconazole

RfD(CHRONIC): .020000 mg/kg/DAY NOEL(CHRONIC): .000000 mg/kg/day

RfD(ACUTE): .002500 mg/kg/DAY NOEL(ACUTE): .000000 mg/kg/day Q*=.0160

Date created/last modified: 02-01-1999/14:21:24/8 Program ver. 6.16

Comment: PAD for acute; Used banana pulp residue levels from field trials

Food Code	Crop Grp	Food Name	RESIDUE (ppm)	RDF #	Adj.Factors #1	#2	Comment
073	A	BANANAS-DRIED	000.560000		03.900	01.000	p, tlt exp 3/31/99 0.1 ppm + n 0.6 ppm, 0E3853
378	A	BANANAS-JUICE	000.560000		01.000	01.000	p, tlt exp 3/31/99 0.1 ppm + n 0.6 ppm, 0E3853
072	A	BANANAS	000.560000		01.000	01.000	p, tlt exp 3/31/99 0.1 ppm + n 0.6 ppm, 0E3853
094	A	PLANTAINS-RIPE	000.560000		01.000	01.000	p, tlt exp 3/31/99 0.1 ppm + n 0.6 ppm, 0E3853
481	A	PLANTAINS-DRIED	000.560000		03.900	01.000	p, tlt exp 3/31/99 0.1 ppm + n 0.6 ppm, 0E3853
480	A	PLANTAINS-GREEN	000.560000		01.000	01.000	p, tlt exp 3/31/99 0.1 ppm + n 0.6 ppm, 0E3853

Attachment 2: Acute Dietary Exposure Analysis - Females 13+

U.S. Environmental Protection Agency Ver. 6.27
DEEM ACUTE analysis for HEXACONAZOLE (1989-92 data)
Residue file name: 128925a.R91 Adjustment factor #2 NOT used.
Analysis Date: 02-02-1999/12:50:28 Residue file dated: 02-02-1999/12:49:05/8
Acute Reference Dose (aRfD) = 0.002500 mg/kg body-wt/day
Run Comment: PAD for acute; Used banana pulp residue levels from field trials

Summary calculations:

	95th Percentile Exposure	95th Percentile % aRfD	99th Percentile Exposure	99th Percentile % aRfD	99.9 Percentile Exposure	99.9 Percentile % aRfD
Females (13+/preg/not nsg):	0.001181	47.23	0.001666	66.64	0.002013	80.51
Females (13+/nursing):	0.001136	45.43	0.001516	60.62	0.001708	68.30
Females (13-19 yrs/np/nn):	0.000892	35.67	0.001533	61.31	0.001953	78.14
Females (20+ years/np/nn):	0.001030	41.18	0.001574	62.97	0.002937	117.46
Females (13-50 years):	0.000954	38.14	0.001558	62.31	0.002727	109.07

Attachment 3: Residue Information - Chronic and Cancer

FILENAME: C:\deem89\resdata\128925c.R91

CHEMICAL NAME: Hexaconazole

RfD(CHRONIC): .020000 mg/kg/DAY NOEL(CHRONIC): .000000 mg/kg/day

RfD(ACUTE): .025000 mg/kg/DAY NOEL(ACUTE): .000000 mg/kg/day Q*=.0160

Date created/last modified: 02-01-1999/14:19:16/8 Program ver. 6.16

Comment: Used banana pulp residue levels from field trials

Food Code	Crop Grp	Food Name	RESIDUE (ppm)	RDF #	Adj.Factors #1	#2	Comment
073	A	BANANAS-DRIED	000.110000		03.900	01.000p,	tlt exp 3/31/99 0.1 ppm + n 0.6 ppm, 0E3853, AR
378	A	BANANAS-JUICE	000.110000		01.000	01.000p,	tlt exp 3/31/99 0.1 ppm + n 0.6 ppm, 0E3853, AR
072	A	BANANAS	000.110000		01.000	01.000p,	tlt exp 3/31/99 0.1 ppm + n 0.6 ppm, 0E3853, AR
094	A	PLANTAINS-RIPE	000.110000		01.000	01.000p,	tlt exp 3/31/99 0.1 ppm + n 0.6 ppm, 0E3853, AR
481	A	PLANTAINS-DRIED	000.110000		03.900	01.000p,	tlt exp 3/31/99 0.1 ppm + n 0.6 ppm, 0E3853, AR
480	A	PLANTAINS-GREEN	000.110000		01.000	01.000p,	tlt exp 3/31/99 0.1 ppm + n 0.6 ppm, 0E3853, AR

Attachment 4: Chronic Exposure Analysis

U.S. Environmental Protection Agency Ver. 6.12
DEEM89N CHRONIC analysis for HEXACONAZOLE (1989-92 data)
Residue file name: 128925C Adjustment factor #2 NOT used.
Analysis Date 02-01-1999 Residue file dated: 02-01-1999/14:19:16/8
Reference dose (RfD, CHRONIC) = 0.020000 mg/kg body-wt/day
Comment: Used banana pulp residue levels from field trials

Total exposure by population subgroup

Population Subgroup	Total Exposure mg/kg body wt/day	Total Exposure Percent of Rfd
U.S. Pop - 48 states - all seasons	0.000033	0.2%
U.S. Population - spring season	0.000033	0.2%
U.S. Population - summer season	0.000029	0.1%
U.S. Population - autumn season	0.000031	0.2%
U.S. Population - winter season	0.000040	0.2%
Northeast region	0.000031	0.2%
Midwest region	0.000030	0.1%
Southern region	0.000036	0.2%
Western region	0.000034	0.2%
Pacific Region	0.000034	0.2%
Hispanics	0.000040	0.2%
Non-hispanic whites	0.000033	0.2%
Non-hispanic blacks	0.000025	0.1%
Non-hispanic other than black or white	0.000050	0.2%
All infants (<1 year)	0.000167	0.8%
Nursing infants (<1 year)	0.000077	0.4%
Non-nursing infants (<1 year)	0.000205	1.0%
Children (1-6 years)	0.000091	0.5%
Children (7-12 years)	0.000037	0.2%
Females (13-19 yrs/not preg. or nursing)	0.000016	0.1%
Females (20+ years/not preg. or nursing)	0.000027	0.1%
Females (13-50 years)	0.000020	0.1%
Females (13+/pregnant/not nursing)	0.000027	0.1%
Females (13+/nursing)	0.000035	0.2%
Males (13-19 years)	0.000024	0.1%
Males (20+ years)	0.000020	0.1%
Seniors (55+)	0.000036	0.2%

Attachment 6: Cancer Exposure Analysis

U.S. Environmental Protection Agency Ver. 6.12

U.S. Environmental Protection Agency Ver. 6.12
DEEM89N CHRONIC analysis for HEXACONAZOLE (1989-92 data)
Residue file name: 128925C Adjustment factor #2 NOT used.
Analysis Date 02-01-1999 Residue file dated: 02-01-1999/14:19:16/8
Q* = 0.016000
Comment: Used banana pulp residue levels from field trials

Total exposure by population subgroup

Population Subgroup	Total Exposure mg/kg body wt/day	Total Exposure Lifetime risk (Q*=0.016000)
U.S. Pop - 48 states - all seasons	0.000033	5.29E-07
U.S. Population - spring season	0.000033	5.31E-07
U.S. Population - summer season	0.000029	4.58E-07
U.S. Population - autumn season	0.000031	4.89E-07
U.S. Population - winter season	0.000040	6.44E-07
Northeast region	0.000031	4.97E-07
Midwest region	0.000030	4.77E-07
Southern region	0.000036	5.74E-07
Western region	0.000034	5.47E-07
Pacific Region	0.000034	5.52E-07
Hispanics	0.000040	6.39E-07
Non-hispanic whites	0.000033	5.28E-07
Non-hispanic blacks	0.000025	4.02E-07
Non-hispanic other than black or white	0.000050	7.97E-07
All infants (<1 year)	0.000167	2.67E-06
Nursing infants (<1 year)	0.000077	1.23E-06
Non-nursing infants (<1 year)	0.000205	3.28E-06
Children (1-6 years)	0.000091	1.46E-06
Children (7-12 years)	0.000037	5.85E-07
Females (13-19 yrs/not preg. or nursing)	0.000016	2.48E-07
Females (20+ years/not preg. or nursing)	0.000027	4.26E-07
Females (13-50 years)	0.000020	3.18E-07
Females (13+/pregnant/not nursing)	0.000027	4.34E-07
Females (13+/nursing)	0.000035	5.62E-07
Males (13-19 years)	0.000024	3.86E-07
Males (20+ years)	0.000020	3.24E-07
Seniors (55+)	0.000036	5.84E-07

ATTACHMENT 4 - Codex Form

Attachment: Page 1 of 1

INTERNATIONAL RESIDUE LIMIT STATUS

CHEMICAL: Hexaconazole (α-butyl-α-(2,4-dichloro-phenyl)-1*H*-1,2,4-triazole-1-ethanol)

CODEX NO. 170

CODEX STATUS:

[ ] No Codex Proposal
Step 6 or Above

Residue (if Step 8): Hexaconazole

Crop(s)	Limit (mg/kg)
banana	0.1

PROPOSED U.S. TOLERANCES:

Petition No. 0E03853

HED Reviewer S. Chun

Residue: Parent hexaconazole only

Crop(s)	Limit (mg/kg)
Bananas	0.1

CANADIAN LIMITS:

[X] No Canadian Limits

Residue:

Crop(s)	Limit (mg/kg)

MEXICAN LIMITS:

[x] No Mexican Limits for banana

Residue: hexaconazole

Crop(s)	Limit (mg/kg)
plantain	0.1

NOTES