United States
Environmental Protection
Agency

Office of Prevention, Pesticides
and Toxic Substances
(7501C)

Pesticide Fact Sheet

Name of Chemical: **Prohexadione Calcium**
Reason for Issuance: **New Chemical Registration**
Date Issued: **April 26, 2000**

DESCRIPTION OF CHEMICAL

Generic Name: calcium 3-oxido-5-oxo-4-propionylcyclohex-3-enecarboxylate

Common Name: prohexadione calcium

Trade Names: Apogee Plant Growth Regulator, Baseline Plant Regulator, K-I Chemical Prohexadione Calcium Manufacturing Use Product

EPA Chemical Code: 112600

Chemical Abstracts Service (CAS) Number: 127277-53-6

Year of Initial Registration: 2000

Pesticide Type: Plant Growth Regulator

U.S. and Foreign Producers: K-I Chemical U.S.A., Inc.

USE PATTERNS AND FORMULATIONS

Prohexadione calcium is foliarly applied plant regulator which reduces vegetative growth by inhibiting the synthesis of gibberellin, a naturally occurring plant hormone. Specifically it decreases the length of shoot internodes. Apogee in apples and pears decreases the need for pruning, allows more light to penetrate the tree canopy increasing fruit coloration, and, due to increased air circulation, decreases the incidence of fire blight, a bacterial disease of apples and pears. Baseline in peanuts decreases vegetative growth and aids mechanical harvesting. The products are dry flowables to be mixed with water and applied with ground spray equipment to wet leaf surfaces. Apogee is a 27.5% active ingredient (a.i.) product applied at a maximum rate of 1.7 pounds a.i./acre/year and Baseline is a 75% a.i. product applied at a maximum rate of 0.375 pounds a.i./acre/year.

SUMMARY SCIENCE FINDINGS

CHEMICAL CHARACTERISTICS

Some of the physical properties of prohexadione calcium are summarized below:

Color: pale yellow brown

Physical State: fine powder

Dissociation Constant: pKa = 5.15

pH: 6.72

Octanol/Water Partition Coefficient: $K_{o/w}$ = 1.25 x 10 exp.-3

Solubility: 174 mg/l in distilled water at 20 degrees C

Hydrolysis: 4.4 to 65 days (pH 5 to 7)

Half-life: 1.4 to 20 days (laboratory and field)

TOXICOLOGY

Subchronic and Chronic Toxicity:

The chronic reference dose (cRfD) of 0.80 mg/kg/day was selected based on both the subchronic and chronic toxicity studies in dogs. Since a similar endpoint of equal severity (minimal and moderate dilation of basophilic tubules) was observed in both studies, the results of the two studies can be evaluated using a single dose-response curve. The no-observed-adverse-effect level (NOAEL) from the subchronic study was used to establish the RfD due to the wider dose spread in the 1-year study. The NOAEL of 80 mg/kg/day was based on histopathological changes (dilated basophilic tubules) in the kidneys and clinical chemistry changes seen at the lowest-observed-adverse-effect level (LOAEL) of 200 mg/kg/day. No additional uncertainty factor is needed because there is no increase in the severity of the lesions over time in the chronic study as compared to the subchronic study. The FQPA Safety Factor Committee determined that the FQPA safety factor of 1x is applicable for chronic dietary risk assessment. Thus, the chronic population adjusted dose (cPAD) is equivalent to the chronic RfD of 0.80 mg/kg/day.

Carcinogenicity:

In 2-year chronic toxicity/carcinogenicity studies in rats and mice, prohexadione calcium was negative for carcinogenicity when administered at dose levels adequate for the testing of carcinogenic potential. In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), the HIARC classified prohexadione calcium as "not likely to be carcinogenic to humans".

Teratology/Reproductive Toxicity:

No treatment-related developmental effects were noted in rats or rabbits, and no treatment-related maternal effects were noted in rats. However, maternal effects in rabbits included increased mortality, increased abortions, and decreased body weight gains (observed at 200 mg/kg/day), and premature deliveries (observed at 350 mg/kg/day). No reproductive toxicity was noted in rats; however treatment-related systemic toxicity was observed in parental animals and pups. Increased mortality was observed in parental males and females at 385 mg/kg/day, and decreased pup body weight was noted at 3850 mg/kg/day. The results of these studies indicated no

quantitative or qualitative increase in susceptibility of rats or rabbits to *in utero* and/or post-natal exposure to prohexadione calcium since no developmental effects were seen at doses up to the limit dose (1000 mg/kg/day) in the rat developmental toxicity study or up to the highest doses tested (150, 200, and 350 mg/kg/day) in three rabbit developmental toxicity studies. In addition, in the two-generation reproduction study in rats, the effects in the offspring were observed only at treatment levels which resulted in evidence of parental toxicity.

Mutagenicity:

Prohexadione calcium was not mutagenic in bacteria or mammalian cells. It did not cause structural chromosomal aberrations in CHO cells *in vitro* or in rats or mice *in vivo*. Although there was significant increase in polyploidy at the highest dose *in vitro* without S9 activation, the mouse micronucleus assay was negative up to the limit dose suggesting the compound has intrinsic activity not expressed *in vivo*. In addition, there was no evidence of carcinogenicity in rats and mice and results in the 2-generation reproduction study do not suggest a genetic component.

Neurotoxicity:

No evidence of neurotoxicity was observed in either the acute or chronic neurotoxicity studies or in any other toxicity studies.

Metabolism:

In a metabolism study in rats, prohexadione calcium was rapidly absorbed with highest tissue/carcass concentrations obtained within 30 minutes; however, absorption became saturated at the highest dose. The test material did not accumulate in the tissues. For low dose animals, renal excretion was the primary route of elimination. At the high dose, fecal excretion became the primary route of elimination. The primary excreta (both urine and feces) metabolite was identified as the free acid.

Dietary Risk*:*

A chronic dietary exposure analysis for prohexadione calcium was performed using the Dietary Exposure Evaluation Model (DEEM™). Tolerance level residues were used and 100% crop treated was assumed for all pome fruit and peanut commodities. The chronic analysis was conducted for the U.S. population and all population subgroups. The chronic exposure estimates (food only) for the U.S. population and all population subgroups were <5% of the cPAD. Therefore, the results of the analysis indicate that the chronic dietary risk estimates (food only) associated with the proposed uses of prohexadione calcium do not exceed HED's level of concern (>100% cPAD) for the U.S. population or any population subgroups. An acute dietary exposure analysis for prohexadione calcium was not performed because no acute dietary endpoints were selected.

OCCUPATIONAL EXPOSURE

Short- and intermediate-term exposures are expected for the commercial handler. Due to seasonal use, long-term exposures are not expected. Since the short-term NOAEL of 100 mg/kg/day (for dermal and inhalation) is based on the maternal effect of premature deliveries, worker exposure is assessed using 60 kg body weight, females 13 - 50 years old as the most sensitive subgroup, and a 25% dermal absorption factor. Exposures from peanut applications by ground boom equipment are expected to be lower than those from pome fruit applications with air blast equipment. All short- and intermediate-term margins of exposure (MOE) are 1400 and above, and, therefore, worker exposure risk estimates do not exceed HED's level of concern (MOE < 100).

Post-application exposure, although occurring for both peanut and pome fruit operations, is expected to be greatest for harvesters of pome fruit due to higher application rates. The estimated intermediate MOE for the post

application scenario is 130. Therefore, it is reasonable to assume that the potential risk for all workers exposed to prohexadione calcium from the proposed uses does not exceed HED's level of concern (MOE < 100).

AGGREGATE RISK

Acute, cancer, and short- and intermediate-term aggregate exposure risk assessments were not performed because an acute dietary endpoint was not selected, prohexadione is not carcinogenic, and there are no residential uses proposed for prohexadione calcium, respectively. Aggregate exposure risk assessment was limited to chronic exposure (food + water) only.

Chronic aggregate risk estimates (food + water) are below the Agency's level of concern**.** A Tier 1 chronic dietary exposure analysis for prohexadione calcium was performed using tolerance level residues and assuming 100% crop treated for all pome fruit and peanut commodities. The chronic analysis was performed for the U.S. population and all population subgroups. The chronic exposure estimates (food only) for the general U.S. population and all population subgroups were <5% of the cPAD. Thus, the chronic dietary risk estimate associated with the proposed uses of prohexadione calcium does not exceed the Agency's level of concern (>100% cPAD). For ground and surface water, the EECs are less than the drinking water levels of comparison (DWLOCs) for prohexadione calcium in drinking water as a contribution to chronic aggregate exposure. Therefore, it is concluded with reasonable certainty that residues of prohexadione calcium in drinking water do not contribute significantly to the chronic aggregate human health risk at the present time.

ECOLOGICAL CHARACTERISTICS

Avian Acute Toxicity:

Bobwhite Quail: LD_{50} = >5250 mg/kg (practically nontoxic)
Mallard Duck: LD_{50} = >5250 mg/kg (practically nontoxic)

Avian Dietary Toxicity:

Bobwhite Quail: LC_{50} = >2000 ppm (practically nontoxic)
Mallard Duck: LC_{50} = >2000 ppm (practically nontoxic)

Reproductive Toxicity:

Bobwhite Quail NOEC = 1000 ppm
LOEC = > 1000 ppm

Mammalian Acute and Chronic Toxicity:

Laboratory rat - acute oral LD_{50} = > 5000 mg/kg (practically nontoxic)
- chronic LD_{50} for reproduction = > 2000 mg/kg

Insect Toxicity:

Honey bee LD_{50} = > 100 mg/a.i./bee (practically nontoxic)

Freshwater Fish Acute Toxicity:

Bluegill Sunfish LC_{50} = 95.6 ppm (practically nontoxic)

Rainbow Trout LC_{50} = 94.6 ppm (practically nontoxic)

Freshwater Invertebrate Acute Toxicity:

Daphnia magna EC_{50} = 90 ppm (practically nontoxic)

Aquatic Invertebrate Life Cycle: Chronic Toxicity

Daphnia magna NOAEC = 12.5 ppm
LOAEC = 25 ppm

Estuarine and Marine Organisms Toxicity:

Sheepshead Minnow	LC_{50} = 122 ppm (practically nontoxic)
	NOAEC = 122 ppm
Eastern Oyster	EC_{50} = 117 ppm (practically nontoxic)
Mysid Shrimp	NOAEC = 125 ppm (practically nontoxic)

Seedling Emergence:

Ten crop plant species including corn, oat, wheat, onion, ryegrass, cucumber, radish, soybean, sunflower, tomato and cabbage were tested. None exceeded the >25% adverse growth level required to trigger the tier two tests, but a 24% reduction in lettuce emergence was recorded.

Vegetative Vigor:

Ten crop plant species (same as above) were tested. None exceeded the >25% adverse growth level required to trigger the tier two tests, but a 23% reduction in rye grass vigor was recorded.

Growth and Reproduction of Aquatic Plants - Acute Toxicity:

Vascular Plant:

Lemma gibba EC_{50} = 1200 ppb

Nonvascular Plants:

Prohexadione calcium is not phytotoxic to any of the following micro-algae at the maximum label dosage.

Diatoms:

Navicula pelliculosa (freshwater) EC_{50} = 1200 ppb
NOAEC/NOAEL = 120 ppb
Skeletonema costatum (marine) NOAEC/NOAEL = 1100 ppb

Algae:

Anabaena flos-aquae (blue-green) NOAEC/NOAEL = 1200 ppb
Selanestrum capricornutum (green) NOAEC/NOAEL = 1100 ppb

Prohexadione calcium has very low toxicity to avian species, mammals, freshwater and estuarine/marine fish and invertebrates, aquatic and terrestrial plants, and honey bees. Acute and chronic risk quotients (RQ) with ranges combining apple/pear and peanut uses are indicated below:

	Acute	Chronic
Avian	0.0 to 0.08	0.004 to 0.4
Mammalian	0.00002 to 0.1	0.004 to 0.2
Aquatic (freshwater)	<0.0004	0.0 to 0.0004
Marine	0.0 to <0.0003	0.0 to 0.0003
Nontarget plants (aquatic)	0.03	

ENVIRONMENTAL CHARACTERISTICS

Prohexadione calcium is not expected to persist in the environment based on laboratory studies submitted. Its low octanol/water partition coefficient and low persistence suggest little or no potential to bioaccumulate. The major route of dissipation is oxidative mineralization to carbon dioxide in the soil. Prohexadione calcium is likely to be mobile in some soils but its rapid degradation suggests little potential to contaminate most ground water. Estimated drinking water concentrations from surface water sources are not likely to exceed 35.61 ug/L The 56-day average chronic concentrations are not likely to exceed 7.73 ug/L. Groundwater monitoring data are unavailable so the SCI-GROW screening model was used to estimate ground water concentrations. Estimated concentrations of prohexadione calcium in drinking water from shallow ground water sources are not expected to exceed 0.001 ppb for application on apples and 0.0003 ppb for peanuts. These concentrations can be considered as both acute and chronic values.

TOLERANCE ASSESSMENT

Tolerances Established:

Peanut ..... 1.0 ppm
Peanut, hay..... 0.60 ppm
Fruit, pome, group..... 3.0 ppm
Cattle, goats, hogs, horses, and sheep, kidney..... 0.10 ppm
Cattle, goats, hogs, horses, and sheep, meat byproducts, except kidney..... 0.05 ppm

Aggregate Risk Exposure:

Acute, cancer, and short- and intermediate-term aggregate exposure risk assessments were not performed because an acute dietary endpoint was not selected, prohexadione is not carcinogenic, and there are no residential uses proposed for prohexadione calcium, respectively. Aggregate exposure risk assessment was limited to chronic exposure (food + water) only.

Chronic aggregate risk estimates (food + water) are below the Agency's level of concern**.** A Tier 1 chronic dietary exposure analysis for prohexadione calcium was performed using tolerance level residues and assuming 100% crop treated for all pome fruit and peanut commodities. The chronic analysis was performed for the U.S. population and all population subgroups. The chronic exposure estimates (food only) for the general U.S. population and all population subgroups were <5% of the cPAD. Thus, the chronic dietary risk estimate associated with the proposed uses of prohexadione calcium does not exceed the Agency's level of concern (>100% cPAD). For ground and surface water, the estimated environmental concentrations (EECs) are less than the drinking water levels of comparison (DWLOCs) for prohexadione calcium in drinking water as a contribution to chronic aggregate exposure. Therefore, it is concluded with reasonable certainty that residues of prohexadione calcium in drinking water do not contribute significantly to the chronic aggregate human health risk at the present time.

Cumulative Toxicity and Metabolism:

In a rat metabolism study, prohexadione calcium is rapidly absorbed with highest tissue/carcass concentrations obtained within 30 minutes; however, absorption became saturated at the highest dose. Test material did not accumulate in the tissues. For low dose animals, renal excretion is the primary route of elimination. The primary excreta (both urine and feces) metabolite is identified as the free acid.

Determination of Safety for Infants and Children:

The Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) concluded the following. The pre- and post-natal toxicology database for prohexadione calcium is adequate for FQPA considerations. The results of these studies indicated no quantitative or qualitative increase in susceptibility of rats or rabbits to *in utero* and/or post-natal exposure to prohexadione calcium. No developmental effects were seen at doses up to the limit dose (1000 mg/kg/day) in the rat developmental toxicity study or up to the highest doses tested (150, 200, and 350 mg/kg/day) in three rabbit developmental toxicity studies. In the two-generation reproduction study in rats, the effects in the offspring were observed only at treatment levels which resulted in evidence of parental toxicity. A developmental neurotoxicity (DNT) study is not required. No neuropathology or central nervous system (CNS) malformations were seen in the developmental toxicity studies. In the two-generation study in rats, there were no findings in pups that were suggestive of changes in neurological development, although no functional assessment was performed. Additionally, there was no evidence of neurotoxicity in either the acute or subchronic neurotoxicty studies in rats and no evidence of neurotoxicity in other studies.

The FQPA Safety Factor Committee determined that the FQPA safety factor of 1x is applicable for chronic dietary risk assessment. The Safety Factor was removed because the pre- and post-natal toxicology database is complete, there is no indication of increased susceptibility, and a developmental neurotoxicity study is not required. The dietary (food and drinking water) exposure assessments will not underestimate the potential exposures for infants and children from the use of prohexadione calcium (currently there are no proposed residential uses and, therefore, non-occupational exposure is not expected).

SUMMARY OF DATA GAPS

Registration is conditional depending on the following: submission of storage stability data on the processed commodities of peanuts within 12 months, submission of a 21-day dermal toxicity study in rabbits within 6 months, and Agency validation of analytical enforcement method for plants.

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