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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: **Cadusafos**: Dietary Risk Assessment Update for FQPA Requirements.
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This memorandum updates the HED risk assessment for Cadusafos, with particular consideration for the requirements of the 1996 Food Quality Protection Act (FQPA). Attachments include the Hazard Identification Assessment Review Committee (HIARC) report (N. Paquette/J. Rowland memo, 5/18/98), the Product and Residue Chemistry report (J. Punzi memo, 4/28/98), and dietary exposure and risk assessment summaries (DEEM). Dietary exposure is the only risk assessment consideration for cadusafos at this time since there are no current registrations for use in the United States so the only possible exposure to U.S. citizens is by way of imported foods. Cumulative risk assessment, considering other pesticides with a common mechanism of effect (cholinesterase inhibition), is not addressed in this memorandum.

Cadusafos [O-ethyl S,S-bis (1-methylpropyl) phosphorodithioate] is a systemic insecticide/nematicide manufactured by the FMC Corporation under the trade name "Rugby". Cadusafos is used to control plant parasitic nematodes and soil insects in/on bananas, plantains, and potatoes. The Biological and Economic Analysis Division estimates (S. Wise memo, 11/18/97) that a maximum of 50% of the bananas grown in the Central American countries of Guatemala, Costa Rica, Ecuador, Mexico, and Hounduras are treated with cadusafos. BEAD was not able to determine whether or not this estimate relates directly to the bananas which are actually imported to the U.S..

The import tolerance for residues of cadusafos in/on bananas was established through a petition (6E03447) submitted by the FMC Corporation in 1986. Establishment of a three-year import tolerance of 0.02 ppm was originally proposed. For purposes of harmonization with the proposed Codex MRL for bananas, the Agency approved a two-year time-limited tolerance of 0.01 ppm. The time-limited tolerance was converted to a permanent tolerance after the Agency reviewed confirmatory usage data (i.e., application rate) required to ensure that cadusafos would be applied to bananas in a manner that would not exceed the residue level proposed for tolerance.

Hazard Identification:

Cadusafos is an aliphatic organophosphate with high water solubility and does not require bioactivation in the liver as do sulfur-organophosphates and is readily absorbed by all routes of exposure. The toxic residue of concern is the parent compound.

It is well documented that Cadusafos is severely acutely toxic and, similar to all organophosphate chemicals, is a potent inhibitor of acetylcholinesterase (AchE) at nerve endings in the central and peripheral nervous systems in mammals. Animal studies (acute) indicate that lethality occurs at low doses regardless of the route of administration. Death results at similar doses in acute oral, dermal and inhalation studies in several mammalian species; oral LD_{50} = 30 mg/kg in rats; dermal LD_{50} = 24 mg/kg in rabbits; acute inhalation = 0.03 mg/L in rats. Death occurred within 24 hours with cholinergic overstimulation (respiratory failure) as the primary cause of death. All animals exhibited the onset of signs of cholinergic toxicity (excess salivation, lacrimation, ataxia, chromodacryorrhea, tremors, decreased activity, labored breathing and finally death) within 2 hours of receiving the oral dose.

In addition to the acute toxicity via the oral, dermal and inhalation routes, death occurred in rabbits receiving a low dose of cadusafos via the eye. Again, signs of cholinergic toxicity were noted prior to death; ataxia, increased locomotion, rales, hypersensitivity, grinding of teeth, and oral discharge. Reviewed data indicates no significant sex-related differences in cadusafos' toxicity. Dose-related inhibition of plasma, red blood cell (RBC) and brain cholinesterase occurs in dogs and rats by all routes following acute, subchronic and chronic exposures. Dogs are the more sensitive species to cholinesterase inhibition in subchronic and chronic oral studies.

Cadusafos is classified as a Group E (i.e. the chemical is characterized as "not likely" to

be a carcinogen in humans via relevant routes of exposure) based on carcinogenicity studies in rats and mice.

Considerations for special sensitivity in infants and children (FQPA)

Developmental toxicity studies in rats and rabbits showed no evidence of additional sensitivity in young rats or rabbits following pre- or post-natal exposure to cadusofos and comparable NOELs were established for adults and offspring. The results of the two-generation reproduction study in rats (MRID 41441803) were re-evaluated during the 4/22/98 HIARC meeting to address an apparent increase in susceptibility (decrease in live birth index) to offspring following exposure to cadusafos. The Committee concluded that although there is an apparent dose-related decrease in the live birth index in the F_{2B} generation, there was no such incident pattern observed in any other generation and no significant increased sensitivity to pups over adults.

However, the potential for increased susceptibility to cadusafos in infants/children cannot be adequately defined because of significant data gaps relative to neurotoxicity. The Agency requires an acute delayed neurotoxicity study in hens (with neuropathology and NTE assessments), an acute neurotoxicty study in rats, and a subchronic neurotoxicity study in rats. The requirement for a developmental neurotoxicity study in rats is reserved pending results of the above studies.

Endpoints / doses for risk assessment:

Acute: The Agency has established an *acute* Reference Dose of 0.00002 mg/kg body weight/day to assess the risk associated with acute dietary exposure(s) to cadusafos. Lacking adequate studies to evaluate the toxicity of cadusafos after a single exposure (acute neurotoxicity in rats), a weight-of-evidence approach was applied to estimate a toxicological end point and dose for acute dietary risk assessment. The acute RfD is based on the results of the 14-day (range finding) oral toxicity study in dogs (MRID 40017902). This study established a NOEL of 0.02 mg/kg/day based on plasma ChE inhibition at 0.1 mg/kg/day (LOEL) in both sexes, observed on Day 3. Plasma ChE inhibition is determined to be the most sensitive indicator of cadusafos toxicity in this study and, based on the onset of signs of cholinergic toxicity noted in other acute toxicity studies (within 2 hours post dose), it is reasonable to assume that this critical effect also occurred on Day 1 although ChE activity was not measured at this point in the study.

An acute RfD uncertainty factor of 1,000 has been determined for cadusafos based on 10x for interspecies extrapolation, 10x for intraspecies variation, and 10x (FQPA) for the lack of neurotoxicity data as summarized above. A retention of the 10x FQPA factor was recommended by the 6/4/98 HIARC *Comprehensive Review of the Organophosphates* and was also recommended by the FQPA Safety Factor Committee.

Chronic: The Agency has established a *chronic* Reference Dose of 0.000001 mg/kg body

weight/day to assess the risk associated with chronic dietary exposure to cadusafos. The chronic RfD is based on the NOEL of 0.001 mg/kg/day (for plasma cholinesterase inhibition observed at 0.005 mg/kg/day) established in a one-year feeding study in dogs (MRIDs 40017901/40017902).

A chronic RfD uncertainty factor of 1,000 has been determined for cadusafos based, as above, on 10x for interspecies extrapolation, 10x for intraspecies variation, and 10x (FQPA) for the lack of neurotoxicity data. Again, the retention of 10x for FQPA considerations was confirmed by the HIARC and the FQPA Safety Factor Committee.

Product Chemistry Data Requirements:

All pertinent data requirements are satisfied for the FMC 92% T/TGAI provided that the registrant submits data required for Guidelines 830.1700 (Preliminary Analysis) and 830.7050 (UV/Visible Absorption).

Dietary Exposure / Residue Estimates for Risk Assessment:

HED concludes (R. Landolt memo, 2/15/91) that terminal residues in banana pulp (hydroxy-2-butyl methyl sulfone and 2-butyl methyl sulfone) are not of toxicological concern. The residue of concern is parent *only*.

The data requirements for "magnitude of the residue" in bananas have been fulfilled. The Agency has evaluated the results of residue field trails conducted in seven sites (in the Ivory Coast, Costa Rica, the Philippines, Guatemala, and Honduras). Residues of cadusafos were not detected (<0.005 ppm) in treated banana pulp samples harvested 1 to 211 days following application of the granular formulation at 6 g ai./mat/year (1x the maximum established seasonal rate) or at exaggerated rates (1.3x and 6.7x). Three samples of treated banana peel exhibited finite residues (0.005 ppm); each of these values resulted from an exaggerated application rate and a short PHI.

Since 1993, the Food and Drug Administration (FDA) has analyzed hundreds of samples, from approximately a dozen countries, for residues of cadusafos. The FDA reports no detections of cadusafos using a Multi Residue Method (MRM) with a 0.001 ppm Limit of Detection (LOD).

Based on the above data, HED concludes that the appropriate residue value for both chronic and acute dietary risk assessment is ½ LOD (0.0005 ppm) and this represents a probable upper-end estimate of cadusafos residues in banana pulp. Use of ½ LOD for chronic/acute risk assessment in this case is consistent with the HED Chemistry Science Advisory Council (ChemSAC) guidance of 5/19/98. The Agency does not have sufficient data to conclude, at this time, that "zero" residue is present in cadusafos-treated bananas.

Dietary Risk Estimates:

The *Dietary Exposure Evaluation Model (DEEM)*, based on 1989-92 USDA food consumption data, was used to estimate acute and chronic risk for cadusafos. DEEM replaces the DRES program which is based on 1977-78 food consumption data. The current DEEM model, like DRES calculates exposures based on single-day (rather than single-serving) consumption data.

Acute risk: The following acute risk estimates are considered a Tier 1 (or upper-end) estimate since the residue level assumed is a point estimate (0.0005 ppm) rather than a range, and percent crop treated information (50% true zeros) is not used.

Based on the above, DEEM estimates that the "Average U.S. Population" and the population subgroup of "All Infants (<1 year)" are exposed to cadusafos (per day) at a level less than the cadusafos acute RfD (less than 60% for both groups). The population group "All Infants" is used since this group is typically estimated to be the most highly exposed group and satisfies the FQPA requirement for the special consideration of pesticide risk to children.

Chronic risk: The following chronic risk estimates are based on the residue level of ½ the LOD (0.0005 ppm), the use estimate of 50% crop treated, and *averaged* food consumption estimates. The resultant risk estimate is not considered upper-end since the estimate is refined by the percent crop treated data.

Based on the above, DEEM estimates that the "Average U.S. Population" and the population subgroup of "All Infants (<1 year)" are chronically exposed to cadusafos at a level less than the cadusafos chronic RfD (less than 50% for all population groups).

The Agency concludes that potential dietary acute or chronic exposure and risk to adults and children from residues of cadusafos on imported bananas does not pose a concern.

Attachments:
Attachment 1 - HIARC reports (10/8/97 and 5/18/98)
Attachment 2 - Product Chemistry report
Attachment 3 - DEEM exposure/risk summaries

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