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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Cover Memo for Fosetyl-AL (Aliette)

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BACKGROUND

Fosetyl-AL is a systemic fungicide registered under a registration standard developed with the cooperation of Rhone-Poulenc, Inc. in 1983. A single end-use product (80% wettable powder) is registered for use on pineapples, ornamentals, turf and citrus. The document now being developed is the final registration standard and tolerance reassessment (FRSTR). There are no major data gaps. Fosetyl-AL is classified as a category C oncogen and poses minimal oncogenic risk from dietary and mixer/loader/applicator exposure.

TOXICOLOGY

Carcinogenicity

The registration standard published in 1983 identified fosetyl-AL as an oncogen. However, based on the low risk levels estimated for dietary, applicator, mixer/loader and planter exposure (range = 1.0×10^{-9} to 6.0×10^{-6}) the Agency determined that the potential adverse effects of the registerable uses were

negligible. To reduce any oncogenic risks to pineapple seed piece treaters and planters, the 1983 standard specified that the following note to users must appear on the label for the pineapple use: "Note to User: Gloves impermeable to fosetyl-AL must be worn during the handling and planting of pineapple crowns (seed pieces)." In addition, the standard specified that "Any request for additional uses of fosetyl-AL must be supported by (a) either an application exposure study or estimates of applicator exposure and (b) either a dermal penetration study or estimates of dermal penetration."

Since issuing the standard, the Toxicology Branch Peer Review Committee considered fosetyl-AL (March 4, 1986) and classified it as a Category C oncogen (possible human carcinogen with limited evidence of carcinogenicity in animals in the absence of human data), according to EPA proposed guidelines (FR November 23, 1984). In addition, Toxicology Branch recalculated the Q^* based on revised histopathological findings in the rat oncogenicity study. The Q^* is 5×10^{-4} and the upper 95% confidence limit on the lifetime human dietary risk calculated from the TMRC is 5×10^{-8}. However, the Toxicology Branch believes (September 3, 1986 memo from M. Jones to H. Jacoby) that a risk assessment for fosetyl-AL does not provide a good basis for numerical extrapolation to humans because the incidence of urinary bladder tumors was not a strictly dose-related phenomenon, the extremely high test dose may have compromised the nutritional status of the experimental animals and fosetyl-AL was negative in all mutagenicity tests. Therefore a risk assessment will not be included in the Standard.

ECOLOGICAL EFFECTS

The honeybee acute contact LD_{50} is the only data gap for ecological effects. Acceptable data are available to fulfill requirements for acute and subacute avian studies, and acute freshwater and estuarine fish and invertebrate studies. The need for further studies to evaluate reproductive or chronic effects is obviated by such factors as the generally low toxicity to most non-target organisms (e.g., birds and mammals) and low expected exposure or bioaccumlation based on the low octanol water partition coefficient (1.7×10^{-3} to 5.2×10^{-3}), high water solubility (120 g/L at 20°C) and short half-life (20 minutes to 14 hours) of fosetyl-AL.

Anticipated hazard to endangered birds and mammals is minimal due to the non-toxic nature of fosetyl-AL and its low exposure and bioaccumulation potential. Hazard to aquatic species is also minimal since the maximum estimated environmental concentration for freshwater fish would be less that 1/10 the LC_{10} for fish.

ENVIRONMENTAL FATE

As stated in the draft 1986 standard: "Fosetyl-AL degrades in the environment through the hydrolysis of the ethyl ester bond with subsequent degradation of the ethanol into carbon dioxide. The phosphorous acid metabolite is expected to form precipitates with aluminum, calcium, or iron in the soil. The half-life of fosetyl-AL under aerobic conditions in the soil is approximately 1.5 hours. The rapid degradation (hydrolysis of microbial origin, because, in sterile soils incubated for 20 to 70 half-lives, fosetyl-Al accounted for over 90 percent of the applied radioactivity.

RESIDUE CHEMISTRY

There were no outstanding residue data requirements when the original standard was issued in 1983. Since then additional uses have been granted (foliar application on pineapple and non-bearing citrus) and additional data are required on storage stability. As stated in the Residue Chemistry Branch chapter:

> "The length and conditions of storage of samples used to generate residue data submitted under PP#2F2702 (residue data in/on pineapples resulting from Aliette® dip and/or foliar treatments), in EPA Accession Nos. 071592 and 259114 (amended registrations for pineapples), and under PP#5F3267 (new use on citrus) must be submitted. These data must be accompanied by data depicting the stability of fosetyl-AL residues on the commodities (pineapples, pineapple forage and fodder, citrus) for the time intervals and under the conditions specified. On receipt of these data the adequacy of established tolerances for residues of fosetyl-AL will be reevaluated."

Fosetyl is not picked up by FDA's multi-residue methods, nor have any specific analyses for the chemical been conducted from 1978 through May 1986. The methods for determination of residues of fosetyl-AL should be entered into the PAM, Vol. II so that FDA may monitor fosetyl-AL residues in pineapples and citrus.

TOLERANCE REASSESSMENT

Tolerances of 0.1 ppm have been established for citrus, pineapple, and pineapple forage. The initial ADI was based on a 2-year rat chronic toxicity/oncogenicity study (NOEL = 2000 ppm). A Toxicology Branch reevaluation of the study concluded that the NOEL = 8000 ppm (tumorigenic effects). The two-year dietary study in dogs demonstrated the lowest (NOEL) and well-defined

toxicity at the next highest level. The NOEL was 10,000 ppm or 250 mg/kg body weight. As stated in the Toxicology Branch review:

> "Using a safety factor of 100 the ADI is set at 2.50 mg/kg/day. This is equivalent to a maximum permissible intake (MPI) of 150 mg/day for a 60 kg individual. The TMRC for Fosetyl-AL based on tolerances for pineapple and citrus and a daily food intake of 1.5 kg is 0.00617 mg/day. Therefore the percent ADI is 0.0025 or essentially 0.00%.

Sufficient data are available to support the established tolerances. However, as noted above, Residue Chemistry Branch has concluded that storage stability data are needed and that "on receipt of these data the adequacy of established tolerances for residues of fosetyl-AL will be reevaluated."