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WASHINGTON, D.C. 20460

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Reregistration of Acephate. 90-Day Response to the Reregistration DCI issued 3/1/94.

List A Case No. 0042; Chemical No. 103301
CBRS No. 14719; DP BARCODE D209342

FROM: Paula A. Deschamp, Team Leader
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Chemistry Branch II: Reregistration Support
Health Effects Division (7509C) *P.A. Deschamp*

THRU: Edward Zager, Chief
Chemistry Branch II: Reregistration Support
Health Effects Division (7509C) *E. Zager*

TO: Robert Richards
Reregistration Branch
Special Review and Reregistration Division (7508W)

SRRD has forwarded Valent USA Corporation's 90-day response to an Agency DCI issued 3/1/94 to CBRS. Valent's 90-day response (dated 5/31/94) was included under cover of a letter dated 10/3/94 requesting Agency comment on their proposed design of plant and livestock metabolism studies and a number of waiver requests. The 5/31/94 DCI response was received in HED on 11/21/94. Presented below are Valent's proposals for modifications to plant/livestock metabolism study designs, their waiver requests, and our comments.

RECOMMENDATIONS

The Valent letter dated 10/3/94 stated that the plant and animal metabolism studies have been initiated. CBRS has significant concerns regarding the registrant's study design. It is therefore important that Valent be informed of our comments on their proposed study design without delay. The registrant should also be advised to refer to the EPA "Guidance for Conducting Plant and Livestock Metabolism Studies", US EPA 738-B-92-001, 1992 and to fully consider this guidance in reporting the results of their studies.

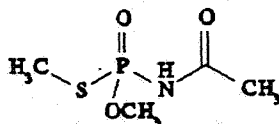
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171-4(a) -- Plant Metabolism:

The 3/1/94 DCI required data depicting the metabolism of S-methyl and carbonyl-labeled [¹⁴C]acephate in a leafy vegetable, a legume vegetable, and in cotton. The chemical structure of acephate is shown below:



In a 5/11/94 meeting between the Valent and the Agency, the registrant was advised that CBRS would consider Valent's proposal to conduct fewer than the required six plant metabolism studies. In their 90-day response dated 5/31/94, Valent proposed to conduct four plant metabolism studies as follows:

Cotton: Mature cotton plants growing in outdoor plots will receive 3 applications of [S-methyl-¹⁴C]acephate and [carbonyl-¹⁴C]acephate (CBRS assumes two separate studies will be conducted) at 1 lb ai/A/application (1x the maximum registered single application rate). Samples of fuzzy cotton seed and cotton gin byproducts will be harvested 21 days after the last application.

Snap Beans: Snap beans growing in a screen-house will receive 3 applications of [S-methyl-¹⁴C]acephate at 1 lb ai/A/application (1x the maximum registered single application rate). Succulent seed (with pod) and semi-dried plant materials will be harvested 21 days after the last application.

Lettuce: Leaf-type lettuce growing in a screen-house will receive 3 applications of [S-methyl-¹⁴C]acephate at 1 lb ai/A/application (1x the maximum registered single application rate). Lettuce will be harvested 14 days after the last application.

The registrant anticipates difficulty in identification of all residues present at ≥ 0.05 ppm. In cases where an isolated residue is not related to a standard, the registrant intends to infer incorporation of radiolabeled material into natural plant products, and proposes to confirm this by isolation of "one (1) radiolabeled natural product for each plant study". No attempt will be made to trap and/or quantitate carbon dioxide or volatile organic degradates.

CBRS Comments:

The proposal to conduct plant metabolism studies using only [S-methyl-¹⁴C]acephate on two different crops and both [S-methyl-¹⁴C]acephate and [carbonyl-¹⁴C]acephate on a single crop for a total of four studies is acceptable.

However, CBRS believes leaf lettuce rather than cotton would be a more appropriate crop to receive application of both [S-methyl-¹⁴C]acephate and [carbonyl-¹⁴C]acephate. CBRS is concerned that treatment at 1x the maximum single application rate, particularly to field grown cotton, may not result in sufficient radioactivity to permit adequate identification/characterization of terminal residues in mature edible crop parts. To ensure

that sufficient radiolabeled material is present in mature RACs, especially cottonseed, the registrant is encouraged to use an exaggerated application rate and/or harvest at intervals shorter than the established 21- and 14-day PHIs. Regarding the information provided on Valent's planned approach to isolate and identify labeled biomolecules, CBRS encourages the registrant to make every effort to provide unequivocal evidence of incorporation into natural products. Also, any loss of radiolabel material from analytical samples must be quantitatively documented.

Valent's description of measures to identify radiolabeled material in plant samples is very general, particularly regarding identification of specific radiolabeled biological macromolecules. The sufficiency of isolation and identification of only one radiolabeled biomolecule will depend on several factors including the presence (or absence) of discreet peaks suggesting the presence of primary metabolites, the percent of identified vs. unidentified residues, the number and range of structures of the standards used, the chromatographic behavior of the unknowns relative to toxic standards, and other factors. CBRS cannot comment further on whether or not the registrant's study design regarding identification/characterization of residues is acceptable.

171-4(b) -- Animal Metabolism

The 3/1/94 DCI required data depicting the metabolism of S-methyl and carbonyl-labeled [¹⁴C]acephate in ruminants and poultry. In their 90-day response dated 5/31/94, Valent proposed to conduct ruminant and poultry metabolism studies using only [S-methyl-¹⁴C]acephate. The registrant did not provide details on the duration or level of radiolabel material to be administered. As with plant studies, the registrant anticipates difficulty in identification of all residues present at ≥ 0.05 ppm. In fractions containing radioactivity not related to a standard, such as a fraction that contains proteins, the registrant proposes hydrolyses of the fraction and isolation and identification of one amino acid. No attempt will be made to trap and/or quantitate carbon dioxide or volatile organic degradates.

CBRS Comments:

CBRS does not agree with the registrant's proposal to conduct ruminant and poultry metabolism studies using only [S-methyl-¹⁴C]acephate. Administration of acephate labeled in both the 1-carbon (S-methyl) and the 2-carbon acetyl positions will allow all cholinesterase inhibiting compounds to be identified and additionally will ensure that all terminal residues are isolated and identified. CBRS has no objection to dosing with a mixture of the two labeled compounds. In selection of the dose rate, the registrant should calculate the maximum anticipated livestock dietary burden using the updated Table II (June, 1994) and include the potential residue exposure from livestock feed items such as peanut hay, soybean forage and hay, bean forage and straw/hay, and cotton gin byproducts. The registrant is reminded that livestock must receive a dose no less than 10 ppm in the diet.

Similar to Valent's plant study, their description of measures to identify specific radiolabeled biological molecules in animal tissues is very general. CBRS cannot comment on the acceptability of this design.

The registrant is also reminded that radiovalidation data are also required. Representative samples from the plant and livestock metabolism studies must be analyzed using a suitable enforcement method. The registrant is encouraged to provide radiovalidation data along with their submission of the plant and livestock metabolism studies.

171-4(k) Crop Field Trials - Rangeland and Pasture Grasses

The 3/1/94 DCI required data on rangeland and pasture grasses reflecting both broadcast application and spot treatments to fireant mounds. In a 5/11/94 meeting between Valent and the Agency, the registrant was advised that field trials for only the broadcast application would be needed provided the application rates for fireant mound and broadcast treatments are the same.

In their 90-day response dated 5/31/94, Valent committed to perform residue trials for range and pasture grass broadcast applications at 0.125 lb ai/A. The registrant requests a waiver from the requirement of data for dry and drench mound application at 0.15 oz ai/gal/mound (not to exceed 13 mounds/A) for fireant control. The registrant presented calculations demonstrating that treatment of 13 mounds/acre is equivalent to 0.122 lb ai/A and that only 0.4% of an acre will be treated. Valent also explained that animals typically avoid fireant mounds while grazing and that active mounds are generally devoid of grass or forage.

CBRS Comments.

CBRS finds the registrant's rationale for waiver of the requirement for data from mound application acceptable; waiver granted.

171-4(k/l) Soybean Processing Study (aspirated grain dust)

The registrant has proposed an amendment to their 75% SC/S product label (EPA Reg. No. 59639-26) to delete soybeans as a use site. They further request that the 1 ppm tolerance for acephate on soybeans (40 CFR 180.108) and 4 ppm feed additive tolerance for acephate in soybean meal (40 CFR 186.100) be retained for a minimum of three years to ensure that any product and/or commodities in the channels of trade can be sold and used legally without risk of violative residues. This amendment request was submitted to Registration Division PM Team 14 (R. Forrest) on 5/31/94.

CBRS Comments. Provided the use on soybeans is removed from all product labels, data on aspirated soybean grain dust will not be required for reregistration. CBRS will consider existing RAC and FAT tolerances for soybeans and soybean meal and concentration factors for additional soybean processed commodities from the existing soybean processing study in its exposure/risk assessment for the RED.

171-4(l) Bean Cannery Waste Processing Study

Valent requests a waiver from the requirement for a bean cannery waste processing study.

CBRS Comments. Bean cannery waste is no longer considered a livestock feed item (Table II; June, 1994); waiver granted.

171-4(k) Crop Field Trials - Winter Wheat

Valent does not wish to support the use of acephate on winter wheat [OK810010 under parent label EPA Reg. No. 59639-26] and has requested that the Oklahoma Department of Agriculture cancel this 24(c) registration.

CBRS Comments. Provided that winter wheat is removed from all 24(c) registrations for use of acephate, residue data from winter wheat field trials will not be required for reregistration of acephate.

171-4(k) Crop Field Trials - Radishes

There is currently no tolerance for residues of acephate on radishes. Valent requests a waiver from the requirement of radish crop field trials to support the 24(c) registration WA810064 for use of acephate on radish grown solely for seed. Valent believes the 24(c) registration meets the requirements of non-food use classification.

The registrant has addressed Agency criteria for a non-food use classification as follows:

1. There is no likelihood of carry-over residue from seed arising from a treated crop. Foliar applications of acephate are only locally systemic and concentration into radish seeds would not be expected.
2. Subsequent to treatment the crop is not fit for human consumption. Post bloom application limits application to radishes at a growth stage which would be commercially unacceptable and inedible as fresh-market radishes. Radishes germinate quickly and grow rapidly, and as a consequence, radishes grown for human consumption are generally harvested within 28 days of seeding. After that time, the radish root becomes woody or pithy and commercially unacceptable.

CBRS Comments.

A specimen label for 24(c) registration WA810064 under EPA Reg. No. 59639-26 was provided in Valent's 90-day response. The 75S (soluble powder) formulation is registered for broadcast applications, as necessary to maintain control, on radish seed crops only at 1 lb ai/A/application using ground or aerial equipment. Treatments are not to be made before or during peak bloom period. The label includes restrictions against use on the Daikon Radish variety and restrictions against feeding crop residues to livestock or allowing animals to graze treated areas.

CBRS cannot recommend for a waiver from the requirement of radish crop field trials to support the 24(c) registration WA810064 for use of acephate on radish grown solely for seed for the following reasons:

1. The registrant did not include calculations or provide data that would permit calculation of a worst-case, theoretical level of acephate residues present in radishes grown from acephate-treated seeds.

2. The existing label restrictions are insufficient to ensure that subsequent to treatment, no parts of the crop will be diverted to use as human food or livestock feed.

CBRS suggests that the label include restrictions against using seed, seed screenings, radishes, and waste from treated fields for human or animal feed. The label should also specify that all radish seed from treated fields be tagged "NOT FOR HUMAN OR ANIMAL CONSUMPTION".

If Valent wishes to support this registration, CBRS recommends that appropriate amendments to the 24(c) registration be submitted to Registration Division along with acceptable calculations/information indicating that residues on the crop grown from treated seed would not be present at detectable levels.

cc: PADeschamp (CBRS), Circulate, Acephate Reg. Std. File, SF, RF, R. Forest/B. Edwards, PM Team 14 (7505C).

7509C:CBRS:PAD:CM#2:Rm804A:703-305-6227:12/07/94
RDI: BCropp-Kohlligian; COlinger; SKnizner; WSmith; LEdwards:12/07/94
MMetzger:12/20/94 EZager:12/20/94