RB-1616
TR-551

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

000551

DATE: November 30, 1979

SUBJECT: Request for Tolerances of 2.0 ppm for Azinphosmethyl[[0,0-Dimethyl S-[4-oxo-1,2,3-benzotriazin-3 (4H)-ylmethyl]]phosphorothioate]] in or on Turnip-Rooted Parsley Roots and Parsley (Fresh Market). PP 9E2233.

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TO: Clint Fletcher
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THRU: M. Adrian Gross, Chief
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Petitioner: Office of IR-4
Rutgers University
New Brunswick, New Jersey

Recommendation:

Issuance of the requested tolerances is concluded not to be toxicologically supported at this time. Further consideration on these tolerances is contingent on the petitioner's acknowledgement that the oncogenicity study in a second species will be started or submitted (if completed) within a reasonable period of time. Furthermore, a conclusion from CHM is requested on the need for a food additive tolerance on dry parsley.

Discussion:

1. Data Considered in Evaluation.

   a. Oral LD50 Study (Rat): 5-6 mg/kg

   b. 30-Day Oral Subacute Neurotoxicity Study (Hen): NEL $\geq$ 100 ppm

   c. Teratology Study (Rabbit): NEL $\geq$ 0.75 mg/kg/day

   d. 2-Year Chronic Feeding Study (Dog): NEL = 5 ppm

   e. 2-Year Chronic Feeding Study (Rat): NEL = 5 ppm; no oncogenicity

   f. 3-Generation Reproduction Study (Mice): NEL $\geq$ 5 mg/kg/day

   g. Teratology Study (Rat): NEL $\geq$ 5 mg/kg/day

   h. Teratology Study (Mouse): NEL $\geq$ 5 mg/kg/day

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1. NCI Oncogenicity Study (Mouse): Negative at 62.5 ppm in males and 125 ppm in females (highest feeding levels).

2. NCI Oncogenicity Study (Rat): Negative at 125 ppm in females (highest level fed); slight statistical increase in both pancreatic islet tumors in males fed 156 ppm (highest level) and thyroid tumors in males given 62.5 and 156 ppm. However, as stated in a memo by R. Engler, 10/4/78, addressing the NCI studies, statistical significance was achgived only when several types of tumors were combined, and NCI concluded that these results are not of sufficient weight in themselves to ascribe an oncogenic potential to azinophosmethyl. Moreover, the NCI pathology report includes conclusions to the effect that azinophosmethyl was not carcinogenic in these bioassays. It is mentioned in the memo by Dr. Engler that NCI would assign a new priority concerning additional testing of testing of azinophosmethyl in the rat. It should be noted that the dosage levels in this rat study were time-weighted.

2. Data Desirable

   a. Oncogenicity Study in a Second Species - To the knowlegde of this reviewer, this request has been outstanding since at least 8/26/76 (letter from EPA to IR-4 on PP Nos. 6E1768 and 6E1881).

   b. Information from NCI, if available, on a decision relative to possible additional oncogenic testing of azinphosmethyl.

   c. Mutagenicity Studies - Deferred until Agency requirements are finalized.

3. Action to Obtain Desired Studies

   Inform registrant and NCI as indicated in point 2.

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4-6. Tolerances previously have been granted under CFR 180.154. The theoretical impact of the maximal residues is calculated as shown in the attached computer printout. The ADI is based on the cholinesterase NEL in the 2-year feeding study in rats and a safety factor of 10. Existing and requested tolerances are equivalent to a TMRC of 0.6835 mg/day/1.5 kg for a 60 kg human or 45.55% of the ADI. The requested tolerances increase the TMRC by only 0.0018 mg/day/1.5 kg and the percentage ADI by only 0.12.

7. No regulatory actions against azinphosmethyl are pending to the knowledge of this reviewer.

8. The risk from addition of the new tolerances is considered acceptable, Chemistry Branch considerations permitting, since exposure from the human food items parsley and parsley roots will increase the TMRC by only 0.0018 mg/day/1.5 kg. Outside of the question on oncogenic potential raised in the NCI rat study, available toxicity data show that azinphosmethyl does not have the potential of inducing carcinogenesis, teratogenesis, adverse effects on reproduction, or delayed neurotoxicity. However, the items addressed under Recommendations must be resolved before the proposed tolerances are issued.

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