3-21-80

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March 24, 1980

SUBJECT: FAP 6H5110 for the Use of Diazinon in Food Handling Establishments

FROM: K. L. Bailey
Toxicology Branch/HED (TS-769)

Caswell #342

TO: Jay S. Ellenberger
PM Team #15, Registration Division (WH-567)

THRU: M. Adrian Gross, Chief
Toxicology Branch/HED (TS-769)

I. Action Requested:

It is proposed that Diazinon 4E (EPA Reg. No. 100-463) and Diazinon 2D (EPA Reg. No. 100-445) be used for crack and crevice and spot application in food handling establishments. For the sake of accuracy, due to the large amount of information, the reader is referred to the attached Section F and labels for pertinent details concerning the proposed use.

II. Summary:

Briefly this action may be summarized as follows:

- There are no significant toxicological data gaps for this compound. However, an additional teratology study and, possibly additional mutagenic studies will be required at re-registration.
- The MTRC exceeds the ADI by %286.
- Based on the T. McLaughlin RCB review, real residues of Diazinon may result from this use.

NOTE to PM: There is a question as to exactly which formulations of Diazinon are to be used. However, the petitioner said in a telephone conversation that Diazinon 4E (100-463) and Diazinon 2D (100-445) are the formulations that will be used - see attached labels. This point should be confirmed.

RCB has suggested that a tolerance would be more appropriate than the exemption from the requirement of a tolerance requested. As no actual numerical tolerance would be established, there is little practical difference between a tolerance or an exemption from the requirement of a tolerance. That is, a tolerance in which no actual numerical value is mentioned is, for all practical purposes, the same as an exemption from the requirement for a tolerance.

EPA Form 1320-6 (Rev. 3-76)

III. History

For pertinent details concerning the history of this food additive petition consult the following:

A. The R. Coberly, Toxicology Branch memo of 10-28-75.

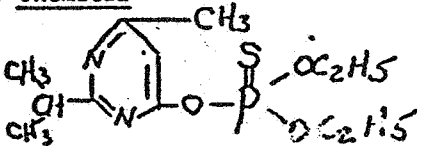
B. The K. Bailey, Toxicology Branch memo of 1-19-77.

C. The A. Rathman, Residue Chemistry Branch memo of 2-23-77.

D. The T. McLaughlin, Residue Chemistry Branch memo of 1-15-79.

E. See also the J. Doherty, Toxicology Branch memo of 12-4-78, concerning other pertinent data.

IV. Chemical



Diazinon

O,O-Diethyl O-(2-isopropyl-6-methyl-4-pyrimidinyl) phosphorthioate

A. Formulations

1. Diazinon 4E (100-463)

	% by Weight
[redacted] technical Diazinon	55.56
Total	100.00

2. Diazinon 2D (100-445)

	% by Weight
[redacted]	4.0
Total	100.0

3. Diazinon MG 50 (100-498)

	% by Weight
Diazinon Technical [redacted]	52.7
	100.0

4. Diazinon 50W (100-460)

Composition of Diazinon 50W
EPA Reg. No. 100-460

	% by Weight
Diazinon Technical	52.7
[redacted]	
Total	100.0

B. Clearance of Inerts:

It is to be noted that at present, there is no formal procedure within the Agency to formally clear inert ingredients that are to be used in pesticide formulations that may be acceptably applied in food handling establishments. Rather, until such time as suitable regulations are published, the question of inerts that are acceptable for use in food handling establishments is being handled on a case by case basis.

In the case of Diazinon 4E (100-463) and Diazinon 2D (100-445), it is the judgement of the Toxicology Branch that the inerts found within these two formulations are acceptable and do not constitute any human health hazard for the following reason:

Considering the extremely low vapor pressure of these compounds and the methods whereby the formulations are to be applied, it is unlikely that any residues of these inerts will result in human food. [redacted]

V. Proposed Numerical Tolerance:

No numerical tolerances are proposed for Diazinon in this case. This is consistent with the similar food additive regulation established for Chlorpyrifos in 21 CFR 193.85.

VI. Petitioner:

Ciba Geigy
Agricultural Division
P. O. Box 11422
Greensboro, N.C. 27409

VII. Established Tolerances

Tolerances have been established for Diazinon on a wide variety of agricultural commodities (40 CFR 180.153) as listed in the attached computer printout.

VIII. MTRC and ADI Considerations

It is to be noted that the calculated MTRC exceeds the ADI by 286%- (see attached computer printout). In the case of the presently accepted diazinon tolerances, this is of slight concern as little if any actual residues of diazinon are found in market basket surveys (Residues in Feed and Food, Pesticide Monitoring Journal, Vol. 1-4). However, T. McLaughlin, in the 1-15-79 Residue Chemistry Branch memo, has concluded that residues of diazinon resulting from this proposed use "may occasionally be present in food items from the proposed treatments in food handling establishments but would not be present for consumption on a continuous basis." Specifically, the T. McLaughlin memo notes that no residues of Diazinon (<.05 ppm) were found in 11 of 13 representative residue studies while residues were found in the two following studies:

1. 0.15 ppm of Diazinon was found in a composite vegetable sample following a 12 hour exposure at a 4X floor application of diazinon.

2. 0.25 ppm of Diazinon was found in an unwrapped ground beef sample exposed for 12 hours, however untreated control values of diazinon varied from .05-.27 ppm in the same study.

As no numerical tolerances are proposed, a comparison of the MTRC and ADI is not pertinent in this case; it is our judgement that residues of Diazinon resulting from this proposed use are not of toxicologic significance especially when considering the recent negative rat and mouse NCI oncogenic studies--see Oncogenic Evaluation .

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IX. Toxicology

A. Toxicologic Problems Raised in Previous Reviews

(Note: For pertinent details consult the K. Bailey 1-19-77 memo)

1. It was noted that Diazinon can decompose to the much more acutely toxic material, sulfotepp. This problem has been solved by the use of adequate stabilizers--Personal Communication W. Greear (TOX/HED).

2. It was noted that no adequate oncogenic study was available. This problem has been resolved by the recent NCI studies-- see Oncogenic Evaluation in this memo.

3. It was noted that no acute studies were available for either Diazinon 4E (100-463) or Diazinon 2D (100-445).

In the case of Diazinon 4E this problem has been resolved by the submission of data; the observed toxicity is what one would expect considering the composition: Tox. Category I on the basis of eye irritation.

In the case of Diazinon 2D, considering that the formulation is [redacted] the toxicity may readily be extrapolated - Tox. Category III - IV.

4. It was noted that no mutagenic studies were available for this compound. However, there are a variety of supplementary mutagenic studies that suggest that Diazinon is not a mutagen-- see the J. Doherty 12-4-78, memo concerning data submitted with 8730-I. Any additional mutagenic studies that will be required will be determined at a later date.

5. It was noted previously that an additional inhalation study was required for Diazinon 4S (EPA Reg. No. 100-456). It is judged that an inhalation study is not required, considering that a coarse spray will be used; thus, inhalation of appreciable material is unlikely.

B. Oncogenic Evaluation

In the K. Bailey 1-19-77, memo it was noted that no adequate Diazinon oncogenic study was available.

Recently, NCI released a negative rat and mouse oncogenic study in which Diazinon (obtained from the petitioner Ciba - Geigy) had been fed to rats and mice in their diets.

Briefly, this study may be summarized as follows:

"A bioassay of diazinon for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and B6C3F1 mice.

Groups of 50 rats and 50 mice of each sex were administered diazinon at one of two doses, either 400 or 800 ppm for the rats and either 100 or 200 ppm for the mice, for 103 weeks and were then observed for an additional 1 to 2 weeks. Matched controls consisted of groups of 25 untreated rats and 25 untreated mice of each sex. All surviving animals were killed at the end of 104 or 105 weeks.

There was no appreciable effect of administration of diazinon on mean body weights of rats or mice of either sex. Mortality was not increased in any of the dosed groups of rats or mice, when related to that in the corresponding controls, and survival was 84% or greater in all dosed and control groups of animals at week 78. Some hyperactivity was noted in the dosed groups of both species; however, both the rats and mice may have been able to tolerate higher doses. Sufficient numbers of animals were at risk in all groups for the development of late-appearing tumors.

No tumors occurred in any of the dosed groups of rats or mice of either sex at incidences that could clearly be related to the administration of diazinon.

It is concluded that under the conditions of this bioassay, diazinon was not carcinogenic for F344 or B6C3F1 mice of either sex."

For other pertinent details consult the detailed summary to be found under Accession No. 238513.

While the chief significance of this study relates to the negative oncogenic findings for Diazinon, it is also of secondary importance in that it is in rough agreement with all other available chronic studies that have been conducted using diazinon . Specifically, the results of other studies suggest that the only effect enduced by Diazinon relates to cholinesterase inhibition. In the NCI study, in which cholinesterase inhibition was not measured per se, the following findings are suggestive of a compound whose only effect at moderate dose is cholinesterase inhibition:

- Hyperactivity, an effect possibly related to cholinesterase inhibition, was noted in some animals.
- No compound related effect was noted on either mortality or body weight suggesting, though by no means proving, that the chronic effects of the compound are relatively benign.

For the record, it is suggested that the complete results of this NCI study be obtained.

It is to be noted that the petitioner is currently conducting a mouse oncogenic study, which we shall review at such time as it is completed.

C. Toxicology Review
Accession No. 232006

Note: All the studies reviewed below are IBT studies conducted with Diazinon 4E (EPA Reg. No. 100-463). These studies have been referred to SPRD for consideration.

1. Diazinon 4E Acute Rat Oral LD 50 study.

2 males and 2 females, were exposed respectively to 400, 600, 900 and 1350 mg/kg of a 25% suspension of Diazinon 4E in corn oil. The animals were observed 5 days and the mortality recorded; the oral LD 50 is 542 mg/kg. It is to be noted that an additional study; using only female rats was conducted. The LD 50 in this female rat study was 217 mg/kg-- see #6 below.

2. Diazinon 4E Acute Rabbit Dermal LD50 Study

In this study 4 groups of rabbits, each group composed of 2 males and 2 females, were dermally exposed respectively to 400, 600, 900 and 1350 mg/kg of Diazinon 4E for 24 hours and subsequently observed for 14 days. The observed dermal LD50 is 600 mg/kg. Considering all other acute studies, this study is core-minimum.

3. Diazinon 4E Rabbit Dermal Irritation Study

In this study, using both abraded and unabraded areas on each animal, 4 rabbits were dermally exposed to 0.5 ml of Diazinon 4E for 24 hours. The dermal irritation, mild, is consistent with the chemical composition and places the product in Tox Categroy III. Considering available data this study is core-minimum.

4. Diazinon 4E Acute Rabbit Eye Irritation Study

In this study, 0.1 ml of Diazinon 4E was instilled into the conjunctival sac of the right eye of 5 rabbits and the animals observed for 7 days. The corneal effects observed at 7 days clearly places this product in Tox. Category I, an effect consistent with the composition. This study is core-minimum.

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5. Diazinon 4E Acute Rat Inhalation Study

In this study two groups of Sprague-Dawley rats, each group composed of 5 males and 5 females, were respectively exposed to 27.9 mg/L of Diazinon 4E and to 27.2 mg/L of a 4% aqueous suspension of Diazinon 4E, both for a duration of 4 hours. Of the animals exposed to undiluted Diazinon 4E, 9 died while only 1 died of the animals exposed to the 4% aqueous suspension of Diazinon. This study is supplementary due to the fact that only one dosage group was used and thus it is impossible to determine the LD50.

according to aug 22, 1978 guidelines the level of 7.5 mg/L meets the requirements 10/30/80 EB

6. Diazinon 4E Female Rat Acute Oral LD 50 Study

In this study 4 groups of Sprague-Dawley rats, each group composed of 5 females, were exposed respectively to 118.5, 177.8, 266.7 and 400 mg/kg of a 25% aqueous suspension of Diazinon 4E via gavage and observed for 14 days— Results expressed in terms of active ingredient. The observed oral LD50 is 218 mg/kg. This study, when considered in conjunction with all others, is core-minimum.

7. Diazinon 4E Rabbit Five Day Subacute Dermal Study

In this study 6 groups of rabbits, each group composed of 2 males and 2 females, were exposed once a day for 5 days respectively to 0, 0.05, 0.1, 0.5, 1.0 and 2.0 g/kg/day of Diazinon 4E. In addition, it is to be noted that one male and one female from each group had abraded skin while in all cases the animals were exposed 7 hours per day to the compound whereupon the product was washed off. The effects observed were weight loss in all groups save the control and the calculated LD50 was 225 mg/kg/day. Considering the absence of a NOEL for weight loss, this study is supplementary.

Body wt loss in dog is not a reason to down grade a study. Upgrade this to minimum 10/30/80 EB

Attachment:

EPA:OPP:HED:TOX:RD KBAILEY:sb 10/22/79 X77395 B1 TS-769 Rm.820 CM 2