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

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Aug 7, 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Submission of the Toxicology Branch Chapter for Registration Standard for Diazinon.

TOX CHEM No. 342
TOX PROJECT NO. 23

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Attached is the Toxicology Branch (TB) Chapter for the Registration Standard for diazinon including the following subparts:

1. Diazinon Policy Discussions
2. Table A: Generic Data Requirements for Diazinon
3. Summary of the Evaluated Data ("one liners" and selected detailed reviews).

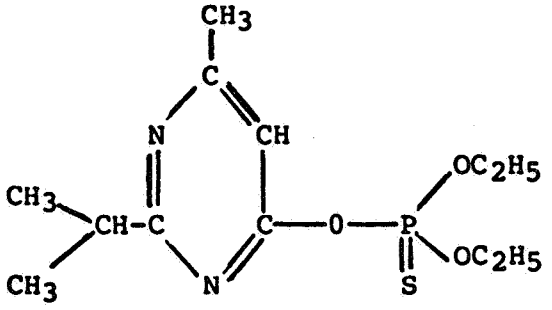
Diazinon Policy Discussions

A. Identification of the chemical and use summary.

Diazinon (see chemical structure below) is an organophosphate insecticide and nematocide which has a variety of agricultural and associated tolerances for residues and other uses including domestic applications. Many formulations containing diazinon are readily available at retail outlets.

The chemical structure and chemical name for diazinon are:

chemical structure:



chemical name: diethyl O-(2-isopropyl-4-methyl-6-pyrimidinyl) phosphorothioate.

Commercially diazinon is also known as Basudin, Dazzel, Diagran, Diaterr-Fos, Diazajet, Diazatol, Diazide, Diazol, Dizinon, Dyzol, Dzn, Fezudin, Nipsan, Serolex, Spectracide, and Knox Out (a microencapsulated product). The principle manufacturer of diazinon used in the United States is the Ciba-Geigy Corporation.

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B. Data Summary

1. One Liners

Attached

2. Policy Discussions of Diazinon Toxicity Problems

The toxicity data base for diazinon consists of a mixture of historical studies (studies circa 1950-1960 which do not have current criteria for investigational endpoints) and several contemporary studies. In addition, review of the published literature suggests that there are some potential or alleged special problems with this chemical. Several of the historical studies with diazinon will have to be repeated. Some special aspects will have to be included in conventional studies to address the alleged potential special problems with diazinon.

A. The data gaps for diazinon are identified as follows:

Delayed type neurotoxicity - hens
Subchronic feeding - rats
Subchronic feeding - dogs
21-day or 90-day dermal - rabbits
21-day or 90-day inhalation - rats
Chronic feeding - rats
Chronic feeding - dogs
Oncogenicity - rats
Multigeneration reproduction - rats (with special assessment of behavioral and endocrine development).
Mutagenicity - Selected study types and summary table of available studies (see below)
Metabolism and Pharmacokinetics

[Note: The technical diazinon used in all studies to satisfy the above data gaps must be identified with respect to percent purity. The percent (or ppm) content of all organophosphorus impurities must be identified. In particular the concentration of sulfotepp must be stated.]

B. Discussions of the Data Gaps.

1. Delayed type neurotoxicity. Since diazinon is an organophosphate insecticide it must be tested in hens for delayed type neurotoxicity. The two studies which attempt to assess this problem which are available to TB do not meet current

CORE MINIMUM criteria. An additional study will have to be submitted.

2. Subchronic Feeding Rats and Dogs. The available subchronic feeding studies in rats and dogs do not meet CORE MINIMUM criteria and usually only ChE activity (and a few other endpoints) were investigated. These subchronic studies are necessary to assist TB in assigning a NOEL for purposes of ADI setting. TB also recommends that subchronic studies in rats and dogs be conducted to assess the appropriate dose levels to be used for the chronic studies.

3. Chronic feeding in dogs and rats. New studies are critically needed to assist in determining the ADI (see Tolerance Reassessment below). The historical studies examined only a limited number of investigational endpoints and used only a few specimens per dose group. The endpoint investigated in these studies was usually ChE inhibition. New chronic feeding studies must establish a NOEL for plasma, RBC and brain ChE inhibition as well as the other investigational endpoints recommended by the current EPA Guidelines for chronic toxicity testing.

4. Oncogenicity testing.

In mice. The NCI study has been assigned CORE MINIMUM status. There was no evidence of an oncogenic response to diazinon in this study.

A second study with mice conducted at Industrial Biotest (IBT) has been determined to be INVALID (refer to the report from the Dynamac Company following page R-38).

In rats. The NCI study could not be accepted as a definitive oncogenicity study in rats. The chronic feeding study requested above should also include a sufficient number of rats to be a combined chronic feeding/oncogenicity study.

5. Teratology and reproduction.

Teratology. Review of the published literature suggests that diazinon (as well as other organophosphates) may be potentially teratogenic because injecting these chemicals directly into developing avian eggs results in chicks with structural malformations. The relevance of these findings, however, to mammals is questionable. The registrant has submitted teratology studies deemed to be CORE MINIMUM or better for both rats and rabbits and has thus met the data requirements for teratology testing. None of the mammalian studies which have been reviewed indicated that diazinon causes structural abnormalities or shows other signs of developmental toxicity. Thus, diazinon is not considered a teratogen in mammals by TB. The apparent positive response noted in avian eggs may relate to the mode of direct admin-

istration, a condition that would not resemble human exposure resulting from the use of diazinon.

Published articles also indicate that diazinon may have effects on the endocrine system (i.e. changes in hepatic metabolism of corticosterone and in plasma levels of this hormone, see Spyker et al in J. Environ. Pathology and Toxicology 2: 357-369, 1978) and on the motor function of pups born of dams dosed with diazinon during gestation. At least one study, however, could not repeat these reported observations as published (see p. R-23 of this Registration Standard).

The possibility that diazinon may be a behavioral teratogen as reported in the literature (Spyker and Avery in J. Toxicol. Environ. Health 3:989-1002, 1977) was deferred to Dr. William Sette of TB for review. Dr. Sette's conclusion (refer to memo from W.F. Sette to J. Doherty dated June 23, 1986) was that "this study provides no convincing evidence of an effect of diazinon on the nervous system".

Because TB already has CORE MINIMUM and higher data on teratology with diazinon, no additional teratology studies will be required to further investigate the alleged endocrine and behavioral effects of diazinon. These parameters should be investigated, however, as a part of the multigeneration reproduction study (see below).

Reproduction. There is no multigeneration reproduction study with diazinon which meets CORE MINIMUM criteria. A second study will have to be provided. This replacement study should include tests to assess the motor function and status of the endocrine systems (including blood levels of several hormones) of the pups for each generation. The registrant is requested to submit a protocol of the planned tests to assess both the behavioral and endocrine aspects of the multigeneration study.

6. 21-day dermal and inhalation studies.

These requirements relate to the many uses of diazinon (both domestic and non-domestic) which result in repeated dermal and respiratory exposure. The studies must demonstrate NOELs for plasma, RBC and brain ChE as well as investigate the usual endpoints recommended by EPA's guidelines.

7. Mutagenicity.

The following study types need to be submitted:

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i. in vitro mammalian gene mutation studies (i.e. mouse lymphoma L5178Y and Chinese hamster type assays)

ii. study assessing the potential effects for structural chromosomal aberrations

iii. studies assessing the potential for inducing sister chromatid exchanges in both in vivo and in vitro systems.

This requirement relates to the inadequate in vivo study (Mutation Research 118:61-68, 1983 see review on page R-51) that reported diazinon at very low concentrations induces sister chromatid exchanges in mudminnows. TB requests that the problem be addressed by assessing the potential for diazinon to induce this chromosome effect in both in vivo and in vitro study systems. One of the in vivo studies should repeat this assay in the same species of mudminnows used in the original report as well as in intact mammals. In vitro assays should be performed both with and without mammalian metbolic activation.

The registrant is also requested to provide a summary table which includes all available studies testing for mutagenic effects of diazinon.

Note: The reviews of the mutagenicity studies were secondarily reviewed by Dr. Irving Mauer of TB and the recommendations for additional testing were also made in collaboration with Dr. Mauer.

8. Metabolism and pharmacokinetics.

Although several studies from the published literature were available for review, there were no studies with supporting data together with methods and procedures. Metabolism and pharmacokinetic studies in rats need to be submitted. Particular attention to identification of the metabolites should be included.

9. Antidote data.

Diazinon is an anticholinesterase organophosphate insecticide and atropine is antidotal to toxicity for this class of insecticides. TB, however, requests that all information that is available on the effectiveness of atropine and 2-PAM as antidotes to diazinon intoxication be submitted to the Agency. In particular, information on the dose levels of these two agents given together or in combination necessary to be effective is especially desired.

C. Risk Assessment/Tolerance Reassessment

1. Risk Assessment

Reviews of the available studies with diazinon have not indicated either an oncogenic or other response which would require a statistical risk assessment.

2. Tolerance Reassessment

There are numerous tolerances established for diazinon for many RACS ranging from 0.1 ppm to as high as 60 ppm (on grass for forage) and some 100 or more commodities are included. Refer to the CFR 180.153 (July 1, 1983) attached.

Historically the Acceptable Daily Intake (ADI) for diazinon was determined using a dog subacute dosing study (of 31 days duration) with a NOEL of 0.02 mg/kg/day based on plasma ChE inhibition and a safety factor of 10. Using this combination and taking into consideration published tolerances only, the percent ADI used up is 351% (refer to the computer printout attached).

The study used in setting the historical ADI (refer to page R-14 of this Registration Standard) does not meet CORE MINIMUM criteria and it is of only 31 days duration.

The ADI for diazinon was reevaluated as of June, 1986 for the TB ongoing RfD/PADI project. The following NOEL and safety factor was recommended for use:

NOEL = 0.009 mg/kg/day based on plasma ChE inhibition noted in a subchronic rat feeding study. [Davies, D.B. and Holub, B.J., Toxicological Evaluation of Dietary Diazinon in the Rat, Arch. Environ. Contam. Toxicol. 9:637-650, 1980).

Safety Factor (or modifying factor) = 10 (this is considered appropriate because the endpoint was plasma ChE inhibition).

PADI = 0.0009 mg/kg/day.

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This PADI will be evaluated by the RfD/ADI Committee in the later part of 1986 or early 1987. Refer to page R-13 for review of the subchronic rat studies. It should be noted that the above rat subchronic study is classified as SUPPLEMENTARY data.

Since both the historical ADI and the PADI calculated using the rat subchronic study (which is in fact lower than the ADI calculated from the dog study) result in greater than 300% of the ADI being used up, no new tolerances should be granted without addressing the problem that the PADI is exceeded.

D. Use Classification and Special Labelling.

Use restrictions. Diazinon is considered by TB to be of moderate acute toxicity. For example the acute oral toxicity in rats for technical grade diazinon is Toxicity Category II and the acute dermal toxicity has been reported as either Toxicity Category II or III. The principle toxicity problems relate to inhibition of ChE and its subsequent effects. No oncogenic or teratogenic effects are currently recognized in mammals. Thus, the use classification of products containing diazinon should follow normal rules for restriction and nonrestriction for usage.

Special Labelling Dermal Sensitization Precautionary Statement. Diazinon was tested with humans for potential sensitization reactions and several of the volunteers showed a positive response which was confirmed by repetition (see p R-44). Therefore, products containing diazinon should have the following precautionary statement (or the equvalent):

"May cause contact sensitization following repeated contact with skin in susceptible individuals. Avoid repeated contact with skin. If sensitization reaction results consult a physician",

E. Special Problem of Contamination with Sulfotepp.

Historically diazinon formulations have also contained quantities of the impurity sulfotepp which is more acutely toxic than diazinon itself. TB understands that the Ciba-Geigy Corporation presently [redacted] or otherwise limits diazinon formulations to a minimal level of sulfotepp such that the small amount of sulfotepp present does not significantly affect the toxicity of the product. Should product chemistry or Residue Chemistry Branch deferrals indicate that significant quantities of sulfotepp will be present, then TB may require specific toxicity studies with this contaminant.

INFORMATION WHICH MAY REVEAL INERT INGREDIENTS IS NOT INCLUDED

Commodity	Parts per million
Pears	3
Peas, shelled	15
Peas, unshelled	15
Peas, vine, with pod	15
Peas, vine, without pod	15
Pecans	0.1
Pineapples	3
Plums	1
Potatoes	10
Poultry, (excluding kidney)	3
Poultry, kidney	9
Sheep, mbyp	0.2
Sheep, meat	0.2
Sorghum	1
Sorghum, forage	5
Soybeans	1
Soybeans, straw	1
Sugarcane	0.1
Tangerines	5
Walnuts	5

(b) Tolerances are established for residues of dalapon (2,2-dichloropropionic acid) resulting from application of dalapon sodium-magnesium salt mixtures to irrigation ditch banks in the western United States in or on the following raw agricultural commodities. Where tolerances are established at higher levels from other uses of dalapon on the subject crops, the higher tolerance applies also to residues from the irrigation ditch bank use.

Commodity	Parts per million
Avocados	0.2
Citrus fruits	0.2
Cottonseed	0.2
Cucurbits	0.5
Flaxseed	2.0
Fruits, pome	0.2
Fruits, small	0.2
Fruits, stone	0.2
Grain crops (exc wheat)	0.5
Grasses, forage	2
Hops	0.2
Legumes, forage	2
Nuts	0.2
Vegetables, fruiting	0.2
Vegetables, leafy	0.5
Vegetables, root crop	0.2
Vegetables, seed and pod	0.5
Wheat	2

[43 FR 22359, May 25, 1978]

§ 180.151 Ethylene oxide; tolerances for residues.

A tolerance of 50 parts per million is established for residues of the antimicrobial agent and insecticide ethylene oxide, when used as a postharvest fumigant in or on the following raw agricultural commodities: Black walnut meats, copra, whole spices.

§ 180.152 Sodium dimethyldithiocarbamate; tolerance for residues.

A tolerance of 25 parts per million is established for residues of the fungicide sodium dimethyldithiocarbamate, calculated as zinc ethylenebisdithiocarbamate, in or on melons.

§ 180.153 O,O-Diethyl O-(2-isopropyl-6-methyl-4-pyrimidinyl) phosphorothioate; tolerances for residues.

Tolerances are established for residues of the insecticide O,O-diethyl O-(2-isopropyl-6-methyl-4-pyrimidinyl) phosphorothioate in or on the following raw agricultural commodities:

Commodities	Parts per million
Alfalfa, fresh	40.0
Alfalfa, hay	10.0
Almonds	0.5
Almonds, hulls	3.0
Apples	0.5
Apricots	0.5
Bananas (NMT 0.1 ppm shall be present in the pulp after peel is removed)	0.2
Beans, forage	25.0
Beans, hay	10.0
Beans, guar	0.1
Beans, guar, forage	0.1
Beans, lima	0.5
Beans, snap	0.5
Beets, roots	0.75
Beets, sugar, roots	0.5
Beets, sugar, tops	10.0
Beets, tops	0.7
Birdsfoot trefoil	40.0
Birdsfoot trefoil, hay	10.0
Blackberries	0.5
Blueberries	0.5
Boysenberries	0.5
Broccoli	0.7
Brussels sprouts	0.7
Cabbage	0.7
Cabbage, Chinese	0.7
Carrots	0.75
Cattle, fat (pre-s appl)	0.7
Cattle, meat (fat basis) (pre-s appl)	0.7
Cattle, mbyp (fat basis) (pre-s appl)	0.7
Cauliflower	0.7
Celery	0.7
Cherries	0.75
Citrus	0.7
Clover (fresh)	40.0
Clover, hay	10.0
Coffee beans	0.2
Collards	0.7
Corn, forage	40.0
Corn (inc sweet k + CWHR)	0.7

Comm
Cottonseed
Cowpeas
Cowpeas, forage
Cranberries
Cucumbers
Dandelions
Dewberries
Endive (escarole)
Figs
Filberts
Grapes
Grass (NMT 40 ppm s appli)
Grass, hay
Hops
Kale
Kiwi fruit
Lespedeza
Lettuce
Loganberries
Melons
Mushrooms
Mustard greens
Nectarines
Olives
Onions
Parsley
Parsnips
Peaches
Peanuts
Peanuts, forage
Peanuts, hay
Peanuts, hulls
Pears
Peavine hay
Peavines
Peas with pods (de moving any shell pro
Pecans
Peppers
Pineapples
Pineapples, forage
Plums (fresh prunes)
Potatoes
Potatoes, sweet
Radishes
Raspberries
Rutabagas
Sheep, fat (pre-s appl)
Sheep, meat (fat basis)
Sheep, mbyp (fat basis)
Sorghum, forage
Sorghum, grain
Soybeans
Soybeans, forage
Spinach
Squash, summer
Squash, winter
Strawberries
Sugarcane
Swiss chard
Tomatoes
Turnips, roots
Turnips, tops
Walnuts
Watercress

(Sec. 408(d), 68 S

[47 FR 42738, Sep
48 FR 14896, Apr.

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Commodities	Parts per million
Cottonseed	0.2
Cowpeas	0.1
Cowpeas, forage	0.1
Cranberries	0.5
Cucumbers	0.75
Dandelions	0.7
Dewberries	0.5
Endive (escarole)	0.7
Figs	0.5
Filberts	0.5
Grapes	0.75
Grass (hMT 40 ppm shall re.. on 24 hours after appli)	60.0
Grass, hay	10.0
Hops	0.75
Kale	0.7
Kiwi fruit	0.75
Lespedeza	1.0
Lettuce	0.7
Loganberries	0.75
Melons	0.75
Mushrooms	0.75
Mustard greens	0.7
Nectarines	0.5
Olives	1.0
Onions	0.75
Parsley	0.75
Parsnips	0.5
Peaches	0.7
Peanuts	0.75
Peanuts, forage	40.0
Peanuts, hay	10.0
Peanuts, hulls	10.0
Pears	0.5
Peavine hay	10.0
Peavines	25.0
Peas with pods (determined on peas after removing any shell present when marketed)	0.5
Pecans	0.5
Peppers	0.5
Pineapples	0.5
Pineapples, forage	40.0
Plums (fresh prunes)	0.5
Potatoes	0.1
Potatoes, sweet	0.1
Radishes	0.5
Raspberries	0.5
Rutabagas	0.75
Sheep, fat (pre-s appli)	0.7
Sheep, meat (fat basis) (pre-s appli)	0.7
Sheep, mbyp (fat basis) (pre-s appli)	0.7
Sorghum, forage	10.0
Sorghum, grain	0.75
Soybeans	0.1
Soybeans, forage	0.1
Spinach	0.7
Squash, summer	0.5
Squash, winter	0.75
Strawberries	0.5
Sugarcane	0.75
Swiss chard	0.7
Tomatoes	0.75
Turnips, roots	0.5
Turnips, tops	0.75
Walnuts	0.5
Watercress	0.7

(Sec. 408(d), 68 Stat. 514 (21 U.S.C. 346a(e)))

[47 FR 42738, Sept. 29, 1982, as amended at 48 FR 14896, Apr. 6, 1983]

§ 180.154 *O,O*-Dimethyl *S*-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl] phosphorodithioate; tolerances for residues.

Tolerances for residues of the insecticide *O-O*-dimethyl *S*-[(4-oxo-1,2,3-benzotriazin-3(4*H*)-yl)methyl] phosphorodithioate in or on the following raw agricultural commodities:

Commodity	Parts per million
Alfalfa	2.0
Alfalfa, hay	5.0
Almonds	0.3
Almonds, hulls	10.3
Apples	2.0
Apricots	2.0
Artichokes	2.0
Barley, grain	0.2
Barley, straw	2.0
Beans (dry)	0.3
Beans, snap	2.0
Birdfoot trefoil	2
Birdfoot trefoil hay	5
Blackberries	2.0
Blueberries	5.0
Boysenberries	2.0
Broccoli	2.0
Brussels sprouts	2.0
Cabbage	2.0
Cattle, fat	0.1
Cattle, mbyp	0.1
Cattle, meat	0.1
Cauliflower	2.0
Celery	2.0
Cherries	2.0
Citrus fruits	2.0
Clover	2.0
Clover, hay	5.0
Cottonseed	0.5
Crabapples	2.0
Cranberries	2.0
Cucumbers	2.0
Eggplants	0.3
Filberts	0.3
Goats, fat	0.1
Goats, mbyp	0.1
Goats, meat	0.1
Gooseberries	5.0
Grapes	5.0
Grass, pasture (green)	2.0
Grass, pasture, hay	5.0
Horses, fat	0.1
Horses, mbyp	0.1
Horses, meat	0.1
Kiwi fruit	10.0
Loganberries	2.0
Melons (honeydew, muskmelons, cantaloups, watermelons, and other melons)	2.0
Nectarines	2.0
Nuts, pistachio	0.3
Oats, grain	0.2
Oats, straw	2.0
Onions	2.0
Parsley, leaves	5
Parsley, roots	2
Peaches	2.0
Pears	2.0
Peas, black-eyed	0.3

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