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

JUN 17 1997

OFFICE OF
INTERNATIONAL ACTIVITIES

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Diazinon {O,O,-diethyl O-[6-methyl-2-(1-methylethyl)-4-pyrimidinyl] phosphorothioate}

CASRN: 333-41-5
EPA Chem. Code: 057801
Caswell No.: 342

FROM: George Z. Ghali, Ph.D. *G. Ghali*
Manager, RfD/QA Peer Review Committee
Health Effects Division (7509C)

THRU: William Burnam *WB*
Chairman, RfD/QA Peer Review Committee
Health Effects Division (7509C)

TO: George LaRocca, PM 13
Insecticide-Rodenticide Branch
Registration Division (7505C)

The Health Effects Division-RfD/Peer Review Committee met on February 19 and 20, 1997 to discuss and evaluate the existing and/or recently submitted toxicology data in support of Diazinon reregistration and to reassess the Reference Dose (RfD) for this chemical. Subsequently, an *ad hoc* meeting convened on March 17, 1997 to address issues relating to the carcinogenicity studies in rats and mice.

Material available for review consisted of data evaluation records (DERs) for chronic toxicity and carcinogenicity studies in rats (83-1a and -2a), a chronic toxicity study in dogs (83-1b), a chronic (nonguideline) study in monkeys, a carcinogenicity study in mice (83-2b), a multi-generation reproductive toxicity study in rats (83-4), developmental toxicity studies in rats (83-1a) and rabbits (83-1b), subchronic toxicity studies in rats and dogs (82-1a and -1b), acute and subchronic neurotoxicity studies in rats (81-8, and 82-7) delayed neurotoxicity studies in hens (81-7) and a battery of mutagenicity studies (84-2).



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A. Chronic and Subchronic Toxicity:

The Committee considered the **chronic toxicity study in rats** (83-1a, 1991, MRID No. 41942002) to be acceptable and the data evaluation record (HED Doc. No. 010331) to be adequate. Diazinon was tested at dietary levels of 0.1, 1.5, 125 and 250 ppm (0.004, 0.06, 5 and 10 mg/kg/day in males and 0.005, 0.07, 6 and 12 mg/kg/day in females). The NOEL/LOEL for plasma cholinesterase inhibition were 0.1/1.5 ppm in both sexes. The NOEL/LOEL for red blood cell and brain cholinesterase inhibition were 1.5 and 125 ppm for both sexes. Systemic effects were not observed in males or females up to and including 250 ppm, the highest dose level tested.

The Committee considered the older chronic toxicity study in rats (83-1a, 1955, MRID No. 00075932, HED Doc. No. 005567) to be superseded with the relatively more recent 1991 study described above.

There were several **subchronic toxicity studies in rats** (82-1a, MRID No. 41886301; 41432301; 41649401; 40815003; HED Doc. Nos. 009372; 007041, 007553) and an open literature study by Davis and Houlb (Arch. Environ. Contam. Toxicol, 9, 1980, HED Doc. No. 005567) available for review by the Committee. These studies appeared to be supportive to the chronic studies but were not evaluated by the Committee.

The Committee considered the **chronic toxicity study in dogs** (83-1b, 1991, MRID No. 41942001) to be acceptable and the data evaluation record (HED Doc. No. 010331 for the original DER and 012219 for updated Executive Summary) to be adequate. Diazinon was tested at dietary levels of 0.1, 0.5, 150 and 200/225 ppm (0.0032, 0.015, 4.7 and 7.7 mg/kg/day in males and 0.0037, 0.02, 4.5 and 9.1 mg/kg/day in females). The following NOEL/LOELs were established:

Plasma ChE: 0.5/150 ppm in males and **0.1/0.5 ppm** in females.
RBC AChE: 0.5/150 ppm in both sexes.

Brain AChE: 0.5/150 ppm in females and 150/200 ppm in males.

Systemic Effects: 0.5/150 ppm for both sexes based on decreased body weight and body weight gain in males and decreased food consumption and increased serum amylase in both sexes.

The overall NOEL and LOEL for this study is thus, 0.1 and 0.5 ppm or **0.0037 and 0.02 mg/kg/day** based on plasma ChE inhibition in females.

The Committee considered the **subchronic toxicity study in dogs** (82-1b, MRID No. 40815004) to be supplementary and the data evaluation record (HED Doc. no. 007041, 007553) to be adequate. Diazinon was tested at dietary level of 0.1, 0.5, 150 and 300 ppm (0.0034, 0.020, 5.9, 10.9 mg/kg/day in males and 0.0037, 0.021, 5.6, 11.6 mg/kg/day in females). The following NOEL and LOELs were set:

Plasma ChE inhibition: 0.0034/0.02 mg/kg/day in males and 0.021/5.6 mg/kg/day in females.

RBC AChE and brain AChE inhibition: 0.02/5.9 mg/kg/day in males and 0.021/5.6 mg/kg/day in females.

Systemic toxicity: 0.02/5.9 mg/kg/day in males and 0.021/5.6 mg/kg/day in females based on emesis/diarrhea, decreased body weight gain, decreased mean total protein and calcium levels and pancreatic atrophy in males.

The Committee considered the 4-week pilot study in dogs (MRID No. 40815004, HED Doc. No. 007041) to be supplementary.

The Committee considered the **chronic cholinesterase inhibition study in monkeys** (nonguideline study, 1966, MRID No. 00057664, 0006419, 00064320, HED Doc. No. 012219) to be ACCEPTABLE. Diazinon was tested orally at 0.05, 0.5 and 5 mg/kg/day for 106 weeks total. For the first 5 weeks of this study, each group received twice the dose listed except the highest dose group which was not dosed on weeks 4-5. The initial dose levels were reduced to one half due to toxicity observed at 10 mg/kg/day. The NOEL/LOEL for plasma ChE and red blood cell AChE inhibition were 0.05 and 0.5 mg/kg/day in both males and females. Brain cholinesterase was assessed for but not demonstrated. The systemic NOEL/LOEL were 5 and 10 mg/kg/day based on body weight decrease and general poor condition of the animals.

The Committee considered the **subacute human exposure study** (Non-guideline, 1966, MRID No. 00091536, HED Doc. No. 012219) to be adequate. The RfD committee concluded that the NOEL and LOEL for plasma ChE were 0.02 and 0.025 mg/kg/day, respectively. The apparent inhibition in two of the three volunteers dosed at 0.02 mg/kg/day was not considered sufficient to conclude that the 0.02 mg/kg/day was a definite effect level. The Committee noted that the dose spacing is too close together and that the NOEL and LOEL established in this study are very close.

B. Carcinogenicity:

Rat and mouse carcinogenicity studies were conducted in 1979 by the National Cancer Institute (83-2a, and -2b MRID No.: 00073372, HED Doc. No.: 005567 and revised Executive Summary in 012219). Diazinon was tested at two dose levels: 20 and 40 mg/kg/day in rats and 14 and 29 mg/kg/day in mice. At the first meeting the Committee questioned the adequacy of dosing and the possibility of tumors in both studies. It was suggested that the chronic toxicity studies be re-evaluated in conjunction with the carcinogenicity studies to resolve the issues of adequacy of dosing and tumors and these issues were referred to a special *ad hoc* committee for review.

Subsequently, an *ad hoc* meeting convened on March 30, to address the above issues relating to the adequacy of dosing and including possible increases in uterine endometrial stromal polyps in rats and mammary gland fibroadenomas in mice. In that meeting, it was determined that the high dose levels tested in both studies were adequate for carcinogenicity testing based on significant cholinesterase inhibition as indicated in the numerous subchronic and chronic feeding studies in rats (see above). Supporting data were found to determine that the dose levels in mice were also adequate based on a preliminary range finding study (Ciba-Geigy Corporation) which demonstrated significant plasma ChE and RBC AChE inhibition in mice at dose levels similar to dose levels assessed in the NCI mouse study. The *ad hoc* committee determined that the carcinogenicity data base for diazinon was acceptable and no further carcinogenicity testing in either the rat or mouse are required at this time. The RfD Committee concluded that diazinon is characterized as "not likely", based on the Proposed Cancer Guideline (FRN April 23, 1996), to be a human carcinogen based on the information provided by the *ad hoc* group (report by J. Doherty, dated April 16, 1997). Neither the rat uterine polyps nor mouse mammary gland tumors attained statistical significance or exceeded historical control frequencies.

C. Reproductive and Developmental Toxicity:

1. Reproductive Toxicity:

The Committee considered the **one-generation reproductive toxicity study in rats** (83-4, 1989, MRID No. 41158102) to be supplementary and the data evaluation record (HED Doc. No. 008415) to be adequate.

Diazinon was tested in Sprague-dawley strain rats at dietary levels of 10, 100, or 1000 ppm (0.49-0.99, 4.88-9.75, or 49.64-93.92 for males and 0.60-0.96, 6.14-9.60, or 65.87-89.48 mg/kg/day for females). Two litters were produced in this study. The LOEL for reproductive toxicity was 10 ppm (0.49-0.99

mg/kg/day for males and 0.60-0.96 mg/kg/day for females), the lowest dose level tested, based on possible decreases in litter size and number of litters; at 100 ppm and higher, there were decreases in relative ovarian weight, female body weight gain during gestation, and pup survival; at 1000 ppm, fertility and mating indices and pup birth weight were decreased, and length of gestation was significantly increased. It was determined to terminate the study due to the excessive toxicity observed at 1000 ppm. Additionally, the possible treatment-related effects on pups at the lowest dose level would have required the study to be repeated to define a NOEL.

The Committee considered the **two-generation reproductive toxicity study in rats** (83-4, 1989, MRID No. 41158101) to be acceptable and the data evaluation record (HED Doc. No. 008415) to be adequate. Diazinon was tested at dietary levels of 10, 100, or 500 ppm (0.67, 6.69, or 35.15 mg/kg/day for males and 0.77, 7.63, or 41.43 mg/kg/day for females). One litter per generation was produced.

The reproductive toxicity NOEL/LOEL were 10 ppm (0.67 for males and 0.77 mg/kg/day for females)/100 ppm (6.69 mg/kg/day for males and 7.63 mg/kg/day for females) based on decreased body weight gain in males, and on pup mortality and decreased postnatal weight gain; at 500 ppm, in addition to the observations listed, tremors were observed, there were effects on mating behavior (decreased male and female mating and fertility indices), gestation length was increased; there was decreased litter size; and absolute testis weight was significantly decreased.

Because both the one- and two-generation studies described above were initiated in the same year (1985), and the rats are from the same source (Charles River Labs, Kingston NY), it was therefore appropriate that the findings of both studies be viewed together. Overall, the results of the two studies are consistent and reproducible in some aspects. The effects noted in the offspring only occur at parental toxic doses, and may be secondary to systemic toxicity in the adults. Whether or not there is a direct toxic effect on the offspring cannot be determined from these data.

The observations of dystocia, which possibly resulted in maternal death of two dams, are assumed to be related to the increases in duration of gestation. Ovarian weight decrements observed in the one-generation study do not occur in the definitive two-generation study. There was a significant decrease in testis weight at the high-dose in the definitive study. This effect was not considered by the scientific reviewer to be definitely treatment related, since the relative weight was equivalent to control and no histopathological abnormalities were observed. However, it is the Committee's opinion that testis is

a highly conserved tissue; even with decreased body weight, the testes will not be much reduced in size/weight, and often a significant increase in relative weight will result. In this case, decreased body weights which occur in the high dose males but not the females may actually be related to decreased testicular hormone levels, since male growth is hormonally regulated. Furthermore, there is an indication in the open literature that testicular effects occur with diazinon administration. It should be noted that cholinesterase inhibition was not measured for pups or adults in either study.

2. Developmental Toxicity:

The Committee considered the **developmental toxicity study in rats** (83-3a, 1985, MRID 00153017) to be tentatively unacceptable until purity data are provided. The data evaluation record (HED Doc. 004979, 005567, 012219) was considered to be adequate with some revisions. These suggested revisions were incorporated into the final version of the DER. The registrant has since provided the information on the purity of the test material and it was 97.4% and the study is now considered ACCEPTABLE.

Diazinon was administered to Sprague-Dawley rats by gavage at levels of 10, 20, or 100 mg/kg/day on gestation days 6-15. The maternal toxicity NOEL/LOEL were considered to be 20/100 mg/kg/day, respectively, based upon decreased body weight gain. The developmental toxicity NOEL/LOEL were considered to be 20 and 100 mg/kg/day, respectively, based upon decreased fetal weight and a "possible" increase in rudimentary ribs.

The Committee considered the **developmental Toxicity study in rabbits** (83-3b, 1981, MRID 0079017) to be acceptable and the data evaluation record (HED Doc. No. 012219) to be adequate.

Diazinon was administered to New Zealand White rabbits by gavage at dose levels of 7, 25, or 100 mg/kg/day on gestation days 6-18. The maternal toxicity NOEL/LOEL were 25/100 mg/kg/day, based on clinical symptoms including tremors and convulsions, mortality in 9/22 does (with gastrointestinal hemorrhage, congestion, or erosion observed in most decedents), and decreased body weight gain. The developmental toxicity NOEL was ≥ 100 mg/kg/day, the highest dose level tested. No evidence of developmental toxicity was observed in this study up to the highest dose level tested.

3. Other Developmental/Reproductive Toxicity Data Reviewed:

The Committee was asked also to comment on a DER for a reproductive toxicity study in rats (83-4, 1994, MRID 43854002, HED Document No.: 012182) that appeared in the literature (*Dtsch. tierartztl. Wschr.* 101:230-232 (1994)).

Diazinon as a 50% formulation was administered to male Wistar rats by gavage at dose levels of 1.5 or 3 mg/kg/day for 65 days pre-mating. The male reproductive toxicity NOEL was reported by the authors to be <1.5 mg/kg/day, the lowest dose level tested.

Summary data demonstrated the following apparently dose-related effects at doses that are lower than those administered in the guideline developmental and reproductive toxicity studies:

1. Decreased organ weights (testes, seminal vesicle, prostate),
2. Decreased sperm count and motility, and increased abnormal morphology,
3. Decreased serum testosterone, and
4. Decreased mating performance.

The Committee generally agreed with the data evaluation record as written. Although there is the suggestion of a diazinon-related effect on male reproductive integrity, there are too many unanswered questions about the study and the data (e.g., amount and/or toxicity of inerts, lack of analytical data, lack of individual animal data, small sample sizes (only five animals) were examined for each parameter, no histopathology to characterize findings in the male reproductive organs). It is noteworthy that a dietary dose of 500 ppm (approximately 35 mg/kg/day) and greater in the one- and two-generation reproduction studies also consistently demonstrated evidence of decreased fertility, but in those studies, technical diazinon was used, leading one to suspect that the effects in this study may be related to, or exacerbated by the inert ingredients. This study can be viewed as starting point for further research as suggested in the memo accompanying the data evaluation record but not be used for regulatory purposes.

D. Neurotoxicity:

The series 81-1 (acute, MRID No.: 413132210, 43132204, HED Document No.: 011375) neurotoxicity studies were reviewed and determined to be acceptable and the DERs adequate. The **acute neurotoxicity study** demonstrated NOEL and LOELs as follows:

Plasma ChE: NOEL < 2.5 mg/kg (27% in males and 47% in females).

RBC AChE: NOEL and LOEL = 2.5 and 150 mg/kg (83% for males and 76% for females).

Brain AChE: Assayed at day 15 and not affected.

Systemic Neurotoxicity: 2.5 and 150 mg/kg (ataxic gait and other related symptoms).

Thus the NOEL and LOEL for the study is < 2.5 mg/kg based on plasma ChE inhibition.

Note: An additional acute study (MRID No.: 44312701, HED Document No.: 012219) demonstrated that the NOEL and LOEL for plasma ChE was 0.15 and 2.5 mg/kg for both sexes.

The **subchronic neurotoxicity study** demonstrated NOEL and LOELs as follows:

Plasma ChE: NOEL and LOEL = 0.3 and 30 ppm or 0.018 and 1.8 mg/kg/day based on 37-45% inhibition in males and 79-86% inhibition in females.

RBC AChE: NOEL and LOEL = 30 and 300 ppm or 1.8 and 18 mg/kg/day based on 37-75% inhibition in males and 53-60% inhibition in females.

Brain AChE: NOEL and LOEL = 300 and 3000 ppm based on 55-75% inhibition in females. Males were considered inhibited at 3000 ppm only (i.e. 62-73%).

Systemic Neurotoxicity: NOEL and LOEL = 300 and 3000 ppm or 18 and 180 mg/kg/day based on weight gain decrease and hyperresponsiveness and tremors and other signs.

The NOEL and LOEL for the study is considered **0.3 and 30 ppm (0.018 and 1.8 mg/kg/day)** based on plasma ChE inhibition.

Diazinon is an organophosphate insecticide and has been tested for **delayed type neurotoxicity in hens (MRID NO.: 44132701)** at 100 mg/kg and vigorously protected by atropine and physostigmine and no evidence of delayed type neurotoxicity was found. The DER was considered adequate (HED Document No.: 012219).

E. Mutagenicity:

Several mutagenicity studies (84-2) were available for review by the Committee. The following is a summary of the studies and Committee's conclusions for each study:

1. Gene Mutations:

a) Salmonella typhimurium/Escherichia coli reverse gene mutation assay (MRID No. 41557404, HED Doc. No. 010062): Independently performed tests were negative in S. typhimurium strains TA1535, TA1537, TA98 and TA100 and E. coli strain WP2 uvrA⁻ up to the highest dose tested (5000 µg/plate +/- S9).

b) Mouse lymphoma L5178Y TK^{+/+} forward gene mutation assay

(MRID Nos. 40660802/41119701; Doc. Nos. 007059/007553): The test was negative up to cytotoxic levels (120 µg/mL -S9; 60 µg/mL +S9).

2. Chromosomal Aberrations:

a) Mouse micronucleus assay (MRID Nos. 40660805, 41603201, HED Doc. Nos. 007229, 010062): The test was negative in male or female CD-1 mice up to lethal doses administered by oral gavage (60 or 120 mg/kg mg/kg). There was, however, no evidence of a cytotoxic effect on the target cells.

3. Other Mutagenic Mechanisms:

a) In vitro sister chromatid exchange (SCE) assay in human lymphocytes assay (MRID No. 41577301, HED Doc. Nos. 010062, 010722): The test was weakly positive, showing reproducible but not dose-related significant increases in the SCE frequency over an S9-activated concentration range of 6.68-66.8 µg/mL. Positive but not dose-related results were also seen without S9 activation at 0.668-20 µg/mL. Higher levels (200 µg/mL +S9 or 66.8 µg/mL - S9) were cytotoxic.

b) In vivo sister chromatid exchange (SCE) assay (MRID No. 41687701, HED Doc. No. 009619): The test was negative and acceptable in male ICR mice at oral gavage doses of 10-100 mg/kg. Overt toxicity and bone marrow cytotoxicity were apparent in the treated males at the highest dose tested.

c) In vivo sister chromatid exchange (SCE) assay (MRID No. 43060601, HED Doc. No. 010945): The test was negative in female CD-1 mice at oral gavage doses of 150-175 mg/kg. Overt toxicity and bone marrow cytotoxicity were apparent in the treated females at concentrations ≥150 mg/kg.

d) Primary rat hepatocyte unscheduled DNA synthesis (UDS) assay (MRID No. 41557405, HED Doc. No. 010062): Independently performed tests were negative up to the highest dose tested (120 µg/mL). Higher levels (>163.1 µg/mL) were insoluble.

4. Other Mutagenicity and Genetic Toxicity Information:

Genetic toxicology studies performed under EPA Contract No. 68-01-2458 also indicated that diazinon was not mutagenic and did not cause DNA damage/repair in bacteria, mitotic recombination in Saccharomyces cerevisiae or UDS in human lung fibroblasts (MRID No. 132952, HED Doc. No. 005567). Several unacceptable in vivo studies suggested that diazinon was negative for micronuclei induction in Chinese hamsters (HED Doc. No. 007229) and dominant lethal mutations in male mice (HED Doc. No. 005567). In addition, summarized results presented in the ATSDR Toxicological Profile for Diazinon (ATSRD, August 1996) were largely negative.

Although two positive studies were cited in the ATSDR document (one mouse lymphoma assay and one in vitro chromosome assay), the results have either not been confirmed in subsequent in vitro testing or not demonstrated in whole animals. Based on the overall data, it was concluded, therefore, that diazinon is at best weakly clastogenic in vitro but its genotoxic potential, if any, has not been demonstrated in vivo.

5. Conclusions (Mutagenicity and Genetic Toxicity):

The Committee overall concluded that the acceptable studies satisfy the pre-1991 mutagenicity initial testing battery guidelines. Based on these studies, there is no concern for mutagenicity at this time. No additional mutagenicity studies are required at this time.

F. Additional Data Required:

Overall, following a review of the available data, the Committee was not convinced that a developmental neurotoxicity study in rats should be conducted with diazinon until more information on diazinon becomes available. Diazinon should be considered within a larger effort to define data needs for organophosphorus pesticides.

In evaluating the developmental and reproductive toxicity data, there were aspects supporting the need for developmental neurotoxicity data and other aspects supporting otherwise. The weight-of-evidence consideration was based upon the following information:

Evidence supporting the requirement to a developmental neurotoxicity study:

1. Diazinon is a an organophosphorus pesticide and thus a neurotoxic chemical. Administration of Diazinon to various species (rat, mouse, dog, monkey) results in cholinesterase inhibition in the plasma, RBCs, and brain. Extensive characterization of the cholinesterase inhibition response has been conducted. Neurotoxic effects (abnormal and ataxic gait, and decreased body temperature) were observed in rats in an acute neurotoxicity study at a gavage dose of 150 mg/kg. Muscle fasciculation, hyperresponsiveness and tremors, and decreased grip strength were observed in the subchronic neurotoxicity study at a dietary level of 3000 ppm (180 mg/kg/day).

2. Some data suggest that diazinon disrupts endocrine function. In the one-generation reproduction study in rats, absolute ovarian weights were decreased at doses of 10 ppm (0.60 mg/kg/day) and higher; relative ovarian weights were decreased at 100 ppm (6.14 mg/kg/day) and greater. In the two-generation reproduction study in rats, absolute testicular weight was

significantly decreased at 500 ppm (35.2 mg/kg/day) for the second generation (F1) males. Indices of fertility are also decreased at this dose level. Delayed parturition, a hormonally mediated event, is also consistently observed in both reproduction studies at doses of 500 ppm (41.4 mg/kg/day in females) and higher. A preliminary review of a study published in the open literature suggests that testosterone levels, testes and accessory gland weights, sperm measures, and male fertility are affected by diazinon exposure, but the conclusions of this study need to be verified with additional data and further research. Additionally, in the subchronic and chronic studies conducted with diazinon, no evidence of toxicity to the reproductive organs was noted for either males or females.

Evidence not supporting the requirement of a developmental neurotoxicity study:

1. No effects on brain weight or histopathology of the brain were observed in any of the numerous studies in which these parameters were measured. Delayed neuropathy was not observed in the hen.

2. No evidence of developmental anomalies, including abnormalities in the development of the fetal nervous system, were observed in the prenatal developmental toxicity studies in either rats, or rabbits, at maternal gavage doses up to 100 mg/kg/day. In the two-generation reproduction study in rats, no clinical evidence suggestive of neurotoxicity was observed grossly in pups, which had been administered diazinon *in utero* and during early and late postnatal development, generally mediated by maternal dietary exposure, but also available in the diet to late lactation pups.

3. There has been no assessment of differential response of fetuses versus adults to cholinesterase inhibition following treatment with diazinon.

In conclusion, the RfD committee does not consider that the weight of evidence justifies requiring a developmental neurotoxicity study at this time.

G. FOPA Considerations:

The data available for review included an acceptable two-generation reproduction study in rats and acceptable prenatal developmental toxicity studies in rats and rabbits, meeting the basic data requirements, as defined for a food-use chemical by 40 CFR Part 158. No further testing was recommended by the Committee at this time. The data provided no indication of increased sensitivity of rats or rabbits to *in utero* and/or postnatal exposure to diazinon.

G. Reference Dose (RfD):

The Committee recommended that an RfD for this chemical be established based on a cholinesterase inhibition study conducted on human volunteers with a NOEL of 0.02 mg/kg/day. Definite plasma cholinesterase inhibition was observed at the next higher dose level of 0.025 mg/kg/day. An Uncertainty Factor (UF) of 10 was applied to account for intraspecies variability. An additional UF of 3 was also recommended to account for the close proximity of the NOEL and LOEL established in this study, the use of only one sex and for the questionable quality of the study. On this basis the RfD was calculated to be 0.0007 mg/kg/day.

The NOEL established in this study was also supported by the findings of chronic and/or subchronic studies in rats, dogs and monkeys.

It should be noted that this chemical has been evaluated by the WHO/FAO Joint Meeting of Pesticide Residues (JMPR) and an Acceptable Daily Intake (ADI) of 0.002 mg/kg/day has been established in 1993.

H. Individuals in Attendance:

Peer Review Committee members and associates present, in at least one meeting, were William Burnam (Chief, SAB; Chairman, RfD/Peer Review Committee), George Ghali (Manager, RfD/Peer Review Committee), Karl Baetcke (Chief, TB I), Mike Ioannou (Actin Chief, TB II), Marion Copley, Nancy McCarroll, Susan Makris, William Sette, Henry Spencer, and Rick Whiting. In attendance also were Karen Hamernik, and Brian Dementi as representatives of the Organophosphorus Pesticide Task Force and Edwin Budd of HED as an observer.

Scientific reviewers (Committee or non-committee member(s) responsible for data presentation; signature(s) indicate technical accuracy of panel report):

John Doherty _____

Marion Copley _____

Respective Branch Chief (Committee member; signature indicates concurrence with the peer review unless otherwise stated)

Karl Baetcke _____

CC: Stephanie Irene
Debra Edwards
Karl Baetcke
Marion Copley
John Doherty
Karen Whitby
Amal Mahfouz (OW)
RfD File
Caswell File.

I. Material Reviewed:

1. U.S. National Institutes of Health (19??). Bioassay of Diazinon for Possible Carcinogenicity (Mice). MRID No. 00073372. HED Doc. No. 005567. Classification: Supplementary. This study (satisfies, does not satisfy) data requirement 83-2a of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in rats.
2. U. S. National Institutes of Health (19??). Bioassay of Diazinon for Possible Carcinogenicity (Rats). MRID No. 00073372. HED Doc. No. 005567. Classification: Supplementary. This study (satisfies, does not satisfy) data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.
3. Kirchner, F. R. et al. (1991). One/Two Year Oral Toxicity Study in Rats. MRID No. 41942002. HED Doc. No. 010331. Classification: Core minimum. This study satisfies data requirement 83-1a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in rats.
4. Horn, A. J. (1955). "Chronic Feeding". MRID No. 00075932. HED Doc. No. 005567. Classification: Core Supplementary. This study does not satisfy data requirement 83-1a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in rats.
5. Trutter, Janet A. (1991). "6-Week Feeding Study in Rats with Diazinon". MRID No. 41886301. HED Doc. No. 009372. Classification: Acceptable. This study satisfies data requirement 82-1a of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in rats.
6. Broadmeadow, Alan (1989). "Diazinon Technical: Comparative Toxicity Study by Dietary Administration to CD Rats for Six Weeks". MRID No. 41432301, 41649401. HED Doc. No. 008374. Classification: Acceptable (according to the DER). This study was not evaluated by the RfD/Peer Review Committee.
7. Singh, A. R. (1988). Diazinon (MG-8): 90-Day Oral Toxicity Study in Rats. MRID No. 40815003. HED Doc. No. 007041, 007553. Classification: Core guideline (according to the DER). This study was not evaluated by the RfD/Peer Review Committee..
8. Barnes, T. B. (1988). Diazinon (MG-8): Pilot 6-Week Oral Feeding Study in Rats. MRID No. 40815003. HED Doc. No. 007041, 007553. Classification: Core Supplementary. (according to the DER). This study was not evaluated by the RfD/Peer Review Committee.

9. Davis, D. B. and Holub, B. J. (1980). Toxicological Evaluation of Dietary Diazinon in the Rat. MRID No. 012219. HED Doc. No. 005567. Classification: Supplementary. (according to the DER). This study was not evaluated by the RfD/Peer Review Committee.
10. Rudzki, M. W. et al. (1991). Diazinon MG-8 52-Week Oral Toxicity Study in Dogs. MRID No. 41942001. HED Doc. No. 010331. Classification: Core guideline.
11. Barnes, T. B. (1988). Diazinon (MG-8): 90-Day Oral Toxicity Study in Dogs. MRID No. 40815004. HED Doc No. 007041, 007553. Classification: Core Supplementary. This study does not satisfy data requirement 82-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in rats.
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