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

FEB 24 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Trichlorfon

CASRN. 52-68-6
EPA Chem. Code: 057901
Caswell No. 385

FROM: George Z. Ghali, Ph.D. G. Ghali 2.17.94
Manager, RfD/Quality Assurance Peer Review
Health Effects Division (H7509C)

TO: Lois Rossi, Chief
Re-registration Branch
Special Review and Re-registration Division (H7508W)

Robert Forrest, PM 14
Insecticide-Rodenticide Branch
Registration Division

The Health Effects Division RfD/Peer Review Committee met on January 13, 1994 to discuss and evaluate the existing toxicology data in support of Trichlorfon re-registration and re-assess the Reference Dose (RfD) for this chemical.

The Committee considered the long-term feeding study in rats **(83-1a)**, the chronic toxicity study in monkeys **(83-1b)**, developmental toxicity studies in rats and rabbits **(83-3a and -3b)** and the reproductive toxicity studies in rats **(83-4)** to be acceptable and the data evaluation records for these studies to be adequate. The Committee recommended to upgrade the most recent developmental toxicity study in rats to a Core-minimum status. The chronic toxicity study in dogs **(83-1b)** was considered to be unacceptable, however the Committee did not ask for another study in dogs since a chronic toxicity study in monkeys was available. The Committee determined that acute and subchronic neurotoxicity studies in a mammalian species are required.

The carcinogenicity studies in rats, mice and monkeys **(83-2a and -2b)** were briefly discussed by the RfD Committee in this meeting. The Committee referred the carcinogenicity issue to the Health Effects Division - Carcinogenicity Peer Review Committee for a weight of the evidence evaluation.

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The Committee recommended that an RfD be established on the basis of an LOEL of 0.20 mg/kg/day, lowest dose tested in a chronic feeding study in Rhesus monkeys, for decreased brain cholinesterase activity observed in males. An uncertainty factor (UF) of 100 was used to account for the inter-species extrapolation and intra-species variability. On this basis the **RfD** was calculated to be **0.002 mg/kg/day.** The Committee considered that the inhibition of cholinesterase at 0.20 mg/kg/day to be marginal and was judged to be a threshold effect. Therefore, the Committee did not feel that any additional uncertainty factor, to compensate for the lack of a no-observable effect level, was necessary. It should be noted that this chemical has been reviewed by the World Health Organization (WHO) and an ADI value of 0.01 has been established for this chemical in 1989.

There was no evidence, based on the available data, to suggest that Trichlorfon was associated with significant reproductive and developmental toxicity. The need for a developmental neurotoxicity study was discussed, but was not recommended.

A. Individual in Attendance

1. Peer Review Committee Members and Associates present (Signature indicates concurrence with the peer review unless otherwise stated).

William Burnam

Marcia Van Gemert

Karl Baetcke

Henry Spencer

Roger Gardner

James Rowe

Esther Rinde

George Ghali

Rick Whiting

2. Scientific Reviewer (Committee or non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report).

Melba Morrow

Joycelyn Stewart

3. Others:

J. Smith, S. Reilly and B. Backus of HED as observers.

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Karl Baetcke
Joycelyn Stewart
Melba Morrow
James Kariya
Flora Chow
RfD File
Caswell File

B. Material Reviewed

Material available for review included data evaluation records for chronic toxicity/carcinogenicity studies in rats **(83-5 or 83-1a and -2a)** and monkeys **(83-1b and -2b)**, a carcinogenicity study in mice **(83-2b)**, a chronic toxicity study in dogs **(83-1b)**, developmental toxicity studies in rats and rabbits **(83-3a and -3b)** and reproductive toxicity studies in rats **(83-4)**, and a tox. one-liner.

1. Hayes, R. H. (1989). Chronic toxicity/oncogenicity study of technical grade trichlorfon (Dylox) with rats. MRID No. 41056201, HED Doc No. 009626.

Core Classification: Guideline data.

Committee's Conclusion and Recommendations:

The chemical was tested in Fischer 344 rats at 100, 300 and 1750 ppm (4.4, 13.3 and 75.5 mg/kg/day in males and 5.8, 17.4 and 93.7 mg/kg/day in females). The NOEL/LOEL were considered to be 100 and 300 ppm based upon decrease in red blood cell and brain cholinesterase activity in both sexes and hyper cholesterolemia in males. The carcinogenicity phase of the study was briefly discussed. The carcinogenicity issue was referred to the Health Effects Division-Carcinogenicity Peer Review Committee for a weight of the evidence evaluation. The Committee generally agreed with the reviewer's evaluation and interpretation of data and the classification of the study. This study satisfies data requirements 83-1a and 83-2a of subpart F of the Pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in rats.

2. Christenson W. R. (1989). A combined chronic toxicity/ oncogenicity study of technical trichlorfon (Dylox) with rats. MRID No. 41973001, HED Doc No. 008845.

Core Classification: Core-supplementary data. This study was conducted with a single dose level.

Committee's Conclusion and Recommendations:

The chemical was tested in Fischer 344 rats at 2500 ppm (129 and 159 mg/kg/day in males and females, respectively). The data presented demonstrated that at this dose level there was a decrease in body weight (about 9% in both sexes) and body weight gain, increased incidence of urine stain, rough coats and paleness of eyes, decreases in erythrocyte parameters (hematocrit, hemoglobin, RBC count and MCV), hypercholesterolemia, increases in hepatic enzymes in males (SAP, AST, ALT and GGT). Decrease in plasma, erythrocyte and brain cholinesterase levels were also reported in both sexes of treated animals. Compound-related non-neoplastic

lesions included duodenal hyperplasia, gastritis, pulmonary hyperplasia and inflammation, nasolacrimal inflammation, hepatocellular hyperplasia and vacuolation, chronic nephropathy and increased incidence of dermal lesions. With regard to neoplastic lesions, an increased incidence in renal tubular adenomas was reported in males. An increase in alveolar/bronchial adenomas was reported in males and an increase in alveolar/bronchial carcinomas was reported in females. It is noted that hyperplasia was observed in lungs at statistically significant levels in treated animals. Hyperplasia was also present in the kidneys, however, there was no significant increase when compared to controls. The carcinogenicity phase of the study was briefly discussed. The carcinogenicity issue was referred to the Health Effects Division-Carcinogenicity Peer Review Committee for a weight of the evidence evaluation. The Committee generally agreed with the reviewer's evaluation and interpretation of data and the classification of the study. This study was conducted to supplement the main study described above, therefore, this study should be viewed together with the main study.

3. **Hayes R. H. (1988). Oncogenicity study of technical grade grade trichlorfon (Dylox) with mice. MRID No. 40782401, 40844301, HED Doc No. 009626.**

Core Classification: Core minimum data.

Committee's Conclusion and Recommendations:

The chemical was tested in CD-1 mice at 300, 900 and 2700 ppm (45, 135, 405 mg/kg/day). A NOEL was not demonstrated for systemic toxicity. The treatment was associated with increased incidence of lung tumors in females, but not in a dose-related manner. Clinical signs of toxicity associated with the administration with the administration of the of the test compound included vaginal discharge in high dose females, urine staining in low and mid dose males and ear lesions in high dose males. Depressed plasma, brain and erythrocyte cholinesterase were reported at all dose levels. The carcinogenicity phase of the study was briefly discussed. The carcinogenicity issue was referred to the Health Effects Division-Carcinogenicity Peer Review Committee for a weight of the evidence evaluation. The Committee generally agreed with the reviewer's evaluation and interpretation of data and the classification of the study. This study satisfies data requirements 83-2b of subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.

4. **Griffen, T. B. (1988). Safety evaluation and tumorigenesis of trichlorfon in rhesus monkeys: a ten year study. MRID No. 40776001, HED Doc No. 009626.**

Core Classification: Core minimum data.

Committee's Conclusion and Recommendations:

The chemical was tested in Rhesus monkeys at 0.2, 1.0 and 5.0 mg/kg/day for ten years. The chemical was administered by gavage six days a week. At these dose levels, the compound did not demonstrate an increase in tumor incidence over the controls. The NOEL for cholinesterase inhibition was considered by the reviewer to be 0.2 mg/kg/day in females. The LOEL was considered to be 0.2 mg/kg/day, lowest dose tested, in males and 1.0 mg/kg/day in females. Additionally, at 5 mg/kg/day, there was a decrease in body weight for both sexes (6-28% in males and 6-33% in females) and anemia as characterized by decreases in erythrocyte counts, hemoglobin and hematocrit values. At this same dose level, transitory cholinergic signs were observed during the first month of dosing in females. These signs consisted of pupillary constriction, muscle fasciculation and diarrhea. Diarrhea was also observed in high dose males. Based on decreases in body weights, decreases in erythrocyte counts, hemoglobin and hematocrit and decreases in plasma, erythrocyte and brain cholinesterase activity, it was concluded that the compound was tested at adequate dose levels. The carcinogenicity issue was referred to the Health Effects Division-Carcinogenicity Peer Review Committee for a weight of the evidence evaluation. The Committee generally agreed with the reviewer's evaluation and interpretation of data and the classification of the study. <u>This study satisfies data requirements 83-1b and 83-2b of subpart F of the Pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in a second species.</u>

5. Doull, J. et al. (1962). Chronic oral toxicity of Dylox to male and female dogs. MRID No. 41056201, HED Doc No. 009626.

Core Classification: Core supplementary data.

Committee's Conclusion and Recommendations:

The chemical was tested in beagle dogs at 50, 250, 500 and 1000 ppm. The NOEL/LOEL were considered to be 250 and 500 ppm based upon decrease in serum and erythrocyte cholinesterase activity and histopathological changes in liver and spleen. The Committee generally agreed with the reviewer's evaluation and interpretation of data and the classification of the study. Deficiencies noted in this study included 1) too few animals were tested, 2) no clinical studies were performed, and 3) histopathological findings were not reported for individual animals. <u>This study does not satisfy data requirements 83-1b of subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs</u>. A new dog study is not required since another a second chronic study was conducted in monkeys as a second species.

6. Eigenberg, D. A. (1991). Two generation reproduction study in rats using technical grade trichlorfon. MRID No. 42228301, HED

Doc. No. 009725.

Core Classification: Guideline data.

Committee's Conclusion and Recommendations:

The chemical was tested in Sprague-Dawley rats at 150, 500 and 1750 ppm (approximately 15, 50 and 175 mg/kg/day) . Parental toxicity LOEL was considered to be 150 ppm , lowest dose tested, based upon decrease in plasma, red blood cell and brain cholinesterase activity in both generations. The reproductive NOEL was considered to be 500 ppm based on decreased pup weights on days 7 and 21 and the presence of dilated renal pelvises. The Committee generally agreed with the reviewer's evaluation and interpretation of data and the classification of the study. The study was considered to be acceptable and the data evaluation record was considered to be adequate. The only recommended revision was to characterize the reproductive NOEL of 500 ppm (25 mg/kg/day) as a "reproductive/systemic" NOEL. It should also be noted that the lowest NOEL was demonstrated by the 3-generation reproduction study discussed below, but the dosage ranges in the two reproduction toxicity studies when considered together indicate that the 500 ppm NOEL is the most appropriate level for a reproductive/systemic toxicity NOEL. This study satisfies data requirements 83-4 of subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

7. Loser, E. (1969). Bay 15 922- general study in rats [Three-generation reproduction assay in rats]. MRID No. 00128682, HED Doc. No. 003267.

Classification: Core minimum data.

Committee's Conclusion and Recommendations:

The chemical was tested in rats (unspecified strain) at 100, 300, 1000 and 3000 ppm (approximately 5, 15, 50 and 150 mg/kg/day) . Maternal and reproductive toxicity NOEL and LOEL were considered to be 15 and 50 mg/kg/day. The only recommended revision was to characterize the reproductive NOEL of 15 mg/kg/day as a "reproductive/systemic" NOEL. It should also be noted that the lowest NOEL was demonstrated by this 3-generation reproduction study, but the dosage ranges in the two reproduction toxicity studies when considered together indicate that the 500 ppm NOEL is the most appropriate level for a reproductive/systemic toxicity NOEL. The Committee generally agreed with the reviewer's evaluation and interpretation of data and the classification of the study. The study was considered to be acceptable and the data evaluation record was considered to be adequate. This study satisfies data requirements 83-4 of subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

8. Kowalski, R. L. et al. (1987). A teratology study with Dylox technical (Trichlorfon) in the rat. MRID No. 40255601, HED Doc. No. 006745.

Core Classification: Core supplementary data.

9. Courtney, K. D. et al. (1983). Assessment of teratogenic potential of trichlorfon in mice and rats. MRID No. 40255601, HED Doc. No. 003267.

Core Classification: Core supplementary data.

10. Machemer, L. (1983). L 13/59 (Trichlorfon) -- studies of embryonic and teratogenic effects on rats following oral administration. MRID No. 00153010, HED Doc No. 003267.

Core Classification: Core minimum data

11. Staples, R. E. et al. (1976). Developmental toxicity in the rat after ingestion or gavage of organophosphate pesticide (Dipterex, ...) during pregnancy. MRID No. 00063192, HED Doc No. 003267.

Core Classification: Core supplementary data

12. Staples, R. E. and Goulding, E. H. (1979). Dipterex teratogenicity in the rat, hamster and mouse when given by gavage. Environmental Health Perspective, 30:105-113. MRID No. 00063192, HED Doc No. 003267.

Core Classification: 1) Rat and mouse studies; supplementary
2) Hamster study; minimum

13. Sulinski, A. et al. (1979). Effect of intoxication of pregnant rats with trichlorfon on the activities of some brain enzymes in progeny during postnatal development. Neuropatologia Polska 17(1): 135-143., HED Doc No. 003267

Core Classification: Core supplementary data

14. Clemens, G. R. et al. (1990). Teratology study in the rabbit with dylox technical (trichlorfon). MRID No. 41565201, HED Doc. No. 008864.

Core Classification: Core minimum data.

15. Machemer, L. (1979). L 13/59 (Trichlorfon). Evaluation for embryonic toxic and teratogenic effects on orally dosed rabbits. MRID No. 00128684, HED Doc. No. 003267.

Core Classification: Core minimum data.

Committee's Conclusions and Recommendations:

There were eight data evaluation records on developmental toxicity considered by the Committee. The data evaluation records, for the most part, are adequate and support NOELs and LOELs for maternal toxicity of 10 and 35 mg/kg/day, respectively. The NOEL and LOEL for developmental toxicity were 35 and 110 mg/kg/day, respectively, and these values were indicated in the rabbit (study No. 14, above).

The data evaluation record for the most recent rat developmental toxicity study (No. 8, above) should be upgraded since the only reason it was classified as supplementary was the lack of a NOEL for cholinesterase inhibition which was demonstrated in other studies. It was also noted in the data evaluation record for this study that the NOEL/LOEL for developmental toxicity were determined on the basis of fetal rather than litter data. Summary tables for the incidences of litters with affected fetuses should be added for effects listed in table 5 of the data evaluation record.

The remaining data evaluation records (9, 10, 11, 12, 13 and 15) are consistent with results reported in DERs 8 and 14 above, but they are done at higher doses, and developmental effects are most frequently seen at lethal doses.

The additional studies were conducted in mice, hamsters, rats and rabbits, and the data from all eight studies suggest that the rabbit is the most sensitive indicator of developmental toxicity in laboratory animals. It was also noted that developmental toxicity always occurred along with maternal toxicity and indicated by delayed development (variation in ossification) and lethality (at relatively high doses).

16. Hayes, R. H. and Ramm, W. W. (1987). Subchronic delayed neurotoxicity study of trichlorfon technical (Dylox) with rats. MRID No. 40351200, HED Doc. No. 006745.

Core Classification: Guideline data

Committee's Conclusions and Recommendations:

The chemical was tested in white leghorn hens at 3, 9, 18 and 45 mg/kg/day. The NOEL/LOEL were considered to be 9 and 18 mg/kg/day based on slight axonal degeneration. The Committee generally agreed with the reviewer's evaluation and interpretation of data and the classification of the study. The study was considered acceptable and the data evaluation record was considered adequate. This study satisfies data requirements 83- of subpart F of the Pesticide Assessment Guideline for subchronic delayed neurotoxicity testing in hens.

C. Conclusions and Recommendations

1. Data Base

The Committee considered the long-term feeding study in rats **(83-1a)**, the chronic toxicity study in monkeys (83-1b), developmental toxicity studies in rats and rabbits **(83-3a and -3b)** and the reproductive toxicity studies in rats **(83-4)** to be acceptable and the data evaluation records for these studies to be adequate. The Committee recommended to upgrade the most recent developmental toxicity study in rats to a Core-minimum status. The chronic toxicity study in dogs **(83-1b)** was considered to be unacceptable, however the Committee did not ask for another study in dogs since a chronic toxicity study in monkeys was available. The Committee determined that acute and subchronic neurotoxicity studies in a mammalian species are required.

2. Carcinogenicity

The carcinogenicity studies in rats, mice and monkeys **(83-2a and -2b)** were briefly discussed by the RfD Committee in this meeting. The Committee referred the carcinogenicity issue to the Health Effects Division - Carcinogenicity Peer Review Committee for a weight of the evidence evaluation.

3. Reference Dose

The Committee recommended that an RfD be established on the basis of a LOEL of 0.20 mg/kg/day, lowest dose tested in a chronic feeding study in Rhesus monkeys, for decrease brain cholinesterase activity observed in males. An uncertainty factor (UF) of 100 was used to account for the inter-species extrapolation and intra-species variability. On this basis the **RfD** was calculated to be **0.002 mg/kg/day.** The Committee considered that the inhibition of cholinesterase at this level to be marginal and can be considered a threshold effect. Therefore, the Committee did not feel that additional uncertainty factor, to compensate for the lack of a no-observable effect level, to be necessary. It should be noted that this chemical has been reviewed by the World Health Organization (WHO) and an ADI value has of 0.01 has been established for this chemical in 1989.

4. Reproductive and Developmental Toxicity

There was no evidence, based on the available data, to suggest that Trichlorfon was associated with significant reproductive and developmental toxicity. The need for a developmental neurotoxicity study was discussed, but was not recommended.