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

SEP 2 1981

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Treflan® PD 4 Draft

FROM: Marcia E. Williams Marcia Williams
Director
Special Pesticide Review Division (TS-791)

TO: Dr. John W. Tollhunter
Assistant Administrator-Designate
for Pesticides and Toxic Substances (TS-733)

THRU: Edwin L. Johnson
Deputy Assistant Administrator
for Pesticide Programs (TS-766C)

Enclosed please find the Position Document (PD 4) concluding the Rebuttable Presumption Against Registration (RPAR) for trifluralin-containing products. The Agency proposed in the PD 1/2/3 that all trifluralin registrations be cancelled unless the registrants amend the terms and conditions of registration to limit the N-nitrosodipropylamine (NDPA) contamination in products containing trifluralin to a level not to exceed 1 ppm. The Agency also indicated that the registrants would be required to conduct studies in order to assess risks due to potential mutagenic, reproductive, and teratogenic effects. Since the PD 1/2/3 was issued in 1979, the principal registrant, Elanco Products Co., has instituted changes in the manufacturing process to reduce the NDPA contamination to an average of 0.1 ppm (range = <0.01 - 0.96 ppm). Because of this reduction, the risks associated with NDPA exposure have been significantly reduced.

However, a new oncogen study, submitted to the Agency last September by Elanco, indicated that trifluralin itself, administered in high doses to rats, was associated with the production of tumors. The Toxicology (TOX) Branch of the Hazard Evaluation Division (HED) has reviewed and interpreted Elanco's chronic feeding study. The Carcinogen Assessment Group (CAG) concurs with their interpretation that trifluralin is associated with a significant increase in the incidence of tumors of the kidney, bladder, and thyroid gland.

The risk estimates calculated in the PD 1/2/3 were due to exposure to the NDPA contamination in Treflan® EC, a formulated product containing trifluralin. Because of the new information on the oncogenicity of trifluralin itself, the Environmental Fate Branch (EFB) of HED recalculated the risk to the general population and workers from exposure to Treflan® EC, taking into account the decrease in NDPA contamination. These estimates were reviewed and approved by the CAG.

514

The new risk estimates associated with exposure to Treflan® EC (containing trifluralin and NDPA as a contaminant) have not changed appreciably when compared to those of the PD 1/2/3. The degree of risk is the same though the source of the risk has changed. The risk is currently associated with the trifluralin in Treflan® EC, rather than the NDPA.

Because the risks have not changed appreciably, the benefits of using trifluralin-containing products continue to outweigh the risks as stated in the PD 1/2/3. The Scientific Advisory Panel (SAP) has reviewed all the studies discussed in the PD 1/2/3, but has not reviewed Elanco's chronic feeding study. Because the benefits continue to outweigh the risks and because the Agency's regulatory position remains the same, it was determined that a review of the study by the SAP was not necessary.

The Agency is currently proposing that registrants of trifluralin-containing products amend their confidential statement of formula to reflect a total N-nitrosamine contamination level of less than 1 ppm. In addition, the Agency is proposing that further testing on trifluralin be done by the registrant to assess potential mutagenic, reproductive, and teratogenic effects. Lastly, the Agency is proposing that a field monitoring study be done to assess possible toxic effects to aquatic organisms in aquifers adjacent to Treflan®-treated fields, since new information on soil runoff has come to our attention subsequent to the issuance of the PD 1/2/3. Table 1 indicates the results of studies supporting the proposed regulatory decision.

These studies impact the proposed regulatory decision as follows:

1. Because NDPA has been shown to be both an oncogen and a mutagen, the level of total N-nitrosamine contamination in trifluralin must not be allowed to exceed 1 ppm.

2. Trifluralin, with an NDPA concentration of less than 0.01 ppm, has been shown to produce tumors in Fischer 344 rats. However, current dietary tolerances and protective clothing for mixer/applicator/loaders result in a risk estimate low enough such that risks are outweighed by the benefits derived from the use of trifluralin-containing products.

3. Because there have been conflicting results concerning the mutagenicity of trifluralin, we are proposing specific studies to test for DNA/gene effects in microbes and mammals and to assess transport to the mammalian gonad.

4. Because the studies done on reproductive and teratogenic effects have been unsatisfactory, further study in these areas is necessary to properly assess potential toxic effects.

5. Lastly, it is necessary for the registrant to perform a field monitoring study to assess potential toxic effects to aquatic organisms for the following reasons:

   a. Trifluralin has been shown to be highly toxic to aquatic organisms.
   b. Aquatic organisms have high bioconcentrating abilities.
   c. Trifluralin has been shown to cause vertebral dysplasia in fish.
   d. Trifluralin has been shown to be transported as bound residues in soil runoff.

Attached please find a bibliography of the cited studies. Please let me know if you require further assistance regarding the proposed regulatory action to conclude the trifluralin (Treflan®) RPAR.

Enclosure

Table 1
Studies Supporting the PD 4 Regulatory Decision

Toxicity	Author (Year)	Results
Oncogenicity of Trifluralin	NCI (1978)	Trifluralin with 84-88 ppm NDPA produces tumors in female B6C3F1 mice.
	Elanco (1980)	Trifluralin with <0.01 ppm NDPA produces tumors in Fischer 344 rats.
Oncogenicity of NDPA	Druckery et al. (1967)	NDPA produces tumors in BD rats.
	Pour et al. (1973)	NDPA produces tumors in Syrian Golden Hamsters.
	Reznick et al. (1975)	NDPA produces tumors in Sprague Dawley rats.
	Dickhaus et al. (1977)	NDPA produces tumors in NMRI mice.
Mutagenicity of Trifluralin	Simmon et al. (1977)	Negative for E. coli, Salmonella typhimurium, B. subtilis, S. Cerevisiae, & human fibroblasts[1/2/]
	Anderson et al. (1972)	Negative for S. typhimurium[3/], and E. coli[3/6/]
	Murnik (1978)	Negative for D. Melanogaster[4/]
	Chan (1979)	Positive in yeast and D. melanogaster[1/]
Mutagenicity of formulated Treflan	Anderson et al. (1972)	Negative for S. typhimurium[1/]
	Murnik (1978)	Negative for gene mutations in D.melanogaster[5/6/] Positive for chromosomal mutations in D. melanogaster[5/6/]
	Yoder et al. (1973)	Positive in humans[4/]
	Griffiths (1978)	Positive in Neurospora[5/]

Table 1
Studies Supporting the PD 4 Regulatory Decision
(continued)

Mutagenicity of NDPA	Kuroki (1977)[5] and Matsuoka (1979)[3]	Positive in mammalian somatic cells in culture.
	McCann et al. (1975), Yahagi et al. (1977), Bartsch et al. (1976, and Olajos and Cornishi (1976)	Positive in S. typhimurium[5]
	Nakajima et al. (1974)	Positive in E. coli[5]
	Brusick and Mayer (1973)	Positive in S. cerevisiae[5]
Reproductive Effects of Trifluralin	Worth et al. (1966)	Results inconclusive due to insufficient number of test animals
	Elanco (1977)	Results negative after one generation, but does not fulfill SAP's recommendation for a multi-generation study
Teratogenicity of Trifluralin	Worth (1966)	Results negative, but a small number of animals, dosing carried out for insufficient period of time, and dams sacrificed prematurely
Ecological Effects of trifluralin (aquatic organisms)	Cope (1966) Macek (1969, 1976) and Parrish (1978)	Acute toxicity of trifluralin to aquatic organisms
	Sanborn (1974) and Parrish (1978)	Aquatic organisms bioconcentrate trifluralin up to 150,000 X
	Couch (1979)	Trifluralin causes vertebral dysplasia in fish
	Wauchope (1978)	Trifluralin is transported as bound residues in soil runoff

Table 1
Footnotes

1/ Strains tested with and without metabolic activation.

2/ Test material contained 87 ppm NDPA as a contaminant.

3/ No metabolic activation used.

4/ Preliminary data - sample of test material with NDPA removed in laboratory

5/ Metabolic activation used.

6/ Test for r-II mutation.

BIBLIOGRAPHY

Anderson, K. J., E. G. Leightly, and M. T. Takahashi (1972) Evaluation of Herbicides for Possible Mutagenic Properties, J. Agr. Food Chem. 20 (3): 649-654.

Bartsch, J., C. Malaveille, and R. Monsanto (1976) Predictive value of tissue-mediated mutagenicity assays to assess the carcinogenic risk of chemicals. IARC Sci. Publ. 12:467-491.

Brusick, D., and V.W. Mayer (1973) New developments in mutagenicity screening techniques with yeast. Envir. Health Perspec., December, 83-96.

Chen, J. (1979) CBIB Virology Unit Report, Product Chemistry Guidelines Test: Microbial Assay of Pesticidal Chemicals.

Cope, O.B. (1966) Contamination of freshwater ecosystems by pesticides. J. Appl. Ecol. 3:33-44.

Couch, J. A., J. T. Winstead, D. J. Hansen and L. R. Goodman, (1979) Vertebral dysplasia young fish exposed to the herbicide trifluralin. J. Fish Diseases, 2:35-42.

Dickhaus, S., G. Reznik, U. Green, and M. Ketkar (1977) The carcinogenic effect of betaoxidized dipropylnitrosamine in mice. Z. Krebsforsch; 90: 253-258.

Druckery, H., R. Preussman, S. Ivankovic, and D. Schmal, (1967) Organotropic Carcinogenic Effects of 65 Different N-nitroso compounds in BD Rats. Z. Krebsforch. (EPA translation from German), 69(2):103-210.

Elanco, (1977) A study of the effects of trifluralin on pregnant rats and their progeny, R.-1265., by Worth, H. M., E.L. Emmerson, and D.M. Morton for Toxicological Division, Lilly Research Laboratories [proprietary].

Elanco, (1980) The chronic toxicity of compound 36352 (trifluralin) given as a component of the diet to the B6C3F1 mouse for 24 months; and the chronic toxicity of compound 36352 (trifluralin) given as a component of the diet to Fischer 344 rats for two years. Toxicological Division, Lilly Research Laboratories, [proprietary].

Griffiths, A., (1978) Personal telephone conversation to T. Miller and letter to D. Kuroda, OGC, EPA., Univ. of Vancouver, British Columbia, Canada, September, 1978.

Kuroki, T., C. Devon, and R. Montesano, (1977) Microsome - mediated mutagenesis in V79 Chinese hamster cells by various nitrosamines. Canc. Res. 37:1044-1050.

Macek, K.J., M.A. Lindberg, S. Sauter, K.S. Buxton and P.A. Costa. (1976) Toxicity of four pesticides to water fleas and fathead minnows. U.S. EPA, Ecol. Res. Series, No. EPA-600/3-76-099, 68 pp.

Macek, K.J., C. Hutchinson and O.B. Cope. (1969) The effects of temperature on bluegills and rainbow trout to selected pesticides. Bull. Environm. contam. Toxicol. 4(3):174-183.

Matsuoka, A., M. Hayashi, and M. Ishidate, Jr., (1979) Chromosomal aberration tests on 29 chemicals combined with S9 mix in vitro . Mut. Research. 66:277-290.

McCann, J., E. Choi., E. Yamasaki, B.N. Ames (1975) Detection of carcinogenic mutagens in the Salmonella microsome test: Assay of 300 chemicals. Proc. Nat. Acad. of Sci., 72(12):5139.

Murnik, M.R., (1979) Letter of April 27, 1978, to T. Miller, Attached data tabulations.

Nakajima, T., A. Tanaka, K. Tojyo (1974) The effect of metabolic activation without liver preparations on the mutagenicity of several N-nitrosamines on a streptomycin dependent strain of Escherichia coli. Mut. Res. 26:361-366.

National Cancer Institute (NCI), (1978) Bioassay of trifluralin for possible carcinogenicity. NCI Carcinogenesis Technical Report Series No. 34.

Olajos, E.J., and H.H. Cornish (1976) Mutagenicity of dialky-nitrosamines, metabolites, and derivatives. Tox. Appli Pharm., 37:109-110.

Parrish, P.R., E.E. Dyar, J.H. Enos, and W.G. Wilson. (1978) U.S. EPA, Gulf Breeze, Fl. EPA-600/3-78-010, 53 pp.

Pour, P., F.W. Kruger, A. Cardesa, J. Althoff, and U. Mohr. (1973) Carcinogenic effects of Di-n-propylnitrosamine in Syrian Golden Hamsters. J. Nat. Canc. Inst., 51:1019-1027.

Reznick, G., U. Mohr, and F.W. Kruger. (1975) Carcinogenic effects of di-n-propylnitrosamine, beta-hydroxydpropyl-n-propylnitrosamine and methyl-n-propylnitrosamine on Sprague-Dawley rats. J. Nat. Canc. Inst., 54:937-941.

Sanborn, J.R. (1974) The fate of select pesticides in the aquatic environment. U.S. EPA, Ecol. Res. Series, No. EPA-660/3-74-025, 83 pp.

Simon, V.E., A.D. Mitchell, and T.A. Jorgenson (1977) Evaluation of selected pesticides as chemical mutagens - in vivo and in vitro studies. Stanford Res. Inst., for EPA, 600/1-77-028.

Wauchope, R.S. (1978) The pesticide content of surface water draining from agricultural fields. A review. J. Environm. Qual., 7(4): 459-472.

Worth, H.M., R.M. Small., P.N. Harris, and R.C. Anderson (1966) Chronic toxicity studies with trifluralin. Eli Lilly Tox. Lab. [proprietary].

Yahagi, T.,M. Magao, Y. Seino, T. Matsushima, T. Sugimura, and M. Okada (1977) Mutagenicities of N-nitrosamines on Salmonella. Mut. Res., 48:121-130

Yoder, J., M. Watson, and W.W. Benson (1973) Lymphocyte chromosome analysis of agricultural workers during extensive occupational exposure to workers. Mut. Res. 21:335-340.