



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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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. Tothunter
Assistant Administrator-Designate
for Pesticides and Toxic Substances (TS-732)

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.

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

<u>Toxicity</u>	<u>Author (Year)</u>	<u>Results</u>
Oncogenicity of Trifluralin	NCI (1978)	Trifluralin with 34-83 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 FMRI 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 ^{3/6/} , and E. coli ^{3/6/}
	Murnik (1978)	Negative for D. melanogaster ^{4/}
	Chen (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 ^{5/6/} 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 <u>S.</u> typhimurium ^{5/}
	Nakajima et al. (1974)	Positive in <u>E. coli</u> ^{5/}
	Brusick and Mayer (1973)	Positive in <u>S.</u> 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 recommenda- tion 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) Nacek (1969, 1976) and Parrish (1978)	Acute toxicity of triflur- alin to aquatic organisms
	Sanborn (1974) and Parrish (1978)	Aquatic organisms biocon- centrate trifluralin up to 150,000 X
	Couch (1979)	Trifluralin causes verte- bral 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.

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