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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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DATE ~~October 23, 1980~~

SUBJECT Section 18 (Emergency Exemption) For the Use of Hydrothal 191 (Endothal) in Irrigation Water. (Caswell # 421)

FROM G.Z. Ghali, Ph.D.
Toxicology Branch, HED (TS-769)

John J. ...

TO Donald R. Stubbs, PM #41
Registration Division (TS-767)

THRU: Christine Chaisson, Acting Branch Chief
Toxicology Branch, HED (TS-769)

C. J. Chaisson
WJ/b

Action Requested:

A request has been submitted by Arizona State Commission of Agriculture and Horticulture for Section 18 (emergency exemption) for the use of Hydrothal 191 (Endothal) at the rate of 3 ppm for 3-8 hours in moving irrigation water for the control of aquatic weeds in Maricopa County, Arizona until a full registration is granted.

Background Information:

Hydrothal 191 is an alkylamine salt of endothal. It is soluble in water. A substantial portion of the treated water for irrigation will be used for domestic purposes. Furthermore, it is possible that treated water might be used on any Arizona crop. These crops include cotton, small grains, alfalfa, vegetables (primarily lettuce, but including broccoli, carrots, cabbage, cauliflower and onion), cantaloups, watermelons, honeydews, sugarbeets, safflower, potatoes and citrus. These crops are not covered by tolerances of Hydrothal 191 in the CFR.

Recommendations:

Section 18 as requested by Arizona State Commission of Agriculture and Horticulture is not toxicologically supported for the following reasons:

- 1) Toxicology data gap exists (oncogenic study, more teratogenic and mutagenic studies.)

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a) Oncogenicity testing:

Only a 53 week interim report of an 18 month oncogenicity study was submitted. A final report of the 18 month mouse oncogenicity study is required to assess this aspect of human safety.

b) Teratogenicity testing:

Teratogenic evaluation in rats (FDRL; November 11, 1976) showed incomplete closure of the skull at all dosage levels which was significantly greater than the controls. It was concluded that endothal was possibly a teratogenic in this study, and this potential teratogenicity needed to be explored. The registrant was requested to provide a teratology study in another species.

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c) Mutagenicity testing:

The mutagenicity studies submitted were acceptable but further mutagenic testing were required, including Ames test with and without metabolic activation.

- 2) An Active ingredient of Hydrothal 191 is N,N-dimethylalkylamine. Open literature indicates that tertiary and quaternary amines, and in particular dimethylamino derivatives, do react with nitrites under digestive processes and other conditions, releasing dimethylnitrosamine (Fiddler, 1972; Greenblatt et al., 1972; Lijinsky et al., 1972; Tinbergen et. al. 1977).
- 3) The tolerances requested are based on NOEL's from IBT studies. These IBT studies need to be validated before use in tolerance settings (SPRD Study Auditing Group).
- 4) As stated by the RCB, the metabolism of andothal in animals is not adequately defined, and therefore, toxicological considerations of potential hazards from unknow residues in meat and milk need to be elucidated.
- 5) Similar actions:
 - a) An EUP was found to be not toxicologically supported for reasons stated in 1-b (W. Dykstra, July 27, 1979).
 - b) A request for permanent tolerances was not recommended for reasons stated in 1- a,b,c, 3 and 4. (W. Dykstra, October 25, 1978).

Conclusion:

Toxicology Branch does not recommend granting this Section 18 request.

References Cited:

- Fiddler, W., (1972) Formation of N-nitrosodimethylamine from naturally occurring quaternary ammonium compounds and tertiary amines. Nature (Lond.), 236:307.
- Greenblatt, M., Kommineni, V., Conrad, E., Wallcave, L.; and Lijinsky, W. (1972) In Vivo conversion of phenmetrazine into its N-nitroso derivative. Nature (New Biol.), 236:25-26.
- Lijinsky, W. Keefer, L.; Conrad, E., and Vande Bogart (1972) Nitrosation of tertiary amines and some biologic implications. J. Natl. Cancer Inst. 49: 1239-49.
- Tinbergen, B.J. and Krol, F. (1977) Nitrite in meat products. Center for Agriculture Publ. and Documentation, Wageningen, Zeist, The Netherland.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: July 27, 1979

SUBJECT: EPA Reg #4581-EUP-32, HydoutTM Aquatic Algicide and Herbicide.
CASWELL #421 (Endothal)

FROM: William Dykstra, Ph.D
Toxicology Branch (TS-769)

WAD 7/27/79

TO: Willa Garner
Product Manager #23

Action Type: EUP (New Routine)

Recommendations:

1. In previously reviewed petitions (1F1105, 2H5016), the report of the teratologic evaluation of Endothal in rats (FDRL; Nov. 11, 1976) showed incomplete closures of the skull in all dose groups which were significantly greater than controls. It was concluded that endothal is possibly teratogenic in this study and this potential teratogenicity needs to be further explored. The registrant is requested to address the teratology study by FDRL and also provide a teratology study in a 2nd species.

2. The EUP is not toxicologically supported for reasons stated in recommendation #1.

Review

1. No additional toxicity data were submitted with this EUP request.

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