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OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Comments on DuPont Response to Toxicology Requirements in Diuron Registration Standard

TO: Robert Taylor/V. Walters
Product Manager #25
Registration Division (TS-767C)

FROM: W. Thomas Edwards, Pharmacologist W. Thomas Edwards 11-27-84
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THRU: Robert P. Zendzian, Acting Section Head 11/28/84
Section III, Toxicology Branch/HED (TS-769C)
and
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Toxicology Branch/HED (TS-769C)

Inhalation LC^{50}

The study by Lomonova et al. (1969) is inadequate to fill the inhalation study requirement principally because a no-observed-effect-level was not found. Also there were no particle size determinations reported.

Skin Sensitization

The study reported in Haskell Laboratory report no. 108-70 is insufficient because no positive control was used, too few animals were used and reporting was unclear.

The brief note (without data) in the report by Lomonova et al. (1969) on the effects of applications of diuron to rabbit skin is not adequate for regulatory purposes.

Mutagenicity

We agree that the suggested mutagenicity studies are needed. They may be enough. This can be determined after results have been received.

Oncogenicity

The two-year rat feeding study (Hodge, July 8, 1963) is inadequate as an oncogenicity study because:

1. There was an inadequate number of survivors as is shown below for survival at 80 weeks.

Dietary level	Males	Females
Control	9	26
25 ppm	13	19
125	14	23
250	20	20
2500	4	23

2. Histopathology was not determined for more than 10 animals per group (8 for male controls and 8 for highest male dosage group). Four animals killed before termination were included in highest dosage male group when results were reported. These numbers are definitely insufficient.

The Innes screening study in mice was planned and conducted as a screening study only. Among the deficiencies of this study are:

1. Only one dosage level.

2. Too few animals per group:

B6CF1 strain males:	17
B6CF1 strain females:	18
B6AKF1 strain males:	17
B6AKF1 strain females:	16

An oncogenicity study in each of two species is required.

Teratogenicity

The mouse study reported in the Report of the Secretary's Commission on Pesticides and their relationship to Environmental Health (USDA, 1969, Exhibit 5) is a screening study. Although no terata were found, only six litters and one dosage level were included. This was not an adequate study.

The rat teratology study (Khera et al., 1979) does not indicate that diuron is a teratogen. However, it is insufficient because it did not find a no-observed-effect-level for fetotoxicity. Anomalies were wavy ribs, extra ribs and delayed ossification of calvaria.

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A rat study which determines the fetotoxicity NOEL in rat as well as a teratology study in another species is needed.

Animal Metabolism

Several useful metabolism studies have been supplied, but in none of them has all (or most) of the ingested diuron been accounted for as could have been done using radioisotope tagged-diuron. The need for such a study can be better evaluated after other data gaps have been filled. Until that time any further metabolism study can be deferred.