

June 8, 2004

MEMORANDUM

SUBJECT: Benfluralin: HED Response to Comments Submitted by the Registrant (Dow Agrosiences) on April 26, 2004.

Case No	2030
PC Code	084301
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Docket ID	OPP-2003-0381

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Dow's comments are summarized first, followed by OPP's response.

Repeat Inhalation Study

Dow Comment: pages 2, 7, 10

Dow does not believe that benfluralin is toxic by the inhalation route as defined by 40 CFR 158.340 (foot note 6) and requests a data waiver from the repeat inhalation study. The reason for requiring the repeat inhalation study is not stated clearly by the Agency and Dow further implies that estimates of systemic toxicity can be made from oral studies by standard methods. The acute inhalation of LC 50 <1.3 to 2.3 mg/L further shows that benfluralin is not likely to be

toxic by the inhalation route.

OPP Response:

The data waiver request is denied. The Agency has no record of a repeat exposure inhalation study with benfluralin. Potential effects from a repeat exposure study are necessary to determine appropriate protection for residential handlers as well as occupational handlers. The Agency requires assurance that effects analogous to the progressively severe skin reactions seen in the 21-day dermal toxicity study in the rabbit (with no NOAEL after repeat exposures) does not occur in the respiratory system after repeat exposure.

Estimates of the severity of potential lung irritation are problematic using estimates from oral studies.

Acute inhalation is not adequate to measure potential effects that may be determined after repeat inhalation exposure. Neither is acute oral exposure adequate to measure potential effects that may be determined in repeat oral exposure studies.

Dow Comment: Pages 11 and 12

Dow objects to the requirement for the 28-day inhalation study recommended by the Hazard Identification Assessment Review Committee (HIARC). They state that the guidelines requiring particle sizes of 1-3µm MMAD would result in an unrealistic risk assessment. In addition, they argue that the particle size from the class of spray nozzles used (approximately 135µm with 0.17% <1µm) are too large to affect the lung.

OPP Response:

This is not the forum for comment on guidelines. Inhalation risk assessment is a complex issue requiring tests for hazard assessment as well as risk assessment if necessary. The relationship between nozzle spray particle size and the particle size inhaled by handlers or bystanders needs evaluation. If Dow wishes to submit the Spray Drift Task Force protocol and data on AgDRIFT® and the DropKick models, OPP will evaluate them. At any rate, prior to consideration of a data waiver, Dow needs to submit the data supporting the 135µm MMAD with less than 0.17% #1µm. The requested data waiver for a 28-day inhalation study is denied. However, OPP agrees that benfluralin has a low acute toxicity in LC50 studies (classified as Group III toxicity).

Dermal Absorption:

Dow Comment: page 9

EPA should have used the dermal absorption study in rats instead of a dermal absorption of 3% from a dermal absorption study on an analogous pesticide. The 8 hour dermal absorption in the rat study was 7% from the 0.2% spray and 2.1% from the 2% spray.

OPP Response:

A search of the OPP toxicity data base yields no such study. OPP will review the study if submitted. In addition, the Agency may require friability studies on the granular products depending on the results from the 28-day inhalation study. Guidance for conducting such studies can be obtained from the American Society of Testing Materials (ASTM) Test Method E-231603; Attrition of Granular Particles.

Dermal Sensitization:

Dow Comment: pages 2, 7 and 14

Dow objects to the labeling of formulations of #60% benfluralin as dermal sensitizers because dermal sensitization studies on these formulations do not support labeling. The dermal effects in the 21-day dermal rabbit study cannot be used as an endpoint for dermal exposure and should be separated from the sensitization effects seen in the technical grade of benfluralin.

OPP Response:

The concern associated with 21-day dermal toxicity study is based on the progressively severe dermal effects, which showed no NOAEL. The object of a toxicity study is to provide information to determine adequate protection for individuals from potential adverse effects. The HIARC could not determine a NOAEL for this 21-day dermal toxicity study.

Labeling formulations as potential skin sensitizers is prudent. Possible interference with the skin sensitization tests by ingredients in the formulations, may result in false negative tests on the #60% benfluralin formulations. Benfluralin in formulations may be a dermal sensitizer.

The dermal sensitization test in Guinea pigs is dependent on the administration of a slightly irritating dose. Ingredients in the formulation may interfere with such a test causing false negative results. Benfluralin is a relatively strong dermal sensitizer and formulations of benfluralin may also be sensitizers. In addition, the cause of the reaction(s) resulting in the dermal effects in the 21-day dermal study in rabbits are unclear and do not exclude an immunological mediated response. The 21-day dermal study is not used as an endpoint for effects, instead it is used to help support the need for labeling and the need for a 28-day inhalation study.

Carcinogenicity Study in Mice:

Dow Comment: page 12

Dow objects to the requirement of a carcinogenicity study in male mice. They state that the LOAEL in males of 185 mg/kg/day based on death by mouse urologic syndrome (all severities) complies with guideline 870.4300. A study at higher dose levels is not warranted and will not show more evidence of cancer in the male mouse.

OPP response:

The Cancer Assessment Review Committee (CARC) does not agree that the dose administered to male mice was sufficiently high and suggested that a study approaching the limit dose of 1000 mg/kg/day would be more appropriate. Another carcinogenicity study in male mice is required. The following is quoted from the CARC report of December 27, 2001 (TXR# 0050378).

The CARC concluded that the highest dose in males may have approached an adequate dose level to assess the carcinogenic potential of benfluralin based on statistically significant increase in absolute and relative liver weight as well as relative brain weight. Urologic syndrome was stated to be a common cause of death in male B6C3F₁ mice. Therefore, the Committee determined that additional data regarding the increased incidence of urologic syndrome and its role in the death of male mice noted in the chronic/carcinogenicity study as well as the results of a 90-day subchronic toxicity study in mice would be required to confirm the adequacy of dosing in male mice.

On Dec 6, 2001, an Ad Hoc Committee reviewed the requested data submitted by the registrant and concluded that the findings of mouse urologic syndrome were not indicative of a compound related effect that showed that the dosing was high enough. It was also determined that 1) the slight decreases in body weight and body weight gain, the small increases in liver weight (both relative and absolute) and minimal increases in liver multifocal hyperplasia were insufficient to determine that dosing was adequate; 2) the results of the 90 day subchronic feeding study indicated that dosing to the males could approach the limit dose of 1000 mg/kg/day rather than the 185 mg/kg used in the cancer study and 3) the metabolism study (in rats) noted no differences in the metabolic profiles between the single low dose of 100 mg/kg/day and the high dose

of 500 mg/kg/day. Saturation was not seen at the high dose. The incidence of liver tumors in females at a slightly higher dose also was a consideration in Committee's conclusion that the dosing in the males was not high enough.

The CARC determined that the liver tumors in female mice were treatment related.

Other:

Dow Comment: pages 13, 19

Dow stated that there was an inconsistency in the NOAEL for the 90-day feeding study and in the 21/28-day dermal study. Dow corrected the LOAEL indicated for the 90-day feeding study in Docket ID OPP-2003-0381-0012 and supplied a reference, Environmental Health Perspectives.105 (#9): (1997).

OPP Response:

The error in the NOAEL for the 90-day feeding study in a draft earlier than OPP-2003-0381-0004 was corrected. There is no inconsistency in the NOAEL in 21-day dermal study. Docket ID OPP-2003-0381-0012 is not used and is of historical interest only. The error in the 90-day feeding study LOAEL was corrected and that endpoint is not used in the only applicable document, "Benfluralin: Human Health Risk Assessment (Revised)" of 10/30/03 (Docket ID OPP-2003-0381-00(0)4 of April 25, 2003). The endpoints for risk assessment are based on the 04/03/2003 document, "Benfluralin: Third Report of the Hazard Identification Assessment Review Committee" (Docket ID, OPP-2003-0381-0013).

Plant-back interval:

Dow Comment, Page 13

Dow objects ("no scientific reasoning") to the Agency requirement for a 12-month plant-back interval on the basis that this interval is inconsistent with the data.

OPP Response:

Currently, the product label specifies a 10-month plant-back interval for wheat, barley, oats, rye, other grasses, onions, corn, milo, spinach, red beets, sugar beets, or other root crops. The label implies that this rotational crop restriction applies only to arid, irrigated areas of the western US, and the restriction is in place to prevent crop toxicity. The confined rotational crop study showed that total radioactive residues (TRR) accumulated at levels above 0.01 ppm in/on the rotational crops of lettuce, mustard, radishes, and wheat planted 28, 91, or 364 days

following application at 1x the maximum rate. The major metabolite found was trifluoroacetic acid and accumulation of TRR was highest in samples from the 91-day group. Considering that current guidance stipulates that TRR should be below 0.01 ppm and that all benfluralin degradates are considered to be not less toxic than parent, HED recommended a plant-back interval of 12 months. HED further recommended that Dow conduct limited rotational crop studies and possibly examine literature sources (or conduct studies) to better define the toxicity of trifluoroacetic acid.