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OFFICE OF  
PESTICIDES AND TOXIC SUBSTANCES

Memorandum:

SUBJECT: 352-366. Methomyl Registration Standard. Evaluation of protocols for cattle feeding study and identification of goat liver metabolite. (RCB#2565, no Acc or MRID#) DuPont response (letter dated 7/1/87) to 3(c)2(B) letter of 1/22/82.

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THRU: Philip V. Errico, Section Head  
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TO: Dennis Edwards, PM-12  
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and

Toxicology Branch  
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In response to EPA 3(c)2(B) letter dated 1/22/82 of data gaps for the reregistration of methomyl (and meeting between EPA and DuPont representatives, See memo of 6/18/87, S. Malak), DuPont has submitted a cover letter (7/1/87, Fredrick O. O'Neal, Reg. Toxicologist) and protocols for 1) a cattle feeding study, and 2) identification of goat liver metabolite, for evaluation/comments by RCB. Registrant also requests the Agency to review its position on the requirement for the goat liver metabolite identification.

Conclusions/Recommendations:

1. RCB agrees that the protocol for the cattle feeding study should supply adequate samples for analytical evaluation. However, the registrant would be advised to properly address the analytical

phase of this experiment, i.e., analytical procedures, validation methods, data handling, etc., before preceding with the animal treatments.

2a. The Agency still requires the identification of the cyclohexane-soluble unknown metabolite(s) reported in AMR-22-80. Analysis of any additional metabolite(s) of toxicological concern must be included in the cow feeding study.

2b. According to the submitted reference, this in vitro procedure may provide useful information in regard to the fate and identification of the  $^{14}\text{C}$ -label in the goat liver, but may not replace a goat metabolism study using  $^{14}\text{C}$ -methomyl. RCB recommends the petitioner run the goat metabolism study using  $^{14}\text{C}$ -methomyl to identify the cyclohexane-soluble unknown metabolite(s). Analysis for acetamide should also be included.

Note to PM: DuPont Report No. AMR-22-80 for a  $^{14}\text{C}$ -methomyl goat metabolism study which was submitted with PP#9F2231 was conducted in part by the now defunct Cannon Laboratories, Inc., Reading, PA. According to 40 CFR 160.190 and 160.195, the registrant must have the original raw data to support a product registration/use, and under 40 CFR 160.195(g), the raw data for the goat metabolism study should be in its possession. The registrant should be asked to respond in writing whether the raw data for the study reported under No. AMR-22-80 is in their possession. If this raw data is not in the possession of the registrant, another goat metabolism study using  $^{14}\text{C}$ -methomyl must be performed. All major metabolites must be identified.

#### Cattle Feeding Study:

##### DuPont's Proposal:

DuPont has submitted a protocol for a cattle feeding study for RCB's evaluation/comments.

##### RCB's Comments:

In accordance with the guidelines in Subdivision 0 the submitted protocol should provide adequate samples for analytical evaluation.

In regard to analytical procedures, validation methods, and data handling, the registrant has not submitted any information. As agreed by the registrant, samples must be analyzed for the metabolites, acetonitrile, and acetamide, in milk and tissues. The registrant would be advised to properly address the analytical phase of this experiment before preceding with the animal treatments.

Identification of Goat Liver Metabolite:DuPont's Proposal:

1. The metabolism of methomyl is adequately understood and meets EPA requirements. DuPont has submitted goat metabolism study (Report No. AMR-22-80, Acc#099952, PP#9F2231). In addition, DuPont has submitted literature references for metabolism of thiodicarb to show that the same intermediate and end products exist for both methomyl and thiodicarb. They do not expect any different metabolites to be produced by the metabolism of methomyl per se. DuPont further reiterated its past contention that in the forementioned goat metabolic study the unknown cyclohexane-soluble metabolite(s) was radiolabeled fatty acids that resulted from  $^{14}\text{C}$ -acetate formed in vivo. DuPont stated that previous data and arguments supplied to the Agency, and the submitted thiodicarb references in regard to metabolism support this theory.

2. If the identification of this unknown(s) is still required by the Agency, then DuPont has proposed to run an in vitro study using goat liver cells (rationale and protocol according to the published report, "Xenobiotic metabolism in suspensions and primary cultures of isolated hepatocytes prepared from the caudate process of bovine liver", American Journal of Veterinary Research, 47,(9), 2043-2052, 1986) and determine the fate of the  $^{14}\text{C}$  label, i.e., formation of  $^{14}\text{C}$ -acetate and incorporation into the liver lipids and other macromolecules.

RCB's Comments:

The Agency still requires the identification of the cyclohexane-soluble unknown(s). According to the submitted reference, this procedure may provide an adequate method to identify the fate of the  $^{14}\text{C}$ -label in the liver. RCB understands the registrant's reasons for their approach, but RCB's reiterates its position that an in vitro study may not exempt them from an in vivo experiment. RCB suggests that any product(s) isolated by this approach should be compared to raw data collected in the goat metabolism (Report No. AMR-22-80) for confirmation. We recommend the petitioner run the goat metabolism study using  $^{14}\text{C}$ -methomyl to identify the cyclohexane-soluble unknown metabolite(s). Analysis for acetamide should also be included.

Note to PM: This study (Report No. AMR-22-80) was run in part by the now defunct Cannon Laboratories, Inc., Reading, PA. According to 40 CFR 160.190 and 160.195, the registrant should have the original data to support a product registration/use, and under 40 CFR 160.195(g) the raw data for the goat metabolism study should be in its possession. The registrant should be asked to respond in writing whether the raw data for the study reported under No. AMR-22-80 is in their possession. If the raw data is

not in their possession, another goat metabolism study using  $^{14}\text{C}$ -methomyl must be performed. All metabolites must be identified, and analysis for acetamide should also be included.

cc: R.F.; S.F.; Circu; PMSD/ISB; PM-12; Methomyl Reg. Std.;  
J. Stokes  
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