



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAY 14 1990

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Methomyl: Registrant's 90-Day Response to the
Methomyl Registration Standard Case (Number 0028)
Dated April 1989.

FROM: Jess Rowland, Toxicologist *Jess Rowland 5/2/90*
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TO: Joanne Edwards
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THRU: K. Clark Swentzel, Section Head *K. Clark Swentzel 5/2/90*
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and
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Health Effects Division (H7509C)
and
William Burnam, Deputy Division Director
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EPA ID.No.: 352-361 Record No.: 251346 Caswell No.: 549C
HED Project No.: 9-2103 Registrant: E.I. Du Pont de Nemours & Co.

ACTION REQUESTED: Respond to comments from the registrant
regarding the following data requirements stipulated in the
Methomyl Registration Standard:

1. 21-Day Dermal Toxicity (82-2)
2. General Metabolism-Rat & Monkeys (85-1)
3. Acute Toxicology for Manufacturing-Use Products
(81-1 thru 81-6).

CONCLUSION:

1. Waiver is granted for the 21-day dermal toxicity study on
abraded skin.
2. The feasibility of granting a waiver for the low-dose rat
metabolism studies is deferred until review and evaluation of
the high-dose rat metabolism study.
3. The requirement for a metabolism study in monkey should stand
as indicated in the Registration Standard.
4. The registrant should be informed that acute toxicity data are
required for all manufacturing-use products.

EVALUATION OF REGISTRANT'S COMMENTS:I. Repeated Dermal Dose Toxicity: 21 Day Study (82-2).Background:

A subchronic 21-day dermal toxicity study on both the intact and abraded skin was requested. An abraded skin study was requested since field workers often work with exposed and "abraded" skin and this study would more closely approximate farm worker exposure conditions.

Registrant's Comments:

The registrant submitted a 21-day study on the intact skin (MRID No. 412515-01) which was reviewed and classified as Core Minimum (Memorandum, L.Taylor, HED to J.Edwards, RD, November 2, 1989).

The registrant is requesting a waiver for the abraded skin study based on the following considerations:

- 1) The repeated-dose study on intact skin is a conservative test that overestimates systemic exposure of workers.
- 2) Farm workers are not likely to work with significant areas of damaged skin exposed and generally protect themselves from contact with scratchy or irritant foliage.
- 3) Abrasion of over 10% of body surface area and maintaining the skin in that state throughout the 21-day test would provide data which cannot be meaningfully extrapolated to the situation with fields workers and results in needless suffering among the test animals.

Response:

Toxicology Branch (HFAS) concurs with the registrant's rationale for not conducting a study on abraded skin and is granting a waiver for the 21-day dermal toxicity study on abraded skin.

II. General Metabolism (85-1)a. Rat StudyBackground:

Rat and monkey metabolism studies were required to fill data gaps as well as to determine the potential tissue levels of the metabolite, acetamide, a possible human oncogen.

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Registrant's Comments:

The registrant proposes to conduct a guideline rat metabolism study at a single oral high dose of 5 mg/kg with [1-¹⁴C]methomyl; the dose level was selected based on a NOEL of 100 ppm (approximately 5 mg/kg for rat) from chronic studies.

Upon completion of the above study, the registrant plans to request a waiver for the low dose metabolism studies (a single low-dose study, an intravenous dose study, multiple low-dose study) and provided the following rationale for such an approach:

- 1) If the low-dose was selected at 10 percent of the high-dose (0.5 mg/kg), cholinesterase would be inhibited, and technical limitations would preclude the discovery of any useful information.
- 2) A dose rate of 0.5 mg/kg would result in dosing 0.1 mg of ¹⁴C-methomyl to a 200 gram rat. Using ¹⁴C-methomyl with a specific activity of 10 uCi/mg would introduce 1.0 uCi (2.2 x 10⁶ dpm) to each animal. This may pose technical (analytical) difficulties in monitoring radioactivity and analyzing metabolites. Similar analytical difficulties would be anticipated in the low dose i.v and multiple low-dose studies.
- 3) The Agency has granted low dose treatment waivers for rat metabolism studies involving other products (Du Pont insecticides) that exhibit high acute toxicity.

Response:

Although the rationale and justification submitted by the registrant in support of a possible data waiver for the low-dose rat metabolism studies can be argued to various extents, from a metabolic point of view, the Agency at this time defers any decision until review and evaluation of the single oral high-dose study.

b. Monkey StudyBackground:

A metabolism study in monkey is required to assess tissue levels of acetamide, a possible human oncogen, in a species more closely related to humans.

Registrant's Comments:

The registrant discussed the evidence for the carcinogenicity of acetamide in humans and animals as well as the sources of acetamide in the diet and concluded that 1) there no reports of carcinogenicity of acetamide in humans, 2) data are equivocal in animals (some evidence of oncogenicity at high doses), and 3) human exposure to acetamide is one to several orders of magnitude greater from natural sources than could possibly be produced from metabolism of methomyl. Based on the above observations the registrant further concludes that it is unreasonable to require a monkey metabolism study.

Response:

The requirement for a metabolism study in this species should stand as indicated in the Registration Standard. The purpose of this study is to investigate the tissue levels of acetamide relative to dietary levels of methomyl.

III. Acute Toxicity Testing for Manufacturing -Use Products(MP)a. Acute Oral, Dermal, and Inhalation Studies(81-1,81-2,81-3)Background:

Data are adequate to support registration of MP products containing 90% Technical Grade Active Ingredient (TGAI); however, additional data (acute oral, dermal, and inhalation) are required for all other MP formulations.

Registrant's Comments

The registrant claims that Methomyl Technical (EPA Reg.No. 352-361) and Methomyl Composition (EPA Reg.No. 352-366) are the only two manufacturing use products being supported at this time. Since data requirements are satisfied for products containing 90% TGAI like Methomyl Composition they do not plan to conduct further acute studies with Methomyl Technical and would like the Agency to reexamine the existing data and withdraw the requirements for these studies.

Response:

Although the registrant claims to support only 2 manufacturing-use products (352-361 and 352-366) in this discussion (Attachment F; Exhibit F.3), a total of 8 Du Pont methomyl products that they intend to support through reregistration was listed in Attachment C (appended). The registrant must clarify this discrepancy. In addition, the registrant should be informed that acute toxicity data are required for ALL MP products that contain Methomyl.

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b. Primary Eye Irritation, Primary Dermal Irritation and Dermal Sensitization Studies (81-4, 81-5, 81-6)

Background:

These studies are required for manufacturing-use products.

Registrants Comments:

The registrant provided brief summaries on "old" studies that "were not conducted according to current guidelines" and claims that these studies (listed below) have already been submitted to the Agency.

<u>Study Title</u>	<u>Study Identification</u>
Eye Irritation, HLR 66-64	MRID 0009224; Accn.No.229706
Untitled, HLR 77-67	MRID 0009225; Accn.No.229708
Primary Skin Irritation and Sensitization Tests on Guinea Pigs, HLR 34-74	MRID 00053405; Accn.No.228667
Skin Primary Irritation and Sensitization Test, HLR 157-67	Accn.No. 106664
Acute Skin Absorption Tests, HLR 155-65	Accn.No. 107774

The registrant concluded that the two eye irritation studies "are adequate to characterize the primary eye irritation potential of technical grade methomyl" and "that the weight of evidence from existing studies on formulations is sufficient to assess the dermal irritation and sensitization potential of technical methomyl and " that no new or useful information would be gained from new studies". Accordingly, they request that the Agency evaluate the studies cited above and withdraw the requirements for further studies.

Response:

The studies cited above have not been previously reviewed or evaluated by the Agency. The registrant can resubmit these studies for Agency review. However, the registrant should be informed that primary eye irritation, primary dermal irritation, and dermal sensitization studies are required for ALL manufacturing-use products that contain methomyl.

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August 20, 1989

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Subject: Methomyl Registration Standard, Case No. 0028
Dated April 19, 1989, Received May 26, 1989
90-Day Response

Dear Ms. Edwards:

E. I. Du Pont de Nemours & Co. (Inc.) is submitting herein our 90-day response to the Methomyl Registration Standard Case (Number 0028) dated April, 1989. This Standard was received by us on May 26, 1989.

This response consists of an administrative package, which accompanies this letter as a series of attachments, and one new submitted study plus its transmittal document. The administrative package is divided into six attachments, A-F. Each of these contains as follows:

Attachment A - Current list of Du Pont methomyl products which are affected by this Registration Standard.

Attachment B - Current list of Du Pont methomyl SLN registrations affected by this Registration Standard. Please note that there are many discrepancies between Du Pont's list of current SLN's and the Agency's list which accompanied the Guidance Document.

Attachment C - Confidential Statements of Formula and Certification Statements for the Du Pont methomyl products we intend to support through reregistration.

Attachment D - Evidence of Compliance with Data Compensation Requirements for manufacturing use products.

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ATTACHMENT C**CONFIDENTIAL STATEMENTS OF FORMULA AND
CERTIFICATION STATEMENTS FOR DU PONT METHOMYL PRODUCTS**

- EXHIBIT C.1 Du Pont Lannate® Insecticide (EPA Reg. No. 352-342)
- EXHIBIT C.2 Du Pont Methomyl Composition for Pesticide Manufacturing Only
(EPA Reg. No. 352-361)
- EXHIBIT C.3 Du Pont Lannate® WP Insecticide (EPA Reg. No. 352-362)
- EXHIBIT C.4 Du Pont Methomyl Technical (EPA Reg. No. 352-366) Basic and
Alternate Formulations
- EXHIBIT C.5 Du Pont Lannate® L Insecticide (EPA Reg. No. 352-370)
- EXHIBIT C.6 Du Pont Lannate® LV Insecticide (EPA Reg. No. 352-384)
- EXHIBIT C.7 Nudrin® 90 Methomyl Insecticide (EPA Reg. No. 352-476)
- EXHIBIT C.8 Nudrin® 1.8 Insecticide Solution (EPA Reg. No. 352-517)