



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: I.D. Nos.: 062719-EUU, 062719-EUG, 062719-EUP-EL. DowElanco/DE-473
Technical and NAF-46 Formulation. Evaluation of Toxicity Data Submitted
and Identification of Outstanding Toxicology Data Requirements

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I. CONCLUSIONS

The existing database supports Registration of the DE-473 Technical (062719-EUU), the NAF-46 0.1030% formulation (062719-EUG), and the EUP on the NAF-46 0.1030% formulation (062719-EUP-EL) for this use pattern. The waiver requests for the acutes on the 0.1030% formulation are also supported.



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II. ACTION REQUESTED

TB-1 received for evaluation the acute and mutagenicity studies on the technical product required to fulfill data requirements for registration of DE-473 Technical and NAF-46 0.1% Formulation for non-food use. In addition, waivers for the acute studies on the 0.1% Formulation were also requested. These data were submitted by Dow Chemical Company.

III. BACKGROUND and PRODUCT INFORMATION

DE-473 or hexaflumuron is a benzoyl phenylurea, a chitin-synthetase inhibiting insecticide. It disrupts the molting process in insects, which results in death at immature stages. It is reportedly highly active against a wide range of pests, primarily in Lepidopter, Coleoptera, Homoptera and Diptera.

DE-473 is a solid at room temperature, with a very low solubility in water of 2.7×10^{-5} g/l. The NAF-46 formulation contains 0.1% a.i. with 99.9% inert ingredients.

The EUPs will allow the Submitter to continue ongoing field research under different conditions. A total of approximately 75 grams of active ingredient will be applied in bait stations throughout 15 states, utilizing a total area of less than 10 acres. Due to the application method in a bait station enclosure, there is expected to be little chance of human and/or environmental exposure to the active ingredient..

IV. DATA REQUIREMENTS (CFR 158.135) for Non-Food Use

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The requirements (CFR 158.135) for Non-Food Use for this chemical, based on the expected exposure scenario are listed on the next page in Table 1.

Table 1.

Test		Technical		0.1% Formulations	
		Required	Satisfied	Required	Satisfied
81-1	Acute Oral Toxicity	Y	Y	Y	Y§
81-2	Acute Dermal Toxicity	Y	Y	Y	Y§
81-3	Acute Inhalation Toxicity	Y	Y	Y	Y§
81-4	Primary Eye Irritation	Y	Y	Y	Y§
81-5	Primary Dermal Irritation	Y	Y	Y	Y§
81-6	Dermal Sensitization	Y	Y	Y	Y§
81-7	Acute Delayed Neurotox. (Hen)	N	-	N	-
82-1	Oral Subchronic (Rodent)	N ¹	-	N	-
82-1	Oral Subchronic (Non-Rodent)	N ¹	-	N	-
82-2	21-Day Dermal	N ¹	-	N	-
82-3	90-Day Dermal	N ¹	-	N	-
82-4	90-Day Inhalation	N	-	N	-
82-5	90-Day Neurotoxicity (hen)	N	-	N	-
82-6	90-Day Neurotoxicity (mammal)	N	-	N	-
83-1	Chronic Toxicity (Rodent)	N	-	N	-
83-1	Chronic Toxicity (Non-rodent)	N	-	N	-
83-2	Oncogenicity (Rat)	N	-	N	-
83-2	Oncogenicity (Mouse)	N	-	N	-
83-3	Developmental Toxicity (one species)	N ¹	-	N	-
83-3	Developmental Toxicity (two species—rodent & non-rodent)	N	-	N	-
83-4	Reproduction	N	-	N	-
83-5	Chronic/Oncogenicity	N	-	N	-
84-2	Mutagenicity—Gene Mutation	Y	Y	N	-
84-2	Mutagenicity—Structural Chromosomal Aberrations	Y	Y	N	-
84-4	Mutagenicity—Other Genotoxic Effects	N	N	N	-
85-1	General Metabolism	N	-	N	-
85-2	Dermal Penetration	N	-	N	-
86-1	Domestic Animal Safety	N	-	N	-
Special Studies for Ocular Effects					
	Acute Oral (Rat)	N	-	N	-
	Subchronic Oral (Rat)	N	-	N	-
	Six-month Oral (Dog)	N	-	N	-

Legend Y = yes N = no

§ Satisfied by the data on the Technical.

¹ Not Required at this time for these actions because of very low human exposure.

V. TOXICITY PROFILE

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A. ACUTE TOXICITY

The Acute toxicity data on DE-473 Technical is summarized below in Table 2. Individual DERs are attached.

TABLE 2. SUMMARY OF ACUTE TOXICITY OF DE-473

TEST	RESULTS	CATEGORY
81-1 Acute Oral Toxicity—Rats Study No.: DR-0210-2650-004A Date: January 21, 1993 MRID No.:426485-14	LD50: >5000 mg/kg (Limit Test) Study is Acceptable Toxic Signs: Urine and fecal perineal staining.	IV
81-2 Acute Dermal Toxicity—Rabbit Study No.: DR-0210-2650-004D Date: January 21, 1993 MRID No.:426485-15	LD50: >2000 mg/kg (Limit Test) Study is Acceptable Toxic Signs: Local scaling and erythema	III
81-3 Acute Inhalation Toxicity—Rat Study No.: DR-0210-2650-005 Date: January 21, 1993 MRID No.:426485-16	LC50: ♂ & ♀: >7.0 mg/l Study is Acceptable Toxic Signs: None significant.	IV
81-4 Primary Eye Irritation—Rabbit Study No.: DR-0210-2650-004C Date: January 21, 1993 MRID No.:426485-17	Primary Irritation Index: 0.0 Study is Acceptable Toxic Signs: Slight redness and chemosis of conjunctivae, resolved within 24 hours.	IV
81-5 Primary Dermal Irritation—Rabbit Study No.: DR-0210-2650-004B Date: January 21, 1993 MRID No.:426485-18	PIS: 0.04 (slightly-irritating) Study is Acceptable Toxic Signs: Slight erythema at 72 hr. Resolved in 7 days.	IV
81-6 Dermal Sensitization—Guinea Pig Study No.: DR-0210-2650-004E Date: January 21, 1993 MRID No.:426485-19	Not a Sensitizer Study is Acceptable Toxic Signs: None except in positive controls	--

B. SUBCHRONIC TOXICITY

Because of the very limited human exposure expected from the requested use of DE-473, subchronic toxicity testing is not required. However, other requests with different exposure patterns would have to be addressed separately.

C. DEVELOPMENTAL TOXICITY

Because of the very limited human exposure expected from the requested use of DE-473, developmental toxicity testing is not required. However, other requests with different exposure patterns would have to be addressed separately.

D. MUTAGENICITY

Four mutagenicity studies are available. They are summarized on Table 3 below. (DERs attached) Data requirements for these FIFRA TOX. Guidelines are satisfied by these submissions; no further studies need be submitted at this time.

TABLE 3. MUTAGENICITY STUDIES CONDUCTED DE-473

STUDY/ LAB/ STUDY # / DATE	MRID	RESULTS	CORE GRADE
Ames Test Hazleton Labs Study # 15138-0-420R 10/12/92	426485-23	Negative for reverse mutation in Salmonella TA strains exposed with/without activation up to 5000 μ g/plate	Acceptable
Gene Mutation Mammalian Cells Hazleton Labs Study # 15138-0-435DR 11/04/92	426485-22	Negative for forward mutation at the HGPRT locus of CHO cells exposed with/without activation up to precipitating concentrations (150 μ g/ml)	Acceptable
Chromosomal Aberrations <u>In Vivo</u> (Mouse MT) Dow Chemical Corp. Study # 2650-003 09/10/92	426485-24	Reported negative for inducing micronuclei in PCE of mice treated orally with single doses up to 5000 mg/kg	Acceptable

STUDY/ LAB/ STUDY # / DATE	MRID	RESULTS	CORE GRADE
Chromosome Damage <u>In Vitro</u> (Rat Lymphocytes) Hazleton Labs Study # 15138-0-444 11/04/92	426485-21	Negative for chromosomal aberrations in rat lymphocyte cultures exposed with/without activation to cytotoxic or precipitating concentrations (100 µg/ml and above)	Acceptable

VI. DATA GAPS

There are no data gaps at this time.

VII. REFERENCE DOSE

An RfD has not been established at this time.

VIII. OTHER TOXICOLOGICAL CONSIDERATIONS

A. WAIVER REQUESTS

It is recommended that the waiver request on the 0.1% formulation concerning the required acute studies (81-1 through 81-6) be granted because:

- | | |
|--------------|---|
| Low Toxicity | The Toxicity Category of the Acutes ^(TG-AT) are IV at the Limit Dose, with the exception of Dermal Irritation, which had a Tox. Category of III at the Limit Dose. Based on the Confidential Statement of Formula there is no reason to believe the inerts would be more toxic than the Technical. |
| Low Exposure | The formulation is not water soluble and is contained in the bait matrix in the soil, with no exposure, drift leach or runoff potential. |

It is further recommended that the waiver request on the 0.1% formulation concerning the delayed neurotoxicity study (81-7) be granted, because the structure of the active ingredient does not raise concern for this endpoint.

B. OECD DATA SUMMARIES

In a separate document (MRID 426485-20), data on studies conducted using DE-473 technical were summarized as follows:

1. DE-473 was not oncogenic in Sprague-Dawley rats at dietary dose levels up to

500 mg/kg/d for 104 weeks. While no gross or clinical signs were noted, an increased incidence and severity of liver pale cell foci were observed at 500 mg/kg/d. the NOEL was 75 mg/kg/d.

2. DE-473 was not oncogenic in CD-1 mice during 80 weeks of treatment at dietary levels up to 25 mg/kg. No other toxic effects were noted.

3. In beagle dogs the target organ was peripheral blood cells. The NOEL for the one year feeding study was 0.5 mg/kg/d, with Heinz body formation and reversible increases in methemoglobin observed at 5 and 25 mg/kg/day.

4. DE-473 was not developmentally toxic in rats or rabbits at oral dose levels up to 1000 mg/kg/day. Furthermore, DE-473 was reported to have no effect on fertility, reproductive performance or fetal development at 125 mg/kg/d, the highest level tested in a two-generation study.

The actual data from these studies were not presented, and these summaries are presented here for general information only.
