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

JUN 29 1989

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: DuPont Escort® RP Herbicide
21-Day Dermal Toxicity Study - Rabbits

TO: Vicky Walters
Product Manager (25)
Registration Division (H7505C)

FROM: Linda L. Taylor, Ph.D. Linda Lee Taylor 6/27/89
Toxicology Branch II, Section II
Health Effects Division (H7509C)

THRU: K. Clark Swentzel K. Clark Swentzel 6/27/89
Acting Section II Head, Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph.D. Marcia van Gemert 6/28/89
Chief, Toxicology Branch/HFAS/HED (H7509C)

Registrant: DuPont
Chemical: Metsulfuron methyl; (methyl-2-[[[[(4-methoxy-6-methyl-1,3,5-triazun-2yl)amino]-carbonyl]-amino]sulfonyl benzoate
Project: none provided
Caswell No.: 419H
Record No.: none provided
Identifying No.: not provided
MRID No.: none provided
Action Requested: Review data.

Comment: The Registrant provided TB II with a copy of the final report of a 21-day dermal toxicity study in rabbits and requested that a prompt response would be appreciated. A copy was also supplied to your Division. To date, I have not received a "bean sheet", although a request was made for one soon after the study was received. This study has been reviewed, and a copy of the DER is attached.

Dermal irritation was observed following repeated applications of INF-6367 (metsulfuron methyl) to the clipped intact skin of New Zealand white rabbits for 6-hours per day for 21 days, at the two highest dose levels (500 and 2000 mg/kg. Following a 14-day recovery period, the skin lesion was still detectable in the 2000 mg/kg group, but it was less severe than immediately after treatment. No skin lesions were detected at 125 mg/kg. No other observations, with the exception of increased incidence of diarrhea at the high-dose level, were related to compound exposure.

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The NOEL for dermal irritation can be set at 125 mg/kg; the LEL at 500 mg/kg. The systemic NOEL can be set at 500 mg/kg; the LEL at 2000 mg/kg, based on the occurrence of diarrhea.

This study is classified as Supplementary, pending the submission of data for confirmation of the test material concentration/homogeneity/stability. The study may be upgraded following submission of such data.

Reviewed by: Linda L. Taylor, Ph.D. Linda L. Taylor 4/27/89
Tox. Branch II, Section II, HED (H7509C)
Secondary reviewer: K. Clark Swentzel K. Clark Swentzel 6/27/89
Acting Head Section II, Tox. Branch II, HED (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: 21-Day Dermal Toxicity - Rabbits TOX. CHEM. NO.: 419H

MRID NO.: 40357803

TEST MATERIAL: INT - 6376

SYNONYMS: DuPont Escort® RP Herbicide

STUDY NUMBER: HLR 35-87

SPONSOR: DuPont

TESTING FACILITY: Haskell Laboratory for Toxicology and Industrial Medicine

TITLE OF REPORT: Repeated Dose Dermal Toxicity: 21-Day Study with INT -6376 in Rabbits

AUTHORS: John W. Sarver

REPORT ISSUED: March 4, 1987, revised March 10, 1987

CONCLUSION: Dermal irritation was observed following repeated applications of INT-6367 (metsulfuron methyl) to the clipped intact skin of New Zealand white rabbits for 6-hours per day for 21 days, at dose levels of 500 and 2000 mg/kg. Following a 14-day recovery period, the skin lesion was still detectable in the 2000 mg/kg group, but it was less severe than immediately after treatment. No skin lesions were detected at 125 mg/kg. No other observations, with the exception of increased incidence of diarrhea at the high-dose level, were related to compound exposure. The NOEL for dermal irritation can be set at 125 mg/kg, the LEL at 500 mg/kg; the system NOEL can be set at 500 mg/kg, the LEL at 2000 mg/kg, based on the occurrence of diarrhea.

This study is classified as Supplementary, pending the submission of data for confirmation of the test material concentration/homogeneity/stability. The study may be upgraded following submission of such data.

Classification: Supplementary, pending submission of analyses data on test material used in this study.

QUALITY ASSURANCE: A quality assurance statement was provided.

A. MATERIALS:

1. Test compound: INT - 6376; Metsulfuron-methyl; Description: white solid; Batch No. 7970-001; Haskell # 16,464; Purity: 99.3%; Stability: assumed to be stable under the conditions of use.

2. Test animal: Species: Rabbit; Strain: New Zealand white; Age: young, not further defined; Weight: 2723-2737 g (males), 2541-2574 g (females); Source: Hare Marland, Hewitt, NJ.

3. Statistics: Data were analyzed by a one-way analysis of variance. Test groups were compared to control values by least significant difference (LSD) and Dunnett's test when the ratio of variance (F) indicated a significant among-to-within group variation. Significant differences were declared at the 0.05 probability level.

B. STUDY DESIGN:

Methodology

No information was provided on how the rabbits were assigned to each group, although it it stated that the study design conformed to the EPA and OECD test guidelines. Purina Certified Rabbit Chow® #5322 and water were provided ad libitum. One day prior to study initiation, the hair was closely clipped to expose the skin (from scapular to lumbar region of the back) of each animal. This was repeated throughout the study as needed. Plastic collars were fitted to prevent test material ingestion and disruption of the wrappings. The test material was made into a paste with distilled water (prepared daily) and applied once daily for 21 days to the intact skin as shown below (individual body weights were measured prior to dosing for calculation of proper dose).

Test Group	Test Material (mg/kg/day)	Males	Females
1	0 (distilled water)	10	10
2	125	5	5
3	500	5	5
4	2000	10	10

The test material was spread evenly over the exposed skin (190 square centimeters), covered with a sterile gauze pad and the animals were wrapped with successive layers of plastic film, stretch gauze bandage, and adhesive bandage and returned to their cages. After 6 hours, the wrappings were removed, and each rabbit was gently washed with warm water to remove excess test material and dried.

RESULTS: No data were provided for confirmation of the test material concentration/homogeniety/stability.

Observations

All rabbits were observed for dermal irritation and clinical signs of toxicity following their bath, and returned to their cages. Thereafter, prior to each exposure, each rabbit was weighed and observed for dermal irritation and clinical signs of toxicity. Dermal irritation was scored according to the Draize scale (Table 1, attached). Five rabbits per sex from the control and high-dose groups were observed for clinical signs and weighed daily (except weekends) during a 14-day recovery period.

RESULTS: No deaths occurred during the study. Body weights were comparable among the groups throughout the study. High-dose animals displayed erythema and edema more frequently than the other dose groups, and an increased incidence of diarrhea was observed at the high dose. Mean body weight, mean organ weight and organ-to-body weight ratios were comparable among the groups.

Clinical Pathology

Blood was collected from each animal 2 days prior to the first treatment, one day following the last exposure, and 14 days following the last exposure from those control and high-dose rabbits used in the recovery phase for hematology and clinical analyses. The CHECKED (X) parameters were examined.

a. Hematology

X	Hematocrit (HCT)	X	Leukocyte differential count
X	Hemoglobin (HGB)	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)	X	Mean corpuscular HGB conc.(MCHC)
X	Erythrocyte count (RBC)	X	Mean corpuscular volume (MCV)
X	Platelet count		Nucleated red blood cell count
			Cellular morphology

RESULTS: Males - The increases noted in MCH and MCHC values in the low- and high-dose males one day following dosing and in the high-dose males following the 14-day recovery period were statistically significant, but not of sufficient magnitude to be toxicologically significant. Additionally, RBC values were decreased in the high-dose males (93% of control values) after the 14-day recovery period, and a decreased percentage of atypical lymphocytes was observed 1 day after the last dose in this same dose group. These are not considered toxicologically significant.

Females - Values for the measured parameters were comparable among the females.

b. Clinical Chemistry

	Electrolytes:		Other:
	Calcium		Albumin
	Chloride	X	Blood creatinine
	Magnesium	X	Blood urea nitrogen
	Phosphorous	X	Cholesterol
	Potassium		Globulins
	Sodium		Glucose

	Enzymes		
X	Alkaline phosphatase		Total Bilirubin
	Cholinesterase	X	Total Serum Protein
	Creatinine phosphokinase		Triglycerides
	Lactic acid dehydrogenase		Serum protein electrophoresis
X	Serum alanine aminotransferase (also SGPT)		
X	Serum aspartate aminotransferase (also SGOT)		
	gamma glutamyl transferase		
	glutamate dehydrogenase		

RESULTS: Males - No significant differences were observed among the groups. Females - Although statistically significant increases were noted in the low-and mid-dose females in ALP values one day after the last dose, both groups had displayed pre-test values above those of control (mid-dose was statistically significant); no significance was placed on this finding. The high-dose females displayed decreases in total protein after one day of recovery, and cholesterol was decreased follo[illegible] the 14-day recovery period. This latter decrease appears related to [illegible]ound administration in that all five values were low compared to controls.

Gross Pathology

On the day following the last exposure and after the 14-day recovery, animals were sacrificed and subjected to gross pathological examination. The liver, kidneys, spleen and testes were weighed at necropsy.

RESULTS: Treatment-related skin lesions were observed grossly at treatment sites in the 2000 mg/kg animals (both sexes). The affected skin was said to be scaly or crusty. The skin lesion was still present in the high-dose animals following the 14-day recovery period, although it was said to be less severe. Organ weights were comparable among the groups.

Histopathology

The following organs and tissues were preserved from all animals, and those of the control and high-dose animals were examined microscopically. The skin and gross lesions were examined for the low- and mid-dose animals also.

	Digestive system		Cardiovasc./Hemat.		Neurologic
	Tongue		Aorta	X	Brain
	Salivary glands	X	Heart		Periph. nerve (sciatic & tibial)
X	Esophagus	X	Bone marrow		Spinal cord
X	Stomach	X	Lymph nodes*		Pituitary
X	Duodenum	X	Spleen	X	Eyes
X	Jejunum	X	Thymus		Glandular
X	Ileum		Urogenital	X	Adrenals
X	Cecum	X	Kidneys		Lacrimal gland (Harderian)
C	Colon	X	Urinary bladder		Mammary gland
X	Rectum	X	Testes		Parathyroids
X	Liver	X	Epididymides	X	Thyroids
X	Gall bladder		Prostate		Other
X	Pancreas		Seminal vesicle	X	Bone (sternebrae)
	Respiratory	X	Ovaries		Skeletal muscle

X	Trachea	X	Uterust	X	Skin
X	Lung	X	Cervix	X	All gross lesions and masses
	Nose	X	Vagina		Head
	Pharynx		Oviduct		Coagulating gland
	Larynx				Mediastinal/mesenteric tissue
				X	Appendix
				X	Sacculus rotundus

* mesenteric
† horn, body, cervix

RESULTS: Microscopically, a treatment-related skin lesion was observed in the 500 and 2000 mg/kg groups (both sexes) at the end of treatment. The microscopic change in the skin was said to be diffuse/multifocal dermatitis manifested by varying degrees of epidermal and dermal necrosis, epidermal hyperplasia, and epidermal infiltration of inflammatory cells, mostly mononuclear round cells, which persisted after the 14-day recovery period, but was less severe (see below).

Treatment period

	Control		Low		Mid		High	
treated skin	M	F	M	F	M	F	M	F
cellular infiltrate, focal, dermis	1	1	1	1	1	2	–	–
dermititis, diffuse/multifocal, epidermis/dermis	–	–	–	–	3	2	5	5
dermititis, dermis		–		–		1		–
dilitation/increased keratin, follicle, focal	–	1	–	–	–	–	–	–
untreated skin*								
cellular infiltrate, focal, dermis	–	1	–	–	1	1	2	3
inflammation, focal, pannicular carnosus	–	–	–	1	–	–	–	–

Recovery phase

	Control		High	
treated skin	M	F	M	F
cellular infiltrate, focal, dermis	1	–	–	–
dermititis, diffuse/multifocal, epidermis/dermis	–	–	4	5
dermititis, dermis	–	–	–	–
dilitation/increased keratin, follicle, focal	–	–	–	–
untreated skin*				
cellular infiltrate, focal, dermis	–	–	–	–
inflammation, focal, pannicular carnosus	–	–	–	–

*term used in report Table 5 (skin-control) is misleading

COMMENT: The original reviewer of the previous 21-day dermal study in rabbits (HRL 137-83; Assession No. 072765) requested the study be repeated due to the testicular degeneration noted in the treated animals. The current reviewer disagreed with this original assessment and concluded that a repeat of the 21-day dermal study was not required (TB II memo dated 11/7/88, copy attached). With regard to testicular degeneration, TB II requested data regarding male fertility in order to assess whether additional testing with respect to male fertility will be required. To date, no such data have been received for review.

CONCLUSION

Dermal irritation was observed following repeated applications of INT-6367 (metsulfuron methyl) to the clipped intact skin of New Zealand white rabbits for 6-hours per day for 21 days, at dose levels of 500 and 2000 mg/kg. Following a 14-day recovery period, the skin lesion was still detectable in the 2000 mg/kg group, but it was less severe than immediately after treatment. No skin lesions were detected at 125 mg/kg. No other observations, with the exception of increased incidence of diarrhea at the high-dose level, were related to compound exposure.

The NOEL for dermal irritation can be set at 125 mg/kg; the LEL at 500 mg/kg. The systemic NOEL can be set at 500 mg/kg; the LEL at 2000 mg/kg, based on the occurrence of diarrhea.

*
This study is classified as Supplementary, since no data were provided for confirmation of the test material concentration/homogeniety/stability. The study may be upgraded following submission of such data.

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

NOV - 7 1988

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: Registration of DuPont Escort® RP Herbicide and Request for Establishemnt of Permanent Tolerance for Residues of Metsulfuron Methyl in or on Grass Forage, Fodder, Hay, and in Milk and Kidney.

TO: Robert J. Taylor
Product Manager (25)
Registration Division (TS-767C)

FROM: Linda L. Taylor, Ph.D. 11/4/88
Toxicology Branch II, Section II
Health Effects Division (TS-769C)

Thru: Marcia van Gemert, Ph.D. 11/7/88
Toxicology Branch II, Acting Head Section II
Health Effects Division (TS-769C)

and

William Burnam, Ph.D. 11/7/88
Acting Chief, Health Effects Division (TS-769C)

Registrant: DuPont
Chemical: (Methyl 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl) amino]-carbonyl]-amino]sulfonyl]benzoate); DuPont Escort® RP Herbicide (60DF Formulation); Metsulfuron Methyl
Project: 8-0991
Caswell No.: 419H
Record No.: 223816/223163

Action Requested: Determination of whether the application for: (1) the registration of DuPont Escort® RP Herbicide, the intended use of which is for the control of broom snakeweed in rangeland and pastures, and for (2) the establishment of a tolerance in or on grass forage, fodder, hay, and milk and kidney, is supported by the available data.

Escort® RP Herbicide is said to be identical in active ingredient (metsulfuron methyl) and formulation (60% dry flowable) to DuPont Escort® Herbicide (EPA Reg. No. 352-EUP-136) and DuPont Ally® Herbicide (EPA Reg. No. 352-435).

The 60DF end-use product (tradename Escort® Herbicide) was evaluated on rangeland and pasture in 1986 and 1987 under an Environmental Use Permit (EUP No. 352-EUP-136), and temporary tolerances were established on grass forage, fodder, hay, and in milk and kidney. The Registrant is now requesting registration of DuPont Escort® RP Herbicide and the establishment of permanent tolerances as follows:

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Commodity	ppm
Grass forage and fodder	15
Grass hay	30
Milk	0.2
Kidney (cattle, goats, hogs, horses, sheep)	0.5

The Registrant is relying on previously submitted toxicology data on Escort® Herbicide (EPA Reg. No. 352-439; identical in active ingredient (metsulfuron methyl) and formulation to Escort® RP Herbicide) and on toxicology data for the formulated end-use product, DuPont Escort® Herbicide.

Tolerances for the active ingredient, metsulfuron methyl, have been approved (0.1 ppm in fat, meat, and meat by-products of cattle, goats, hogs, horses, and sheep; 0.05 ppm in milk; 0.05 ppm in or on barley and wheat grain; 5.0 ppm in or on barley and wheat green forage; 20 ppm in or on barley and wheat hay; and 0.1 ppm in or on barley and wheat straw) and are listed in 40 CFR 180.428. The proposed permanent tolerance for residues of metsulfuron methyl for milk (0.2 ppm) is greater than that currently listed (0.05), and the proposed tolerance for kidney is new. Additionally, the proposed permanent tolerance for grass forage/fodder (15 ppm) is the same as the existing temporary tolerance, while that for dried hay (30 ppm) is one-half of the existing temporary tolerance.

With regard to the available toxicology data and the requirements for the proposed use, several studies are classified as supplementary/unacceptable/ missing. These include:

1. Acute inhalation study on the 60% formulation - not available

There is an acute inhalation study available on the TGAI, which falls into Tox. Category IV. All other acute studies show comparable toxicity between the TGAI and the formulations (60% and 70% AI formulations); i.e., they all fall into the same Tox. Category. At this time, there appears to be no need to conduct an acute inhalation study on the 60% formulation.

2. Acute delayed neurotoxicity of TGAI - not available

Since metsulfuron methyl is not an organophosphate and is apparently not related to a chemical that shows neurologic effects, there is no need, at this time, to perform an acute delayed neurotoxicity study.

3. 90-day rat feeding study - supplementary;

There is an adequate chronic rat study available; therefore, there is no need to repeat the 90-day rat feeding study.

4. 2 mutagenicity studies - unacceptable

a) CHO/HGPRT gene mutation assay
b) UDS/primary rat hepatocytes

The acceptable mutagenicity studies available on metsulfuron methyl are (see overview of submitted mutagenicity studies, Dearfield to Taylor, dated October 31, 1988; copy attached) the Salmonella assay, rat bone marrow/aberrations, and CHO/aberrations assays. The latter study was positive with and without metabolic activation. It was concluded that metsulfuron methyl has been adequately tested in two of the three areas for mutagenicity testing, i.e., gene mutations and structural chromosomal aberrations (both in vivo and in vitro). The third area, "other genotoxic effects" requires further testing before a final conclusion on the potential genotoxic activity of metsulfuron methyl can be made.

As noted in the original review of the UDS assay, no cytotoxicity was noted, and the test compound was not tested up to high enough concentrations (top concentration should elicit some signs of toxicity). Although the Registrant responded that they tested up to the limit of solubility, this was not reported in the original final report and no substantiation was ever provided. With this lack of such documentation, as well as an apparent lack of toxicity, the study is reclassified as unacceptable, and a study in the "other genotoxic effects" category remains a data requirement.

5. 21-day dermal study - supplementary

The original TB reviewer concluded that this study would have to be repeated. because of the testicular effects observed. The current reviewer disagrees.

The Registrant has provided a discussion/explanation regarding the testicular effects observed in the 21-day dermal study. It is argued that, although there were only 3 males/group at termination (2/group were used for the recovery phase), the testicular degeneration was not dose-related; the highest dose tested was twice the [illegible] effects were reported at the 2-g/kg dose level in the [illegible] and the interval between dose levels was large. Additionally, the [illegible] said to be prepubertal/young, which, it is suggested, makes it difficult to distinguish between the testis undergoing regeneration (adult) and the immature testis.

At this time, TB cannot conclude [illegible] ation regarding the observed testicular effects [illegible] porting data regarding male fertility. Although there [illegible] study available on metsulfuron methyl, there were no [illegible] ith which to determine the male fertility index. The Registrant should be requested to provide these data, if available; otherwise it will be necessary to perform a study to investigate male fertility. It will be necessary to repeat the 21-day dermal study, however.

CONCLUSION: The data do not support the application for registration of DuPont Escort® RP herbicide, or the establishment of a permanent tolerance for residues of metsulfuron methyl in or on grass forage, fodder, hay, and in milk and kidney, at this time. Two issues require resolution before approval can be granted.

(1) The mutagenicity data requirement: "other genotoxic effects" will need to be satisfied. Following the submission of the necessary data regarding "other genotoxic effects", an evaluation of the entire mutagenicity package will be made to determine whether additional mutagenicity testing will be necessary.

(2) A determination of whether additional testing will be necessary with respect to male fertility (question raised by the 21-day dermal study in rabbits) must await the Registrant's response to the request for such data from the rat reproduction study already submitted and reviewed.

It will not be necessary to repeat the 21-day dermal study in rabbits, as previously requested by the original study reviewer.

Tox Chem No. Metsulfuron methyl 419H File Last Updated _____ Current Date 6/14/89

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
21-day dermal-rabbit Haskell Lab. Tox & IM HLR 35-87; 3/4, 10/87	technical 99.3%	MRID # 40357803	Dermal irritation observed at 500 & 2000 mg/kg (6 hours/day for 21 days) & at 2000 mg/kg following a 14-day recovery period; increased incidence of diarrhea at 2000 mg/kg (HDT); no effects at 125 mg/kg. No data were provided to confirm test material concentration/stability/homogeneity. NOEL-(dermal irritation) 125 mg/kg; LEL - 500 mg/kg; NOEL (systemic toxicity) - 500 mg/kg; LEL (systemic) 2000 mg/kg		Supplementary