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

007618

NOV 17 1989

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: DuPont Escort® RP Herbicide (Rangeland and Pastures)
Registrant's Response to Agency's Reviews

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

FROM: Linda L. Taylor, Ph.D. 11/13/89
Toxicology Branch II, Section II
Health Effects Division (H7509C)

THRU: K. Clark Swentzel 11/15/89
Section II Head, Toxicology Branch II
Health Effects Division (H7509C)

AND

Marcia van Gemert, Ph.D. 11/17/89
Chief, Toxicology Branch/HFAS/HED (H7509C)

REGISTRANT: DuPont
CHEMICAL: (METHYL-2-[[[[(4-METHOXY-6-METHYL-1,3,5-TRIAZIN-2-YL) AMINO]-CARBONYL]-AMINO]SULFONYL BENZOATE; METSULFURON METHYL
PROJECT No.: 9-1773A
CASWELL No.: 419H
RECORD No.: 247852 & 247853
IDENTIFYING No.: 8F3647 & 352-LEU
MRID No.: 411180-02 & 403578-03
ACTION REQUESTED: Nothing specified. A mutagenicity study and the Registrant's response to the Agency's reviews of previously submitted data were received.

COMMENT: The submission is in response to the Agency reviews of previously submitted data. This memo responds only to the issues regarding toxicology.

The first issue concerns the results of the *in vitro* CHO assay, in which a positive response was observed. The Registrant contends that the negative results found in the previously submitted *in vivo* bone marrow cytogenic assay (HLO 22-83) and the recently submitted *in vivo* mutagenicity study (*In Vivo* Mouse Micronucleus Assay HLO 433-84) provide a better indication of clastogenic potential of Escort® than the *in vitro* CHO study. The Registrant contends that although the *in vitro* study provides a determination of inherent clastogenic potential, it does not present an appropriate basis for extrapolation to the whole animal.

1

AS STATED IN THE SACB OVERVIEW MEMO DATED 10/31/88 (TB II COVER MEMO DATED 11/7/88), IT IS POSSIBLE THAT THE BONE MARROW MAY NOT BE THE APPROPRIATE TARGET FOR POSSIBLE IN VIVO CLASTOGENIC ACTIVITY. IT WAS FURTHER CONCLUDED THAT A FINAL DETERMINATION OF THE POTENTIAL GENOTOXIC ACTIVITY OF METSULFURON METHYL WILL BE MADE FOLLOWING SUBMISSION OF THE REQUIRED "OTHER GENOTOXIC EFFECTS" DATA. TO DATE, TB II IS NOT AWARE THAT ANY SUCH DATA HAVE BEEN SUBMITTED TO ADDRESS THIS CATEGORY.

NOTE: ON PAGE 4 OF THE JUNE 2, 1989 LETTER FROM THE REGISTRANT, THE RESPONSE TO THE AGENCY'S COMMENT ON THE UDS/PRIMARY RAT HEPATOCYTE ASSAY WAS:

"TO FURTHER SATISFY THE 'OTHER GENOTOXIC EFFECTS' REQUIREMENT", THE MOUSE BONE MARROW MICRONUCLEUS ASSAY WAS SUBMITTED. THIS ASSAY DOES NOT FULFIL THIS REQUIREMENT.

THE IN VIVO MOUSE MICRONUCLEUS ASSAY HAS BEEN REVIEWED AND THE DER IS ATTACHED. THE RESULTS INDICATE THAT THE TEST MATERIAL WAS NOT CLEARLY TOXIC TO THE TEST ANIMALS OR CYTOTOXIC TO THE TARGET ORGAN, AND IT DID NOT CAUSE A SIGNIFICANT INCREASE IN THE FREQUENCY OF MICRONUCLEATED POLYCHROMATIC ERYTHROCYTES AT AN ACCEPTABLE HIGH DOSE. THE STUDY IS CLASSIFIED AS ACCEPTABLE.

WITH REGARD TO THE 21-DAY DERMAL STUDY [ORIGINALLY SUBMITTED TO THE AGENCY 3/87 (MRID # 40357803) AND DELIVERED TO THIS REVIEWER ON 3/28/89 BY THE REGISTRANT], THE 1987 STUDY WAS REVIEWED (TB II MEMO DATED 6/29/89), AND IT WAS CONCLUDED THAT THE NOEL FOR DERMAL IRRITATION CAN BE SET AT 125 MG/KG AND 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. THESE DATA WERE SUBMITTED TO THE AGENCY (COVER LETTER DATED 9/25/89; HED PROJECT NO. 0-0091, RECEIVED IN TB II ON 11/2/89) AND ARE DISCUSSED ELSEWHERE UNDER THAT PROJECT NUMBER.

IN TB II MEMO DATED 11/7/88, IT WAS CONCLUDED THAT IT WAS NOT NECESSARY TO REPEAT THE 21-DAY DERMAL STUDY, AS HAD BEEN REQUESTED PREVIOUSLY BY THE ORIGINAL TOXICOLOGY REVIEWER, BUT DATA ON MALE FERTILITY FOLLOWING EXPOSURE TO METSULFURON METHYL WERE REQUIRED. ALTHOUGH THE 1987 21-DAY DERMAL STUDY DID NOT SHOW THE TESTICULAR EFFECT (NOTED IN THE FIRST STUDY) TO BE REPRODUCIBLE, THE QUESTION OF MALE FERTILITY REMAINS UNANSWERED. IN THE ORIGINAL STUDY, THE TESTICULAR CHANGES NOTED BY THE ORIGINAL REVIEWER WERE NOT DOSE-RELATED, BUT THEY ONLY APPEARED IN THE TREATED ANIMALS. THE ACUTE DERMAL TOXICITY CATEGORY FOR METSULFURON METHYL IS III, FOR WHICH THE PRECAUTIONARY STATEMENT READS "HARMFUL IF ABSORBED THROUGH THE SKIN. AVOID CONTACT WITH SKIN, EYES OR CLOTHING. WASH THOROUGHLY WITH SOAP AND WATER AFTER HANDLING." BASED ON THE FACTS THAT THE ORIGINAL TESTICULAR CHANGES WERE NOT REPRODUCIBLE, NOR WERE THEY DOSE-RELATED, AND SINCE THE LABEL CAUTIONS AGAINST DERMAL CONTACT, FURTHER INVESTIGATION INTO THIS ASPECT WILL NOT BE REQUIRED FOR THE CURRENT ACTION.

WITH REGARD TO THE ADDITIONAL INFORMATION SUBMITTED ON THE TEST MATERIAL TO UPGRADE THE SECOND 21-DAY DERMAL STUDY (HED PROJECT # 0-0091;RECEIVED IN TB II ON NOVEMBER 2, 1989), THE REGISTRANT STATED THAT AN APPROPRIATE AMOUNT OF THE TEST MATERIAL WAS WEIGHED OUT FOR EACH ANIMAL ON EACH EXPOSURE DAY AND MIXED WITH WATER TO FORM A PASTE, WHICH WAS THEN PLACED ON THE ANIMAL IN TOTO; THEREFORE, THERE WAS NO NEED TO ANALYZE FOR CONCENTRATION/ STABILITY/HOMEOGENIETY. WITH REGARD TO STABILITY OF THE TEST MATERIAL ITSELF, INFORMATION WAS PROVIDED AS TO ITS HALF-LIFE AT VARIOUS PH'S. ALTHOUGH THE PH OF THE PASTE WAS NOT MEASURED, IT WAS THOUGHT TO BE WITHIN THE RANGE WHERE THE TEST MATERIAL WAS STABLE. THE DATA ARE ADEQUATE, AND THE STUDY CAN BE UPGRADED TO CORE MINIMUM.

THE TOXICOLOGY DATA AVAILABLE ON METSULFURON METHYL AND ESCORT® RP HERBICIDE ARE SUMMARIZED BELOW.

METSULFURON METHYL (92.9%) - DPX (ALLY)

1. ACUTE ORAL LD_{50} - RAT	LD_{50} > 5000 MG/KG; TOX. CAT. 4
2. ACUTE DERMAL LD_{50} - RABBIT	LD_{50} > 2000 MG/KG; TOX. CAT. 3
3. ACUTE INHALATION LC_{50} - RAT	LC_{50} >5.3 MG/L/4 HR.; TOX. CAT. 4 (DUST INHALATION)
4. 21-DAY DERMAL - RABBIT	DERMAL IRRITATION AT 500 & 2000 MG/KG (6 HRS./DAY) & AT 2000 MG/KG AFTER 14-DAY RECOVERY PERIOD; DERMAL IRRITATION NOEL = 125 MG/KG, LEL = 500 MG/KG; SYSTEMIC NOEL = 500 MG/KG, LEL = 2000 MG/KG, BASED ON DIARRHEA
5. 90-DAY ORAL - RAT	ALTHOUGH THIS STUDY IS CLASSIFIED SUPPLEMENTARY, THERE IS AN ADEQUATE CHRONIC STUDY IN RATS AND THIS IS NOT A DATA GAP
6. 90-DAY ORAL - DOG	THERE IS A ONE-YEAR DOG STUDY
7. TERATOLOGY - RAT	MATERNAL NOEL < 40 MG/KG/DAY (HYPERACTIVITY, UNGROOMED COAT); FETOTOXIC NOEL > 1000 MG/KG/DAY; DEVELOPMENTAL NOEL > 1000 MG/KG DAY
8. TERATOLOGY - RABBIT	MATERNAL NOEL = 25 MG/KG/DAY, LEL = 100 MG/KG/DAY, BASED ON DECREASED BODY WEIGHT AND DEATH; FETOTOXIC NOEL > 700 MG/KG/DAY; DEVELOPMENTAL NOEL > 700 MG/KG/DAY (HDT)
9. 1-YEAR CHRONIC - DOG	NOEL = 50 PPM, LEL = 500 PPM, BASED ON DECREASED SERUM LDH

10. 2 GENERATION REPRODUCTION - RAT — REPROD. NOEL > 5000 PPM (HDT); MATERNAL NOEL = 500 PPM, LEL = 5000 PPM, BASED ON DECREASED BODY-WEIGHT GAIN; FETOTOXIC NOEL > 5000 PPM

11. 2-YEAR CHRONIC/CARCINOGENIC - RAT — SYSTEMIC NOEL = 500 PPM, LEL = 5000 PPM, BASED ON DECREASED BODY WEIGHT; CARCINOGENIC NOEL > 5000 PPM (HDT)

12. CARCINOGENIC - 18-MONTH - MOUSE — CARCINOGENIC NOEL > 5000 PPM (HDT) SYSTEMIC NOEL = 500 PPM, LEL = 5000 PPM. BASED ON BODY WEIGHT DECREASES

13. MUTAGENICITY

CATEGORIES	ACCEPTABLE STUDIES	OVERALL CATEGORY ASSESSMENT
A) GENE MUTATION	AMES TEST - NEGATIVE	NEGATIVE
B) CHROMOSOMAL ABERRATIONS	1) CHROMOSOME ABERRATION/CHO POSITIVE, WITH/WITHOUT S-9 2) RAT BONE MARROW/ABERRATIONS NEGATIVE 3) MOUSE MICRONUCLEUS - NEGATIVE	NEGATIVE
C) OTHER GENOTOXIC EFFECTS	NONE	UNKNOWN

14. METABOLISM - RAT — RAPID ELIMINATION, MOSTLY VIA URINE, LARGELY UNCHANGED

METSULFURON METHYL (60%) - DPX (ALLY)

1. ACUTE ORAL LD_{50} - RAT — LD_{50} > 5000 MG/KG; Tox. Cat. 4
2. ACUTE DERMAL LD_{50} - RABBIT — LD_{50} > 2000 MG/KG; Tox. Cat. 3
3. PRIMARY DERMAL IRRITATION - RABBIT — SLIGHTLY IRRITATING; Tox. Cat. 4
4. PRIMARY EYE IRRITATION - RABBIT — CORNEAL OPACITY IN ONE EYE AT 24 HRS.; CLEARED IN 48 HRS. Tox. Cat. 3
5. DERMAL SENSITIZATION - GUINEA PIG — NO SENSITIZATION

NOTE: ACUTE INHALATION - TB II MEMO DATED 11/7/88 CONCLUDED THAT, BASED ON THE TECHNICAL PRODUCT TOXICITY CATEGORY 4 STATUS FOR ACUTE INHALATION AND COMPARABLE ORAL AND DERMAL ACUTE TOXICITY BETWEEN THE 60% FORMULATION AND THE TECHNICAL PRODUCT, THIS STUDY WAS NOT NECESSARY.

2. DATA GAPS: BY CURRENT STANDARDS, THE "OTHER GENOTOXIC EFFECTS" CATEGORY IS A DATA GAP.

3. TOLERANCE SUMMARY: THE DIETARY RESIDUE EVALUATION STAFF (DRES) HAVE PROVIDED THE DIETARY EXPOSURE ANALYSIS FOR PUBLISHED TOLERANCES AND PROPOSED TOLERANCES OF METHYLSULFURON METHYL (SEE MEMO DATED JULY 3, 1989, COPY ATTACHED).

4. ACCEPTABLE DAILY INTAKE (ADI): THE ADI FOR METSULFURON METHYL IS 0.25 MG/KG BODY WEIGHT/DAY, BASED UPON A NOEL OF 25 MG/KG BODY WEIGHT/DAY AND AN UNCERTAINTY FACTOR OF 100 FROM A 2-YEAR RAT FEEDING STUDY. THIS VALUE HAS BEEN APPROVED BY HED (6/12/87) AND AGENCY (8/12/87) REFERENCE DOSE COMMITTEES.

5. EFFECT OF TOLERANCE ON ADI: DRES HAS DETERMINED THAT THE EXPOSURE TO METSULFURON METHYL FROM PUBLISHED TOLERANCES REPRESENTS AN INSIGNIFICANT PORTION OF THE REFERENCE DOSE (0.0008-0.003 MG/KG; (0.3-1.4% OF ADI), AND THE EXPOSURE THAT WOULD BE ADDED FROM THE PROPOSED TOLERANCE IN KIDNEY OF CATTLE, GOAT, HORSE, SHEEP, AND HOGS RESULTS IN A SMALL INCREASE IN THE TOTAL EXPOSURE (<0.000001 MG/KG). ADDITIONALLY, SINCE THE ASSUMPTION IS MADE THAT 100 PERCENT OF ALL COMMODITIES WOULD CONTAIN TOLERANCE LEVEL RESIDUES, ACTUAL EXPOSURE WOULD BE EVEN LESS.

007618

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

JUL 3

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Dietary Exposure Analysis for the Proposed Use of Metsulfuron Methyl (Ally/Escort) on Grasses with Residues in Kidney, PP#8F3647

FROM: J. Robert Tomerlin, Ph.D. J.R. Tomerlin 7/3/89
Tolerance Assessment System Staff
HED/SACB (H7509C)

THROUGH: Reto Engler, Ph.D.
Chief, Science Analysis and Coordination Branch
Health Effects Division (H7509C)

TO: Robert Taylor/V. Walters PM 25
Registration Division (H7505C)

Action Requested

Provide a dietary exposure analysis for published tolerances and proposed tolerances in milk and kidney resulting from the use of metsulfuron methyl on grass forage and fodder.

Discussion

1. Toxicology Endpoint: The routine chronic TAS analysis used a reference dose (ADI) of 0.25 mg/kg body weight/day, based upon a NOEL of 25.0 mg/kg body weight/day and an uncertainty factor of 100 from a 2 year rat feeding study. This value has been approved by HED (6/12/87) and Agency (8/12/87) reference dose committees.

2. Residue Information: Food uses evaluated were published tolerances from 40 CFR 180.428 and the proposed tolerance in kidney (J. Garbus memo, 3/30/89). A tolerance of 0.1 ppm exists for kidney and petition PP#8F3647 requests a tolerance of 0.5 ppm resulting from treated grasses used for forage and fodder. In this analysis, a new tolerance of 0.4 ppm was used, which when added to the existing tolerance of 0.1 ppm gives the total magnitude of the requested tolerance, and also calculates the incremental increase in exposure from this tolerance. The requested milk tolerance of 0.2 ppm was not included in the analysis because the current published tolerance of 0.05 ppm in milk is not expected to be exceeded by the proposed use. The registrant was advised to submit a revised Section F withdrawing the request for an increased tolerance on milk (J. Garbus memo, 3/30/89). A summary of the residue information used in the analysis is attached as Table 1.

3. Exposure Analysis: The TAS chronic exposure analysis uses tolerance level residues and 100 per cent crop treated to estimate the Theoretical Maximum Residue Contribution (TMRC) for the overall U.S. population and 22 population subgroups. A summary of the TMRCs for the overall U.S. population and all 22 TAS population groups is shown in Table 2. The TMRC information for the overall U.S. population and the two most highly exposed TAS population groups is given in the following table.

Metsulfuron Methyl Exposure Summary

	Overall U.S. Population	Non-Nurs. Infants	Children Aged 1 - 6
Published Tolerances	0.000824[a] 0.3[b]	0.003537 1.4	0.002114 0.8
PP#8F3647 Kidney	< 0.000001 0	0 0	< 0.000001 0
TOTAL	0.000824 0.3	0.003537 1.4	0.002115 0.8

[a]Estimated exposure in mg/kg body weight/day.
[b]Exposure expressed as a per cent of the ADI.

4. Comments: Exposure from published tolerances represents an insignificant portion of the reference dose. Likewise, the exposure that would be added from the proposed tolerance in kidney of cattle, goat, horse, sheep, and hogs results in a small increase in the total exposure. Since this analysis assumed that 100 per cent of all commodities would contain tolerance level residues, actual exposure would be even less.

US 0.05 on front page

Note that the analysis did not include the proposed increased tolerance in milk. The DEB memo (J. Garbus, 3/30/89) stated that the current tolerance of 0.1 ppm would not be exceeded from the proposed use on grass forage and fodder and directed the registrant to submit a revised Section F withdrawing the increased tolerance on milk. This analysis was conducted assuming that this submission would be made.

ER .05

Attachments

cc: TAS File, DEB, Caswell #419H, Van Gamert (TOX-HFASB)

CHEMICAL INFORMATION FOR CASWELL NUMBER 419H DATE: 06/30/89 PAGE: 1

CHEMICAL	STUDY TYPE	EFFECTS	REFERENCE DOSES	DATA GAPS/COMMENTS	STATUS
Ally (DPX-T6376) Caswell #419H CAS No 74223-64-6 A I CODE. 122010 CFR No 180 428	2yr feeding- rat NOEL= 25 0000 mg/kg 500 00 ppm LEL= 250.0000 mg/kg 5000.00 ppm ONCO: Negative- 2 species	Decreased body weight gain. No evidence of oncogenicity in rats or mice, however mouse study may not have an MTD.	ADI UF -->100 OPP RfD= 0.250000 EPA RfD= 0.250000	No data gaps.	HED complete 03/21/86. EPA pending 04/22/86. HED reassess 06/12/87. EPA verified 08/12/87. On IRIS

FOOD CODE	FOOD NAME	PETITION NUMBER	TOLERANCE (PPM) NEW	PENDING	PUBLISHED
24001AA	BARLEY	8F3647			0.050000
24007AS	WHEAT-ROUGH				0.050000
24007CS	WHEAT-GERM				0.050000
24007HA	WHEAT-BRAN				0.050000
24007WA	WHEAT-FLOUR				0.050000
50000DB	MILK-NON-FAT SOLIDS				0.050000
50000FA	MILK-FAT SOLIDS				0.050000
50000SA	MILK SUGAR (LACTOSE)				0.100000
53001BA	BEEF-MEAT BYPRODUCTS				0.100000
53001BB	BEEF(ORGAN MEATS)-OTHER				0.100000
53001DA	BEEF-DRIED				0.100000
53001FA	BEEF(BONELESS)-FAT (BEEF TALLOW)	8F3647	0.400000		
53001KA	BEEF(ORGAN MEATS)-KIDNEY				0.100000
53001KA	BEEF(ORGAN MEATS)-KIDNEY				0.100000
53001LA	BEEF(ORGAN MEATS)-LIVER				0.100000
53001MA	BEEF(BONELESS)-LEAN (W/O REMOVEABLE FAT)				0.100000
53002BA	GOAT-MEAT BYPRODUCTS				0.100000
53002BB	GOAT(ORGAN MEATS)-OTHER				0.100000
53002FA	GOAT(BONELESS)-FAT	8F3647	0.400000		
53002KA	GOAT(ORGAN MEATS)-KIDNEY				0.100000
53002KA	GOAT(ORGAN MEATS)-KIDNEY				0.100000
53002LA	GOAT(ORGAN MEATS)-LIVER				0.100000
53002MA	GOAT(BONELESS)-LEAN (W/O REMOVEABLE FAT)				0.100000
53003AA	HORSE	8F3647	0.400000		
53003AA	HORSE				0.100000
53005BA	SHEEP-MEAT BYPRODUCTS				0.100000
53005BB	SHEEP(ORGAN MEATS)-OTHER				0.100000
53005FA	SHEEP(BONELESS)-FAT	8F3647	0.400000		
53005KA	SHEEP(ORGAN MEATS)-KIDNEY				0.100000
53005KA	SHEEP(ORGAN MEATS)-KIDNEY				0.100000
53005LA	SHEEP(ORGAN MEATS)-LIVER				0.100000
53005MA	SHEEP(BONELESS)-LEAN (W/O REMOVEABLE FAT				0.100000
53006BA	PORK-MEAT BYPRODUCTS				0.100000
53006BB	PORK(ORGAN MEATS)-OTHER				0.100000
53006FA	PORK(BONELESS)-FAT (INCLUDING LARD)	8F3647	0.100000		
53006KA	PORK(ORGAN MEATS)-KIDNEY				0.100000
53006KA	PORK(ORGAN MEATS)-KIDNEY				0.100000
53006LA	PORK(ORGAN MEATS)-LIVER				
53006MA	PORK(BONELESS)-LEAN (W/O REMOVEABLE FAT)				

CHEMICAL INFORMATION	STUDY TYPE	EFFECTS	REFERENCE DOSES	DATA GAPS/COMMENTS	STATUS
Ally (DPX-T6376)	2yr feeding- rat	Decreased body weight	ADI UF -->100	No data gaps.	HED complete 01/21/86
Caswell #419H	NOEL- 25 0000 mg/kg	gain	OPP RfD= 0.250000		EPA pending 04/22/86
CAS No 74223-64-6	500 00 ppm	No evidence of oncogeni-	EPA RfD= 0.250000		HED reassess 06/12/87
A I CODE 122010	LEL- 250 0000 mg/kg	city in rats or mice,			EPA verified 08/12/87
CFR No 180 478	5000 00 ppm	however mouse study may			
	ONCO Negative- 2 species	not have an MTD			On IRIS

POPULATION SUBGROUP	TOTAL TMRC (MG/KG BODY WEIGHT/DAY) CURRENT TMRC*	NEW TMRC**	NEW TMRC AS PERCENT OF RFD	DIFFERENCE AS PERCENT OF RFD	EFFECT OF ANTICIPATED RESIDUES ARC	%RFD
U S POPULATION - 48 STATES	0.000823	0 000823	0.329391	0.000080		
U S POPULATION - SPRING SEASON	0 000782	0 000783	0 313001	0.000075		
U S POPULATION - SUMMER SEASON	0 000817	0 000817	0 326803	0.000191		
U S POPULATION - FALL SEASON	0 000854	0 000854	0 341438	0.000032		
U S POPULATION - WINTER SEASON	0 000841	0.000841	0 336380	0.000021		
NORTHEAST REGION	0 000851	0 000851	0 340292	0.000043		
NORTH CENTRAL REGION	0 000860	0 000860	0 343901	0 000000		
SOUTHERN REGION	0 000738	0 000738	0 295338	0 000178		
WESTERN REGION	0 000881	0 000881	0 352548	0.000077		
HISPANICS	0 001008	0 001008	0 403301	0 000092		
NON HISPANIC WHITES	0 000822	0 000822	0 328698	0.000008		
NON HISPANIC BLACKS	0 000738	0 000739	0.295603	0.000501		
NON-HISPANIC OTHERS	0 000897	0 000898	0.359018	0 000358		
NURSING INFANTS (< 1 YEAR OLD)	0 000833	0 000833	0.333341	0.000000		
NON-NURSING INFANTS (< 1 YEAR OLD)	0 003537	0 003537	1 414724	0.000000		
FEMALES (13+ YEARS, PREGNANT)	0 000587	0 000587	0 234994	0.000000		
FEMALES 13+ YEARS, NURSING	0 000718	0 000718	0 287063	0.000000		
CHILDREN (1-6 YEARS OLD)	0 002114	0 002114	0.845710	0.000306		
CHILDREN (7-12 YEARS OLD)	0 001369	0 001370	0 547843	0.000194		
MALES (13-19 YEARS OLD)	0 000915	0 000915	0 366191	0 000028		
FEMALES (13-19 YEARS OLD, NOT PREG OR NURSING)	0 000700	0 000701	0.280205	0.000019		
MALES (20 YEARS AND OLDER)	0 000551	0 000551	0.220592	0 000021		
FEMALES (20 YEARS AND OLDER, NOT PREG OR NURS)	0 000462	0 000462	0.184706	0 000058		

*Current TMRC does not include new or pending tolerances.
**New TMRC includes new, pending, and published tolerances.

Tox Chem No. METSULFURON METHYL

File Last Updated 6/14/89

Current Date 11/13/89

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD50, LC50, PIS, NOEL, LEL	Tox Category	CURE Grade/ Doc. No.
21-Day Dermal Species: Rabbit Haskell Lab. Tox & IM HLR 35-87; 3/4, 10/87	Technical 99.5%	403578-03 412478-01	Dose levels: 0, 125, 500, 2000 mg/kg Dermal irritation at 500 & 2000 mg/kg Dermal irritation NOEL: 125 mg/kg, LEL: 500 mg/kg; systemic NOEL: 500 mg/kg, LEL: 2000 mg/kg, based on occurrence of diarrhea Supplemental submission: study can be upgraded		Minimum
Mutagenic - In vivo Mouse micronucleus assay Pharmakon Res. Intern. 4581-205; 4/11/89	INT-6376-22 92.9%	411180-02	Test material not clearly toxic to test animals or cytotoxic to target organ; did not cause significant increase in frequ[illegible] of micro- nucleated polychro[illegible]c erythrocytes ar acceptably high dose		Acceptable

007618

EPA No.: 6F0080056
DYNAMAC No.: 246-A
TASK No.: 2-46A
November 1, 1989

DATA EVALUATION RECORD

INT-6376-22 (METSULFURON)

Mutagenicity--In vivo Mouse Micronucleus Assay

APPROVED BY:

Robert J. Weir, Ph.D.
Program Manager
Dynamac Corporation

Signature: Lauren J. Puente for

Date: 10-31-89

00761 8

EPA No.: 68D80055
DYNAMAC No.: 246-A
TASK No.: 2-16A
November 1, 1989

DATA EVALUATION RECORD

INT-6376-22 (METSULFURON)

Mutagenicity--In vivo Mouse Micronucleus Assay

REVIEWED BY:

Nancy E. McCarroll, B.S.
Principal Reviewer
Dynamac Corporation

Signature: Nancy E. McCarroll
Date: 10-31-89

I. Cecil Felkner, Ph.D.
Independent Reviewer
Dynamac Corporation

Signature: Roman J Prienta for
Date: 10-31-89

APPROVED BY:

Roman Pienta, Ph.D.
Department Manager
Dynamac Corporation

Signature: Roman J Prienta
Date: 10-31-89

Linda Taylor, Ph.D.
EPA Reviewer, Section II
Toxicology Branch II
(H-7509C)

Signature: Linda Taylor
Date: 11-13-89

K. Clark Swentzel
EPA Section Head, Section II
Toxicology Branch II)
(H-7509C)

Signature: K. Clark Swentzel
Date: 11/15/89

12

DATA EVALUATION RECORD

CHEMICAL: INT-6376-22(Metsulfuron).

STUDY TYPE: In vivo mouse micronucleus assay.

ACCESSION NUMBER: 411180-02.

TEST MATERIAL: INT-6376-22 (H-14,418).

SYNONYMS/CAS NO. Benzoic acid, 2-[[[[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]amino]sulfonyl]-,methyl ester/74223-64-6.

SPONSOR: E. I. duPont de Nemours and Company, Inc., Wilmington, DE.

TESTING FACILITY: Pharmakon Research International, Inc., Waverly, PA.

TITLE OF REPORT: Mouse Bone Marrow Micronucleus Assay of INT-6376-22.

AUTHOR(S): Vlachos, D.A.

STUDY NUMBER(S): 4581-205.

REPORT ISSUED: April 11, 1989.

13

CONCLUSION(S)/EXECUTIVE SUMMARY: Thirty mice (15 males and 15 females) received a single oral gavage administration of 5000 mg/kg INT-6376-22. Bone marrow cells were harvested from five males and five females at 24, 48, and 72 hours postexposure to the test material. Results indicated that the test material was not clearly toxic to the test animals, cytotoxic to the target organ, or caused a significant increase in the frequency of micronucleated polychromatic erythrocytes (MPEs). In the absence of overt animal toxicity or detectable target organ cytotoxicity, 5000 mg/kg can be considered as an acceptable high dose. It was concluded, therefore, that INT-6376-22 was adequately tested and found to be nongenotoxic in a well-controlled mouse micronucleus assay.

Study Classification: The study is acceptable.

A. MATERIALS:

1. Test Material: INT-6376-22 (H-14,418).
   Description: White solid.
   Other code Nos.: DPX-T6376; N.B. 8660-5.
   Purity: 92.9%
   Contaminants: Not provided.
   Solvent used: Corn oil.
   Other comments: The test material was stored at room temperature in an amber bottle. Suspensions of the test material were prepared immediately prior to use.

2. Control Materials:

   Negative/Route of administration: None.

   Vehicle/Final concentration/Route of administration: Corn oil at a dosing volume of 20 mL/kg was administered by oral gavage to fasting mice.

   Positive/Final concentration/Route of administration: Triethylenemelamine (TEM) was administered intraperitoneally at a dose of 0.5 mg/kg.

3. Test compound:

   Route of administration: Oral gavage to 4-hour fasted mice.

Dose levels used:

a. Preliminary toxicity study: Single oral gavage administrations of 166, 500, 1666, 3000, and 5000 mg/kg.

b. Micronucleus assay: Single oral gavage administration of 5000 mg/kg.

4. Test animals:

a. Species ___mouse___ Strain ___CD-1___ Age 7 weeks.

Source: Charles River Breeding Laboratories, Wilmington, MA.

b. No. animals used per dose: ___4___ male; ___4___ female--Preliminary Toxicity Study; ___5___ male, ___5___ female per harvest interval--Micronucleus Assay.

B. TEST PERFORMANCE

1. Treatment and Sampling Times:

a. Test compound
Dosing: ___x___ once _____ twice (24 hr apart)
___N/A___ other (describe): _____.
Sampling (after last dose): _____ 6 hr _____ 12 hr
___x___ 24 hr ___x___ 48 hr ___x___ 72 hr.

b. Vehicle control
Dosing: ___x___ once _____ twice (24 hr apart)
___N/A___ other (describe): _____.
Sample (after last dose): ___x___ 48 hr.

c. Positive control
Dosing: ___x___ once _____ twice (24 hr apart)
___N/A___ other (describe): _____.

Sampling (after last dose): _____ 6 hr _____ 12 hr
___x___ 24 hr _____ 48 hr _____ 72 hr
___N/A___ other (describe): _____.

2. Tissues and Cells Examined:

x bone marrow N/A others (list):
No. of polychromatic erythrocytes (PCEs) examined per animal: 1000.
No. of normochromatic erythrocytes (NCEs, more mature RBCs) examined per animal: 1000.

3. Preliminary Toxicity Assay: Five groups of four male and four female mice were fasted for 4 hours and were administered single oral gavage doses of 166, 500, 1666, 3000, or 5000 mg/kg of the test material. Mortality and clinical signs were monitored for 72 hours posttreatment. No deaths occurred in any treatment group. The author indicated that signs of decreased body tone, piloerection, and abnormal gait were seen over the 72 hour observation period. Based on these findings, 5000 mg/kg was the dose selected for the micronucleus assay.

4. Micronucleus Assay: Thirty fasted mice (15 males and 15 females) received a single oral gavage dose of 5000 mg/kg INT-6376-22. At 24, 48, and 72 hours after administration of the test material, five males and five females were sacrificed by cervical dislocation. Ten mice receiving the vehicle control (corn oil) and the 10 mice administered the positive control (0.5 mg/kg TEM) were sacrificed 48 and 24 hours, respectively, after dosing.

One female in the test group died 24 hours posttreatment. Other clinical signs included ptosis, lacrimation, and decreased body tone and activity for one female at 48 hours and ptosis and decreased body tone and activity for one male at 72 hours. Representative results from the multiple-harvest micronucleus assay are presented in Table 1.

As shown, 5000 mg/kg of the test material did not induce a significant increase in the frequency of MPEs in cells harvested 24, 48, or 72 hours postexposure. The ratio of PCEs to NCEs in test groups was comparable to the vehicle control group value indicating that the test material had no adverse effects on hematopoiesis. By contrast, MPEs were significantly increased ($p<0.01$) and PCEs:NCEs were significantly reduced ($p<0.01$) in mice receiving the positive control (0.5 mg/kg TEM). The study author concluded, "The results for test article, H #14,418, were negative in the Micronucleus Test at a dose level of 5000 mg/kg at all of the time

TABLE 1. Representative Results of the Multiple-Harvest Mouse Micronucleus Assays with INT-6376-22 (H-14,418)

Substance	Dose	Harvest Time[a] (hours)	No. of Mice per Group[b]	No. of PCEs[c] Analyzed per Group	Mean MPEs per Group ± Standard Deviation	Ratio of PCEs to NCEs per Group ± Standard Deviation
Vehicle Control						
Corn oil	20 mL/kg	48	10	10,000	0.80 ± 0.63	1.54 ± 0.35
Positive Control						
Triethylenemelamine	0.5 mg/kg	24	10	10,000	56.50 ± 22.48*	0.91 ± 0.49*
Test Material						
INT-6376-22	5000 mg/kg	24	10	10,000	1.40 ± 1.35	1.28 ± 0.69
		48	10	10,000	1.11 ± 1.36	1.32 ± 0.68
		72	10	10,000	1.20 ± 1.23	1.40 ± 0.24

[a]Time after compound administration.

[b]Five male and five female mice/group.

[c]Abbreviations used:
PCEs--Polychromatic erythrocytes
MPEs--Micronucleated polychromatic erythrocytes
NCEs--Normochromatic erythrocytes.

*Significantly different than the control value ($p<0.01$) by t-tests.

intervals evaluated. These findings are based on the inability of the test article to produce a statistically significant increase in the number of micronuclei in 1000 polychromatic erythrocytes in the treated versus the negative control group."

C. Reviewers' Discussion/Conclusions: We assess that the study was properly conducted and that the study author interpreted the data correctly. Although the assayed dose of INT-6376-22 (5000 mg/kg) did not induce clear toxic effects and had no detectable cytotoxicity toward the target organ, this level is considered an appropriate dose for nontoxic and noncytotoxic compounds. It was, therefore, concluded that INT-6376-22 was assayed up to an adequate dose with no indication of a genotoxic effect. The sensitivity of the test system to detect micronuclei induction was demonstrated by the significant results obtained with the positive control (0.5 mg/kg TEM).

D. Quality Assurance Measures: A quality assurance statement was signed and dated August 31, 1989.

E. CBI Appendix: Appendix A, Materials and Methods, CBI pp. 10-13.

APPENDIX A
Materials and Methods

TOXR 007618

METSULFURON-METHYL 122010

Page _____ is not included in this copy.

Pages 20 through 23 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

X FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.
