



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 (H75056)

FROM: LINDA L. TAYLOR, PH.D. *Linda Taylor* 11/14/89
TOXICOLOGY BRANCH II, SECTION 41
HEALTH EFFECTS DIVISION (H7509C)

THRU: K. CLARK SWENTZEL *K. Clark Swentzel* 11/15/89
SECTION II HEAD, TOXICOLOGY BRANCH II
HEALTH EFFECTS DIVISION (H7509C)

AND

MARCIA VAN GEMERT, PH.D. *Marcia van Gemert* 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
9-1773A
PROJECT No.: 419H
CASWELL No.: 247852 & 247853
RECORD No.: 8F3647 & 352-LEU
IDENTIFYING No.: 411180-02 & 403578-03
MRID No.:
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 CONTENTS 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.

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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 5/87 (MRID # 40357803) AND DELIVERED TO THIS REVIEWER ON 3/28/89 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 # 9-0091; 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/HOMOGENEITY. 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 LD50 - RAT
2. ACUTE DERMAL LD50 - RABBIT
3. ACUTE INHALATION LC50 - RAT

LD50 > 5000 MG/KG; TOX. CAT. 4
 LD50 > 2000 MG/KG; TOX. CAT. 3
 LC50 > 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

<u>CATEGORIES</u>	<u>ACCEPTABLE STUDIES</u>	<u>OVERALL CATEGORY ASSESSMENT</u>
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 LD50 - RAT

LD50 > 5000 MG/KG; TOX. CAT. 4

2. ACUTE DERMAL LD50 - RABBIT

LD50 > 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 (IRES) 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: IRES 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 PIGS 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.



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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. Tomerlin 7/3/89*
Tolerance Assessment System Staff
HED/SACB (H7509C)

THROUGH: Reto Engler, Ph.D. *Reto Engler*
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.

Metsulfuron Methyl Dietary Exposure Analysis, page 2

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

	<u>Overall U.S. Population</u>	<u>Non-Nurs. Infants</u>	<u>Children Aged 1 - 6</u>
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

^aEstimated exposure in mg/kg body weight/day.

^bExposure expressed as 1 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, 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.

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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.

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 CAPS/COMMENTS	STATUS
ALL7 (DPX-T6376)	2 yr feeding- rat	Decreased body weight	ADJ UP -->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 06/12/87.
CFR NO 180 428	5000 00 ppm	however mouse study may			
	ONCO: Negative- 2 species	not have an MTD.			On IRIS

FOOD CODE	FOOD NAME	PETITION NUMBER	TOLERANCE (PPM)	PENDING	PUBLISHED
24001AA	O-RILEY	8F3647			0.050000
24007AA	WHEAT-ROUGH				0.050000
24007AA	WHEAT-GERM				0.050000
24007AA	WHEAT-BRAN				0.050000
24007AA	WHEAT-FLOUR				0.050000
5000008	MILK-NON-FAT SOLIDS				0.050000
50000FA	MILK-FAT SOLIDS				0.050000
50000SA	MILK SUGAR (LACTOSE)				0.100000
51001BA	BEEF-MEAT BYPRODUCTS				0.100000
51001BB	BEEF (ORGAN MEATS)-OTHER				0.100000
51001DA	BEEF-DRIED				0.100000
51001FA	BEEF (BONELESS)-FAT (BEEF TALLOW)		0.100000		0.100000
51001KA	BEEF (ORGAN MEATS)-KIDNEY	8F3647			0.100000
51001LA	BEEF (ORGAN MEATS)-LIVER				0.100000
51001MA	BEEF (BONELESS)-LEAN (W/O REMOVABLE FAT)				0.100000
51002BA	COAT-MEAT BYPRODUCTS				0.100000
51002BB	COAT (ORGAN MEATS)-OTHER				0.100000
51002FA	COAT (BONELESS)-FAT				0.100000
51002KA	COAT (ORGAN MEATS)-KIDNEY	8F3647	0.400000		0.100000
51002LA	COAT (ORGAN MEATS)-LIVER				0.100000
51002MA	COAT (BONELESS)-LEAN (W/O REMOVABLE FAT)				0.100000
51003AA	HORSE	8F3647	0.400000		0.100000
51003BA	SHEEP-MEAT BYPRODUCTS				0.100000
51003CA	SHEEP (ORGAN MEATS)-OTHER				0.100000
51003FA	SHEEP (BONELESS)-FAT	8F3647	0.400000		0.100000
51003KA	SHEEP (ORGAN MEATS)-KIDNEY				0.100000
51003LA	SHEEP (ORGAN MEATS)-LIVER				0.100000
51003MA	SHEEP (BONELESS)-LEAN (W/O REMOVABLE FAT)				0.100000
51003PA	PORK-MEAT BYPRODUCTS				0.100000
51003RA	PORK (ORGAN MEATS)-OTHER				0.100000
51003TA	PORK (BONELESS)-FAT (INCLUDING LARD)	8F3647	0.100000		0.100000
51003UA	PORK (ORGAN MEATS)-KIDNEY				0.100000
51003VA	PORK (ORGAN MEATS)-LIVER				0.100000
51003WA	PORK (BONELESS)-LEAN (W/O REMOVABLE FAT)				0.100000
51003XA	PORK (BONELESS)-LEAN (W/O REMOVABLE FAT)				0.100000

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CHEMICAL INFORMATION	STUDY TYPE	EFFECTS	REFERENCE DOSES		DATA GAPS/COMMENTS	STATUS
			ADI	UF		
Allyl (DPX-76376)	2yr feeding - rat	Decreased body weight	OPP RID= 0.250000	-->100	No data gaps.	HED complete 01/21/86
Caswell #419H	NEL- 25 0000 mg/kg	gain	EPA RID= 0.250000			EPA pending 01/22/86
CAS NO 74223-84-6	500 00 ppm	No evidence of oncogen-				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 4-8	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)		NEW TMRC		DIFFERENCE		EFFECT OF ANTICIPATED RESIDUES	
	CURRENT TMRC*	NEW TMRC**	AS PERCENT OF REF	AS PERCENT OF REF	AS PERCENT OF REF	AS PERCENT OF REF	ARC	ARC
U S POPULATION - 48 STATES	0.000823	0.000823	0.129391	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	0.000861	0.000861	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	0.000738	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	0.001369	0.547843	0.000194				
MALES (13-19 YEARS OLD)	0.000915	0.000915	0.366191	0.000028				
FEMALES (13-19 YEARS OLD)	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)	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.

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Tox Chem No. METSULFURON METHYL FILE LAST UPDATED 6/14/89 CURRENT DATE 11/13/89

EPA
ACCESSION No. RESULTS: LD50, LC50, PIS, NOEL, LEL TOX CATEGORY CURE GRADE/Doc. No.

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 HUR 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 FREQUENCY OF MICRO- NUCLEATED POLYCHROMATIC ERYTHROCYTES AT ACCEPTABLY HIGH DOSE		ACCEPTABLE

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EPA No.: 6PD80056
DYNAMAC No.: 246-A
TASK No.: 2-46A
November 1, 1989

CONFIDENTIAL BUSINESS INFORMATION
DO NOT CONTAIN
NATIONAL SECURITY INFORMATION (EO 12065)

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: *Ramona Penta for*
Date: 10-31-89

007618

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. Pienta for
Date: 10-31-89

APPROVED BY:

Roman Pienta, Ph.D.
Department Manager
Dynamac Corporation

Signature: Roman J. Pienta
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

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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.

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 PERFORMANCE1. 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 $\pm$ Standard Deviation	Ratio of PCEs to NCEs per Group $\pm$ Standard Deviation
<u>Vehicle Control</u>						
Corn oil	20 mL/kg	48	10	10,000	0.80 $\pm$ 0.63	1.54 $\pm$ 0.35
<u>Positive Control</u>						
Triethylenemelamine	0.5 mg/kg	24	10	10,000	56.50 $\pm$ 22.48*	0.91 $\pm$ 0.49*
<u>Test Material</u>						
INT-6376-22	5000 mg/kg	24	10	10,000	1.40 $\pm$ 1.35	1.28 $\pm$ 0.69
		48	10	10,000	1.11 $\pm$ 1.36	1.32 $\pm$ 0.68
		72	10	10,000	1.20 $\pm$ 1.23	1.40 $\pm$ 0.24

^aTime after compound administration.^bFive male and five female mice/group.^cAbbreviations 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.

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APPENDIX A
Materials and Methods

BOX 2 007618

METSULFURON-METHYL

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