CASWELL FILE 007883

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

APR 26 1990

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: F-6594, AN IMPURITY IN METSULFURON METHYL; SUBMISSION OF AN ACUTE LETHAL DOSE STUDY AND AN AMES ASSAY.

TO: VICKY WALTERS
PRODUCT MANAGER (25)
REGISTRATION DIVISION (H7505C)

FROM: LINDA L. TAYLOR, PH.D. Linda Lee Taylor 4/19/90
TOXICOLOGY BRANCH II, SECTION II
HEALTH EFFECTS DIVISION (H7509C)

THRU: K. CLARK SWENTZEL K. Clark Swentzel 4/20/90
SECTION II HEAD, TOXICOLOGY BRANCH II
HEALTH EFFECTS DIVISION (H7509C)

AND

MARCIA VAN GEMERT, PH.D. Marcia van Gemert 4/25/90
CHIEF, TOXICOLOGY BRANCH/HFAS/HED (H7509C)

REGISTRANT: DU PONT
CHEMICAL: METSULFURON METHYL - IN F6594 IS AN IMPURITY
SYNONYM: [redacted]
PROJECT NO.: 0-0969A
CASWELL NO.: 419H
RECORD NO.: 261716 & 261717
IDENTIFYING NO.: 352-512 & 352-439
MRID NO.: 413932-02 & 413932-03
ACTION REQUESTED: ADDITIONAL INFORMATION ON IMPURITY.

COMMENT: IN RESPONSE TO AN EPA LETTER DATED 10/3/89, THE REGISTRANT HAS SUBMITTED AN ACUTE LETHAL DOSE STUDY AND AN AMES ASSAY BOTH PERFORMED ON THE IMPURITY [redacted] IN A PREVIOUS SUBMISSION BY THE REGISTRANT, IT WAS STATED THAT THE "NEW" IMPURITY (F-6594) IS EXPECTED TO CONVERT TO A-4098. TOXICITY DATA AVALIABLE ON THIS LATTER COMPOUND INCLUDE RAT ACUTE DATA (ORAL LD_{50} = 1680 MG/KG FOR MALES) AND A NEGATIVE AMES ASSAY (DOSES UP TO 10,000 UG/PLATE, WITH AND WITHOUT METABOLIC ACTIVATION.

THE TWO NEW STUDIES HAVE BEEN REVIEWED AND THE DER'S ARE ATTACHED.

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

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In the acute lethal study, one male rat was dosed per dose level (100, 500, 1000, 2000, or 4000 mg/kg). No deaths occurred at the three lowest dose levels, but both rats died at the other two levels. Although this study does not satisfy the guideline requirements (81-1) for an acute oral study, but it does provide information about a lethal dose of F-6594 for comparison with the acute oral dose of [redacted] (LD_{50} = 1680 mg/kg - males), another impurity in metsulfuron methyl.

In the Ames assay, IN F6594 was not mutagenic to tester strains TA97, TA98, TA100, or TA1535 of Salmonella Typhimurium with and without metabolic activation at concentrations up to 500 ug/plate for each strain.

CONCLUSION

Provided data have been submitted to demonstrate conversion of F-6594 to A-4098, the limited toxicology data available do not raise any concern regarding minimal exposure to the "new' impurity. The acute lethal dose study does not fulfill the Guideline requirement 81-1 for acute oral exposure; it is classified as core supplementary and is not upgradeable. The Ames assay does not fulfill the Guideline requirement 84-2(a) for gene mutation; it is classified as unacceptable, pending submission of data regarding the solubility and Batch number of IN F6594 and information for confirming the genotypes of the tester strains.

REVIEWED BY: LINDA L. TAYLOR, PH.D. Linda Lee Taylor 4/17/90
TOX. BRANCH II, SECTION II, (H7509C)
SECONDARY REVIEWER: JOHN H.S. CHEN, D.V.M. John H.S. Chen 4/19/90
TOX. BRANCH II, SECTION I, (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: SALMONELLA/MAMMALIAN ACTIVATION GENE MUTATION ASSAY

TOX. CHEM. NO.: 419H

MRID NO.: 413932-03

TEST MATERIAL: [redacted]

(NOTE: THE TEST MATERIAL IS AN IMPURITY OF THE HERBICIDE, METSULFURON METHYL)

SYNONYMS: IN F6594

STUDY NUMBER: MR 4581-689; H# 17,649

SPONSOR: AGRICULTURAL PRODUCTS DEPARTMENT EXPERIMENTAL STATION

TESTING FACILITY: HASKELL LABORATORY FOR TOXICOLOGY & INDUSTRIAL MEDICINE

TITLE OF REPORT: MUTAGENICITY TESTING OF IN F6594 IN THE SALMONELLA TYPHIMURIUM PLATE INCORPORATION ASSAY

AUTHORS: VINCENT L. REYNOLDS

REPORT ISSUED: FEBRUARY 24, 1989

QUALITY ASSURANCE: A QUALITY ASSURANCE STATEMENT WAS PROVIDED.

CONCLUSIONS: IN F6594 WAS NOT MUTAGENIC TO TESTER STRAINS TA97, TA98, TA100, OR TA1535 OF SALMONELLA TYPHIMURIUM WITH AND WITHOUT METABOLIC ACTIVATION AT CONCENTRATIONS UP TO 500 UG/PLATE FOR EACH STRAIN.

CLASSIFICATION: UNACCEPTABLE, PENDING SUBMISSION OF INFORMATION ON THE SOLUBILITY OF IN F6594.

SALMONELLA

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

A. MATERIALS

1. TEST MATERIAL: NAME: IN F6594 [redacted] DESCRIPTION: WHITE SOLID, ASSUMED STABLE
BATCH #: NOT PROVIDED; PURITY: 91%.
SOLVENT USED: DMSO
OTHER COMMENTS: THE TEST MATERIAL IS AN IMPURITY OF THE HERBICIDE METSULFURON METHYL.

2. CONTROL MATERIALS:
NEGATIVE: DMSO
SOLVENT/FINAL CONCENTRATION: DMSO* (BAKER LOT # B02339)/???????
POSITIVE: NON-ACTIVATION:
SODIUM AZIDE 2 UG/PLATE TA100, TA1535
2-NITROFLUORENE 25 UG/PLATE TA98
ICR-191 ACRIDINE 2 UG/PLATE TA97
OTHER (LIST):

ACTIVATION:
2-AMINOANTHRACENE (2-ANTHRAMINE) 1 (TA97) UG/PLATE
2 (TA98,TA1535) UG/PLATE
USUALLY ALL STRAINS
OTHER (LIST):

* SOLVENT FOR SODIUM AZIDE WAS DISTILLED DEIONIZED WATER

3. ACTIVATION: S9 DERIVED FROM

X AROCLOR 1254	X INDUCED	X RAT(MALE)	X LIVER
PHENOBARBITAL	NON-INDUCED	MOUSE	LUNG
NONE		HAMSTER	OTHER
OTHER		OTHER	

THE S9 MIX COMPOSITION WAS AS FOLLOWS: 8MM $MgCl_2$, 33MM KCL, 5MM GLUCOSE-6-PHOSPHATE, 4MM $NADP^+$, 100MM SODIUM PHOSPHATE (PH=7.4), 1.6 MG S-9 FRACTION/1.0ML S-9 MIX. THE S-9 FRACTION (SITEK RESEARCH LABORATORIES, ROCKVILLE, MD, LOT # 880809) WAS THE 9,000 X G SUPERNATANT OF LIVER HOMOGENATE (1 G WET LIVER: 3.0 ML PBS). THE LIVERS WERE FROM MALE CRL: CD®BR RATS INJECTED I.P. 5 DAYS BEFORE SACRIFICE.

4. TEST ORGANISMS: S. TYPHIMURIUM STRAINS

X TA97	X TA98	X TA100	TA102	TA104
X TA1535	TA1537	TA1538; LIST ANY OTHERS.		

NO INFORMATION WAS PROVIDED AS TO WHETHER THE TEST ORGANISMS WERE CHECKED FOR APPROPRIATE GENETIC MARKERS OR HOW THEY WERE MAINTAINED.

5. TEST COMPOUND CONCENTRATIONS USED:
NON-ACTIVATED CONDITIONS: 0, 50, 75, 100, 250, 500 UG/PLATE

ACTIVATED CONDITIONS: 0, 50, 75, 100, 250, 500 UG/PLATE

SALMONELLA

B. TEST PERFORMANCE

1. TYPE OF SALMONELLA ASSAY:
   - X STANDARD PLATE TEST
   - ___ PRE-INCUBATION (___ MINUTES)
   - ___ "PRIVAL" MODIFICATION (I.E., AZO REDUCTION METHOD)
   - ___ SPOT TEST
   - ___ OTHER (DESCRIBE)

PROTOCOL: THE ASSAY WAS PERFORMED WITH AND WITHOUT A RAT LIVER HOMOGENATE ACTIVATION SYSTEM (S-9 MIX) SIMILAR TO THE METHOD OF AMES, ET AL., [MUTAT. RES. 113, 173-215 (1983)]. POSITIVE INDICATORS AND NEGATIVE CONTROLS WERE INCLUDED IN ALL ASSAYS. NON-ACTIVATED TREATMENTS WERE CONDUCTED BY ADDING 0.1 mL OF SOLVENT OR SOLUTION OF TEST MATERIAL AND 0.1 mL OF AN OVERNIGHT CULTURE CONTAINING APPROXIMATELY 10^8 BACTERIA TO 2 mL OF TOP AGAR (0.6% AGAR, 0.6% NaCl, 0.05 mM L-HISTIDINE, 0.05 mM BIOTIN). THESE COMPONENTS WERE MIXED AND POURED ON THE SURFACE OF A PLATE CONTAINING 25 mL OF DAVIS MINIMAL AGAR. TREATMENTS WITH ACTIVATION WERE CONDUCTED BY ADDING 0.5 mL OF S-9 MIX TO THE BACTERIA/TEST SAMPLE/TOP AGAR AS DESCRIBED ABOVE AND POURING THE MIXTURE ONTO A MINIMAL AGAR PLATE. REVERTANT COLONIES WERE COUNTED AFTER THE INDIVIDUALLY-LABELED PLATES WERE INCUBATED AT 37°C FOR 48 HOURS.

2. PRELIMINARY CYTOTOXICITY ASSAY: THE CYTOTOXICITY OF IN F6594 (WITH AND WITHOUT AN ACTIVATION SYSTEM) WAS MEASURED IN STRAIN TA98, USING THE SAME PROCEDURE AS IN THE MAIN STUDY EXCEPT THAT APPROXIMATELY 10^3 RATHER THAN 10^8 BACTERIA WERE USED PER PLATE, EXCESS HISTIDINE WAS PRESENT, AND NO POSITIVE INDICATORS WERE TESTED. THE DOSES TESTED WERE 0, 1, 5, 10, 50, 100, 500 UG/PLATE. THE AUTHOR STATED THAT SOLUBILITY OF IN F6594 PROHIBITED DOSING ABOVE 500 UG/PLATE. THE RESULTS ARE PRESENTED IN TABLE 1, COPY ATTACHED. IN F6594 DID NOT EXHIBIT TOXICITY AT ANY OF THE DOSE LEVELS, WITH OR WITHOUT ACTIVATION. THE 500 UG/PLATE DOSE WAS CHOSEN AS THE HIGHEST DOSE FOR THE MUTAGENICITY ASSAYS.

SALMONELLA

3. MUTAGENICITY ASSAY : THE MUTAGENICITY OF IN F6594 WAS EVALUATED USING FOUR TESTER STRAINS OF SALMONELLA TYPHIMURIUM (TA97, TA98, TA100 AND TA1535) AT CONCENTRATIONS OF 500 UG/PLATE AND BELOW, SINCE THE TEST MATERIAL IS APPARENTLY NOT SOLUBLE ABOVE THIS LEVEL. NO SOLUBILITY DATA WERE PROVIDED TO SUBSTANTIATE THIS. PLATING WAS PERFORMED IN DUPLICATE.

THE RESULTS INDICATE THAT COUNTS OF REVERTANT COLONIES FOR EACH TESTER STRAIN TREATED WITH TEST MATERIAL WERE SIMILAR TO THE CORRESPONDING SOLVENT CONTROLS AT THE CONCENTRATIONS TESTED, BOTH WITH AND WITHOUT METABOLIC ACTIVATION [SEE ATTACHED TABLES - TABLES II & III (TA1535), TABLES IV & V (TA97), TABLES VI & VII (TA98), AND TABLES VIII & IX (TA100)]. THE STRAIN SPECIFIC CONTROL COMPOUNDS AND THE POSITIVE CONTROL COMPOUND TO ENSURE THE EFFICACY OF THE ACTIVATION SYSTEM GAVE THE POSITIVE RESPONSES EXPECTED.

4. REVIEWER'S DISCUSSION/CONCLUSION

A. THE SPONTANEOUS REVERTANT COLONIES FOR EACH OF THE FOUR TESTER STRAINS OF SALMONELLA TYPHIMURIUM WERE WITHIN THE NORMAL RANGES OF REVERTANTS RECOMMENDED BY AMES, ET AL. (MUTATION RES. 31, 347-364 (1975); MUTATION RES. 113, 173-215 (1983). THE INFORMATION FOR CONFIRMING THE GENOTYPES OF THESE TESTER STRAINS SHOULD BE INCLUDED.

B. THE RESPONSES OBSERVED WITH THE STRAIN SPECIFIC CONTROLS AND THE POSITIVE CONTROL COMPOUND INDICATE THAT THE ASSAY SYSTEMS WERE SENSITIVE ENOUGH TO DETECT REVERSE MUTATIONS UNDER THE CONDITIONS OF THE ASSAYS.

C. THE RATIONALE USED TO DETERMINE THE MAXIMUM DOSE LEVEL TO BE USED IN THE ASSAYS IS BASED ON THE SOLUBILITY OF THE TEST MATERIAL. THE REGISTRANT SHOULD PROVIDE DATA/INFORMATION TO SUBSTANTIATE THE CHOICE OF 500 UG/PLATE DOSE AS THE MAXIMUM SOLUBLE LEVEL.

D. SINCE NO STATISTICALLY SIGNIFICANT INCREASES IN THE NUMBER OF REVERTANT COLONIES FOR ANY OF THE FOUR TESTER STRAINS WERE OBSERVED FOLLOWING EXPOSURE TO THE TEST MATERIAL, WITH AND WITHOUT METABOLIC ACTIVATION, IT IS CONCLUDED THAT THE RESULTS OF THE TWO TRIALS WITH IN F6594 DO NOT SUGGEST A POSITIVE EFFECT.

E. THIS STUDY IS CLASSIFIED AS UNACCEPTABLE PENDING SUBMISSION OF INFORMATION ON THE SOLUBILITY AND BATCH NUMBER OF IN F6594. THE STUDY MAY BE UPGRADED UPON RESOLUTION OF THESE ASPECTS.

REVIEWED BY: LINDA L. TAYLOR, PH.D. Linda Lee Taylor 4/17/90
TOX. BRANCH II, SECTION II (H7509C)
SECONDARY REVIEWER: K. CLARK SWENTZEL K. Clark Swentzel 4/20/90
HEAD SECTION II, TOX. BRANCH II (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: ACUTE ORAL LD_{50} - RATS TOX CHEM NO: 419H

ACCESSION/MRID NO.: 413932-02

TEST MATERIAL: [redacted]

SYNONYMS: IN F6594

STUDY NUMBER: MEDICAL RESEARCH # 4581-689; HASKELL # 17,649; REPORT # 96-89

SPONSOR: DUPONT

TESTING FACILITY: HASKELL LABORATORY FOR TOXICOLOGY AND INDUSTRIAL MEDICINE

TITLE OF REPORT: APPROXIMATE LETHAL DOSE OF IN F6594 IN RATS

AUTHORS: JOHN W. SARVER

REPORT ISSUED: FEBRUARY 21, 1989; REVISED FEBRUARY 19, 1990

QUALITY ASSURANCE: A QUALITY ASSURANCE STATEMENT WAS PROVIDED.

CONCLUSIONS: NO LD_{50} VALUE FOR THE IMPURITY WAS DETERMINED. UNDER THE CONDITIONS OF THE STUDY, THE LOWEST LETHAL DOSE WAS 2000 MG/KG.

CLASSIFICATION: CORE SUPPLEMENTARY, NOT UPGRADEABLE.

TOXICITY CATEGORY:

A. MATERIALS:

1. TEST COMPOUND: IN F6594
   BATCH #: NOT PROVIDED
   DESCRIPTION: WHITE SOLID
   PURITY: APPROXIMATELY 91%

2. TEST ANIMALS:
SPECIES: RAT
STRAIN: CRL: CD®BR
AGE: 8 WEEKS OLD
WEIGHT: 243-276 GRAMS
SOURCE: CHARLES RIVER BREEDING LABORATORIES, NC

STUDY DESIGN: ONE MALE RAT PER DOSE GROUP WAS ADMINISTERED (GAVAGE) THE TEST MATERIAL SUSPENDED IN MAZOLA® CORN OIL IN SINGLE DOSES OF 100, 500, 1000, 2000, OR 4000 MG/KG (DOSE VOLUME VARIED WITH DOSE). FEW ANIMALS WERE USED DUE TO THE LIMITED SUPPLY OF TEST MATERIAL, WHICH IS AN IMPURITY IN THE HERBICIDE METSULFURON METHYL. ALL ANIMALS WERE OBSERVED FOR CLINICAL SIGNS OF TOXICITY FOLLOWING DOSING AND DAILY THEREAFTER UNTIL SIGNS SUBSIDED, AND THEN 3 TIMES PER WEEK UNTIL DAY 15.

RESULTS: NO DEATHS OCCURRED AT THE 100, 500, OR 1000 MG/KG DOSE LEVELS. BOTH OF THE ANIMALS AT THE TWO HIGHEST DOSE LEVELS DIED.

CONCLUSION: THIS STUDY DOES NOT SATISFY THE GUIDELINE REQUIREMENTS (81-1) FOR AN ACUTE ORAL STUDY, BUT IT DOES PROVIDE INFORMATION ABOUT A LETHAL DOSE FOR COMPARISON WITH THE ACUTE ORAL DOSE OF [redacted] (LD_{50} = 1680 MG/KG - MALES), ANOTHER IMPURITY IN METSULFURON METHYL. IT IS TO BE NOTED THAT THE TEST MATERIAL IS AN IMPURITY OF METSULFURON METHYL; THEREFORE, THIS STUDY IS NOT A DATA REQUIREMENT, AS SUCH.

THIS STUDY IS CLASSIFIED SUPPLEMENTARY, NOT UPGRADEABLE.

Metsulfuron-methyl / toxicology review

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