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

005113

MAY 15 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCE

MEMORANDUM

SUBJECT: 524-EUP-AT (PP 6G 3345) and Temporary Tolerances for Acetochlor on corn and in eggs, poultry and meat.

Caswell # 38

TO: Robert Taylor (25)
Registration Division (TS-767C)

FROM: Winnie Teeters, Ph.D. W. Teeters, 4-16-86
Pharmacologist, Section V
Tox/HED (TS-769C)

THRU: Laurence D. Chitlik, D.A.B.T.
Head, Section V
Tox/HED (TS-769C) J. D. Chitlik. 4/30/86

and

Theodore M. Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

CHEMICAL: Acetochlor (2-chloro-N-[ethoxymethyl]-N-[2-ethyl-6-methyl phenyl] acetamide), MON 097, CP 55097; Harness® and Top-Hand® are EC formulations

ACTION REQUESTED: Review submitted studies to support Monsanto's request for an EUP for Top-Hand® and Top-Hand® tank mixes in corn (field) and an application for temporary tolerances for Acetochlor in or on the raw agricultural commodities as follows:

Corn (field) grain	0.1 ppm
Corn forage and fodder	0.5 ppm
Eggs	0.02 ppm
Milk	0.02 ppm
Beef tissue	0.02 ppm
Hog tissue	0.02 ppm
Chicken tissue	0.02 ppm
Goat tissue	0.02 ppm
Horse tissue	0.02 ppm
Sheep tissue	0.02 ppm

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Residue tolerances for atrazine on corn are established (40 CFR 180.220):

Corn grain	0.25 ppm
Corn forage and fodder	15.0 ppm

Residue tolerances for cyanazine on corn are established (40 CFR 180.307):

Corn grain	0.05 ppm
Corn forage and fodder	0.2 ppm

Residue tolerances for simazine on corn are established (40 CFR 180.213):

Corn grain	0.25 ppm
Corn forage	15.0 ppm
Corn fodder	0.25 ppm

Residue tolerances for glyphosate on corn are established (40 CFR 180.364):

Grain crops	0.1[N] ppm

Residue tolerances for paraquat on corn are established (40 CFR 180.205):

Corn grain	0.05[N] ppm
Corn forage and fodder	0.05[N] ppm

The EUP Program: Monsanto requests 35,000 pounds active ingredient (Acetochlor) of Top-Hand® for use in a two-year program which will treat 10,500 acres in 30 states (21,000 lbs.) and allow for bulk storage assessment (14,000 lbs.).

An exemption has been requested [redacted] from the requirement of a tolerance for residues of the inert ingredient [redacted] when used in formulations of Acetochlor applied to corn. This has been denied (see No. 2 below in Recommendations).

INERT INGREDIENT INFORMATION IS NOT INCLUDED

Recommendations: The studies reviewed in this action for MON 8449 formulation and those in our files on Acetochlor are adequate to support the requested EUP and temporary tolerances, except for an acute inhalation study with the formulation (a waiver for which was denied) and a subchronic or longer-term feeding study in a non-rodent (the 119-day dog feeding study [Pharmacopathics Res. Labs. #7920, 10-10-80] did not establish a NOEL and the 1-year dog feeding study [Pharmacopathics Res. Labs. #PR-80-008, 10-14-81] was classified as Supplementary Data. Furthermore, the status of mutagenicity studies for chromosome aberration (Hazleton Labs. America # 83-006, 5-24-83) and other genotoxic effects (Pharmacon Res. Internat'l # PK-52-151) are presently under review.

However, the following information should be considered when decisions are made regarding these requests:

1. Acetochlor has been found in chronic studies to be oncogenic in both

rats and mice (memo of Teeters to Taylor, 8-5-85) and chronic systemic toxicity has not been adequately defined. A new study is necessary to establish a NOEL for chronic toxicity.

A risk assessment (memo of Lacayo to Teeters, signed by the former on 5-4-86) based on the findings in these oncogenic studies estimates a worst case potency of Q_1^* (mg/kg/day) to be 10^{-2} for humans; the worst case Q_1^*s for mice and rats are 10^{-3} and 10^{-4}, respectively.

In an informal note from Lacayo using the tolerances requested in this action, the dietary risk to humans was estimated to be 3.3×10^{-6}, indicating there appears to be only a minor risk from dietary exposure at the requested tolerance levels. However, the risks to applicators have not been assessed.

Furthermore, Acetochlor is one of a series of closely related analogs having oncogenic activities (memo of Teeters to Engler, 8-23-85). Others in this series are Alachlor, Metolachlor and Butachlor. Additionally, Propachlor and Allidochlor, also of this series, may be positive oncogens but were tested by Industrial Bio-Test Laboratories and these long term studies must be repeated.

2. [redacted] weight of the Top-Hand® formulation (MON 8449), a requested waiver for the requirement for an acute inhalation study for this formulation has been denied (see pages 12-14 for details).

Summary of reviews for studies accompanying this action (all studies were conducted with MON 8449, an EC formulation containing 74-76% (Certified Limits) of Acetochlor and have the same Acc. No. 260748):

1. Acute Oral Toxicity Study in Rats, Bio/Dynamics, Inc., #6067-85, 12-6-85.

   The acute oral LD_{50}s for rats are as follows:

Males	2400 mg/kg
Females	1550 mg/kg
Combined	1900 mg/kg

   These data require Toxicity Category III for acute oral toxicity. The study is classified as Core Minimum.

2. Acute Dermal Toxicity Study in Rabbits, Bio/Dynamics, Inc., 6068-85, 11-7-85.

   The acute dermal LD_{50} in rabbits is greater than 2000 mg/kg but less than 5000 mg/kg.

These data require Toxicity Category III for acute dermal toxicity. The study is classified as Core Minimum.

3. Eye Irritation Study in Rabbits, Bio/Dynamics, Inc., #6070-85, 11-7-85.

Corneal opacity and ulceration, and irritation of the iris and conjunctivae were present in 6/6 rabbits; opacity persisted through 72 hrs. in 4/6 and through 7 days in 3/6 and had disappeared by Day 30.
These data require Toxicity Category I for ocular irritation.
The study is classified as Core Minimum.

4. Primary Dermal Irritation Study in Rabbits (4 Hour Exposure/Semi-Occulsive Covering), Bio/Dynamics, Inc., #6069-85, 12-7-85.

In 6/6 rabbits there were irritation effects of slight to mild erythema and edema which persisted in some animals through 72 hours, and by Day 14, two rabbits still had minimum erythema.

These data require Toxicity Category IV for dermal irritation.
The study is classified as Core Minimum.

5. A Closed-Patch Insult Dermal Sensitization Study in Guinea Pigs, Bio/Dynamics, Inc., #6071-85, 11-7-85.

Each of 10 tested pigs gave a positive reaction to the challenge dose. These data indicate that MON 8449 may have the potential to sensitize humans upon repeated dermal contact.

The study is classified as Core Guideline.

6. A requested waiver for the requirement for an acute inhalation toxicity study with MON 8449 was considered.

The waiver is denied. The basis for the denial is that the proposed formulation for MON 8449 contains [redacted] ingredients for which we have no information, and the combined contribution of these [redacted] amounts to greater than [redacted] by weight of the total formulation. Although this is a relatively low percentage, if these ingredients were to have grave respiratory effects their influence could markedly alter the respiratory toxicity of the formulation. This possibility cannot be assessed from the data referenced by the sponsor.

Summary of data in our files:

Memo of Teeters to Taylor, 8-5-85. (Petition 3F2966 & 524-GUI and 524-EUP-56/2G2797 and 3G2791). Studies with Acetochlor (MON 097, CP 55097)

1. Subchronic 21-day dermal, IRDC Study #IR 80-356, 12-11-81.
   LOEL for systemic effects (mortality and decreased weight gain): 1200 mg/kg (HDT).
   NOEL for systemic effects: 400 mg/kg
   LOEL for dermal irritation: 100 mg/kg (LDT)
   NOEL for dermal irritation: not established

Core minimum.

2. Dermal sensitization, (MON 097 technical). Bio/Dynamics, Inc. Study #BD-82-204, 4-13-83.
   Positive dermal sensitizer
   Core minimum

3. Dermal sensitization, (MON 097, 8 lbs/gal EC formulation, Harness®). Bio/Dynamics, Inc. Study #BD-82-205, 4-13-83.
   Positive dermal sensitizer
   Core minimum

4. In Vivo bone marrow chromosome study, Hazleton Labs. America, Inc. Study #HL83-006, 5-24-83.
   No evidence of chromosome abnormalities induced, but the study is Unacceptable; however, results of study audit are under review.

5. Rat hepatocyte primary culture/DNA repair test, Pharmacon Res. Internat'l, Inc. Study #PK-52-151, 2-17-83.
   No evidence of inducement of unscheduled DNA synthesis, but the study is Unacceptable; however, additional material is under review.

6. Mouse lymphoma assay, SRI Internat'l Study #SR-81-150, Aug.-82.
   Positive mutagen only in the presence of metabolic activation.
   Study is Acceptable.

7. CHO/HGPRT gene mutation assay, Monsanto Environmental Health Lab. Study #ML-82-281, 6-9-83.
   Weakly positive at near-toxic doses, but the vehicle used (alcohol) did not appear to be inert in the assay.
   Study is Acceptable.

8. Rabbit teratology studies, IRDC, Pilot Studies #IR-79-292, Primary Study #IR-79-293, 11-24-81.
   Two pilot studies are Invalid Data; the third pilot study is Supplementary Data as a range-finding study.

   The primary study is also Supplementary Data and a new study is requested; insufficient numbers of litters were available to fully assess the teratogenic potential.

9. Two generation reproduction study in rats, IRDC Study #IR-80-053, 12-16-82.
   Reproductive NOEL: 500 ppm
   Reproductive LOEL: 1500 ppm (based on decreased body weight gain of F_{2b} pups)
   Systemic NOEL: <500 ppm based on absolute and relative organ weight: decreases for ovary weights in F_1 females, decreases for pituitary weights for F_1 and F_{2b} males, increases for thyroid weights in F_{1b} and F_{2b} pups.

   Supplementary Data, but additional material is under review.

10. Metabolism study with rats, Hazleton Raltech, Inc. Study #MSL-2824, June-83.

Little (0.5%) eliminated via lungs; >70% excreted within 48 hrs., preferentially in urine. Elimination is biphasic with a fast half-life of < 10 hrs. and a slow half-life of 128-286 hrs. Early metabolites are mainly mercapturates; later ones were sulfoxides, sulfones, and sulfates; over 20 metabolites were identified. Less than 1% of parent compound is excreted unchanged in feces. There was retention of 2-2.5% of dose in RBC due to covalent binding to hemoglobin.

Core Guideline

11. One year feeding study in dogs, Pharmacopathics Res. Lab. Study #PR-80-008, 10-14-81.
Dogs at 40 mg/kg (HDT) showed testicular atrophy accompanyied by decreased absolute and relative (to body weight) testicular weight, decreased body weight gain of males and decreased terminal body weight of females. There is also suggestive evidence at this level for anemia and hepatotoxicity but a NOEL and LOEL cannot conclusively be determined for these effects at lower levels because of control data variability and the wide range of normal values for these parameters established at the testing facility.

Supplementary Data

12. Chronic toxicity and oncogenicity study in rats, Pharmacopathics Res. Labs. Study #PR-80-006, 5-20-83.
Oncogenic NOEL: 1500 ppm
Oncogenic LOEL: 5000 ppm -increased incidence of liver carcinomas and thyroid follicular cell adenomas in males.
There were positive trends for hepatic carcinomas in females and thyroid follicular cell adenomas in males.
Systemic LOEL: 500 ppm (LDT) based on organ weight effects and decreased body weight in males.
Systemic NOEL was not established. One must be established in a new study.
The high level (5000 ppm) also increased incidences of polyarteritis of the testes and arteries of males and liver necrosis and alveolar histiocytosis in females. Mortality was increased in females and food consumption was decreased in both sexes.

Minimum Data

13. Oncogenicity study in mice, Pharmacopathics Res. Labs. Study #PR-80-007, 5-4-83.
Oncogenic NOEL: < 500 ppm (LDT). There were increased incidences of: liver carcinomas in high level males, total tumors in females of all levels, carcinomas of the lungs in low and high level females, uterine histiocytic sarcomas in females of all levels and total benign ovarian tumors in mid level females. There were positive linear trends for: liver carcinomas in both sexes, and pulmonary carcinomas, total lung tumors, ovarian benign tumors and kidney adenomas in females.
Non-neoplastic lesions included an increase in interstitial nephritis in both sexes of the high level(5000 ppm).
Systemic LOEL: 500 ppm(LDT) based on increased liver and kidney weights in males.

Minimum Data

Memo of Dykstra to Taylor, dated 3-21-84 for PP# 1G 2454. These data are summarized as follows:

1. Acute oral LD_{50}, Rat, Mon 097, 2953 mg/kg (both sexes), Category II, Minimum Data. Environmental Health Laboratory Report #80-49, 10-15-80.
2. Acute dermal LD_{50}, Rabbit, Mon 097, 3667 mg/kg (both sexes), Category III, Minimum Data. Environmental Health Laboratory Report #80-48, 10-15-80.
3. Primary dermal irritation, Mon 097, P.I.=0.6/8.0, Category IV, Minimum Data. Environmental Health Laboratory Report #80-50, 10-15-80.
4. Primary eye irritation, Mon 097, scores for unwashed= 18.8/110, for washed=1.2/110, Category II, Minimum Data. Environmental Health Laboratory Report #80-51, 10-15-80.
5. 91-Day feeding, Rat, CP-55097, NOEL = 800 ppm
   LOEL = 2000 ppm based on body weight loss and food consumption decrease, Minimum Data. Pharmacopathics Report #7914, 10-10-80.
6. 119-Day feeding, Dog, CP-55097, NOEL <25 mg/kg/day (LDT), dose-related elevated SGPT - Minimum Data. Pharmacopathics Report #7920, 10-10-80.
7. Teratology, Rat, CP-55097, Negative at 400mg/kg/day
   Fetotoxic NOEL = 200 mg/kg/day
   Maternal NOEL = 200 mg/kg/day
   Minimum Data. IRDC Report #401-066, 10-15-80.
8. Mutagenicity, Ames Salmonella Assay, CP-55097, Negative for strains TA-98, 100, 1535 and 1537, with and without mouse and rat microsomal preparations. Minimum Data. Monsanto Report # MRC-DA-838, 12-5-78.

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Data Evaluation Record

Study Title: Acute Oral Toxicity Study In Rats
Accession No.: 260748
Sponsor/Contracting Lab.: Monsanto Co./ Bio/Dynamics, Inc.
Study No.: 6067-85
Report Date/Submitted: 12-6-85 / 12-20-85
Test Material: MON 8449, Lot XLF-274 (Top-Hand®)
Although the composition was not identified in this report, the sponsor's submission included the composition of MON 8449
Test Animal: Albino rats, CD^R (Sprague-Dawley derived)
5/level/sex, except that only females were tested at the lowest dose
Test Doses: 625, 1250, 2500 & 5000 mg/kg, orally

Quality Assurance: A brief, general statement about this subject was in the report introduction.

Comments on Methods and Reporting: The study included four dose levels. Two were run simultaneously, and one about a month later and one about two weeks earlier. These animals used at different times were from different shipments. This is undesirable procedural practice. Also, 5 animals/sex/level should have been used, but only females were used at the lowest level.

The report states that 20 males and 15 females were used whereas 15 males and 20 females were used. Table III (page 10) gives postmortem observations for males but no males at this level died, and even if one assumes the data are for females, one of the animal numbers in incorrect (No. 2875 should be 2973, according to Table 1). There is yet another typo on page 5 under "A. Mortality", where 3/3 (should be 3/5) males at 2500 mg/kg are listed as dying.

Methods: The rats received a single dose of the neet material by oral intubation after an overnight fast following a 14-16 day equilibration period. Doses were based on fasted weights. Weights were taken pre-fast, post-fast, and on 7 and 14 days postdose. Observations were made 1, 2, and 4 hours after dosing and daily thereafter for 14 days, when surviving rats were sacrificed and necropsied. Rats that died were necropsied also.

Results: The mortality data were as follows:

Dose Level mg/kg	Mortality Males	Females	Combined
625		0/5	0/5
1250	0/5	3/5	3/10
2500	3/5*	3/5	6/10
5000	5/5	5/5	10/10
LD_{50}(mg/kg)	2400	1550	1900
95% Conf. Limits	1128-3672	760-2340	1094-2760

* Listed as 3/3 on page 5 of report

Signs noted were primarily those associated with dying animals, seen from 23 hours to Day 6, and included hypoactivity, prostration, respiratory abnormalities and evidence of anal, oral, ocular and nasal discharges. Necropsy findings were most prevalent for lungs and gut, and signs suggestive of irritation were seen in the latter. All survivors gained weight by Day 14.

These data require Toxicity Category III for oral toxicity.
The study is classified Core Minimum.

Data Evaluation Record.

Study Title:	Acute Dermal Toxicity Study In Rabbits
Accession No.:	260748
Sponsor/Contracting Lab.:	Monsanto Co./ Bio/Dynamics; Inc.
Study #:	6068-85
Report Date/Submitted:	11-7-85 / 12-20-85
Test Material:	MON 8449, Lot XLF-274 (Top-Hand®) Although the composition was not identified in this report, the sponsor's submission included the composition of MON 8449.
Test Animal:	New Zealand white albino rabbits, 5/sex/level
Test Doses:	2000 or 5000 mg/kg
Quality Assurance:	There was a very brief, general statement on this subject in the introduction of the report.

Comments on Methods: Only two dose levels were used; they were run over two weeks apart using animals of different shipments. This is poor procedural practice. Our Guidelines suggest using a minimum of three dose levels. However, our Guidelines also state that a "limit test" using at least 2000 mg/kg with no compound related mortality may be sufficient and this study meets this qualification.

Methods: A single dose of the neet material was applied to a clipped dorsal area; the animal was then wrapped in gauze to cover the site and then overwrapped in an impervious plastic sleeve. A collar was fitted to prevent ingestion of test material and to maintain the wrappings for 24 hours, after which they were removed and the site wiped free of excess material. The rabbits had been acclimated for 23-24 days before dosing. Weights were recorded at time of clipping, pre-dose and at 7 and 14 days postdose. Observations were made 1, 2 and 4 hours after dosing and daily thereafter. Necropsies were performed on animals that died or were sacrificed at study termination.

Results: No animal died at the 2000 mg/kg level and all died between Days 1 and 2 when dosed at the 5000 mg/kg level. Thus the LD_{50} is greated thar 2000 and less than 5000 mg/kg. Some of the lower level group lost 0.1 kg by Day 7 but each had gained this amount by Day 14, except one male (change measured from pre-test weight). At 2000 mg/kg, there was a single occurance of nasal discharge or wet rales and a few rabbits showed signs of dermal necrosis and irritation. At the high level, signs included fine tremors, ataxia, decreased food consumption, hypoactivity, prostration, nasal or oral discharge, dyspnea and wet rales.

At necropsy of the low dose group the only findings related to exposure were those of dermal effects. Findings at necropsy of the high level group were consistent with postmortem autolysis and antemortem stress, the one exception being that 2/10 were noted to have unilateral renal pelvis dilation.

These data require Toxicity Category III for dermal toxicity.
The study is classified as Minimum Data.

Data Evaluation Record

Study Title:	Eye Irritation Study In Rabbits
Accession No.:	260748
Sponsor/Contracting Lab.:	Monsanto Co. / Bio/Dynamics, Inc.
Study No.:	6070-85
Report Date/Submitted:	11-7-85 / 12-20-85
Test Material:	MON 8449, Batch XLF-274 (Top-Hand®) Although the composition was not identified in this report, the sponsor's submission included the composition of MON 8449.
Test Animal:	New Zealand white albino rabbits, 3 males and 3 females
Test Dose:	0.1 ml instilled into the conjunctival sac of the right eye.
Quality Assurance:	A brief, general statement on this subject was in the report introduction.

Methods: The test dose was instilled into the lower conjunctival sac of the right eye and the lids were held together for 1 sec.; a wash was not used until 24 hours later to remove any residual material. The eyes had been checked with flourescein dye the day before dosing. Irritation was graded 1, 24, 48 and 72 hours and 7, 14, 21 and 30 days after dosing or until no evidence of irritation was present.

Results: Each rabbit exhibited corneal opacity and ulceration, iris effects and conjunctival redness and chemosis. Corneal effects were still present at 72 hours in 4/6 and at 7 days in 3/6. At 14 days, conjunctival irritation was present in 4/6 and corneal effects in 2/6. At 21 days, all eyes were normal except for corneal effects in one and insignificant conjunctival redness in another rabbit. The corneal effects has disappeared by Day 30. Other effects were pannus in one rabbit on Days 7 and 14 and alopecia around the eye in another animal.

These results place MON 8449 in Toxicity Category I for ocular irritation.
The study is classified as Minimum Data.

Data Evaluation Record

Study Title:	Primary Dermal Irritation Study In Rabbits (4-Hour Exposure/ Semi-Occlusive Covering)
Accession No.:	260748
Sponsor/Contracting Lab.:	Monsanto Co./ Bio/Dynamics, Inc.

Study No.:	6069-85
Report Date/Submitted:	12-7-85 / 12-20-85
Test Material:	MON 8449, Batch XLF-274 (Top-Hand®) Although this report did not identify the test material, the sponsor's submission included the composition of MON 8449.
Test Animal:	New Zealand white albino rabbits, 4 males and 2 females
Test Dose:	0.5 ml to each of two intact dermal sites per animal
Quality Assurance:	A brief, general statement about this subject was in the report introduction.

Methods: The day before dosing the hair of the dorsal area of the trunk was clipped to expose at least 10% of the body surface. A volume of 0.5 ml of neet test material was applied to each of two intact skin sites of each rabbit. The dose was placed beneath a 1" X 1" gauze square placed on the test site and held with tape. The sites were then wrapped with gauze surrounding the animal's trunk and covered with porous tape; collars were placed on each animal. After 4 hours, the wrappings and gauze squares were removed and the sites wiped free of excess test material using dry gauze. After 30 minutes, the first dermal observations were made and were repeated at 24, 48 and 72 hours and at 7, 10 and 14 days, or until no signs of irritation were present.

Results: Each rabbit showed slight to mild erythema or edema on one or both test sites through 72 hours. On Day 7, one animal had no effects on either site and two each had one site that was normal. By Day 14, minimal erythema still persisted in one or both sites of two rabbits and desquamation was noted for one or both sites of 4 rabbits.

These data place MON 8449 in Toxicity Category IV for dermal irritation. The study is classified as Minimum Data.

Data Evaluation Record

Study Title:	A Closed-Patch Repeated Insult Dermal Sensitization Study In Guinea Pigs.
Accession No.:	260748
Sponsor/Contracting Lab.:	Monsanto Co. / Bio/Dynamics, Inc.
Study No.:	6071-85
Report Date/Submitted:	11-7-85 / 12-20-85
Test Material:	MON 8449, Lot XLF-274 (Top-Hand®, 92% Acetochlor) Although the study report did not identify the test material other than as MON 8449, the sponsor's submission included the composition.
Test Animal:	Hartly albino guinea pigs Range-finding: 3 males and 3 females Sensitization study: 20 test pigs, two groups of 5 males and 5 females; 20 irritation controls for challenge, two groups of 5 males and 5 females
Test Doses:	Range finding- 0.3 ml of 100, 50, 25 and 10% v/v in acetone

Induction- 0.3 ml of 50% v/v in 80% ethanol
Challenge- 0.3 ml of 25% v/v in acetone

Quality Assurance: A brief, general statement about this subject was in the report introduction.

Methods: A range-finding test to select a slightly irritating concentration for induction and a non-irritating concentration for challenge was conducted by testing each of 6 guinea pigs with 4 concentrations of test material in acetone for 6 hours beneath a Hilltop Chamber on clipped skin and observing for irritation at 24 and 48 hours.

The induction phase of the main study was conducted as for the range-finding test three times per week for 3 weeks (9 exposures of 6 hours each). Test sites were varied to avoid placing patches over skin damaged by irritation from a previous exposure. MON 8449 and dinitrochlorobenzene (DNCB), the positive control, were tested this way. Fourteen days after the last induction exposure, the pigs were challenged in the same manner as for a single induction exposure, but at a new site. Irritation control pigs were treated only as for the challenge procedure.

Pigs of the main study were checked twice daily for viability and were weighed the day prior to first induction and prior to challenge.

Results:

Range-finding: A 50% v/v solution of MON 8449 in 80% alcohol was selected as the slightly irritating concentration for induction and a 25% v/v concentration in acetone was selected for the non-irritating challenge dose.

Main Study: Mild to moderate dermal irritation was seen after the first exposure to MON 8449 and severe irritation occurred with repeated exposures. All 10 pigs gave a definite response to the challenge dose whereas the irritation control pigs did not show a significant response, thus indicating that the test material is a positive dermal sensitizer in guinea pigs.

Pigs treated with DNCB exhibited slight irritation after the first or second induction dose and severe responses beginning after the third dose. Each pig also reacted positively to the challenge dose whereas none of the irritation controls gave a significant response. These data demonstrate that this group of animals are susceptible to sensitization.

All pigs treated with the test material or positive control gained weight during the study.

Conclusion: MON 8449 is a positive dermal sensitizer to guinea pigs, thus may have the potential to sensitize humans upon repeated contact.

The study is classified as Core Guidelines.

Subject: Rationale on why Monsanto should not conduct an acute inhalation toxicity study (CFR 40, §158.135, ref. No. 81-3) with Top-Hand®.

Monsanto provided references for acute inhalation studies with MON 097, 8 lb/gal EC formulation and with [redacted] technical material (98%).

MON 097 Inhalation Study (MON 097, 8 lb/gal EC formulation of Acetochlor)

There is not a DER for this study but the report was obtained from our files by this reviewer. It appears to be a well conducted study. There were no deaths among groups of 5 rats of each sex tested at average maximum concentrations of 3.50, 3.79, 3.82 or 3.85 mg/l. Consequently, the LC_{50} must be greater than 3.85 mg/l for a four-hour exposure. These data indicate a toxicity category of III for acute inhalation toxicity of MON 097, 8 lb/gal EC.

[redacted] Acute Inhalation Study:

This study with [redacted] was reviewed in the memo from Ritter to Taylor, initialed by the former on 12-5-85. The subject was: [redacted]

The maximum concentration attainable was 0.27 mg/l and rats were exposed for 4 hours. No deaths occurred and salivation was the only effect noted. The LC_{50} was concluded to be greater that 0.27 mg/l, the maximum attainable concentration. The study was Core rated as Guideline and the Toxicity Category was stated as III, but should have been II (from 0.2 through 2 mg/l). However, this categorization has little practical meaning in this instance since the maximum attainable concentration was so low. The pertinent fact relative to inhalation toxicity is that it was impossible to attain a significant airborne concentration thus indicating from a practical aspect that inhalation exposure will be low.

Additionally, the formulation ingredients for Top-Hand® and MON 097, 8lb/gal EC were provided by the sponsor as follows:

Top-Hand®

7 lb/gal EC with active ingredient (MON 097) labelled at 75.2%

	%
Mon 097, 91.3 %	82.2
[redacted]	

MON 097 ——— 8lb/gal EC formulation

	%
MON 097*, 94.6%	91.37
[redacted]	

*current label is 85.5% active ingredient

Furthermore, the sponsor referenced the recent EPA Guidelines on acute toxicity testing (Oct.,1984) wherein the Agency discourges animal testing solely to obtain a median lethal dose if toxicity can be predicted from available data. The sponsor contends that enough data are available to evaluate the inhalation toxicity of Top-Hand®.

On the basis of data in our files indicating the relatively low acute in-

[redacted]

INERT INGREDIENT INFORMATION IS NOT INCLUDED

halation toxicity (Category III) for MON 097 and the difficulty in obtaining a significant airborne concentration for MON 8449, the waiver appears justified.

However, on the other hand, there are [redacted] ingredients in the MON 8449 formulation for which we have no information (see attached copy of Exemption status of Inert Ingredients). These 3 ingredients are: [redacted], and the combined contribution of the [redacted] ingredients amounts to over [redacted] by weight of the total formulation. Although the contributed percentage is low, if the ingredients were to induce grave respiratory effects they could markedly influence the toxicity of the formulation. This possibility cannot be assesssed from the data referenced by the sponsor. Consequently, the waiver for the requirement for an acute inhalation toxicity study for MON 8449 is denied.

Moreover, the formulation ingredients shown on the previous page for MON 097, 8lb/gal EC provided by the sponsor differ from the Confidential Statement of Formula on file with Registration Division of EPA for this EC formulation. The difference amounts to more than just the footnoted change indicated on the previous page.

INERT INGREDIENT INFORMATION IS NOT INCLUDED

ACETOCHLOR

Page 15 is not included in this copy.

Pages _____ through _____ are not included.

The material not included contains the following type of information:

X 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.

____ 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.