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

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OCT -7 1991

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: Ignite 1SC Herbicide - Evaluation of Acute Data: Acute Oral, Dermal, and Inhalation Studies in Rats; Primary Eye and Dermal Studies in Rabbits; and Dermal Sensitization Study in Guinea Pigs

ToxChem No.: 580I

Accession (MRID) Nos. 417961-01, 417961-02, 417961-03, 417961-04, 417961-05, 417961-06, and 418463-02
HED Project No.: 1-1604

FROM: Susan L. Makris, M.S. Susan L Makris 10/1/91
Review Section III
Toxicology Branch II
Health Effects Division (H7509C)

TO: Joanne Miller/Jesse Mayes (PM-23)
Fungicide/Herbicide Branch
Registration Division (H7505C)

THRU: James N. Rowe, Ph.D., Section Head James N. Rowe 10/1/91
Review Section III
Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph.D., Branch Chief
Toxicology Branch II
Health Effects Division (H7509C) Marcia van Gemert 10/1/91

Registrant: Hoechst Celanese Corporation
Route 202-206, P.O. Box 2500
Somerville, New Jersey 08876-1258

Action Requested: Review the following studies conducted on the chemical Ignite 1SC Herbicide:

1. Acute Oral Toxicity in Rats
2. Acute Dermal Toxicity in Rats
3. Acute Inhalation Toxicity in Rats
4. Primary Eye Irritation in Rabbits
5. Primary Dermal Irritation in Rabbits
6. Dermal Sensitization in Guinea Pigs

In addition to the above studies, a Summary of Acute Toxicity (MRID No. 417961-01) was submitted to EPA by the registrant. This document was not evaluated as part of the acute package, and no Data Evaluation Report was generated.

Printed on Recycled Paper

Conclusions:

1. Acute Oral Toxicity in Rats (Guideline 81-1) - MRID No. 417961-02, Caswell No. 580I, HED Project No. 1-1604

   The test material was administered to male and female Wistar rats, Hoe: WISKf(SPF71), by a single oral gavage at dosages of 2500, 3150, and 4000 mg/kg. An addition dose level of 5000 mg/kg was administered to male rats only.

   LD_{50} - Males: 4010 mg/kg, Females: 3030 mg/kg, Males & Females: 3570 mg/kg
   Toxicity Category: III (from 500 through 5000 mg/kg)

   CORE Classification: Supplementary - This study can be upgraded to "Guideline" upon clarification of discrepancies regarding the date that the Quality Assurance Statement was signed.

2. Acute Dermal Toxicity in Rats (Guideline 81-2) - MRID No. 417961-03, Caswell No. 580I, HED Project No. 1-1604

   The test material was administered to male and female Wistar rats, Hoe: WISKf(SPF71), by a single 24-hour dermal application at a dosage of 2000 mg per rat (a dosing error that delivered actual dosages to the rats greatly in excess of the limit dose of 2000 mg/kg body weight). There were no mortalities, dermal irritation, or other signs of toxicity at these doses.

   LD_{50} - greater than 2000 mg/kg
   Toxicity Category: III (from 2,000 through 20,000 mg/kg)

   CORE Classification: Supplementary - This study can be upgraded to "Guideline" upon clarification of discrepancies regarding the date that the Quality Assurance Statement was signed.

3. Acute Inhalation Toxicity in Rats (Guideline 81-3) - MRID 418463-02, Caswell No. 580I, HED Project No. 1-1604

   The test material was administered by 4-hour nose only exposure to male and female Wistar rats, Hoe: WISKf(SPF71), at aerosol exposure levels of 0.82, 1.60, 1.90, 3.30, 3.60, and 4.20 mg/L. Although deaths were noted at all exposure levels except 0.82 mg/L, the maximum mortality rate achieved was 50%, and no clear dose-related trend in mortality was demonstrated by the data. Median lethal concentration values cannot be calculated with a high degree of confidence from the mortality patterns observed in this study.

   CORE Classification: Not Acceptable

4. Primary Eye Irritation in Rabbits (Guideline 81-4) - MRID 417961-04, Caswell No. 580I, HED Project No. 1-1604

   Nine New Zealand albino rabbits were exposed for 1 minute or 24 hours to a 0.1 ml single dose of the test material in the conjunctival sac of the left eye.

   Toxicity Category: I; corneal opacity was not reversible within 7 days but was reversible within 14 days

   CORE Classification: Supplementary - This study can be upgraded to "Guideline" upon clarification of discrepancies regarding the date that the Quality Assurance Statement was signed.

5. Primary Dermal Irritation in Rabbits (Guideline 81-5) - MRID 417961-04, Caswell No. 580I, HED Project No. 1-1604

Six New Zealand albino rabbits received a single 0.5 ml dermal dose of the test material, with exposure lasting 4 hours.

Toxicity Category: IV (mild or slight irritation at 72 hours)

CORE Classification: Supplementary - This study can be upgraded to "Guideline" upon clarification of 1) discrepancies regarding the date that the Quality Assurance Statement was signed and 2) an explanation of the method of control comparison.

6. Dermal Sensitization in Guinea Pigs (Guideline 81-6) - MRID 417961-04, Caswell No. 580I, HED Project No. 1-1604

For the induction phase, the test material was administered, as a 20% solution in physiological saline, by nine dermal applications at 2-3 day intervals to Pirbright-White guinea pigs. A single 10% saline solution served as the challenge dose, administered dermally 17 days after the last induction treatment.

The test material was determined not to be a sensitizing agent.

CORE Classification: Supplementary - This study can be upgraded to "Guideline" upon clarification of discrepancies regarding the date that the Quality Assurance Statement was signed.

Reviewed by: Susan L. Makris, M.S. Susan L Makris 10/1/91
Section III, Toxicology Branch II (H7509C)
Secondary reviewer: James N. Rowe, Ph.D. James N. Rowe 10/1/91
Supervisor, Section III, Toxicology Branch II (H7509C)

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DATA EVALUATION REPORT

STUDY TYPE:	Acute Oral Toxicity in Rats (Guideline 81-1)
EPA IDENTIFICATION NOS.:	MRID NO.: 417961-02 HED PROJECT NO.: 1-1604 CASWELL NO.: 580I
TEST MATERIAL:	HOE 039866 Liquid Water-Soluble Concentrate 120 (g/l)
SYNONYMS:	Ignite 1SC Herbicide Monoammonium [2-amino-4-(hydroxymethylphosphinyl) butanoate]
STUDY NUMBER:	85.0496 A35436 Report No. 85.0804
SPONSOR:	Hoechst Celanese Corporation Route 202-206, P.O. Box 2500 Somerville, New Jersey 08876-1258
TESTING FACILITY:	Pharma Research Toxicology and Pathology Hoechst Aktiengesellschaft Postfach 80 03 20 6230 Frankfurt am Main 80 West Germany
TITLE OF REPORT:	HOE 039866-Liquid Water-Soluble Concentrate 120 (g/l) (Code: HOE 039866 OH SL11 A202) Testing for Acute Oral Toxicity in the Male and Female Wistar Rat
AUTHORS:	Dr. K.-H. Diehl Dr. K.-H. Leist
DATE REPORT ISSUED:	August 5, 1985

CONCLUSION:

Toxicity Category:	III (from 500 through 5000 mg/kg)
Median Lethal Dose:	
LD_{50} (Males)	= 4010 mg/kg body weight
LD_{50} (Females)	= 3030 mg/kg body weight
LD_{50} (Males and Females)	= 3570 mg/kg body weight
Core Classification:	Supplementary - This study can be upgraded to "Guideline" upon clarification of discrepancies regarding the date that the Quality Assurance Statement was signed.

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MATERIALS:

1. Test compound: Description: Bluish-green liquid
   Code No.: Hoe 039866 OH SL11 A202
   Purity: 11.4%

2. Test animals: Species: Wistar rat
   Strain: Hoe: WISKf(SPF71)
   Source: HOECHST AG, Kastengrund, SPF breeding colony
   Age: Males - 6-7 weeks; Females - 8 weeks
   Weight: Males - 159-184 g; Females - 159-186 g

METHODS:

Rats were fasted for approximately 16 hours before dosing. The test material was dissolved in deionized water and administered by oral gavage to the following test groups.

Dose (mg/kg)	Concentration % (w/v)	Volume Applied (ml/kg)	No. of Animals	
			Male	Female
2500	25	10	5	5
3150	25	12.6	5	5
4000	25	16	5	5
5000	25	20	5	-

Animals were observed at 10 and 30 minutes after dosing; 1, 2, 4, and 6 hours after dosing; and daily for a total of 14 days. Body weights were recorded immediately prior to dosing on Day 0, and on Days 7 and 14 of study. A gross necropsy was performed on all animals that died on study and on all survivors which were sacrificed on Day 14.

RESULTS:

Mortality data and median lethal dose:

Numerical mortality data and calculated LD_{50} values are presented in Tables 1 and 2.

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Table 1. Mortality (deaths/dosed)

Dose (mg/kg)	Males [number (%)]	Females [number (%)]
2500	1 / 5 (20)	2 / 5 (40)
3150	1 / 5 (20)	2 / 5 (40)
4000	2 / 5 (40)	4 / 5 (80)
5000	4 / 5 (80)	--

Note: Data were extracted from report No. 85.0804, page 12.

The LD_{50} value and the 95% confidence limits were established on the basis of mortality rate by probit analysis.

One male was inadvertently killed 5 days postdose. Because this rat had been free of clinical signs 3 days postdose, and had shown normal weight gain following test material administration, it was counted as a survivor for the purposes of LD_{50} calculation.

The value for an additive LD_{50} (male and female mortality combined) was calculated because the comparison of both probit lines showed that the value "1" was within the 95% confidence range of the coefficient of both LD_{50} values (the relative effect).

Table 2. Median Lethal Dose Values

Sex	LD_{50} (mg/kg)	95% Confidence Limits (mg/kg)
Male	4010	2600 - 3550
Female	3030	731 - 6440
Male and female	3570	2460 - 10900

Clinical signs of toxicity:

The following clinical observations were noted on the day of treatment for both male and female rats: reduced or enhanced spontaneous activity, enhanced startle reflexes, contracted flanks, piloerection, squatting position, periodic prone position, straddling of legs, uncoordinated gait, narrowed or widened palpebral fissures, abnormal respiratory sounds, reduced respiratory rate, bizarre movements, trembling, tonic or tonoclonic convulsions, and salivation.

During the period of Day 1-9, the following observations were reported: lateral position, ataxia and high-legged gait, drowsiness, negative placing reflexes, jerky respiration, grinding of teeth, hypersensitivity

to touch, blood-encrusted snout and eye margins, poor general health condition and persistent attempts to escape when the cage was open. All deaths occurred through Day 9 postdose; from Day 10 through study termination, no clinical signs were noted in the surviving rats.

Body weight data:

Mean body weight data are presented in Table 3. Rats that survived to study termination generally gained body weight. Severe body weight depression was observed in those animals that were found dead and weighed postmortem (data not included in Table 3).

Table 3. Mean body weight and body weight change data - grams (mean percent change from Day 0)a

Dose (mg/kg)		Males			Females		
		Day 0	Day 7	Day 14	Day 0	Day 7	Day 14
2500	Mean	167	214 (31)	253 (55)	173	177 (4)	14)
	S.D.	8.5	7.2	7.0	4.9	29.2	
	N	5	4	4	5	3	
3150	Mean	171	212 (26)	239 (41)	173	175 (0.8)	19c (21)
	S.D.	7.3	9.7	24.7	8.3	45.4	39.0
	N	5	4	4	5	4	3
4000	Mean	174	218 (25)	259 (49)	168	140 (-20)	208 (15)
	S.D.	3.5	4.5	6.1	8.8	60.1	-
	N	5	3	3	5	2	1
5000	Mean	176	b	-	-	-	-
	S.D.	6.6	-	-	-	-	-
	N	5	0	0	-	-	-

a Calculated by reviewer.
b One surviving rat was inadvertently killed on Day 5 postdose.
Note: Data were extracted from report No. 85.0804, pages 14-15.

Gross necropsy data:

The following observations were noted in rats found dead during the study: gastrointestinal tract filled with blackish-brown mass or reddish fluid, reddening of the intestine or pancreas, dark discoloration of the liver or adrenal glands, and congestion of the lungs.

No macroscopic abnormalities were observed in rats that survived to study termination.

DISCUSSION:

Based upon the criteria presented in 40 CFR Part 156.10, the Toxicity Category for acute effects following oral administration of the test material, Hoe 039866 OH SL11 A202, is III (from 500 through 5000 mg/kg).

DEVIATION:

The Quality Assurance Statement contains a signature, but not a valid date. Two conflicting dates are typed at the top of the page, not handwritten in conjunction with the signature.

COMPLIANCE:

The following signed and dated statement was included:
GLP Compliance Statement

Reviewed by: Susan L. Makris, M.S. Susan L Makris 10/1/91
Section III, Toxicology Branch II (H7509C)
Secondary reviewer: James N. Rowe, Ph.D. James N. Rowe 10/1/91
Supervisor, Section III, Toxicology Branch II (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Acute Dermal Toxicity in Rats (Guideline 81-2)

EPA IDENTIFICATION NOS.:
MRID NO.: 417961-03
HED PROJECT NO.: 1-1604
CASWELL NO.: 580I

TEST MATERIAL:
HOE 039866
Liquid Water-Soluble Concentrate 120 (g/l)

SYNONYMS:
Ignite 1SC Herbicide
Monoammonium [2-amino-4-(hydroxymethylphosphinyl) butanoate]

STUDY NUMBER:
86.0696
A35435
Report No. 86.0815

SPONSOR:
Hoechst Celanese Corporation
Route 202-206, P.O. Box 2500
Somerville, New Jersey 08876-1258

TESTING FACILITY:
Pharma Research Toxicology and Pathology
Hoechst Aktiengesellschaft
Postfach 80 03 20
6230 Frankfurt am Main 80
West Germany

TITLE OF REPORT:
HOE 039866-Liquid Water-Soluble Concentrate 120 (g/l)
(Code: HOE 039866 OH SL11 A205)
Testing for Acute Dermal Toxicity in the Male and Female Wistar Rat

AUTHORS:
Dr. K.-H. Diehl
Dr. K.-H. Leist

DATE REPORT ISSUED: August 5, 1986

CONCLUSION:

Toxicity Category: III (from 2,000 through 20,000 mg/kg).

Median Lethal Dose: The LD_{50} is greater than 2000 mg/kg in male and female Wistar rats. Although a dosing error resulted in dermal administration of the test material to study animals far in excess of the limit dose, there were no mortalities or other signs of toxicity; therefore, further acute dermal toxicity testing in the rat is not required.

Core Classification: Supplementary - This study can be upgraded to "Guideline" upon clarification of discrepancies regarding the date that the Quality Assurance Statement was signed.

MATERIALS:

1. Test compound: Description: Bluish-green liquid
Code No.: Hoe 039866 OH SL11 A205
Purity: 12.0%.

2. Test animals: Species: Wistar rat
Strain: Hoe: WISKf(SPF71)
Source: HOECHST AG, Kastengrund, SPF breeding colony
Age: Males - 7 weeks; Females - 11 weeks
Weight: Males - 250-269 g; Females - 196-218 g

METHODS:

Ten rats (five per sex) were shaved over a dorsal area of approximately 30 cm^2. Undiluted test material was applied evenly to the intact, shaved skin. The treated skin was covered with a 6 x 8 cm patch of aluminum foil, and an elastic plaster bandage. The test material was allowed to remain in contact with the skin for 24 hours, after which time all remnants were removed from the skin with warm tap water.

The intended dosage level was 2000 mg/kg body weight. According to the report, the volume of the dose was calculated on the basis of the density (1.06 g/ml), yielding a 1.89 ml dose. This volume of test material delivered 2000 mg of Hoe 039866 OH SL11 A205 to the skin of each animal, but was not based upon the individual body weights of the rats, and was therefore not the intended dose. Actual dosages to the animals are as follows:

Rat No.	Actual Dose Administered (mg/kg)	
	Male	Female
1	7663	9174
2	7905	9804
3	8000	10204
4	7663	9756
5	7435	9852

Animals were observed at 10 and 30 minutes after dosing; 1, 2, 4, and 6 hours after dosing; and daily for a total of 14 days. Body weights were recorded immediately prior to dosing on Day 0, and on Days 7 and 14 of study. A gross necropsy was performed on all animals that were sacrificed on Day 14.

RESULTS:

Mortality data, clinical signs of toxicity, and gross necropsy observations:

No rats died during the course of the study. There were no signs of toxicity noted for any of the test subjects at any time following test material administration. No macroscopic abnormalities were observed in rats that were necropsied at study termination.

Body weight data:

Mean body weight data are presented in Table 1. All rats on study gained body weight following test material administration.

Table 1. Mean body weight and body weight change data - grams (mean percent change from Day 0)a

Sex		Day 0	Day 7	Day 14
Males	Mean	259	276 (7)	297 (15)
	S.D.	7.5	10.0	14.4
	N	5	5	5
Females	Mean	205	213 (4)	221 (8)
	S.D.	8.0	9.4	10.8
	N	5	5	5

a Calculated by reviewer.
Note: Data were extracted from report No. 86.0815, page 12.

DEVIATIONS:

1. The Quality Assurance Statement contains a signature, but not a valid date. Two conflicting dates are typed at the top of the page, not handwritten in conjunction with the signature.
2. The test animals were administered dermal doses of the test material that were far in excess of the intended dose of 2000 mg/kg. This dosage error was not reported.

DISCUSSION:

1. In view of the fact that FIFRA guideline 81-2 defines 2000 mg/kg as the limit dose for dermal acute studies, and since there were no signs of toxicity noted in any of the rats dosed in excess of that amount, the conclusion of the study authors, that the dermal LD_{50} of Hoe 039866 OH SL11 A205 is greater than 2000 mg/kg, remains valid. Further acute dermal toxicity testing in the rat is not required.

2. Based upon the criteria presented in 40 CFR Part 156.10 and the results of this study, the test material, Hoe 039866 OH SL11 A205, falls within Toxicity Category III (from 2,000 through 20,000 mg/kg).

COMPLIANCE:

The following signed and dated statements were included:
GLP Compliance Statement
Statement of Data Confidentiality (none claimed)

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Reviewed by: Susan L. Makris, M.S. Susan L Makris 10/1/91
Section III, Toxicology Branch II (H7509C)
Secondary reviewer: James N. Rowe, Ph.D. James N. Rowe 10/1/91
Supervisor, Section III, Toxicology Branch II (H7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Acute Inhalation Toxicity in Rats (Guideline 81-3)
EPA IDENTIFICATION NOS.:	MRID NO.: 418463-02 HED PROJECT NO.: 1-1604 CASWELL NO.: 580I
TEST MATERIAL:	HOE 039866 Liquid Water-Soluble Concentrate 120 (g/l)
SYNONYMS:	Ignite 1SC Herbicide Monoammonium [2-amino-4-(hydroxymethylphosphinyl) butanoate]
STUDY NUMBER:	86.0697 A35305 Report No. 86.0754
SPONSOR:	Hoechst Celanese Corporation Route 202-206, P.O. Box 2500 Somerville, New Jersey 08876-1258
TESTING FACILITY:	Pharma Research Toxicology and Pathology Hoechst Aktiengesellschaft Postfach 80 03 20 6230 Frankfurt am Main 80 West Germany
TITLE OF REPORT:	HOE 039866-Liquid Water-Soluble Concentrate 120 (g/l) (Code: HOE 039866 OH SL11 A200) Testing for Acute Aerosal Inhalation Toxicity in the Male and Female SPF Wistar Rat - 4-Hour LC 50
AUTHORS:	Dr. H. Hollander Dr. W. Weigand
DATE REPORT ISSUED:	November 10, 1986

CONCLUSION:

Core Classification: Not acceptable

Although deaths were noted at all dose levels except the lowest (0.82 mg/l) tested, the maximum mortality rate achieved was 60%, and no clear dose-related trend in mortality was demonstrated by the data. Median lethal concentration values cannot be calculated with a high degree of confidence from the mortality patterns observed in this study.

MATERIALS:

1. Test compound: Description: Blue liquid
   Code No.: Hoe 039866 OH SL11 A205; Purity: 12.0%
   Hoe 039866 OH SL11 A206; Purity: 11.8%

2. Test animals: Species: Wistar rat
   Strain: Hoe: WISKf(SPF71)
   Source: HOECHST AG, Kastengrund, SPF breeding colony
   Age: 8-10 weeks
   Weight: Males - 187-209 g; Females - 181-203

METHODS:

The test material was aerosolized and administered by nose-only inhalation for a 4-hour interval to the following test groups:

Group	Chamber Concentration (mg/l)a	Volume Applied (ml/hr)	No. of Animals	
			Male	Female
1	0.82	6	5	5
2	1.60	12	5	5
3	1.90	30	5	5
4	3.30	120	5	5
5	3.60	120	5	5
6	4.20	90	5	5

a Actual measured exposure chamber concentration.

Hoe 039866 OH SL11 A205 was administered to Groups 1-3 and 5-6, and Hoe 039866 OH SL11 A206 was administered to Group 4. No explanation was given as to why two lots of test material were used.

The exposure chamber consisted of a stainless steel and glass cylinder with a volume of 60 l, standing in a vent pipe with a volume of approximately 4 m³. The rats were placed in individual plastic tubes, arranged to allow nose-only exposure to the chamber atmosphere. Filtered air was pumped into the chamber at a pressure of 4 bar and a measured rate of 800 l/h. The test material was injected into the air supply at a constant speed by means of a continuous infusion apparatus. The primary aerosal formation took place in a 10-liter flask. Smaller aerosal particles (secondary aerosal) entered the exposure chamber through a rising tube. Air was suctioned from the bottom of the exposure chamber at a rate of 1100 l/h, ensuring a slight negative pressure in the inhalation chamber.

During the exposures, CO, CO_2, and O_2 in the chamber were monitored continuously. Atmospheric humidity and temperature of the chamber were also measured continuously for all groups except 1 (humidity was not measured), 2, and 4. The absence of temperature and/or humidity monitoring for Groups 1, 2, and 4 is a deviation from FIFRA Guideline 81-3 requirements. Samples (31 liters) of chamber atmosphere were collected over a 60-minute period during testing. The active ingredient of the test material was determined by gas chromatography, using a P-mode flame photometric detector and a packed column. Aerosol particle size distribution was performed with an APS 33 Aerodynamic Particle Sizer; samples were taken at 30-minute intervals, results were stored once per hour, and mean values of 4 designated measurement times were calculated. Aerodynamic diameters within the range of 0.486 to $\geq$ 15.4 μm were measured, and between 61.07 and 74.40% were less than 1.03 μm in diameter, indicating a high probability of adequate delivery of the test material to the alveolar regions of the lung in the test animals.

Rats were not fasted prior to dosing. During the exposures, the behavior of the animals was observed for at least 6 separate observation intervals; and twice daily for a further 14 days. Body weights were recorded immediately prior to dosing on Day 0, and on Days 7 and 14 of study. A gross necropsy was performed on all animals that died on study and on all survivors which were sacrificed (by CO_2 asphyxiation) on Day 14.

RESULTS:

Mortality data and median lethal dose:

Numerical mortality data and calculated LC_{50} values are presented in Tables 1 and 2.

Table 1. Mortality (deaths/dosed)

Dose (mg/l)	Males [number (%)]	Females [number (%)]	Males & Females [number (%)]
0.82	0 / 5 (0)	0 / 5 (0)	0 / 10 (0)
1.60	3 / 5 (60)	1 / 5 (20)	4 / 10 (40)
1.90	1 / 5 (20)	3 / 5 (60)	4 / 10 (40)
3.30	2 / 5 (40)	2 / 5 (40)	4 / 10 (40)
3.60	1 / 5 (20)	2 / 5 (40)	3 / 10 (30)
4.20	3 / 5 (60)	2 / 5 (40)	5 / 10 (50)

The LC_{50} value and the 95% confidence limits were established on the basis of mortality rate by probit analysis according to the method of Linder and Weber. The limits of confidence were calculated by the method of Fieller and Sidak.

The value for an additive LC_{50} (male and female mortality combined) was

calculated because the comparison of both probit lines showed that the value "1" was within the 95% confidence range of the coefficient of both LC_{50} values (the relative effect).

Table 2. Median Lethal Concentration Values

Sex	LC_{50} (mg/l)	95% Confidence Limits (mg/l)
Male	4.40	-1.0×10^{75} - 3.63×10^{-2} and $1.93 - 1.0 \times 10^{75}$
Female	4.43	-1.0×10^{75} - 3.35×10^{-2} and $1.94 - 1.0 \times 10^{75}$
Male and female	4.42	$2.69 - 0.184 \times 10^{1}$

FIFRA Guideline 81-3 clearly states that at least three exposure levels should be used and that they should be spaced between the 10% and 90% mortality range of toxic effects and mortality. Although deaths were noted at all dose levels except the 0.82 mg/l level, the maximum mortality rate achieved was 60%, and no clear dose-related trend in mortality was demonstrated by the data. The median lethal concentration values calculated from these mortality rates are, therefore, judged by the reviewer to be unacceptable. This opinion is substantiated by the wide 95% confidence limits calculated by the analysis programs employed at the testing facility.

Clinical signs of toxicity:

The following clinical observations were noted following treatment: "irregular and jerky breathing, reduced respiratory rate, increased rhinorrhea, increased salivation, blood-crusted snout, narrowed or closed palpebral fissures, blood-crusted eye margins, uncoordinated, ataxic and high-legged gait, paresis of hindlimbs, squatting position, lying on side, contracted flanks, piloerection, tonoclonic spasms, aggressiveness, incipient cannibalism, weakening of corneal, placing and paw-pinch reflexes, reduced spontaneous activity, hyperreflexia, enhanced startle reaction and poor general health condition" (from Report No. 86.0754, page 14). Recovery from adverse effects was noted in those rats that survived to study termination.

Body weight data:

Mean body weight data are presented in Tables 3A and 3B (males and females, respectively).

Table 3A. Mean male body weight and body weight change data - grams (percent change from Day 0)

Dose (mg/l)		Day 0	Day 7	Day 14	Day 21a
0.82	Mean	199	221 (11)	266 (34)	-
	S.D.	5.9	13.8	23.6	-
	N	5	5	5	-
1.60	Mean	204	194 (-4)	235 (4)	276 (32)
	S.D.	3.6	29.0	18.4	25.5
	N	5	2	2	2
1.90	Mean	201	206 (3)	242 (20)	-
	S.D.	4.0	21.0	25.9	-
	N	5	4	4	-
3.30	Mean	207	229 (11)	264 (28)	-
	S.D.	2.7	10.1	14.2	-
	N	5	3	3	-
3.60	Mean	198	202 (3)	245 (23)	-
	S.D.	5.8	14.4	18.1	-
	N	5	4	4	-
4.20	Mean	190	199 (5)	241 (27)	-
	S.D.	0.7	12.0	13.4	-
	N	5	2	2	-

Table 3B. Mean female body weight and body weight change data - grams (percent change from Day 0)

Dose (mg/l)		Day 0	Day 7	Day 14	Day 21a
0.82	Mean	191	208 (9)	218 (14)	-
	S.D.	5.5	4.3	4.5	-
	N	5	5	5	-
1.60	Mean	196	204 (4)	227 (16)	241 (24)
	S.D.	5.4	12.2	22.2	26.5
	N	5	4	4	4
1.90	Mean	197	146 (-26)	207 (6)	-
	S.D.	1.6	24.1	8.5	-
	N	5	5	2	-
3.30	Mean	191	159 (-17)	217 (13)	-
	S.D.	2.2	43.7	17.3	-
	N	5	5	3	-
3.60	Mean	190	152 (-20)	200 (5)	-
	S.D.	3.4	44.1	2.6	-
	N	5	5	3	-
4.20	Mean	188	176 (-7)	200 (6)	-
	S.D.	3.8	16.3	4.0	-
	N	5	3	3	-

a Group 2 rats were observed for 21 days due to clinical observations noted at 14 days.

Gross necropsy data:

In rats found dead during the study, abnormalities were noted in the lung, including discolorations (light-red, orange, red, or dark-red) and foamy fluid in the pulmonary lobes. In addition, observations of inflated, discolored, and/or foam-filled gastrointestinal tract were recorded.

Dark foci were noted on the lungs of one animal killed at study termination. No macroscopic abnormalities were observed in any other rats examined.

DEVIATIONS/COMMENTS:

1. The Quality Assurance Statement contains a signature, but not a valid date. Two conflicting dates are typed at the top of the page, not handwritten in conjunction with the signature.
2. The code number for the test material used in this study is not consistently referenced throughout the study. For example: 1) on the cover page of the report (page 1) and in the summary (page 6), the code name HOE 039866 OH SL11 A200 appears, 2) in the summary (page 6) the LD_{50} values are presented for HOE 039866 OH SL11 A205, and 3) in the material and methods section (page 9) as well as in the description of the test groups (page 11), HOE 039866 OH SL11 A206 also appears.
3. Body weight change was not reported, as required by Guideline 81-3. The reviewer calculated percent weight change for purposes of study evaluation.
4. The absence of temperature and/or humidity monitoring for Groups 1, 2, and 4 is a deviation from FIFRA Guideline 81-3 requirements.
5. Nominal exposure chamber concentration, i.e., the total amount of test substance fed into the inhalation equipment divided by the volume of air, was not presented in the report for any dose level, although it can be calculated from the information presented in the analytical method (report No. 86.0754, page 78).
6. FIFRA Guideline 81-3 clearly states that at least three exposure levels should be used and that they should be spaced between the 10% and 90% mortality range of toxic effects and mortality. Although deaths were noted at all dose levels except the 0.82 mg/l level, the maximum mortality rate achieved was 60%, and no clear dose-related trend in mortality was demonstrated by the data. The median lethal concentration values calculated from these mortality rates are, therefore, judged by the reviewer to be unacceptable.

COMPLIANCE:

The following signed and dated statements were included:
GLP Compliance Statement
Statement of Data Confidentiality (none claimed)

Reviewed by: Susan L. Makris, M.S. Susan L. Makris 10/1/91
Section III, Toxicology Branch II (H7509C)
Secondary reviewer: James N. Rowe, Ph.D. James N. Rowe 10/1/91
Supervisor, Section III, Toxicology Branch II (H7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Primary Eye Irritation in Rabbits (Guideline 81-4)
EPA IDENTIFICATION NOS.:	MRID NO.: 417961-04 HED PROJECT NO.: 1-1604 CASWELL NO.: 580I
TEST MATERIAL:	HOE 039866 Liquid Water-Soluble Concentrate 120 (g/l)
SYNONYMS:	Ignite 1SC Herbicide Monoammonium [2-amino-4-(hydroxymethylphosphinyl) butanoate]
STUDY NUMBER:	86.0695 A35438 Report No. 86.0805
SPONSOR:	Hoechst Celanese Corporation Route 202-206, P.O. Box 2500 Somerville, New Jersey 08876-1258
TESTING FACILITY:	Pharma Research Toxicology and Pathology Hoechst Aktiengesellschaft Postfach 80 03 20 6230 Frankfurt am Main 80 West Germany
TITLE OF REPORT:	HOE 039866-Liquid Water-Soluble Concentrate 120 (g/l (Code: HOE 039866 OH SL11 A205) Testing for Primary Eye Irritation in the Rabbit
AUTHORS:	Dr. K.-H. Diehl Dr. K.-H. Leist
DATE REPORT ISSUED:	July 15, 1986

CONCLUSION:

Toxicity Category:	I; corneal opacity was not reversible within 7 days but was reversible within 14 days.
Core Classification:	Supplementary - This study can be upgraded to "Guideline" upon clarification of discrepancies regarding the date that the Quality Assurance Statement was signed.

MATERIALS:

1. Test compound: Description: Blue liquid
Code No.: Hoe 039866 OH SL11 A205
Purity: 12.0%

2. Test animals: Species: Rabbit
Strain: New Zealand albino
Source: HOECHST AG, Kastengrund, conventional breed
Age: Approximately 3-5 months
Weight: 2.8-3.4 kg

METHODS:

Nine young adult rabbits, confirmed to be free of ocular lesions, received a 0.1 ml single dose of the undiluted test material in the conjunctival sac of the left eye. The right eye was left untreated and served as the control. The treated eyes of three animals were washed with physiological saline one minute after dosing; the treated eyes of the other six animals were left unwashed for 24 hours.

The eyes were examined 1, 24, 48, and 72 hours after test material application, and at days 7, 14, and 21 due to effects that were still present in the eyes. At 24 and 72 hours, the eyes were also examined for corneal lesions under UV light after installation of fluorescein-sodium solution. Lesions in the cornea, iris, or conjunctiva were graded numerically according to the methods of Draize. The eyes were washed following any examination in which fluorescein dye was applied or discharge was noted.

An irritancy index was calculated by adding scores obtained from the grades for the cornea, iris, and conjunctiva at observation time:

cornea	:	degree of opacity x area involved x 5	=	max. 80
iris	:	degree of irritation x 5	=	max. 10
conjunctiva	:	(redness + chemosis + discharge) x 2	=	max. 20
				max. 110

The irritancy score for each observation period was the mean of the total scores of all rabbits at that observation time. The severity of irritation was defined on the basis of the maximum irritancy index, as follows:

Irritancy Index	Classification
0 - 10	non-irritating
11 - 25	slightly irritating
26 - 56	moderately irritating
57 - 110	severely irritating

RESULTS:

No signs of overt systemic toxicity were noted in the rabbits following administration of the test substance.

In the eyes washed out after 1 minute, a maximum irritancy index of 7 was obtained after 1 hour. No corneal effects were noted, and discharge or irritant effects to the conjunctiva or iris were not severe. All signs of irritation had disappeared by Day 7 after treatment

In the eyes washed out after 24 hours, a maximum irritancy index of 22.3 was noted at the 24-hour observation interval, and all six rabbits showed signs of discharge, conjunctival chemosis and redness, and iritis during the first 72 hours after treatment. Signs of corneal opacity were noted in four of the six rabbits at 24 hours postdose, and continued for two of those animals through the Day 7 observation interval. Corneal opacity and discharge/irritation were reversed by the Days 14 and 21 observation intervals, respectively.

DISCUSSION:

The study authors stated that in the eyes exposed to contact with the test material, Hoe 039866 OH SL11 A205, for 1 hour, there were no irritant effects, based upon the defined criteria of evaluation and the maximum irritancy index of 7. For the eyes washed out after 24 hours, the test material was a slight irritant, based upon the same evaluation criteria and a maximum irritancy score of 22.3. The evaluation criteria used by the study authors are not required by FIFRA Guideline 81-4 nor by FIFRA GLP, and they tend to minimize the corrosive effects to the eye. According to 40 CFR Part 156.10, observations noted on this study, specifically corneal opacity which was not reversible within 7 days, would place the test material into Toxicity Category I.

DEVIATION:

The Quality Assurance Statement contains a signature, but not a valid date. Two conflicting dates are typed at the top of the page, not handwritten in conjunction with the signature.

COMPLIANCE:

The following signed and dated statements were included:
GLP Compliance Statement
Statement of Data Confidentiality (none claimed)

Reviewed by: Susan L. Makris, M.S. Susan L Makris 10/1/91
Section III, Toxicology Branch II (H7509C)
Secondary reviewer: James N. Rowe, Ph.D. James N Rowe 10/1/91
Supervisor, Section III, Toxicology Branch II (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Primary Dermal Irritation in Rabbits (Guideline 81-5)

EPA IDENTIFICATION NOS.:
MRID NO.: 417961-05
HED PROJECT NO.: 1-1604
CASWELL NO.: 580I

TEST MATERIAL:
HOE 039866
Liquid Water-Soluble Concentrate 120 (g/l)

SYNONYMS:
Ignite 1SC Herbicide
Monoammonium [2-amino-4-(hydroxymethylphosphinyl) butanoate]

STUDY NUMBER:
86.0694
A35437
Report No. 86.0782

SPONSOR:
Hoechst Celanese Corporation
Route 202-206, P.O. Box 2500
Somerville, New Jersey 08876-1258

TESTING FACILITY:
Pharma Research Toxicology and Pathology
Hoechst Aktiengesellschaft
Postfach 80 03 20
6230 Frankfurt am Main 80
West Germany

TITLE OF REPORT:
HOE 039866-Liquid Water-Soluble Concentrate 120 (g/l)
(Code: HOE 039866 OH SL11 A205)
Testing for Primary Dermal Irritation in the Rabbit

AUTHORS:
Dr. K.-H. Diehl
Dr. K.-H. Leist

DATE REPORT ISSUED: July 8, 1986

CONCLUSION:

Toxicity Category: IV (mild or slight irritation at 72 hours)

Core Classification: Supplementary - This study can be upgraded to "Guideline" upon clarification of 1) discrepancies regarding the date that the Quality Assurance Statement was signed and 2) an explanation of the method of control comparison, a FIFRA Guideline 81-5 requirement.

MATERIALS:

1. Test compound: Description: Blue liquid
   Code No.: Hoe 039866 OH SL11 A205
   Purity: 12.0%

2. Test animals: Species: Rabbit
   Strain: New Zealand albino
   Source: HOECHST AG, Kastengrund, conventional breed
   Age: Not reported, but assumed to be young adults, based upon body weight data
   Weight: 2.3-2.7 kg

METHODS:

Six rabbits of unspecified age and sex were shaved (over a dorsal area of approximately 25 cm^2). Approximately 24 hours later, the intact, shaved skin was treated with a single 0.5 ml dose of undiluted test material. The test material was applied under a surgical plaster with a 2.5 x 2.5 cm cellulose patch, and a semi-occlusive bandage covered the area. The test material was allowed to remain in contact with the skin for 4 hours, after which time all remnants were removed from the skin with warm tap water.

The skin was examined at 30-60 minutes, and 24, 28, and 72 hours after removal of the patches and test material. Further examinations were conducted on Days 7 and 14 due to dermal findings noted after 72 hours. Erythema, eschar formation, and edema were evaluated numerically according to the technique of Draize. All other dermal changes were also recorded.

An irritancy index was calculated from the individual scores for erythema and edema noted at the designated observation intervals. The index for each time-period was obtained by totalling the scores for each rabbit, determining a mean score per observation period, and dividing by a factor of 4.

The following evaluation criteria were used to interpret the study results:

Irritancy Index	Classification
0.0 - 0.5	non-irritating
0.6 - 3.0	slightly irritating
3.1 - 5.0	moderately irritating
5.1 - 8.0	severely irritating

RESULTS:

Within the first 72 hours after removal of the test material, some of the animals showed slight erythema and edema. These signs had reversed 7 days after application. Other dermal observations included dry and chapped skin in some cases with fine or coarse scales, hardening, and a light-brown discoloration over large areas. No clinical signs of toxicity were noted in any of the rabbits over the duration of the study.

Based on the scores for erythema and edema after 30 - 60 minutes, and 24, 48, and 72 hours, an irritancy index of 0.7 was calculated.

DISCUSSION:

Based upon the criteria presented in 40 CFR Part 156.10, the Toxicity Category for skin effects following dermal administration of the test material, Hoe 039866 OH SL11 A205, is IV (mild or slight irritation at 72 hours).

DEVIATIONS:

1. The Quality Assurance Statement contains a signature, but not a valid date. Two conflicting dates are typed at the top of the page, not handwritten in conjunction with the signature.
2. The report does not mention the use of untreated areas of skin of each animal, adjacent to treated areas, as controls for the test. It cannot be determined if this Guideline 81-5 requirement was met.

COMPLIANCE:

The following signed and dated statements were included:
GLP Compliance Statement
Statement of Data Confidentiality (none claimed)

Reviewed by: Susan L. Makris, M.S. Susan L Makris 10/1/91
Section III, Toxicology Branch II (H7509C)
Secondary reviewer: James N. Rowe, Ph.D. James N. Rowe 10/1/91
Supervisor, Section III, Toxicology Branch II (H7509C)

008640

DATA EVALUATION REPORT

STUDY TYPE:	Dermal Sensitization in the Guinea Pig (Guideline 81-6)
EPA IDENTIFICATION NOS.:	MRID NO.: 417961-06 HED PROJECT NO.: 1-1604 CASWELL NO.: 580I
TEST MATERIAL:	HOE 039866 Liquid Water-Soluble Concentrate 120 (g/l)
SYNONYMS:	Ignite ISC Herbicide Monoammonium [2-amino-4-(hydroxymethylphosphinyl) butanoate]
STUDY NUMBER:	86.0698 A35434 Report Nos. 86.0845 and 86.0798
SPONSOR:	Hoechst Celanese Corporation Route 202-206, P.O. Box 2500 Somerville, New Jersey 08876-1258
TESTING FACILITY:	Pharma Research Toxicology and Pathology Hoechst Aktiengesellschaft Postfach 80 03 20 6230 Frankfurt am Main 80 West Germany
TITLE OF REPORT:	HOE 039866-Liquid Water-Soluble Concentrate 120 (g/l) (Code: HOE 039866 OH SL11 A205) Testing for Sensitizing Properties in the Pirbright-White Guinea Pig According to the Techniques of BUEHLER
AUTHORS:	Dr. K.-H. Diehl Dr. K.-H. Leist
DATE REPORT ISSUED:	August 6, 1986

CONCLUSION:

Skin Sensitization Potential:	Not a sensitizing agent (at an induction dose of 20% test material in saline and a challenge dose of 10% test material in saline)
Core Classification:	Supplementary - This study can be upgraded to "Guideline" upon clarification of discrepancies regarding the date that the Quality Assurance Statement was signed.

008649

MATERIALS:

1. Test compound: Description: Blue liquid
Code No.: Hoe 039866 OH SL11 A205
Purity: 12.0%

2. Vehicle control: Material: isotonic saline, sterile, pyrogen free
Source: Fresenious AG, Bad Hamburg

3. Positive control: Material: 2,4-dinitrochlorobenzene (DNCB)
Description: yellowish crystals
Code No.: Hoe 083957
Purity: > 99%

4. Test animals: Species: Pirbright-White guinea pig
Strain: Hoe: DHPK (SPFLac)
Source: HOECHST AG, Kastengrund, SPF breeding colony
Age: approximately 8-10 weeks
Weight: 330-410 g (main study)
230-376 g (positive control)
Sex: female

METHODS:

Positive control:

The positive control testing was initiated approximately 2.5 months prior to the study on the test material. It was conducted as a separate sensitization study under the laboratory project ID No. 86.0594, and is presented as report No. 86.0798, part of study No. 86.0698, pages 23-43. In this Data Evaluation Report, it will be discussed as if it were conducted simultaneously with the main sensitization study on the test material.

Range-finding primary irritation studies:

Dose selections for the induction and challenge phases were based on the results of range-finding tests in which 0.5 ml aliquots of test or positive control substance dilutions were applied via a 2 x 2 cm cellulose patch to the shaved left flank of guinea pigs. Animals were assigned to range-finding test groups according to the following scheme:

Material	Vehicle	Doses (%)	No. of Animals per Dose
Test material: Hoe 039866 OH SL11 A205	physiological saline	1, 10, 50, 100	3
Positive control: 2,4-dinitrochlorobenzene (DNCB)	acetone	0.1, 0.05, 0.02	2
		1.0, 0.5	5

The test substance, Hoe 039866 OH SL11 A205, was applied three times at two-day intervals, the positive control material, 2,4-dinitrochlorobenzene (DNCB) was applied once. The treated area was occluded for 6 hours; after 24 hours, the treated skin was examined for erythema and edema according to the method of Draize.

Induction phase:

In order to assess the sensitizing properties of the test material and the positive control material, guinea pigs were assigned to the following treatment groups:

Material	Vehicle	Group	Doses (%)	No. of Animals per Dose
Test material: Hoe 039866 OH SL11 A205	physiological saline	Control	0	10
		Treated	20	20
Positive control: 2,4-dinitrochlorobenzene (DNCB)	acetone	Control	0	10
		Treated	0.5a 0.05b	20

a This dosage was applied from the first through the fourth treatment.
b This dosage was applied from the fifth through the final treatments. Presumably, the dosage was lowered due to severe dermal effects noted in treated animals beginning with the third treatment.

Initial body weight values were recorded for each animal, and on Day 1 of study, the front part of each left flank was shaved. 0.5 ml of the test substance (20% Hoe 039866 OH SL11 A205 in physiological saline) or the positive control material (0.5% or 0.05% DNCB in acetone) were applied as appropriate to the treated animals. In addition, 0.5 ml of the appropriate vehicle material was applied to the guinea pigs in each control group. The test or control substances were applied evenly over a 2 x 2 cm cellulose patch which was fixed to the front part of the left flank and then occluded. Following 6 hours of exposure, the occlusive bandage was removed, and the flank skin was washed. Clinical signs and irritant effects were recorded. These procedures were repeated on Days 3, 5, 8, 10, 12, 15, 17, and 19 of study.

From Days 20 through 35 of study, treatment was discontinued and the animals were observed daily (except weekends).

Challenge phase:

The challenge treatment was conducted on Day 36 of study under identical conditions for the negative controls, positive control, and treated animals. The hair on the front part of the previously untreated right flank was shaved. Challenge treatment was performed with the primary non-irritant concentration of the test material (10% Hoe 039866 OH SL11 A205 in physiological saline) or the positive control material (0.02% DNCB in acetone) as appropriate. 0.5 ml of the

challenge concentration was applied to a cellulose patch which was placed on the skin and covered with an occlusive bandage. After 6 hours of exposure, the occlusive bandage was removed, remnants of the substance were washed off with warm water, and the flank was re-shaved.

On Day 37 of study (24 hours posttreatment), the skin was examined macroscopically, and on Day 38 (48 hours posttreatment) the skin was re-shaved and evaluated again. A terminal body weight value was recorded.

RESULTS:

Range-finding primary irritation study:

Hoe 039866 OH SL11 A205: Application of the undiluted test material caused a very slight (barely perceptible) to well-defined erythema on the treated areas of skin. Clinical observations indicative of toxicity in one animal included prone and lateral positioning and "jumping and rolling spasms." In addition, the skin areas treated with the undiluted test material were hardened, cracked, and discolored (brown) over large areas. The 50% solution of the test material caused areas of hardened, cracked, dry, and chapped skin with fine or coarse scales. Due to the signs of irritation and toxicity noted, a 20% solution of Hoe 039866 OH SL11 A205 in physiological saline was chosen for induction treatment in the main sensitization study.

DNCB: Very slight erythema and yellow discoloration of the skin was observed following application of the 1.0 and 0.5% solutions of DNCB. No irritant effects were observed at the 0.1, 0.05, or 0.02% dose levels. Based on these results, a 0.5% solution of DNCB was selected for the induction treatment.

Main test for sensitization:

Body weight and clinical observation data:

Body weight gains were similar between control and treated animals (Table 1).

Table 1. Mean percent body weight increases

Material	Group	Doses (%)	Mean % Increase
Test material: Hoe 039866 OH SL11 A205	Control	0	56.8
	Treated	20	59.1
Positive control: 2,4-dinitrochlorobenzene (DNCB)	Control	0	69.3
	Treated	0.5	75.8

Note: Data were extracted from report No. 86.0845, pages 15 and 35.

Clinical observations:

Hoe 039866 OH SL11 A205: During the sensitization phase of the study (Days

1-19), signs of dermal irritation were noted in guinea pigs treated with the test substance. These included: 1) dry/chapped, cracked, hardened skin with fine and/or coarse scales and 2) one animal with very slight, barely perceptible erythema. Based upon these findings, a 10% solution of the test material in saline was selected as the challenge dose.

DNCB: Very slight to marked erythema and hardened, cracked, dry/chapped skin with coarse scales and yellow discoloration were noted on the DNCB-treated skin during the sensitization phase of the study Days 1-19. Following the third treatment, open lesions, peeling of large scales, eschar formation, and scars were also reported.

Challenge phase:

Hoe 039866 OH SL11 A205: Following challenge treatment on Day 36 of the study, examination at 24 and 48 hours posttreatment showed no effect on the skin of the control animals or those treated with 10% Hoe 039866 OH SL11 A205.

DNCB: Very slight or well-defined erythema was observed in 70% of the treated animals at both 24 and 48 hours posttreatment, following challenge treatment on Day 36 with 0.02% DNCB. Discoloration of the treated skin caused by the color of the DNCB was not judged to have had an effect on evaluation of erythema. No edema was observed in treated animals, and neither erythema nor edema was noted in controls.

DISCUSSION:

The criteria used to determine whether or not a substance is considered to be a sensitizing agent are that 15% or more of the treatment animals show a positive reaction and at the same time no irritant effects emerge in the control group. Therefore, 2,4-dinitrochlorobenzene (DNCB), the positive control material, showed clear evidence of sensitization, while the test material, Hoe 039866 OH SL11 A205, did not meet those criteria and was not considered to be a sensitizing agent under the conditions of this study.

DEVIATIONS/COMMENTS:

1. The Quality Assurance Statement contains a signature, but not a valid date. Two conflicting dates are typed at the top of the page, not handwritten in conjunction with the signature.
2. Individual data for the range-finding primary irritation portions of the positive control and main sensitization studies were not provided, although textual summaries of the data allowed evaluation of the dosage selection process.

COMPLIANCE:

The following signed and dated statements were included:
GLP Compliance Statement
Statement of Data Confidentiality (none claimed)