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

MAY 2 1984

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of acute toxicity data submitted with an application for an Experimental Use Permit for DPX-H6573 to be used on peanuts (crop destruct). Reg #352-EUP-RRI, Tox. Chem. No. 419K, Accession #252481.

TO: Henry Jacoby, PM #21
Registration Division (TS-767C)

FROM: Marion P. Copley, D.V.M.
Toxicology Branch/HED (TS-769C)

THRU: Albin B. Kocialski, Acting Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769C)
and
William L. Burnam, Branch Chief
Toxicology Branch
Hazard Evaluation Division (TS-769C)

E. I. du Pont de Nemours and Co. has submitted toxicology data for review to satisify the requirement for their Experimental Use Permit application (crop destruct). DPX-H6573 is a new triazol chemical to be used as a fungicide on peanuts.

The studies submitted are:

Study type	Category of Toxicity	Classification
Acute oral LD_{50} - rat	III	core-minimum
Acute dermal LD_{50} - rabbits	IV	core-guideline
Skin Irritation - rabbits	IV	core-guideline
Eye Irritation - rabbits	I	core-minimum
Acute Inhalation LC_{50} - rats	II	core-minimum
Sensitization - Guinea pigs	non-sensitizing	core-supplementary

1. The registrant needs to answer the following questions which have been raised in the course of the review:

°For all studies

Completely identify the material tested including the percent of active ingredient and the percent of each inert ingredient.

°Acute Oral LD_{50} - rats — Haskell Lab. Report No. 412-83

1) Please identify by sex and dose those surviving animals which had pink and/or dark red thymus glands.

124

°Eye irritation - Rabbits Haskell Lab. Report No. HLO 517-83

1) Why does the protocol indicate 1 male/1 female with rinsed eyes when there are 2 females and 1 male in the results with rinsed eyes.

°Primary skin irritation and sensitization test - Guinea pigs

Haskell Lab. Report No. 418-83, Hazelton Project No. 201-640

Questions: During the course of reviewing this study, certain assumptions were made by the Toxicology Branch reviewer. These need to be clarified and either confirmed as correct or corrected.

1) Where was the challenge dose applied (flank?).
2) How were the primary irritation and challenge doses applied (topically?).
3) Give a reference or rationale for the use of dimethyl phthalate as the contr substance in the Primary Skin Irritation and Sensitization Study.

2. The signal word and precautionary statements listed on the label are supported by the test results.

Description of the EUP Program

The experimental use permit program proposes that DPX-H6573 be applied about 30 days after crop emergence. It would be repeated every 2 - 3 weeks until 2 weeks before harvest for a maximum of 8 applications. The objectives listed by the registrant are:

"-Evaluate disease control at various rates
-Compare performance to existing standards
-Monitor occurrence of crop injury on major varieties
-Compare intervals between applications
-Compare methods of application, ground vs. aerial
-Evaluate performance under varied climatological and geographical conditions
-Collect crop samples for residue analysis from commercial applications
-Monitor effects on non-target organisms such as insect and wildlife
-Evaluate effect of addition fo surfactants to spray mixture."

STUDY TYPE: Acute oral LD_{50} - Rats

TOX. CHEM. NO.: 419K

STUDY NUMBER: Haskell Lab. Report No. 412-83

ACCESSION NUMBER: 252481

SPONSOR: E. I. du Pont de Nemours and Co.

STUDY PERFORMED AT: Haskell Labs. for Tox and Indust. Med., Newark., Del. 19711

AUTHORS: C.N.Wylie, R.L.Ferenz, B.A.Burgess, G.L.Kennedy

DATE REPORT SUBMITTED: Oct. 24, 1983

TEST MATERIAL: DPX-H6573 (40% active ingredient; 60% inerts)

SYNONYMS: [Bis(4-fluorophenyl)](methyl)-(1H-1,2,4-triazol-1-ylmethyl), silane.
INH-6573-43
NB 9146-17

MATERIALS AND METHODS: Male and female Crl:CD rats, 7 to 9 weeks of age were housed singly and quarantined for one week prior to compound administration. Animals were fed standard laboratory chow ad libitum and had free access to water. The animals were fasted twenty-four hours prior to administeration of a single oral dose of compound in corn oil (150 mg/ml). The rats were then observed for clinical signs, body weight changes and mortality for a 14 day period. All animals were subjected to necropsy. The experimental design and mortality ratios are indicated as follows:

	Mortality ratio (dead/dosed)	
Dose (mg/ml)	Males	Females
1200	0/10	3/10
1300		6/10
1500	4/10	9/10
1700	3/10	
2000	4/10	
2300	9/10	

RESULTS: The $AOLD_{50}$ for male rats was reported to be 1865 mg/kg (95% CL 1669-2163) with a slope of 8.7 probits/log (mg/kg). Deaths occurred 1 to 8 days post-dosing.

The $AOLD_{50}$ for females was reported to be 1272 mg/kg (95% CL 1119-1368) with a slope of 18.6 probits/log (mg/kg). Deaths occured 1 to 5 days post dosing.

The following clinical signs were observed at the doses indicated as well as at all higher doses.

MALES

1200 mg/kg and above: diarrhea and stained wet perineal area
1500 mg/kg and above: salivation, weakness, stained face, alopecia, prostration, lacrimation
1700 mg/kg and above: lethargy
2000 mg/kg and above: chromodacryorrhea and hunched posture
Males at all dose levels exhibited slight to moderate weight loss.

FEMALES

1200 mg/kg and above: salivation, stained face, stained and wet perineal area, weakness, lethargy
1300 mg/kg and above: diarrhea, alopecia
1500 mg/kg and above: prostration
Females at all dose levels tested exhibited slight to severe weight loss.

126

Gross Pathology: The most common gross pathological changes observed and reported were as follows: pink or dark red thymuses, lungs which were moist, contained bright to dull red mottling, and failed to collapse, digestive tracts that were distended with brown, oily fluid, corneal opacity, hydronephrosis and small spleens. It was noted that most of the observations applied to rats that had died following dosing and not to those rats examined after the 14 day recovery period.

CONCLUSIONS: The $AOLD_{50}$ for males and females is as follows:
Males: 1865 mg/kg (1669-2163 mg/kg, 95% CL)
Slope: 8.7 probits/log (mg/kg)
Females: 1272 mg/kg (1119-1368 mg/kg, 95% CL)
Slope: 18.6 probits/log (mg/kg)
Females appeared to be more sensitive than males as reflected by:
- °severity of weight loss
- °lower LD_{50} values
- °steepness of slope
- °females dying earlier in time than males

Category of Toxicity: III

CLASSIFICATION OF STUDY: core-minimum

Reviewer's Question:

- °Identify the inert ingredients and the percentage of each ingredient in the formulation tested.

- °Please identify by sex and dose those surviving animals which had pink and/or dark red thymus glands.

STUDY TYPE: Acute dermal LD_{50} - Rabbits

TOX. CHEM. NO.: 419K

STUDY NUMBER: Haskell Lab. Report NO. HLO 326-83
Hazleton Project No. 201-639

ACCESSION NUMBER: 252481

SPONSOk: E. I. du Pont de Nemours and Co.

CONTRACTING LAB.: Hazleton Lab. America, Inc., Vienna,Va. 22180

AUTHORS: J.L.Gargus, J.C.Strausburg, S.K.Connor

DATE REPORT SUBMITTED: Aug. 9, 1983

TEST MATERIAL: DPX-H6573 (40% active ingredient; 60% inerts)[NOTE: A value of 100% a.i. was assumed for purposes of dosage calculations.]

SYNONYMS: [Bis(4-fluorophenyl)](methyl)-(1H-1,2,4-triazol-1-ylmethyl), silane.
INH-6573-43
NB 9146-17

MATERIAL AND METHODS: DPX-H6573 was applied to 5 male (2215-2238 gm) and 5 female (2091-2414 gm) New Zealand White rabbits using the method of Draize. The backs of the animals were clipped and abraded with small incisions sufficiently deep to penetrate to stratum corneum but not deep enough to disturb the dermis or produce bleeding. A single dose of test compound (5000 mg/kg, equivalent to 4.808 ml/kg) was then applied to the back of each rabbit and covered by a non-absorbent rubber dam. The test material remained in contact with the skin for 24 hours at which time the residual amount of test meterial was estimated. The exposure sites were then wiped clean to preclude further exposure of the animals to the test compound. It is noted here that a plastic collar restrainer was placed on each animal at the time of compound application and remained in place for 7 days post-treatment. Animals were observed for 14 days on a daily basis for mortality and clinical signs. The dermal responses (erythema and edema) were reported on days 1, 3, 7, 10 and 14. All animals were necropsied on day 14.

All animals were individually housed and had free access to food and water during the experimental period. Individual body weights were recorded prior to treatment, on day 7 and at termination.

RESULTS: Most of the test material was found in situ at 24 hours post application. Males: Five of 5 males manifested a well-defined erythema by day 3. The erythema gradually diminished and disappeared by day 14. Slight to very slight edema was observed in 3 of 5 animals on day 3 which was then not observed at subsequent readings. However, at the time the erythema and edema were disappearing, epidermal scaling, atonia and fissuring appeared. Atonia and fissuring disappeared by day 14 while epidermal scaling was still in evidence. Some skin sloughing was also evident in 2 of 5 animals.
Females: Five of 5 females manifested a slight to well defined erythema by day 3 which disappeared by day 14. Three of 5 animals had slight to very slight edema by day 3. The edema was no longer evident by day 7. However, at the time erythema and edema disappeared, epidermal scaling, atonia and fissuring appeared. Epidermal scaling was still evident on day 14 in all animals.

Most of the animals remained either depressed or slightly depressed from day 2 (post-dosing) through termination. Generally, rabbits were anorexic till day 10 of the study. All rabbits lost weight during the first week of the study followed by some recovery from day 7 through day 14. Some animals were also observed as being thin or cyanotic.

Mortality: No animals died during the course of the experiment.

DISCUSSION: A single application of test material (5000 mg/kg) produced a well defined to slight erythema and edema in all rabbits by day 3. Epidermal scaling, atonia, and fissuring were then reported for subsequent readings. Atonia and fissuring disappeared by day 14, but epidermal scaling was still in evidence.

The anorexia, weight loss and depression were probebly due primarily to the presence of the test material. Males appeared to be more sensitive to the compound as based upon weight loss. However, as noted earlier, the dermal irritation appeared comparable between sexes.

The $ADLD_{50}$ is greater than 5000 mg/kg since no animals died at this single administered dose.

CONCLUSION: The Acute Dermal LD_{50} is greater than 5000 mg/kg. Dermal lesions reported under the test were erythema and edema progressing to atonia, fissuring and epidermal scaling.

Category of Toxicity: IV

CLASSIFICATION: core-guideline

NOTE: Table 1 had an error on DAY 6 (males). Table 1 showed 5/5 males with slight depression and 1/5 with depression.

STUDY TYPE: Primary Skin Irritation Study - Rabbits TOX. CHEM. NO.: 419K

STUDY NUMBER: Haskell Lab. Report No. HLO 285-83
Hazleton Project No. 201-638 ACCESSION NUMBER: 252481

SPONSOR: E. I. du Pont de Nemours and Co.

CONTRACTING LAB.: Hazleton Lab. America, Inc., Vienna, Va. 22180

AUTHORS: J.L.Gargus, J.C.Strausburg, S.E.Gluck

DATE REPORT SUBMITTED: Jul. 22, 1983

TEST MATERIAL: DPX-H6573 (40% active ingredient; 60% inerts)[NOTE: a value of 100% a.i. was assumed for the purpose of dosage calculation.]

SYNONYMS: [Bis(4-fluorophenyl)](methyl)-(1H-1,2,4-triazol-1-ylmethyl), silane.
INH-6573-43
NB 9146-17

METHODS: DPX-H6573 was applied to 6 individually housed male, New Zealand White rabbits using the method of Draize. The backs of the animals were clipped the day before the study. Two of the four application sites for each rabbit were abraded with small incisions which did not penetrate the dermis. The compound (0.5 ml) was then applied to all 4 sites and covered by gauze and a nonabsorbent cover. The test animals were then immobilized and not fed or watered for 24 hr. Twenty-four hours later the chemical was wiped off and the animals had free access to food and water. Dermal responses were recorded at 24, 48, 72, 96 hr and 7 days using Draize'(1959) method. All rabbits were sacrificed without necropsy on day 7.

RESULTS: All 6 rabbits had a barely perceptable erythema (score = 1) lasting 96 hr in both abraded and intact areas. Edema was not in evidence for any animal for any time period (score = 0). Epidermal scaling in 5 of 6 rabbits was recorded on day 7.

CONCLUSIONS: DPX-H6573 had a PIS (primary irritation score) of 1. Epidermal scaling was the only other sign observed.

PIS: 1

Category of Toxicity: IV

CLASSIFICATION OF STUDY: core-guideline

STUDY TYPE: Primary Eye Irritation Study - Rabbits TOX. CHEM. NO.: 419K

STUDY NUMBER: Haskell Lab. Report No. HLO 517-83
Hazleton Project No. 201-671 ACCESSION NUMBER: 252481

SPONSOR: E. I. du Pont de Nemours and Co.

CONTRACTING LAB.: Hazleton Lab. America, Inc., Vienna, Va. 22180

AUTHORS: J.L.Gargus, J.C.Strausburg, J.A.Groves

DATE FINAL REPORT SUBMITTED: December 19, 1983

TEST MATERIAL: DPX-H6573 (40% active ingredient; 60% inerts)[NOTE: a value of 100% a.i. was assumed for the purpose of dosage calculation.]

SYNONYMS: ° [Bis(4-fluorophenyl)](methyl)-(1H-1,2,4-triazol-1-ylmethyl), silane.
° INH-6573-43
° NB 9146-17

MATERIAL AND METHODS: DPX-H6573 was applied to 4 male and 5 female, individually housed, New Zealand White rabbits according to the method of Draize. Prior to treatment and at each observation interval, all eyes were examined after staining with 2% fluorescein sodium solution to determine corneal integrity. DPX-H6573 (0.1 ml) was placed in the left conjunctival sac of all rabbits and the lid held closed for about one second. According to the protocol, the treated eyes of one male and female were rinsed with water 10 seconds after compound placement for 60 seconds. The right eye of each rabbit was used as a control and remained untreated. Eye irritation was reported at 24, 48, and 72 hr as well as 7, 10, 14 and 21 days using Draize' method of scoring (1959). Animals were sacrificed without necropsy at 21 days. Standard deviation of the mean eye irritation scores was calculated.

RESULTS: Unwashed eyes: Scattered or diffuse corneal opacities lasted 72 hr in 4 animals, persisted in a 5th for 10 days and was present at the 21 day reading for the remaining animal (the area involved went from 75-100% on day 14 to <25% on day 21). Iritis occured in 3 animals and disappeared after 3 days. Conjunctival irritation persisted for 72 hr in all animals and was manifested by redness, chemosis and discharge. Conjunctival irritation was absent at the 7 day reporting period. Washed eyes: Washing after treatment decreased lesions to minimal conjunctival redness lasting less than one week.

CONCLUSIONS: Unwashed eyes: DPX-H6573 produced corneal opacities which were reversible by 21 days in all but 1 animal. Mild iritis and conjunctivitis were present for only 3 days. Washed eyes: Washing after 10 seconds was effective in preventing corneal lesions and keeping conjunctivitis to a minimum.

Eye irritation score:

	24hr	48hr	72hr	7d	10d	14d	21d	
unwashed	29.7	27.7	24.8	3.7	3.7	3.3	0.8	n=6
washed	2.0	2.0	1.3	0	0	0	0	n=3

Toxicity Category: I

CLASSIFICATION OF STUDY: core-minimum

Question - 1) Why does the protocol incicate 1 male/1 female with rinsed eyes when there are 1 male/2 females in the results with rinsed eyes.

12

STUDY TYPE: Acute inhalation - Rats TOX. CHEM. NO.: 419K

STUDY NUMBER: Haskell Lab. Report No. HLO 437-83 ACCESSION NUMBER: 252481

SPONSOR: E. I. du Pont de Nemours and Co.

STUDY PERFORMED AT: Haskell Labs. for Toxicity and Industrial Medicine

AUTHORS: G.L.Kennedy, B.A.Burgess, L.A.Kinney

DATE REPORT SUBMITTED: Nov. 9, 1983

TEST MATERIAL: DPX-H6573; Silane, [bis(4-fluorophenyl)](methyl)-(1H-1,2,4-triazol-1-yl-methyl)-; 40% a.i.

SYNONYMS: ° INH-6573-43
° NB 9146-17

METHODS: Seven - 9 week old Crl:CD® strain rats, 10 male/10 female/dose received nose only exposures of DPX-H6573 for 4 hr. Controls received air only. A Solo-Sphere® Nebulizer was used for aerosol generation. The dose levels generated were 0.82, 1.2, 2.4, 5.3 mg/L (actual concentrations). Atmospheric (analysis) concentrations were measured at 15-20 minute periods. A Sierra Cascade Impactor was used to determine particle size and percent respirable aerosol (see table). Chamber temperature was maintained at 27-30°C, oxygen levels were maintained at 20% and relative humidity was 52-80%. The rats received food and water ad libitum. Animals were weighed and observed daily daily for 14 days at the end of which time 3 survivors/sex/dose were necropsied and examined for gross lesions. Up to 3 animals/sex/dose of the non-survivors were also necropsied. Lungs, kidney, liver and gross lesions were examined microscopically. LC_{50}s were calculated using the method of Finney (1971)*.

RESULTS: The registrant reported "A slight to heavy cloud was visible ... during exposure".

Exposure/Mortality Data

Actual (mg/L) Concentration	Deaths/exposed male	female	MMD**(% respirable) um	
0.82	0/10	0/10	2.8	(86)
1.2	7/10	2/10	1.6	(93)
2.4	7/10	5/10	2.6	(78)
5.3	10/10	10/10	1.6	(84)

All high dose tested (HDT) male rats and 8/10 females died during the exposure. The other deaths (including lower doses) occured during the exposure period or within 3 days. The registrant reported a moderate-severe dose dependent weight loss for the first day and a slight-moderate loss for the next two days after which time weight gain was normal in survivors of all groups.

Signs

Dose (mg/l)	Exposure	Post-exposure
control	red nasal discharge slight weight loss	
0.82	reddish-brown nasal discharge	wet perineum, dry red nasal, ocular and oral discharge, lung noise and/or gasping- all at 1-7 days low incidence of hair loss and/or cloudy eyes
1.20	reddish-brown nasal discharge labored breathing, gasping	same as above
2.40	reddish brown nasal discharge labored breathing, gasping crystal formation on whiskers/nose	same as above plus decreased muscle tone at 2 days post exposure
5.30		clear nasal discharge, cyanosis, lung noise or labored breathing, lethargy, wet perineal areas, no righting rflex prior to death

Pathologic changes in the non-survivors were: edematous, heavy, hemorrhagic lungs; hepatocytes with lipid like vacuolation; and thymic lymphoid cell necrosis. One surviving male had a foreign body type microgranulomata in the lung.

CONCLUSIONS:

LC_{50}: female - 2.4 (1.8 - 3.8) mg/L (95% CL)
male - approximately 1.2 mg/ 1 (the LC_{50} for the males could not be calculated because of the mortality distribution)
NOTE: Males appear to be more sensitive than females.

Slope: female - 1.0519 mg/l
male - could not be determined

Toxicity Category: II (based on male LC_{50})

CLASSIFICATION OF STUDY: core-minimum

*Finney, D.J., Probit analysis, 3rd Ed., 1971, Cambridge University Press
**Mass Median Diameter of respirable particles

STUDY TYPE: Primary skin irritation and sensitization test - Guinea pigs

TOX. CHEM. NO.: 419K

STUDY NUMBER: Haskell LAb. Report No. 418-83
Hazelton Project No. 201-640

ACCESSION NUMBER: 252481

SPONSOR: E. I. du Pont de Nemours and Co.

CONTRACTING LAB.: Hazleton Labs. Americe, Inc., Vienna, Va. 22180

AUTHORS: J.L.Gargus, J.C.Strausburg, J.D.Sutherland

DATE FINAL REPORT SUBMITTED: Oct. 26, 1983

TEST MATERIAL: DPX-H6573; [bis(4-fluorophenyl)](methyl)-(1H-1,2,4-triazol-1-yl-methyl)-silane; 40% a.i., 60% inerts

SYNONYMS: ° INH-6573-43
° NB 9146-17

MATERIALS AND METHODS: Twenty-three (23) young male albino Guinea pigs of the Hartley strain were individually housed and had free access to food and water. Animals were acclimated to laboratory conditions for 7 days prior to study initiation. The animals were then randomly assigned (random number generator) to one of the 3 experimental groups - as follows:

°range finding study - 3 animals
°primary irritation and induction study - 10 animals for the control group, 10 animals for the treatment group.

Dimethyl phthalate (DMP) was used as the vehicle. DMP is non-irritating and not absorbed.

Range-finding Study for Determination of Irritation Concertration: The backs of 3 Guinea pigs were shaved from shoulder to flank and 0.05 ml aliquots of the test material at concentrations (w/v) of 100% (pure test substance, not diluted with vehicle, that is to say it was applied "neat"), 75% and 50% in DMP were applied to the separate test sites on the back of each animal. Skin reactions were then graded at 24 and 48 hours following application using the method of Draize. These animals were not used again.

Primary Irritation: Ten (10) Guinea pigs were then shaved (clipped) from the shoulder to mid-back and 2 sites on each animal were chosen for a single application. Two concontrations [10% in DMP and 100% test substance (neat)] of the test substance were then applied (surface application*) to separate test sites on each animal. The resulting irritation scores were then compared to the challenge scores as determined at the end of the sensitization period. Ten control animals were treated identically with DMP alone.

Induction of Sensitization: The same ten (10) test animals that were used in the primary irritation phase were treated during the induction phase. The sacral/hip area was then shaved (clipped) and a 0.010 ml aliquot of 1% concentration of test compound in DMP was injected intradermally alternately at 2 hip sites for a period of 4 weeks. The 10 control animals were injected with DMP. A 14 day rest period followed.

Challenge Phase: Fourteen days after the final sensitization injection the backs of all animals were reshaved. A 0.05 ml aliquot of the challenge test solution

at 10% and 100% was applied topically* to the two assigned flank test sites* on each animal. The 10 test animals, as well as the 10 control animals were exposed to the same challenge doses.

RESULTS: Mortality: No animals died during the course of the study.
Range-finding Phase: It was stated in the report that dermal irritation was not observed in any of the animals.
Primary Irritation: The mean primary irritation scores (erythema) were as follows:

Application site (dose)	Control Group Mean Scores Erythema 24 hr ($\bar{x}$)	Erythema 48 hr ($\bar{x}$)
left flank (LS) (0%)	0.80	0.00

Application site (dose)	Treated Group Mean Scores 24 hr ($\bar{x}$)	48 hr ($\bar{x}$)
left flank (LS)(10%)	0.00	0.00
right flank (RS) (100%)	0.40	0.00

Induction of Sensitization: The mean ($\bar{x}$) scores recorded during the period of induction (by injection) were as follows:

Induction Phase	Control Group Erythema ($\bar{X}$)	Necrosis ($\bar{x}$)
Injection # 1 (LS)	2.2	0.0
Injection # 2 (RS)	2.0	0.0
Injection # 3 (LS)	2.0	0.0
Injection # 4 (RS)	2.0	0.0
	Treated Group	
Injection # 1 (LS)	2.2	0.2
Injection # 2 (RS)	1.9	0.1
Injection # 3 (LS)	2.0	0.0
Injection # 4 (RS)	2.0	0.0

Challenge Dose: The mean ($\bar{x}$) scores recorded during the challenge phase (surface application) were as follows:

Application site (dose)	Control Group Mean Scores Erythema 24 hr ($\bar{x}$)	Erythema 48 hr ($\bar{x}$)
left flank (LS)(10%)	0.0	0.0
Right flank (RS)(100%)	0.0	0.1)

Application site (dose)	Treated Group Mean Scores 24 hr ($\bar{x}$)	48 hr ($\bar{x}$)
left flank (LS)(10%)	0.0	0.0
right flank (RS)(100%)	0.0	0.1

DISCUSSION: Comparison of the results issued for the challenge doses against the reported results for both primary irritation and induction phases indicated no increase in responsiveness. It therefore appears that the compound (formulation) tested is not a sensitizer under the test conditions.

CONCLUSION: Non-sensitizing

CLASSIFICATION: Core-supplementary, pending satisfactory clarification of methods used in applying the test compound.

Questions: During the course of reviewing this study, certain assumptions were made by the Toxicology Branch reviewer. These need to abe clarified and either confirmed as correct or corrected.

1) Where was the challenge dose applied (flank?).
2) How were the primary irritation and challenge doses applied (topically?).
3) Give a reference or rational for the use of dimethyl phthalate as the control substance in the Primary Skin Irritation and Sensitization Study.

Marion P. Copley, D.V.M.
Section II, Toxicology Branch
Hazard Evaluation Division (TS769C)

ABL for MPC 5/11/84

* see below

*assumption made by the reviewer