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WASHINGTON, D.C. 20460

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CASWELL FILE

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OFFICE OF  
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

**SUBJECT:** EPA REG. NO.: 33694-1. Diazinon: Acute toxicity and dermal sensitization studies submitted in support of the product DIANON, technical grade diazinon manufactured by the Nippon Kayaku Co. Ltd. (Japan).

TOX CHEM No.: 342  
TOX PROJECT No.: 0-0888  
Record No.: 261230

**FROM:** John Doherty *John Doherty 7/19/90*  
Section I, Toxicology Branch I  
Health Effects Division (H7509C)

**TO:** Dona Williams  
Product Manager #74  
Special Review and Reregistration Division  
(H7508C)

**THROUGH:** *for* Roger Gardner *Roger Gardner 11/26/90*  
Acting Section Head *KRS 11/26/90*  
Section I, Toxicology Branch I  
Health Effects Division (H7509C)

The Nippon Kayaku Chemical Co. (Japan) is attempting to register their technical grade of diazinon named Dianon (87.84% diazinon) and has submitted six acute toxicity studies including a dermal sensitization study in guinea pigs. These studies were reviewed and the following comments apply.

1. The acute oral toxicity study, the primary ocular and dermal irritation studies and the sensitization study in guinea pigs were reviewed and determined to be ACCEPTABLE. Refer to the DERS attached.
2. The acute inhalation toxicity study with rats was determined to be UNACCEPTABLE. More detailed information on the particle size distribution will have to be provided. Toxicology Branch I (TB-I) needs to know the percentage distribution of particles of each size and in particular the percentage of particles less than

1 um in diameter. The approximations and implications noted in the text of the study report (page 17) are not supported by data. The supplementary report should include the methods and results of the analysis of the cascade impactor filters and the data on distribution of the particles.

3. The acute dermal toxicity study was determined to be ACCEPTABLE. There were no deaths among the females when the rabbits were dosed with 2000 mg/kg. In males, however, There were 2 deaths among the 5 rabbits treated. The GUIDELINES provide that when there are deaths in the limit test (2000 mg/kg), then a full study using a minimum of three dose levels may be necessary. Since there were 2 deaths at 2000 mg/kg in the male group, it is implied that this level is near the LD<sub>50</sub>, TB-I will assume that the product DIANON is toxicity category II (for example, the LD<sub>50</sub> including a significant portion of its 95% confidence limits is < 2000 mg/kg) and a new study will not be required.

If, however, the registrant wishes to have their product classified as toxicity category III based on dermal toxicity, a new study with multiple dose levels with male rabbits which clearly demonstrates that the LD<sub>50</sub> is > 2000 mg/kg will have to be provided.

4. The registrant has not submitted a six week rat feeding study designed to assess for blood ChE/AChE and brain AChE inhibition as previously requested by the Agency.

Reviewed by: John Doherty *John Doherty 7/19/90*  
Section I, Toxicology Branch I (H7509C)  
Secondary reviewer: Roger Gardner *Pamela M. Hurley 4/26/96*  
Section I, Toxicology Branch I (H7509C)

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DATA EVALUATION REPORT

STUDY TYPE: 81-1. Acute oral toxicity - rats

MRID NO.: 413346-07 TOX. CHEM. NO.: 342

TEST MATERIAL: Dianon. Manufacturing Use Product of diazinon.  
87.84% diazinon.

TEST ANIMALS: Sprague-Dawley rats obtained from the Charles  
River Laboratories, Raleigh, North Carolina.  
Males ranged in weight from 316- 397 gm and  
females ranged in weight from 232 - 275 gm.

STUDY NUMBER(S): HLA #2132-110

SPONSOR: Nippon Kayaku Co. Ltd., Tokyo, Japan.

TESTING FACILITY: Hazleton Laboratories America, Inc.

TITLE OF REPORT: "Acute Oral Toxicity Study with Dianon in Rats".

AUTHOR(S): Janet A. Trutter, M.S., D.A.B.T.

REPORT ISSUED: November 28, 1989

CONCLUSIONS: The following LD<sub>50</sub> data were obtained (including  
the 95% confidence interval) and are adjusted to 100% diazinon:

Males	882	(587-1326)	mg/kg
Females	968	(731-1283)	mg/kg
Combined	936	(742-1180)	mg/kg

The symptoms resulting included: tremors, ataxia, salivation  
and other generalized reactions. Necropsy was unremarkable for  
the survivors, organ discoloration and abnormal contents in the  
stomach and intestines were noted in the decedents. There was a  
transient body weight decrease in males. Toxicity Category III.

Classification: ACCEPTABLE

Quality Assurance Statement: A statement signed by Janet Milazzo  
attested that four inspections/reviews were made and four reports  
filed. No adverse comments were made by the QAU regarding this  
study.

## REVIEW

The basic design of this study consisted of dosing three groups of 5 rats of each sex with either 450, 750 or 1250 mg/kg of Dianon. These dose levels were selected based on the results of a preliminary dose range finding study. The test material was dissolved in 4% aqueous carboxymethylcellulose and administered at a volume of 10 ml/kg body weight. The rats were fasted approximately 21-22 hours prior to dosing. Following dosing the rats were monitored for signs of toxicity at least once daily for 14 days.

### Results

1. Analytical chemistry data indicated that the samples of diazinon were stable and the product was homogeneous in the solution.
2. In the range finding study (one male and one female per group dosed with either 250, 500, 750, 1000 or 1250 mg/kg), rats dosed with 1000 (one male) or 1250 mg/kg (one male and one female) died within the two day observation period.

In the main study, none of the rats dosed with 450 mg/kg died. Two males but no females dosed with 750 mg/kg died and 4 of 5 males and all of the 5 females died when dosed with 1250 mg/kg. The deaths occurred on days 1, 2 or 5 for the males and on days 2, 3, or 4 for the females.

The symptoms noted in the dosed animals included tremors, hunched appearance, urine staining, rough coat, soft feces, ataxia, gasping, salivation, depression, and red stains on nose/eyes. The animals were reported as not completely recovering from the signs until day 6 for females and by day 13 for males. The lone surviving male dosed with 1250 mg/kg/day still exhibited red stains on the nose/eyes at day 14. Necropsy of the survivors was unremarkable. The rats which died had discolored lungs, liver, spleen and kidneys and the stomach and intestines had "abnormal contents". There was also a transient body weight loss in males.

The LD<sub>50</sub>s with 95% confidence limits were reported as follows:

Males	882 (587-1326) mg/kg
Females	968 (731-1283) mg/kg
Combined	936 (742-1180) mg/kg

The data are adjusted to 100% diazinon.

CONCLUSION. This study is ACCEPTABLE. Sufficient data were generated to classify the test material as Toxicity Category III.

Reviewed by: John Doherty  
Section I, Toxicology Branch I (H7509C)  
Secondary reviewer: Roger Gardner  
Section I, Toxicology Branch I (H7509C)

*John Doherty 7/19/90*

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*for*  
*Parrot M. Hurley 11/26/90*

DATA EVALUATION REPORT

STUDY TYPE: 81-2. Acute dermal toxicity - rabbits

MRID NO.: 413346-08

TOX. CHEM. NO.: 342

TEST MATERIAL: Dianon. Manufacturing Use Product of diazinon.  
87.84% diazinon.

TEST ANIMALS: Adult New Zealand White rabbits (Hra:(NZW)SPF  
obtained from Hazleton Research Products Inc,  
Denver, Penn.. They weighted 2251 - 2307 (males)  
and 2110 - 2158 (females) at the start of dosing.

STUDY NUMBER(S): HLA #2132-111

SPONSOR: Nippon Kayaku Co. Ltd., Tokyo, Japan.

TESTING FACILITY: Hazleton Laboratories America, Inc.

TITLE OF REPORT: "Acute Dermal Toxicity Study with Dianon in  
Rabbits".

AUTHOR(S): Janet A. Trutter, M.S., D.A.B.T.

REPORT ISSUED: November 28, 1989

CONCLUSIONS:

The LD<sub>50</sub> for males could not be determined based on the  
observation that 2 of 5 males dosed with 2000 mg/kg/day died.  
The LD<sub>50</sub> for females was determined to be > 2000 mg/kg.

Classification: UNACCEPTABLE for males. ACCEPTABLE for females.

Quality Assurance Statement: A statement signed by Janet Milazzo  
attested that four inspections/reviews were made and four reports  
filed. No adverse comments were made by the QAU regarding this  
study.

## REVIEW

This study consisted of two parts: a dose range finding study and a limit test main study. For both studies the rabbits were prepared by clipping (without abrading the skin). The rabbits were wrapped with a nonabsorbent binder (rubber dam) and the test material was injected under the binder and onto the skin. After application, the dermal binder was held in place with staples and porous tape. The test material was kept in contact with the rabbit for twenty four hours. After removal the rabbits were observed for signs of toxicity for 14 days.

None of the rabbits dosed with either 500, 1000, 1500 or 2000 mg/kg in the dose range finding study died (one male rabbit per dose group). Since none of the rabbits died, it was determined that a limit test of 2000 mg/kg could be run with 5 males and 5 females per dose group.

In the limit test 2 males but no females died. The males died on days 1 and 3 postdosing. The LD<sub>50</sub> for females is established as > 2000 mg/kg or toxicity category III. The symptoms resulting included depression, soft feces, urine stains, anorexia, and thin appearance. Some symptoms (depression, soft feces, urine stains and thin appearance) persisted to day 11 for males and to day 14 for females. Necropsy revealed some organ discoloration in the two males found dead.

CONCLUSION. This study is ACCEPTABLE. Based on these data the product Dianon is classified as toxicity category II via the dermal route for males and toxicity category III for females. The product will have to be labeled as toxicity category II based on acute dermal toxicity.

Note: When acute dermal toxicity studies are tested at the limit dose (2000 mg/kg) and deaths occur, the guidelines provide that a second study with at least three dose levels may be required. TB-I considers that the two deaths in the males resulting is sufficient to classify the product as toxicity category II without the additional study. For example, the LD<sub>50</sub> in males is probably borderline between toxicity category II and III and the 95% confidence limits would be within the toxicity category II range.

Reviewed by: John Doherty *John Doherty 7/19/90*  
Section I, Toxicology Branch I (H7509C)  
Secondary reviewer: Roger Gardner *Ronnie M. Hurley*  
Section I, Toxicology Branch I (H7509C)

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DATA EVALUATION REPORT

STUDY TYPE: 81-3. Acute Inhalation Toxicity - rats

MRID NO.: 413346-09 TOX. CHEM. NO.: 342

TEST MATERIAL: Dianon. Manufacturing Use Product of diazinon.  
87.84% diazinon.

TEST ANIMALS: Rats. Sprague-Dawley obtained from Charles-River  
Laboratories, Portage, Michigan or from Raleigh,  
North Carolina. They were young adults (39-52  
days of age).

STUDY NUMBER(S): HLA #2132-115

SPONSOR: Nippon Kayaku Co. Ltd., Tokyo, Japan.

TESTING FACILITY: Hazleton Laboratories America, Inc.

TITLE OF REPORT: "Acute Inhalation Toxicity Study with Dianon in  
the Rat".

AUTHOR(S): Janes B. Terrill, Ph.D., D.A.B.T.

REPORT ISSUED: November 22, 1989

CONCLUSIONS:

The following LC<sub>50</sub>s with 95% confidence limits were  
generated from this study.

Combined	9.36 (0.355-247) mg/l
Males	6.76 (0.189-242) mg/l

Note the LC<sub>50</sub> for females could not be determined.  
These data would indicate that Dianon is Toxicity Category IV via  
inhalation toxicity. The broad range of the confidence limits  
results from there being one death for each sex in the lowest  
test group and only 2 deaths for each sex in the highest dose  
test group.

Classification: UNACCEPTABLE.

Quality Assurance Statement: A statement signed by Carl Hay  
attested that three inspections/reviews were made and four  
reports filed. No adverse comments were made by the QAU regarding

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this study.

## REVIEW

In this study three groups of rats (5 male and 5 female) were exposed to atmospheres containing the test material for four hours and the animals observed for signs of toxicity at least once daily for 14 days. All animals including those that died prior to termination of the study were subjected to gross postmortem examination.

The test atmosphere was generated from undiluted stock material into a 100 liter chamber by means of a FMI metering pump to an atomizer where it was mixed with compressed air and forced through a flowmeter which caused atomization of the liquid test material which in turn was directed into the exposure chamber. The settings of the metering pump, compound flow rate and air flow atomizer were varied such that the chamber atmospheres were 5.0, 2.5, and 0.75 mg/l.

The chamber atmosphere was sampled at least four times during each exposure for determination of the atmospheric concentration of diazinon. The samples were reportedly drawn from the breathing zone of the test animals from a port located at the "front center of each chamber". The test aerosol was drawn through a 25 mm Gelman glass fiber filter at a rate of 5 Lpm for 2 or 5 minutes by means of a vacuum pump. The filters were weighted for gravimetric determination of the atmospheric concentration and the samples were analyzed by gas chromatography to determine the content of diazinon. The mean analytical and nominal concentrations of diazinon were reported as follows:

<u>Group</u>	<u>Analytical</u>	<u>Nominal</u>
1	4.30 ± 0.183	107
2	2.33 ± 0.071	37.4
3	0.82 ± 0.084	6.93

Particle size distribution was reportedly determined twice by sampling a measured volume of the atmosphere through an Anderson (Model 2000) Cascade impactor. The filters were again weighted gravimetrically and analyzed by gas chromatography to determine the distribution of the particles by size. Data on the particle size distribution was incomplete. The results of the individual analyses were not presented. The study report indicated that the mass median aerodynamic diameter ranged from 1.97 to 2.56 microns and the geometric standard deviation was from 1.77 to 1.96 for all groups. This information does not demonstrate that 25% of the particles were 1 um or less in

diameter one of the criteria for a GUIDELINE study.

#### RESULTS.

Two rats (a male and a female) exposed to 0.82 mg/l died. Three rats (2 males and a female) exposed to 2.33 mg/kg died and 4 rats (2 males and 2 females) exposed to 4.3 mg/l died. The rats were found dead on days 2, 3 and 5. The survivors were reported as not being returned to normal until day 13 for some symptoms. The symptoms included salivation, languid behavior, urine stained fur, squinted eyes, crusts, rhinorrhea and respiratory distress. Body weight was reduced during the first week postexposure for two rats in the high dose exposure group, body weight in the two other groups was considered unremarkable. Necropsy of the animals which were found dead indicated fluid in the trachea, dark areas of the lungs, stomach and nasal turbinates and "a failure of the lungs to collapse". Necropsy of the survivors did not indicate treatment related lesions.

The following LC<sub>50</sub>s with 95% confidence limits were generated from this study.

Combined	9.36 (0.355-247) mg/l
Males	6.76 (0.189-242) mg/l

Note the LC<sub>50</sub> for females could not be determined. These data would indicate that Dianon is Toxicity Category III or IV via inhalation toxicity. TB-I considers that an accurate LC<sub>50</sub> determination cannot be made utilizing the available data. For example, notice the broad range of 95% the confidence limits.

CONCLUSION. This study is UNACCEPTABLE. The registrant must submit more detailed information on the particle size distribution and demonstrate the particle size distribution with respect to the percentage of particles less than 1 um in diameter.

Reviewed by: John Doherty *John Doherty 7/19/90*  
Section I, Toxicology Branch I (H7509C)  
Secondary reviewer: Roger Gardner *Pamela M. Hurley 4/26/90*  
Section I, Toxicology Branch I (H7509C)

006172

#### DATA EVALUATION REPORT

STUDY TYPE: 81-4. Primary eye irritation - rabbits

MRID NO.: 413346-10

TOX. CHEM. NO.: 342

TEST MATERIAL: Dianon. Manufacturing Use Product of diazinon.  
87.84% diazinon.

TEST ANIMALS: Adult New Zealand White rabbits (Hra:(NZW)SPF  
obtained from Hazleton Research Products Inc, Denver, Penn..

STUDY NUMBER(S): HLA #2132-112

SPONSOR: Nippon Kayaku Co. Ltd., Tokyo, Japan.

TESTING FACILITY: Hazleton Laboratories America, Inc.

TITLE OF REPORT: "Primary Eye Irritation Study with Dianon in  
Rabbits"

AUTHOR(S): Janet A. Trutter, M.S., D.A.B.T.

REPORT ISSUED: October 27, 1989

CONCLUSIONS: No corneal involvement. Transient conjunctivae  
irritation of low intensity only at 1 hour. Toxicity Category  
IV.

Classification: ACCEPTABLE.

Quality Assurance Statement: A statement signed by Janet Milazzo  
attested that four inspections/reviews were made and four reports  
filed. No adverse comments were made by the QAU regarding this  
study.

#### REVIEW

In this study the eyes of six adult male rabbits were  
instilled with a 0.1 ml aliquot of the test material by insertion  
into the conjunctival sac. The upper and lower lids of the eye  
were held together for approximately 1 sec and the eyes were  
examined for reaction at 1, 24, 48 and 72 hours after  
instillation. Fluorescein dye was used at the 24 hour  
observation period to aid in revealing possible corneal injury.

None of the rabbits developed corneal opacity. There was some transient conjunctival irritation that was evident at the one hour observation period. The eman total score at 1 hour was 7 for conjunctivae. The test material is considered minimally irritating.

This study is ACCEPTABLE. Sufficient data were generated to classify the test material into toxicity category IV based on ocular irritation.

**HAZLETON**

LABORATORIES AMERICA, INC.

9200 LEESBURG TURNPIKE VIENNA, VIRGINIA 22182, USA

HLA 2132-112

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RESULTS  
Table 1  
Individual Eye Irritation Scores  
Test Material: Dianon<sup>a</sup>

Animal Number	Sex	PRIMARY EYE IRRITATION SCORES					Total <sup>b</sup> Score
		Cornea	Iris	Conjunctivae		Discharge	
				Redness	Chemosis		
1 Hour							
E49667	M	0	0	1	1	1	6
E49668	M	0	0	1	1	1	6
E49669	M	0	0	2	1	1	8
E49670	M	0	0	1	1	2	8
E49671	M	0	0	1	1	1	6
E49672	M	0	0	1	1	1	6
						Mean Total Score:	7
24 Hours <sup>c</sup>							
E49667	M	0	0	0	0	0	0
E49668	M	0	0	0	0	0	0
E49669	M	0	0	0	0	0	0
E49670	M	0	0	0	0	0	0
E49671	M	0	0	0	0	0	0
E49672	M	0	0	0	0	0	0
						Mean Total Score:	0
48 Hours							
E49667	M	0	0	0	0	0	0
E49668	M	0	0	0	0	0	0
E49669	M	0	0	0	0	0	0
E49670	M	0	0	0	0	0	0
E49671	M	0	0	0	0	0	0
E49672	M	0	0	0	0	0	0
						Mean Total Score:	0
72 Hours							
E49667	M	0	0	0	0	0	0
E49668	M	0	0	0	0	0	0
E49669	M	0	0	0	0	0	0
E49670	M	0	0	0	0	0	0
E49671	M	0	0	0	0	0	0
E49672	M	0	0	0	0	0	0
						Mean Total Score:	0

<sup>a</sup> Excessive blinking/rubbing of the treated eye upon instillation was noted in all rabbits.

<sup>b</sup> Same as the subtotal score for the conjunctivae.

<sup>c</sup> Fluorescein staining of eyes did not reveal any corneal injuries.

M = Male

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Reviewed by: John Doherty *John Doherty 7/19/90*  
Section I, Toxicology Branch I (H7509C)  
Secondary reviewer: Roger Gardner *Amelia M. Hurley 11/26/90*  
Section I, Toxicology Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: 81-5. Primary dermal irritation - rabbits

MRID NO.: 413346-11 TOX. CHEM. NO.: 342

TEST MATERIAL: Dianon. Manufacturing Use Product of diazinon.  
87.84% diazinon.

TEST ANIMALS: Adult New Zealand White rabbits (Hra:(NZW)SPF  
obtained from Hazleton Research Products Inc,  
Denver, Penn..

STUDY NUMBER(S): HLA #2132-113

SPONSOR: Nippon Kayaku Co. Ltd., Tokyo, Japan.

TESTING FACILITY: Hazleton Laboratories America, Inc.

TITLE OF REPORT: "Primary Dermal Irritation Study with Dianon in  
Rabbits"

AUTHOR(S): Janet A. Trutter, M.S., D.A.B.T.

REPORT ISSUED: October 27, 1989

CONCLUSIONS:

No signs of irritation. PIS = 0. Toxicity Category IV.

Classification: ACCEPTABLE

Quality Assurance Statement: A statement signed by Janet Milazzo  
attested that four inspections/reviews were made and four reports  
filed. No adverse comments were made by the QAU regarding this  
study.

REVIEW

In this study the backs of six rabbits were prepared by  
clipping but not abrading and a dose of 0.5 gm of the test  
material was applied to an area approximately 6 cm<sup>2</sup> and kept in  
contact with the rabbits skin by means of a gauze patch secured  
with transparent tape and further wrapped with a nonabsorbent  
binder (rubber damming) which was held in place with staples and  
1 inch tape for a four hour period. After removal, the area was

evaluated for signs of reaction or irritation at 30-60 minutes and at 24, 48, and 72 hours.

None of the rabbits showed signs of irritation or erythema or edema. All the scores were zero at all time points.

CONCLUSION. This study is ACCEPTABLE. Sufficient data were generated to classify the test material as Toxicity Category IV.

Reviewed by: John Doherty  
Section I, Toxicology Branch I (H7509C)  
Secondary reviewer: Roger Gardner  
Section I, Toxicology Branch I (H7509C)

*John Doherty 9/19/90*

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*Pamela M. Hurley 11/26/90*

**DATA EVALUATION REPORT**

**STUDY TYPE:** 81-6. Dermal sensitization - guinea pigs.

**MRID NO.:** 413346-12

**TOX. CHEM. NO.:** 342

**TEST MATERIAL:** Dianon a manufacturing use formulation of 87.84% purity provided by the sponsor. It was described as a pale-yellow liquid.

**TEST ANIMALS:** Hartley outbred strain guinea pigs (adults) obtained from the Hazleton Research Products, Inc. Denver, Penn.

**STUDY NUMBER(S):** HLA # 2132-114

**SPONSOR:** Nippon Kayaku Co. Ltd., Tokyo, Japan

**TESTING FACILITY:** Hazleton Laboratories America

**TITLE OF REPORT:** "Dermal Sensitization Study in Guinea Pigs with Dianon".

**AUTHOR(S):** Janet A. Trutter, M.S., D.A.B.T.

**REPORT ISSUED:** December 6, 1989

**CONCLUSIONS:**

Not demonstrated to be a sensitizer.

Classification: ACCEPTABLE.

**Quality Assurance Statement:** A statement signed by Janet Milazzo attested that three inspections/reviews were made and three reports prepared. No adverse comments were made in the QAS regarding the conduct of this study.

**REVIEW**

In this study one group of 10 (5 male and 5 female) guinea pigs was dosed with the test material (neat Dianon), a second group of 4 (2 males and 2 females) were dosed with the positive control (1-chloro-2,4-dinitrobenzene, DNCB, 0.15% w/v concentration in 80% aqueous ethanol) and a third group of 10 (5 male and 5 female) served as negative controls and were not

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treated during the induction phase. The method used was a modified Buehler technique. A preliminary test was conducted to determine the most appropriate dose level for the induction phase.

The induction phase consisted of dosing the guinea pigs on their shaved backs (the left quadrant) by applying 0.5 ml of either the test material or the positive control substance. The induction solutions were kept in place by means of rubber dam and cotton pads for six hours. After six hours the remaining test material was washed off. Three induction applications were made at one week intervals. The guinea pigs were given a 2-week rest period prior to subjecting to the challenge application.

The challenge phase consisted of making an application of the test material on the upper right quadrant. The test material was applied as a 50% dilution of the neat material in acetone and the positive control was applied as a 0.05% acetone solution in 0.5 ml of solution. The non-induced control group was dosed with the 50% Dianon. The challenge dose was also kept in contact with the guinea pig for six hours.

The application sites were scored according to the Draize technique approximately 24 hours after each induction phase and again at 24, 48 and 72 hours after the challenge dose.

#### RESULTS

The positive control produced the expected positive response in the development of well defined erythema noticeable at 24, 48 and 72 hours. One incident of very slight edema was evident at 24 hours.

The Dianon treated animals were not reported as having either erythema or edema at any time following the challenge dose. There was some slight erythema reported at the 24 hour observation period following the third induction phase (a score of 1 in two animals). All other scores were zero. No other adverse effects on the guinea pigs were noted.

**CONCLUSION.** This study is ACCEPTABLE. Sufficient data were generated to demonstrate that DIANON is not a sensitizer under the conditions in this study.