CIBA-GEIGY

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8EHQ-0486-0585
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[illegible] Control Officer (WH-557)
Information Management Division
Office of Toxic Substances
U. S. Environmental Protection Agency
401 "M" Street, S. W.
Washington, D. C. 20460

Att: Mr. Frank D. Kover

Re: 8EHQ-0186-0585S

Dear Mr. Kover:

This is in response to your letter of February 25, 1986 asking CIBA-GEIGY Corporation to:

A. Submit complete copies of the final reports from all studies cited in Part IV ("Health Hazard Data") of the Tinuvin(R) 144 Material Safety Data Sheet.

B. Describe the nature and available results of all other toxicity or exposure studies with Tinuvin 144 that CIBA-GEIGY has conducted, is conducting, or plans to conduct.

C. Describe the nature and available results of all toxicity studies (other than those previously submitted to the Agency) for PMN Substance No. 81-495 that CIBA-GEIGY has conducted, is conducting, or plans to conduct.

With regard to A, copies of the following reports for Tinuvin 144 (identified as TK 1192 in the reports) are enclosed:

1. Acute Oral LD_{50} in the Rat, November 15, 1976.

2. Acute Dermal LD_{50} in the Rat, January 3, 1976.

3. Acute Aerosol Inhalation Toxicity in the Rat, August 14, 1978.

4. Acute Inhalation Toxicity in the Rat as Determined in the Thermal Decomposition Apparatus, October 18, 1978.

5. Eye Irritation in the Rabbit, June 24, 1976.

6. Skin Irritation in the Rabbit after Single Application, June 24, 1976.

7. Skin Sensitizing Effect in Guinea Pigs, March 18, 1977.

8. Skin Photoallergenicity Study in the Guinea Pig, June 13, 1980.

9. Skin Phototoxicity Study in the Mouse, April 14, 1980.

10. Salmonella/Mammalian-Microsome Mutagenicity Test, January 29, 1979.

11. Human Repeat Insult Patch Test in Polypropylene, May 9, 1979.

With regard to B, rather than describing the information, we are submitting copies of the following reports:

12. Acute Toxicity to Rainbow Trout, Carp, Catfish and Bluegill, May 24, 1979.

13. Japanese MITI Fish Bioaccumulation Results (we only have the test results in our possession).

We are not aware of any other toxicity or exposure studies conducted by CIBA-GEIGY or any other entity. CIBA-GEIGY has no further studies underway nor are any planned at this time.

With respect to C, the only studies conducted with PMN Substance No. 81-495, which were not submitted with the PMN, are as follows, along with a description of the results:

14. Salmonella/Mammalian-Microsome Mutagenicity Test - Negative, with and without activation, in all four strains tested (TA 98, TA 100, TA 1535 and TA 1537).

15. Skin Sensitizing (Contact Allergenic) Effect in Guinea Pigs: Maximization Test - No animal was sensitized by the PMN substance under the experimental conditions employed. The PMN substance was classified to the lowest sensitization grade according to Magnussen and Kligman.

16. Another skin sensitization study, also negative, has not yet been received by CIBA-GEIGY Corporation.

We are unaware of any other studies conducted with the PMN substance or any studies in progress or planned at this time.

We trust that this letter and its enclosures adequately respond to your information request. None of the submitted information is considered to be Confidential Business Information.

Sincerely yours,

A. Di Battista

A. Di Battista
Manager, Toxic Substances Compliance
Safety, Health & Ecology

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Att.

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CIBA-GEIGY Limited
Basle, Switzerland

November 15, 1976/wu

Toxicology/Pathology
PH 2.635

TIMMVIN 144

ACUTE ORAL LD_{50} IN THE RAT OF TK 11927

Batch No.: [illegible]

Project No.: Siss 5628

1. Summary and Conclusion

The acute oral LD50 of TK 11927 in rats of both sexes observed over a period of 14 days is 1490 (1300-1708) mg/kg*. The test material has therefore a slight acute toxicity to the rat by this route of administration.

2. Method

a) Test material and formulation

TK 11927 was suspended with carboxymethyl-cellulose 2 %. Before treatment the suspension was homogeneously dispersed with an Ultra-Turrax and during treatment it was kept stable with a magnetic stirrer.

b) Animals

Healthy random bred rats of the Tif: RAIf (SPF) strain raised on our premises were used for these experiments. They were kept at a room temperature of 22 ± 1° C, at a relative humidity of 55 ± 5 % and on a 14 hours light cycle day. They received ad libitum rat food - NAFAG, Gossau SG - and water. Prior to treatment the animals were adapted to our laboratories for a minimum of 4 days and the initial body weight ranged from 160 to 180 grams.

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* LD 50 including 95 % confidence limits were calculated by the probit analysis method (Goulden A., Methods of Statistical Analysis, John Wiley and Sons, 1960, 3rd printing, pages 404-408).

Siss 5628

c) Treatment and observations

During the treatment and observation period the animals were housed in groups of 5 in Macrolon cages (type 3).

Animals fasted overnight were treated by oral intubation. Physical condition and rate of deaths were monitored throughout the whole observation period.

3. Results

a) Rate of deaths - Table 1

b) Signs and symptoms

Within 2 hours after treatment the rats in all dosage groups showed sedation, dyspnoea, exophthalmus, curved position and ruffled fur. Between the fourth and seventh day after intubation diarrhoea was also observed in animals of the four highest dosage groups.

The surviving animals recovered within 9 to 14 days. They were submitted to a necropsy whenever they died, survivors at the end of the observation period.

c) Autopsies

Dead and killed Animals: No substance related gross organ changes were seen.

K. Sachsse D.V.M. R. Bathe D.V.M.

Table 1 - Rate of deaths

Dose mg/kg	Concentration % of Formulation	No. of Animals		Died within 1 hr.		24 hrs.		48 hrs.		7 days		14 days	
		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
464	5	5	5	0	0	0	0	0	0	0	0	0	0
1000	10	5	5	0	0	0	0	0	0	0	0	1	0
1470	20	5	5	0	0	0	0	0	0	0	1	1	2
1670	20	5	5	0	0	0	0	1	1	1	3	3	5
2150	20	5	5	0	0	0	0	0	4	0	4	4	5
4640	50	5	5	0	0	0	0	1	1	4	4	5	5

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Basle, Switzerland

January 3, 1976/wu

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615-144 = TINUVIN 144

ACUTE DERMAL LD_{50} IN THE RAT OF TK 11927

Batch No.: EN 6398

Project No.: Siss 5628

1. Summary

The acute dermal LD50 of TK 11927 in rats of both sexes observed over a period of 14 days is greater than 3100 mg/kg.

2. Method

a) Test material and formulation

TK 11927 was suspended with carboxymethyl-cellulose 2 %. Before treatment the suspension was homogeneously dispersed with an Ultra-Turrax and during treatment it was kept stable with a magnetic stirrer.

b) Animals

Healthy random bred rats of the Tif:RAIf (SPF) strain raised on our premises were used for these experiments. They were kept at a room temperature of 22 ± 1° C, at a relative humidity of 55 ± 5 % and on a 14 hours light cycle day. They received ad libitum rat food - NAFAG, Gossau SG - and water. Prior to treatment the animals were adapted to our laboratories for a minimum of 4 days and the initial body weight ranged from 180 to 200 grams.

a) Treatment and observations

During the treatment and observation period the rats were housed individually in Macrolon cages (type 2). Approximately 24 hours before treatment an area on the back of the rats of approximately [illegible] hours [illegible] was shaved with an electric clipper. For treatment the test material was evenly dispersed on the skin with a syringe and was covered with an occlusive dressing which was fastened around the trunk with an adhesive elastic bandage. After 24 hours the dressing was removed, the skin was cleaned with lukewarm water and the reaction of the skin was appraised.

3. Results

a) Rate of deaths - Table 1

b) Signs and symptoms

No symptoms and no local skin irritation were seen.

The animals were submitted to a necropsy at the end of the observation period.

c) Autopsies

Killed Animals: No substance related gross organ changes were seen.

K. Sachsse D.V.M. R. Bathe D.V.M.

* Noakes, D.N. and Sanderson, D.M.
A method for determining the dermal toxicity of pesticides.
Brit. J. Industr. Med., 26, 59-64, 1969

Siss 5628

Table 1 - Rate of deaths

Dose mg/kg	Concentration % of Formulation	No. of Animals		Died within									
				1 hr.		24 hrs.		48 hrs.		7 days		14 days	
		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
2150	50	5	5	0	0	0	0	0	0	0	0	0	0
3170	50	5	5	0	0	0	0	0	0	0	0	0	0
No higher doses were possible.													

August 17, 1978/wu

[illegible]

[illegible] IN THE RAT OF TK 11927

[illegible]

[illegible]

1. [illegible]

[illegible] exposure for rats of both [illegible] air, when evaluated [illegible] 14 day posttreatment observation period.

2. Method

Inhalation toxicity was tested according to the method of Sachsse et al. (1973, 1976)*.

a) Animals

The test was performed with 10 male and 10 female rats of the Tif: RAIf (SPF) strain, raised on the premises. Before and after the inhalation the animals were kept at a room temperature of 22 ± 1° C, at a relative humidity of 55 ± 5 % and on a 10 hours light cycle day. They received ad libitum rat food - NAFAG, Gossau SG - and water. Prior to treatment they were adapted to our laboratories for a minimum of 4 days. Bodyweights were recorded immediately prior to exposure (control weights) and at day 14. The males and females were segregated and kept in Macrolon cages, type 4, (10 animals to a cage).

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* K. Sachsse, L. Ullmann, G. Voss and R. Hess: Measurement of inhalation toxicity of aerosols in small laboratory animals. In: Proceedings of the Europ. Soc. for the Study of Drug Toxicity. Vol XV, pp. 239-251, Zurich, June 1973.

K. Sachsse, L. Ullmann, K. Zbinden: Toxikologische Prüfungen von Aerosolen im Tierexperiment: Aus "Chemische Rundschau" 29 (1976), Nr. 38 Seite 1-4.

b) Testing procedures

For inhalation the rats were kept in separate PVC tubes positioned radially around the exposure chamber such that snout and nostrils of the animals only were exposed to the aerosol.

During the exposure period the following parameters were controlled inside the inhalation cylinder: temperature, relative humidity and oxygen content. The values were: temperature: 24° C; humidity: 46 %; oxygen: 20 Vol.%. After a 4 hour inhalation the rats were returned to their cages. Physical condition and incidence of death were monitored throughout an observation period of 14 days.

c) Preparation of aerosol

The aerosol was generated by injecting the solid test material with the help of a "Grafix Exaktomat Injector" into an air stream which was discharged into the exposure chamber through a nozzle under a pressure of 2 atm. at a rate of 20 l/min.

The concentration and the particle size distribution of the aerosol in the vicinity of the animals was monitored at 1 hour intervals throughout the aerosol exposure. The concentration was determined gravimetrically by sampling the test atmosphere through a selectron filter of 50 mm diameter and with a pore size of 0.2 µm (Schleicher and Schuell, Feldbach, Switzerland) at an air flow rate of 10 l/min. The size distribution of the particles was measured with a Cascade Impactor with selectron filters of 25 mm diameter and with a pore size of 0.2 µm (Schleicher and Schuell) at an air flow rate of 17.5 l/min. Fig. 1 contains data on the particle size of the test material.

3. Results

a) Rate of deaths - Table 1

b) Signs and symptoms - Table 2
No symptoms were seen during the exposure and observation period. The animals were submitted at random to a necropsy at the end of the observation period.

c) Autopsies

Killed Animals: No substance related gross organ changes were seen.

Dr. med. vet. K. Sachsse

L. Ullmann

781656

Table 1 - Rate of deaths

Concentration* mg/m³	Exposure Time (hrs)	No. of Animals		Died within 0-4 hrs		24 hrs.		48 hrs.		7 days		14 days	
		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
460 ± 70	4	10	10	0	0	0	0	0	0	0	0	0	0
No higher concentrations were possible.													

* Average aerosol concentration, gravimetrically determined.

[illegible]

Table [illegible] - Signs and symptoms

Signs and symptoms	Dose (mg/m²)						
	[illegible]						
Sedation							
[illegible]							
[illegible]							
Chromodacryorrhoea							
Rhinorrhoea							
Epistaxis							
Exophthalmos							
Salivation							
Ruffled fur							
Pallor							
Cyanosis							
Diarrhoea							
Body position (ventral)							
Body position (lateral)							
Body position (curved)							
Ataxia							
Trismus							
Tremor							
Tonic-clonic muscle spasms							
Convulsions							

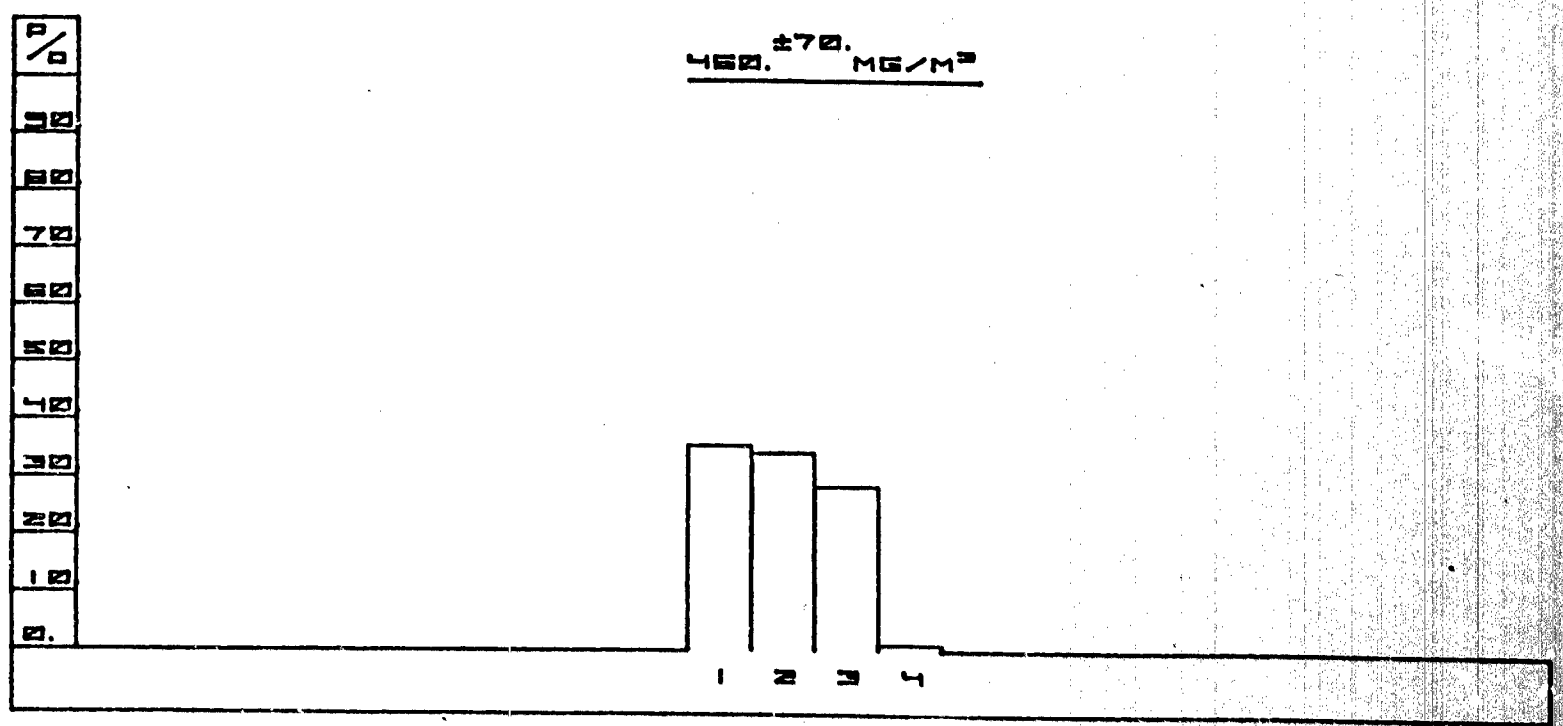
Day 1 ♂	Mean Bodyweight g	185						
Day 1 ♀		180						
Day 7 ♂								
Day 7 ♀								
Day 14 ♂		317						
Day 14 ♀		254						

Key: + = slight, ++ = moderate, +++ = severe

EXP.704656. TK 11927

FIG. 1.

MEAN PARTICLE SIZE DISTRIBUTION
CASCADE IMPACTOR
AIR FLOW RATE 17.5 L/MIN



1 = ABOVE 7 µM / 2 = 3-7 µM / 3 = 1-3 µM / 4 = 0-1 µM

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[illegible] Limited
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October 18, 1978/wu

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FIDAVIN 144

ACUTE INHALATION TOXICITY IN THE RAT OF TK 11927 AS DETERMINED IN THE THERMAL DECOMPOSITION APPARATUS

Batch No.: 21177-11190

Project No.: 784944

1. Summary and Conclusion

Rats were exposed for 60 minutes to the volatile materials of TK 11927 produced in the thermal decomposition apparatus at 200° C. Exposures to the volatile materials were tolerated by the animals.

2. Method

Inhalation toxicity was tested according to the method of Sachsse et al. (1973, 1976)*.

a) Animals

The test was performed with 10 male and 10 female young adult rats of the Tif: RAIf (SPF) strain, raised on the premises. Before and after the inhalation procedure the animals were kept at a room temperature of 22 ± 1° C, and a relative humidity of 55 ± 5 % on a 10 hours' light cycle. They received rat food (NAFAG, Gossau SG) and water ad libitum. Prior to treatment they were kept in the laboratory for at least 4 days to accustom them to the environment. The initial body-weights ranged from 195 to 228 grams. The males and females were segregated and housed 10 to a cage in Type 4 Macrolon cages.

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* K. Sachsse, L. Ullmann, G. Voss and R. Hess: Measurement of inhalation toxicity of aerosols in small laboratory animals. In: Proceedings of the Europ. Soc. for the Study of Drug Toxicity. Vol XV, pp. 239-251, Zurich, June 1973.

K. Sachsse, L. Ullmann: K. Zbinden: Toxikologische Prüfungen von Aerosolen im Tierexperiment: Aus "Chemische Rundschau" 29 (1976), Nr. 28 Seite 1-4.

b) Test procedures

A 10 g sample of the test material was evenly distributed in a glass vessel (30 cm in length), which was inserted into a glass tube 25 mm in diameter and 120 cm in length. The tube was heated in a cylindrical oven (DIN 53436; H. Born, mech. Werkstatt, Möhlin AG, Switzerland). The oven was driven by an electric motor and travelled over the tube containing the glass vessel and the product to be incinerated at a rate of 1 cm/min. Air was blown through the tube in the direction of movement of the oven at a rate of 100 l/hr. At the opposite end of the tube, the air jet containing the volatile material of decomposition was mixed with fresh air introduced at a rate of 100 l/hr. This jet of fresh air provided sufficient oxygen for the animals' respiration, and also cooled the fumes to a tolerable temperature.

The gases were produced at a temperature of 200° C. The gases were mixed with air as descrived above blown into the exposure chamber, around which the rats were kept in separate PVC tubes radially around the exposure chamber such that only their snouts and nostrils were exposed. The duration of exposure was 60 minutes.

The temperature inside the glass tube over the oven on the top of the substance was controlled at 80; 122; 201 and 354° C in comparison with the melting points of the chemical reference substances Naphtalin, Benzoic acid, Isatin and Acridon and the indicating instruments. The accuracy of the temperature in this system was established to be +5° C.

c) Gas analysis

In this experiment carbon monoxide (CO), carbon dioxide (CO_2), hydrochloric acid (HCl) and ammonia (NH_3) contents were measured with DRAEGER analyzer tubes, oxygen (O_2) was measured with a Draeger E 15 stationary control system (Draegerwerk AG, Lübeck, Germany) within the inhalation cylinder.

d) Temperature and humidity control

The temperature and the humidity inside the test chamber was controlled continuously during the exposure period in close vicinity of the test animals.

Temperature was measured with a THERM 2104 Contact thermometer (Ahlborn Mess- und Regeltechnik, [illegible] Holzkirchen, Germany).

Humidity was measured with a VÄISALA Humidity Indicator [illegible] 11 (Kelag AG, 8057 Zurich, Switzerland).

3. Results

a) Conditions of test and death rate - Table 1

b) Signs and symptoms

After the 60 minutes exposure period and the following observation period no toxic symptoms were observed. No irritations of the mucous membranes of the eyes and nose were seen.

The bodyweight gain of all rats was within physiolgocial limits during the test and observation period.

The animals were submitted at random to a necropsy at the end of the observation period.

c) Substance behaviour

At the end of the test period 9.8 g of the test material remained in the glass vessel. The test material had changed from a white solid at the beginning of the test to a colorless liquid at termination.

d) The following gas concentrations were measured within the cylinder

Temperature °C	O_2 Vol. %	CO ppm	CO_2 Vol. %	NH_3 ppm	HCl ppm
200	20	<5	0.2	<2	<2

f) Temperature and relative humidity

The temperature and relative humidity inside the inhalation cylinder was measured to be 24° C and 85 %.

g) Autopsies

Killed Animals: No substance related gross organ changes were seen.

Dr. med. vet. K. Sachsse

L. Ullmann

Table 1 - Conditions of test and death rate

Temperature °C	Duration of Exposure	No. of Animals		Died within									
				0-60 min.		24 hrs.		48 hrs.		7 days		14 days	
		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
[illegible]	60 min.	10	10	0	0	0	0	0	0	0	0	0	0

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Basle, Switzerland

June 24, 1976/wu

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EYE IRRITATION IN THE RABBIT OF TK 11927

Batch No.: EN 6003

Project No.: Siss 5261

1. Summary and Conclusion

Under the conditions of this experiment the test preparation was found to cause a minimal irritation when applied to the rabbit eye mucosa.

2. Method

The procedure used was the test for eye irritants described in the "Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics" (1959), the US Association of Food and Drug Officials (AFDO).

The test was performed on 3 male and 3 female rabbits of the Himalayan breed weighing 1.5 to 2 kg. The animals were housed individually in metal cages, were kept at a constant room temperature of 18 ± 1° C, at a relative humidity of 55 ± 5 % and on a 14 hour light cycle day. The animals had ad libitum access to standard rabbit food - NAFAG, Gossau SG - and water. Prior to treatment they were adapted to our laboratories for a minimum of 8 days. Only rabbits with normal ophthalmic findings were used for these tests.

The test material in an amount of 0.1 g was inserted into the conjunctival sac of the left eye of the 6 rabbits and the lids were gently closed for one second. The right eye was not treated and served as an untreated control. In 3 of the 6 rabbits approximately 30 seconds after treatment the treated eye was flushed with 10 ml of lukewarm water. The eye irritation was appraised with a slit-lamp on day 1, 2, 3, 4 and 7 and was scored for each individual rabbit as outlined in table 1. The primary eye irritation index represents the sum of the mean values for cornea, iris and conjunctivae. This procedure was carried out separately for unrinsed and rinsed eyes respectively.

[illegible] in rabbits (Table 1)

[illegible]:

A [illegible] (most dense area scored)
[illegible] 0
[illegible] area, details of iris clearly visible .. 1
[illegible] areas, details of iris [illegible] 2
[illegible] details of iris visible, size of pupil [illegible] 3
Opaque, iris invisible 4

B Area of cornea involved
One quarter (or less) but not zero 1
Greater than one quarter, but less than half 2
Greater than half, but less than three quarters 3
Greater than three quarters, up to whole area 4

A x B x 5 Maximum possible score = 80

IRIS:

A Values
Normal 0
Folds above normal, congestion, swelling, circumcornea injection (any or all of these or combination of any thereof) iris still reacting to light (sluggish reaction is positive . 1
No reaction to light, hemorrhage, gross destruction (any or all of these) 2

A x 5 Maximum possible score = 10

CONJUNCTIVAE:

A Redness (refers to palpebral and bulbar conjunctivae [illegible] cornea and iris)
Vessels normal 0
Vessels definitely injected above normal 1
More diffuse, deeper crimson red, individual vessels not easily discernible 2
Diffuse beefy red 3

B Chemosis
No swelling 0
Any swelling above normal (includes nictitating membrane) ... 1
Obvious swelling with partial eversion of lids 2
Swelling with lids about half closed 3
Swelling with lids about half closed to completely closed ... 4

C Discharge
No discharge 0
Any amount different from normal (does not include small amounts observed in inner canthus of normal animals) 1
Discharge with moistening of the lids and hairs just adjacent to lids 2
Discharge with moistening of the lids and hairs, and considerable area around the eye 3

(A + B + C) x 2 Maximum possible score = 20

Siss 5261

The total maximum score was thus 80 for the cornea, 10 for the iris, 20 for the conjunctivae and 110 for the entire eye. The severity of overall eye irritation was rated as:

0 - 10	minimal
11 - 25	slight
26 - 56	moderate
57 - 84	marked
above 84	extreme

The ratio $R = \frac{\text{unrinsed}}{\text{rinsed}}$ eyes indicates the effect of rinsing the eyes 30 seconds after instillation of the compound.

R =	<1	= rinsing increased the effect of the compound
	1.1 - 1.5	= practically no effect
	1.6 - 2	= little but assessable effect
	2.1 - 4	= good effect
	4.1 - 10	= very good effect
	>10	= action of the compound practically abolished

3. Results - Tables 2 and 3

In the present experiments the irritation index was established as 0.15 for the cornea, 0 for the iris and 0.8 for the conjunctivae. The substance caused therefore a minimal overall eye irritation to rabbits.

K. Sachsse D.V.M.

L. Ullmann

[illegible]

[illegible]

[illegible]

[illegible] Eye irritation in individual rabbits with eyes rinsed [illegible] after treatment

Days after Appl.	Rabbit 1 ♀			Rabbit 2 ♀			Rabbit 3 ♀		
	Cornea	Iris	Conjunct.	Cornea	Iris	Conjunct.	Cornea	Iris	Conjunct.
1	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0

Cornea: 0; Iris: 0; Conjunctivae: 0

Table 3 Eye irritation in individual rabbits with eyes not rinsed after treatment

Days after Appl.	Rabbit 4 ♂			Rabbit 5 ♂			Rabbit 6 ♂		
	Cornea	Iris	Conjunct.	Cornea	Iris	Conjunct.	Cornea	Iris	Conjunct.
1	5	0	10	0	0	0	0	0	0
2	0	0	8	0	0	0	0	0	0
3	0	0	6	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0

Cornea: 0.3; Iris: 0; Conjunctivae: 1.6

effect of rinsing $R = \frac{\text{unrinsed eyes}}{\text{rinsed eyes}} \quad \frac{0.63}{0} =$

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Basle, Switzerland

June 24, 1976/wu

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TINUVIN 144
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SKIN IRRITATION IN THE RABBIT AFTER SINGLE APPLICATION OF

TK 11927

Batch No.: EN 6003

Project No.: Siss 5261

1. Summary and Conclusion

The primary irritation index, a measure of the acute irritation to the rabbit skin was 0. This indicates that the substance is not an irritant to the rabbit skin.

2. Method

The procedure used was the patch test technique described in the "Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics" (1959), the US Association of Food and Drug Officials (AFDO).

The test was performed on 3 male and 3 female rabbits of the Himalayan breed weighing 1.5 to 2 kg. They were housed individually in metal cages, were kept at a constant room temperature of 18 ± 1° C, at a relative humidity of 55 ± 5 % and on a 14 hours light cycle day. The animals received ad libitum standard rabbit food - NAFAG, Gossau SG - and water. Prior to treatment they were adapted to our laboratories for a minimum of 8 days.

Two days before treatment the entire back and the flank of the rabbits were shaved with an electric clipper and immediately before treatment the shaven skin on the left side was slightly scarified. For treatment gauze patches of 2.5 x 2.5 cm with test substance were applied to the prepared abraded and non abraded skin, in quantities of 0.5 g.

The patches were covered with an impermeable material and were fastened to the body of the rabbit with adhesive tape. The dressings were removed after a 24 hour exposure.

The skin irritation was scored immediately and 48 hours after removal of the dressings (24 and 72 hours after initiation of treatment). Skin irritation was scored in accordance with the irritation score from table 1.

The severity of skin irritation was rated as follows: A mean value of less than 2 indicated mild, from 2 to 5 moderate and above 6 severe skin irritation.

<u>Score for skin irritation in rabbits</u> (Table 1)

Erythema and eschar formation

No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4
Maximum possible erythema score	4

Edema formation

No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond area of exposure)	4
Maximum possible edema score	4

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Siss 5261

3. **Results** - Table 2

The primary irritation index is the mean value of the sum of the scores for erythema and edema from all 6 rabbits 24 and 72 hours after initiation of treatment. The maximum possible score is 8.

The primary skin irritation index in this experiment was established to be 0. The substance caused therefore no skin irritation to rabbits.

K. Sachsse D.V.M.

L. Ullmann

Size 5261

Skin irritation in individual rabbits - Table 2

Animal No. Sex	Skin Reaction	24 hrs after application		72 hrs after application	
		intact skin	scarified skin	intact skin	scarified skin
1 ♂	Erythema	0	0	0	0
	Edema	0	0	0	0
2 ♂	Erythema	0	0	0	0
	Edema	0	0	0	0
3 ♂	Erythema	0	0	0	0
	Edema	0	0	0	0
4 ♀	Erythema	0	0	0	0
	Edema	0	0	0	0
5 ♀	Erythema	0	0	0	0
	Edema	0	0	0	0
6 ♀	Erythema	0	0	0	0
	Edema	0	0	0	0

CIBA-GEIGY Limited
Basle, Switzerland

March 18, 1977/wu

Toxicology/Pathology
PH 2.635

SKIN SENSITIZING (CONTACT ALLERGENIC) EFFECT IN GUINEA PIGS OF

TK 11927 6 15 - 144

TINUVIN 144

Batch No.: EN 6398

Project No.: Siss 5628

1. Summary and Conclusion

Under the experimental conditions employed, significant differences between the test group and the vehicle-treated controls were only seen after intradermal challenge administration of preparation TK 11927, i.e. when the skin barrier was intentionally by-passed.

No difference between the test and the control group was seen after epidermal challenge administration. The negative results upon epidermal challenge demonstrate that, in artificially sensitized guinea-pigs, exposure of the intact skin to the test compound does not provoke contact dermatitis.

2. Method

The optimization test[1] was used, an intracutaneous sensitization procedure similar to the method recommended in the "Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics" (1959), the US Association of Food and Drug Officials (AFDO).

---

1 Maurer, Th., Thomann, P., Weirich, E.G. and Hess, R. (1975) The Optimization test in the guinea pig. A method for the predictive evaluation of the contact allergenicity of chemicals.
Agents and Actions Vol. 5 (2), 174-179, 1975

[illegible]

[illegible]

[illegible] test was performed on groups of 10 male and 10 female [illegible] of the [illegible] white strain bred on our [illegible] between 400 to 450 grams. The animals were housed individually in Macrolon cages, type 3, kept at a constant room temperature of 22 ± 1° C, at a relative humidity of 55 ± 5 % and on a 10 hours light cycle day. The animals received ad libitum standard [illegible] pellets - NAFAG, No. 830, Gossau SG - and water.

b) Testing procedure

During the induction period the animals received one injection every second day (except weekends) to a total of 10 intracutaneous injections of a freshly prepared 0.1 % dilution in polyethylene glycol (PEG 400) + saline (70 : 30 parts).

On the first day, injections of 0.1 ml were administered into the shaven skin of the right flank and the back, while on the following days a single intracutaneous injection was given into the back.

During the second and third week of the induction period the test material was incorporated in a mixture of the normal vehicle with complete Bacto Adjuvant[2]

(vehicle : adjuvant = 1 : 1).

Fourteen days after the last sensitizing injection, a challenge injection of 0.1 ml of a freshly prepared 0.1 % dilution of TK 11927 in polyethylene glycol (PEG 400) + saline (70 : 30 parts) was administered into the skin of the left flank.

Twenty-four hours after each injection during the first week of the induction period and 24 hours after the challenge injection the reactions were recorded. Before examination, the reaction sites were depilated chemically (Butoquick®, 5 minutes).

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2 Bacto Adjuvant, complete Freund (Difco, Michigan, USA).

The two largest perpendicular diameters (in mm) and the increase in the skin- fold thickness (in mm) were measured and by multiplication of these values "reaction volume" was obtained (in µl) for each reading from each animal. The mean volume plus one standard deviation of the induction reactions observed in the individual animal in the first week was taken as representing the skin irritation "threshold" for each animal. Any challenge reaction greater than this threshold value in the induction period was graded as an allergic reaction and the animal termed "positive". The number of "positive" animals in the test group was compared with the number of animals in the control group (treated with the vehicle alone) that showed a non-specific reaction of at least the same magnitude ("negative control")[3].

Ten days after the intracutaneous challenge injection a subirritant dose of the test compound was applied epicutaneously under occlusive dressings which were left in place for 24 hours.

3. Results

Intradermal injection of the vehicle alone failed to induce sensitization.

Table 1 summarizes the incidence of positive reactors after intradermal and epidermal challenge application.

Tables 2 and 3 show the reaction volumes for individual animals of the test and control group.

K. Sachsse D.V.M.

L. Ullmann

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[3] The exact Fisher test for comparison of the basic probability of two binominal distributions; L. Sachs, Statistische Auswertungsmethoden, Thieme Verlag, Stuttgart, 1971. A probability of $\leq$ 0.01 was considered to indicate a significant difference.

[illegible] intradermal

	No. of positive animals/ No. of treated animals	P
[illegible] control	1/20	0.75
[illegible]	13/20	<0.001

[illegible] positive animals per group after occlusive [illegible] application

	No. of postive animals/ No. of treated animals	P
[illegible] control	0/20	-
[illegible]	0/20	-

[illegible] reactions after occlusive epicutaneous [illegible] of the test compound

Erythema score (Draize Score) 24 hours after removal of the [illegible]

Animal No.	1	2	3	4	5	6	7	8	9	10
	0	0	0	0	0	0	0	0	0	0

Animal No.	11	12	13	14	15	16	17	18	19	20
	0	0	0	0	0	0	0	0	0	0

Table 2 - Reaction volumes (µl) after intradermal injection of Polyethylene glycol (PEG 400) + saline (70 : 30 parts) Control

Animal No.	INDUCTION Application No. 1	2	3	4	mean ($\bar{x}$)	standard deviation (s)	($\bar{x}$ + s)	after skin sensitization	+ = positive reactor
1 ♂	58	73	66	69	66	6.3	72.3	0.2	-
2	77	54	12	110	63	41	104	94	-
3	59	18	38	30	36	17	53	27	-
4	121	50	70	170	103	54	157	90	-
5	81	97	81	100	90	10	100	99	-
6	79	45	73	60	64	15	79	160	+
7	70	83	70	52	69	13	82	78	-
8	108	50	40	134	83	45	128	112	-
9	79	40	98	84	75	25	100	96	-
10	81	40	129	296	136	112	248	120	-
11 ♀	12	0	63	101	44	47	91	90	-
12	32	22	32	90	44	31	75	72	-
13	88	16	79	35	54	34	88	24	-
14	89	57	104	130	95	30	125	120	-
15	36	62	109	168	94	58	152	92	-
16	40	18	96	130	71	51	122	96	-
17	8.4	11	73	48	35	31	66	60	-
18	45	0	126	71	60	53	113	104	-
19	60	0	96	13	42	44	86	79	-
20	34	7.2	48	110	50	44	94	88	-
Group-mean	62.9	37.1	75.1	100				85	1/20

[illegible] (x1) after intradermal injection [illegible] in polyethylene glycol (PEG 400) + [illegible]

[illegible]	[illegible]					standard deviation (s)	$(\bar{x} + s)$	after skin sensitization	+ = positive reactor
	1	2	3	4	[illegible]				
1 ♂	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	49	110	110	-
2	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	7	53	48	-
3	65	42	49	88	61	20	81	168	+
4	[illegible]	73	50	187	90	65	155	120	-
5	45	115	32	32	56	40	96	80	-
6	20	34	7	99	40	41	81	80	-
7	55	84	8	122	67	48	115	45	-
8	20	22	0	86	32	37	69	276	+
9	13	29	19	58	30	20	50	168	+
10	26	13	38	39	29	12	41	27	-
11 ♀	70	29	49	49	49	17	66	251	+
12	58	44	81	82	66	19	85	210	+
13	50	33	14	21	29	16	45	108	+
14	12	25	19	80	34	31	65	150	+
15	69	84	28	48	57	24	81	121	+
16	81	69	121	29	75	38	113	112	-
17	90	38	32	31	48	28	76	138	+
18	72	90	24	96	70	33	103	140	+
19	43	34	5.6	57	35	22	57	108	+
20	27	46	19	31	31	11	46	126	+
Group-mean	48.3	49.1	33.2	70.9				129	12/20

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CIBA-GEIGY LIMITED
BASEL, SWITZERLAND

Test No.: 800354

Toxicology GU 2.5 / ek

SKIN PHOTOALLERGENICITY STUDY IN THE GUINEA PIG OF TK 11'927

Sponsor: Plastics and Additives Division

TINUVIN 144

Test material received: 21.02.1980

Validity: Determined by sponsor

Study initiated: 14.04.1980

Study completed: 13.06.1980.

Summary and conclusion

Under the experimental condition employed, no differences between the test group and the vehicle-treated controls were seen, after epidermal challenge application either followed by UV-B and UV-A irradiation or followed by UV-A irradiation alone.

TK 11'927 was found to be devoid of a photoallergenic potency in albino guinea-pigs.

Study director: Th. Maurer
Dr. Th. Maurer

Approved by: R. Hess
Prof. Dr. med. R. Hess
(Head of Toxicology)

Reported and archivated: June 13, 1980; R-1062.3.07.

Test No.: 800354

[illegible]: TK 11'927

[illegible]: [illegible] 21175

[illegible]: white powder

Concentration: Epidermal application of freshly prepared 0.1 % solution of TK 11'927 in 80 % DAE433.

Vehicles: - 80 % DAE433 / 20 % physiological saline (DAE433 = 40 % Dimethylacetamide, 30 % Acetone, 30 % Ethanol)
- Adjuvant complete Freund (Difco).

[illegible] Animals

Strain: Guinea pigs of the Pirbright white strain bred on our premises were used.

Animals received: 08.04.1980

Acclimatisation period: 7 days.

The test was performed on 10 male and 10 female guinea pigs per group weighing between 300 - 370 g (~ 10 weeks old). The animals were housed individually in Macrolon cages (type 3), assigned to the different groups by means of random numbers generated by the random number generator incorporated in the Hewlett-Packard desk computer, identified with individual ear tags, kept at a constant room temperature of 20 ± 1° C, at a relative humidity of 50 ± 5 % and on a 14 hours light cycle day. The animals received ad libitum standard guinea pig pellets - NAFAG No. 830, Gossau SG - and fresh water, supplemented with fresh carrots.

3. Light Source Characteristics

Burner: Special irradiation chamber with a water cooled 6000 W Xenon burner (Osram)

Distance between burner and animals: 80 cm

Maximal irradiation intensity used:

280 - 320 nm	(UV-B)	785 µW/cm2
320 - 400 nm	(UV-A)	4.55 mW/cm2
400 - 700 nm	(visible)	23.64 mW/cm2

Energy output controlling system:

Spectroradiometer EG & G, Model No. 585

4. Method

Induction: 4 days before starting the induction, the animals were shaven on the neck and chemically depilated (Veet^R). During the whole induction period the animals were only shaven (Aesculap^R, V20 mm).

4 times a week for three weeks the animals were treated by epidermal open exposure with a 0.1 % solution of TK 11'927 in 80 % DAE433 (0.1 ml per application; 2 x 2 cm application area on the animals' neck).

One hour after application the animals were irradiated for 10 minutes during the first induction week (UV-A, visible), 10 minutes during the second and third week (UV-B, UV-A, visible).

During the irradiation process the animals were immobilized in a special animal holder. In order to protect the skin surrounding of the irradiated area, this part was covered with a lightproof bandage.

[illegible] each of the first four induction [illegible] the skin reactions were evaluated according the Draize Scoring Scale (see appendix). [illegible], during the second and third induction week [illegible] extended.

A total of 4 adjuvant injections were made to [illegible] of the application site on Monday and Wednesday of the second and third induction week (0.1 ml suspension of adjuvant complete Freund and physiological saline per injection).

Challenge I: 12 days after the last induction irradiation, the animals were shaven on the back and the skin was chemically depilated (Veet^{R}, 5 min.). 7 days later the animals were treated by epidermal open exposure for three days as during the induction period. One hour after each application the animals were irradiated for 3 minutes with a sub-erythematogenic dose of UV-B, UV-A and visible light (lamp filtered with a Schott filter WG 280, 3 mm).

Challenge II: A second challenge was done after a rest period of 14 days. The substance was applied again three times on the shaven skin of the animals' back: the test site was irradiated after each application for 10 minutes with a suberythematogenic dose of UV-A and visible light (lamp filtered with a Schott filter WG 320, 3 mm).

24 hours after each application of both challenges, the skin reactions were evaluated according the Draize Scoring Scale.

Every animal with one or more score values higher at the end of the two challenge periods than that obtained at the end of the first induction week was termed positiv. The number of

positive animals in the test group was compared with the number of animals in the control group treated with the vehicle alone*.

5. Results

Table I summarizes the incidences of positive animals per group after challenge I and II.

In Table II, the individual erythema reactions are listed as evaluated 24 hours after the last irradiation of either the induction, challenge I or challenge II.

In the control group only one animal showed a weak skin reaction during challenge I.

In the test group one animal showed scaling formation at the end of the first induction week. Slight scaling formation was observed in the test group at the end of the second challenge. Erythema formation was not observed.

The intensity of the skin reactions and the incidence does not show a significant difference to the control group.

* The exact Fisher test for comparison of the basic probability of the binomial distributions; L. Sachs, Statistische Auswertungsmethoden, Thieme Verlag, Stuttgart, 1971. A probability of $P \leq 0.01$ was considered to indicate a significant difference.

Toxicology GU 2.5 Test No.: 800354

T A B L E I

Incidence of positive animals after challenge I and challenge II

	No. of positive animals / No. of treated animals	P
Challenge I		
DAE433	1/20	
TK 11'927	1/20	
Challenge II		
DAE433	0/20	
TK 11'927	5/20	>0.01

T A B L E I I

Individual erythema reaction score 24 hours after the last irradiation of the induction, challenge I and challenge II

Control group DAE433	Animal number																			
	572	573	574	575	576	577	578	579	580	581	582	583	584	585	586	587	588	589	590	591
Induction	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Challenge I	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Challenge II	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Test group TK 11'927	612	613	614	615	616	617	618	619	620	621	622	623	624	625	626	627	628	629	630	631
Induction	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	S	0	0
Challenge I	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
Challenge II	0	0	0	0	S	0	0	0	S	0	S	0	0	0	0	0	S	0	S	0

S = scaling formation

Toxicology OM 7.5 Test No.: 800354

Evaluation of skin reactions according to Draize[1)]

	Score
Erythema and eschar formation	
No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4

1) in Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics (1959), the US Association of Food and Drug Officials (AFDO).

Toxicology GU 2.5 Test No.: 800354

Verteiler:

Dr. Th. Maurer (Original)
Dr. A. von Schulthess

TK 11'927

[illegible]

[illegible] Test No.: 800353

[illegible]

TINUVIN 144

SKIN PHOTOTOXICITY STUDY IN THE MOUSE OF TK 11'927

Sponsor: Plastics and Additives Division

Test material received: 21.02.80

Validity: not determined

Study initiated: 24.03.80

Study completed: 28.03.80

Summary and Conclusion

Under the experimental conditions employed, TK 11'927 was found to cause neither erythema nor edema in hairless mice when applied topically followed by UV irradiation.

TK 11'927 was found to be devoid of a phototoxic potency in hairless mice.

Study director: Dr. Th. Maurer

Approved by: Prof. Dr. med. R. Hess (Head of Toxicology)

Reported and archivated: April 14, 1980; R-1062.3.07.

1. Materials

Test material: TK 11'927.

Identification: EN 21175.

Concentrations: 0.3 %, 1 % and 3 %.

Positive control: 0.1 % 8-methoxypsoralene (Sigma), 8-MOP.

Test vehicle: 50 % Acetone / 50 % Ethanole.

2. Animals

Strain: Mouse, SC: hairless HR/HR.

Breeder: Bomholtgard.

Animals received: 13.03.80.

Acclimatisation period: 10 days.

3. Light source characteristics

Solar Ultraviolet Simulator (Solar Light Company, 6655 Lawnton Ave, Philadelphia, Pennsylvania 19126).

Burner: 150 W Xenon.

Wavelength range for irradiation: 320 - 400 nm.

Irradiation intensity at focused distance: 35 mW/cm^2.

4. Method

The test was performed on 3 male and 3 female mice per group (SC: hairless HR/HR outbred mice) weighing 20 - 27 g (2 to 2½ months old). They were housed individually in wire cages (size 1), assigned to the different cages by means of random numbers generated by the random number generator incorporated in the Hewlett-Packard desk computer, kept at a constant room temperature of 24 ± 1° C, at a relative humidity of 50 ± 5 % and on a 14 hours light cycle day. The animals recieved ad libitum standard mouse pellets No. 890 - Nafag Gossau SG - and water.

[illegible] was diluted to concentrations of 0.3 %, [illegible] a mixture of 50 % acetone and 50 % ethanole. [illegible] of [illegible] µl of each concentration were applied evenly [illegible] the skin of both flanks of the mice. For [illegible] level a separate group of animals was [illegible] and positive control groups treated either with the vehicle or a solution of 0.1 % 8-methoxypsoralene [illegible] were included in the test system.

Half an hour after application the animal was fixed in front of the light source in an animal holder at a distance of 5.6 cm from the lamp box and a circular skin area of 1 cm in diameter of one side of the mouse was exposed to UV-light for a duration of 2 minutes. The contralateral side, not exposed to light, served as the control.

The skin reactions were evaluated 24, 48 and 72 h after the irradiation according to the Draize Scoring system for primary irritation reactions (Appendix).

5. Results

No adverse skin reaction was observed when TK 11'927 was applied topically to hairless mice followed by UV-irradiation.

Moderate oedema reactions were seen 24 h after application of 0.1 % 8-methoxypsoralene topically to hairless mice followed by UV-irradiation. Fresh necrosis surrounded by erythema was observed 48 and 72 h after irradiation in the 0.1 % 8-methoxypsoralene group.

Table 1: Number of positive animals per group

	No. of positive animals/ No. of treated animals irradiated flank	No. of positive animals/ No. of treated animals non irradiated flank
24 h after irradiation		
vehicle control	0/6	0/6
0.1 % 8-MOP	6/6	0/6
0.3 % TK 11'927	0/6	0/6
1.0 % TK 11'927	0/6	0/6
3.0 % TK 11'927	0/6	0/6
48 h after irradiation		
vehicle control	0/6	0/6
0.1 % 8-MOP	6/6	0/6
0.3 % TK 11'927	0/6	0/6
1.0 % TK 11'927	0/6	0/6
3.0 % TK 11'927	0/6	0/6
72 h after irradiation		
vehicle control	0/6	0/6
0.1 % 8-MOP	6/6	0/6
0.3 % TK 11'927	0/6	0/6
1.0 % TK 11'927	0/6	0/6
3.0 % TK 11'927	0/6	0/6

Every animal with a defined erythema or edema was evaluated as a positive animal.

Table 2: Evaluation of skin reactions

Preparation	Sex		24 h ♂ 1	24 h ♂ 2	24 h ♂ 3	24 h ♀ 1	24 h ♀ 2	24 h ♀ 3	48 h ♂ 1	48 h ♂ 2	48 h ♂ 3	48 h ♀ 1	48 h ♀ 2	48 h ♀ 3	72 h ♂ 1	72 h ♂ 2	72 h ♂ 3	72 h ♀ 1	72 h ♀ 2	72 h ♀ 3
50% Acetone / 50% Ethanole	Erythema	i	0	0	0	0	0	0	0	0	0	0	0	0						
		ni	0	0	0	0	0	0	0	0	0	0	0	0						
	Edema	i	0	0	0	0	0	0	0	0	0	0	0	0						
		ni	0	0	0	0	0	0	0	0	0	0	0	0						
	Total	i	0	0	0	0	0	0	0	0	0	0	0	0						
		ni	0	0	0	0	0	0	0	0	0	0	0	0						
0.1 % 8-MOP	Erythema	i	0	0	0	0	0	0	3	0	1	0	0	0	3	0	0	0	3	0
		ni	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Edema	i	2	3	2	2	3	2	2	2	2	2	2	1	2	2	2	2	6	1
		ni	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Total	i	2	3	2	2	3	2	5	2	3	2	2	1	5	2	2	2	6	1
		ni	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

i = irradiated flank ni = non irradiated flank

Table 3: Evaluation of skin reactions

Preparation	Sex		Skin reaction after 24 h ♂ 1	♂ 2	♂ 3	♀ 1	♀ 2	♀ 3	48 h ♂ 1	♂ 2	♂ 3	♀ 1	♀ 2	♀ 3	72 h ♂ 1	♂ 2	♂ 3	♀ 1	♀ 2	♀ 3
0.3 % TK 11'927	Animal No.		1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
	Erythema	i	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		ni	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Edema	i	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		ni	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Total	i	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		ni	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1.0 % TK 11'927	Sex		♂			♀			♂			♀			♂			♀		
	Animal No.		1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
	Erythema	i	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		ni	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Edema	i	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		ni	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Total	i	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		ni	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

i = irradiated flank ni = non irradiated flank

Table 4 : Evaluation of skin reactions

Preparation		Skin reaction after 24 h							48 h						72 h					
3.0 % TK 11'927	Sex		♂			♀			♂			♀			♂			♀		
	Animal No.		1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
	Erythema	i	0	0	0	0	0	0	0	0	0	0	0	0						
		ni	0	0	0	0	0	0	0	0	0	0	0	0						
	Edema	i	0	0	0	0	0	0	0	0	0	0	0	0						
		ni	0	0	0	0	0	0	0	0	0	0	0	0						
	Total	i	0	0	0	0	0	0	0	0	0	0	0	0						
		ni	0	0	0	0	0	0	0	0	0	0	0	0						

Sex		♂			♀			♂			♀			♂			♀		
Animal No.		1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
Erythema	i																		
	ni																		
Edema	i																		
	ni																		
Total	i																		
	ni																		

i = irradiated flank ni = non irradiated flank

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Page 001353

Toxicology GU 2.5 Test No.: 800353

Evaluation of skin reactions according to Draize[1)]

	Score
Erythema and eschar formation	
No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4
Edema formation	
No edema	0
Very slight edema (barely perceptible)	1
Slight edema (edges of area well defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond area of exposure	4

1) in Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics (1959), the US Association of Food and Drug Officials (AFDO).

Case No.: 800353

Ex 11'327

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CIBA-GEIGY Limited
Basle, Switzerland

SALMONELLA/MAMMALIAN-MICROSOME MUTAGENICITY TEST

with

TK 11 927

(Test for mutagenic properties in bacteria)

TINUVIN 144

GU 2.3
January 29, 1979

Salmonella/Mammalian-Microsome Mutagenicity Test

No. of experiment: 78/2596
Batch: EN.6003

SUMMARY AND CONCLUSIONS

TK 11 927 was tested for mutagenic effects on histidine-auxotrophic mutants of Salmonella typhimurium. The investigations were performed with the following concentrations of the trial substance with and without microsomal activation: 25, 75, 225, 675 and 2025 µg/0.1 ml.

These tests permit the detection of point mutations in bacteria induced by chemical substances. Any mutagenic effects of the substances are demonstrable on comparison of the numbers of bacteria in the treated and control cultures that have undergone back-mutation to histidine-prototrophism. To ensure that mutagenic effects of metabolites of the test substances formed in mammals would also be detected, experiments were performed in which the cultures were additionally treated with an activation mixture (rat liver microsomes and co-factors)[1,2,3].

In the experiments on Strains TA 98, TA 1535 and TA 1537 without microsomal activation, comparison of the numbers of back-mutant colonies in the controls and the cultures treated with the various concentrations of TK 11 927 revealed a reduction in the colony count due to a growth-inhibiting effect of the compound at the concentrations of 225 µg/0.1 ml and above. This effect was also

observed in the experiments with microsomal activation on Strains TA 98 and TA 1537 at the concentrations of 675 and 2025 µg/0.1 ml.

No evidence of the induction of point mutations by TK 11 927 or by the metabolites of the substance formed as a result of microsomal activation was detectable in the strains of S. typhimurium used in these experiments.

(Dr. P. Arni)

(Prof.Dr.D.Müller)

Date January 29, 1979

CIBA-GEIGY Limited
Basle, Switzerland
Protection of Health
and Environment
Toxicology

MATERIALS AND METHODS

The materials on which the tests were performed were the histidine auxotrophic TA 98, TA 100, TA 1535, and TA 1537 strains of Salmonella typhimurium. Cultures were prepared from frozen stocks, and on the following days the Standard Plate Test was carried out with and without the addition of activation mixture (rat liver microsomes and co-factors)[1,2,3].

The test was performed with the following concentrations of the trial substance with and without microsomal activation: 25, 75, 225, 675, and 2025 µg/0.1 ml. The substance was dissolved in acetone. Acetone alone was used for the negative controls (the substances and vehicles used for the positive controls are indicated below). Each Petri dish contained: 1) approx. 20 ml of minimum agar (Agar purified, "Difco" certified, Difco Laboratories, Detroit, Michigan, U.S.A., Art.No.0560, plus salts (Vogel-Bonner Medium E) and glucose), 2) 0.1 ml of the solution of the test substance or the vehicle and 0.1 ml of a bacterial culture (in nutrient broth: Bacto Nutrient Broth dehydrated, Difco Laboratories, Detroit, Michigan, U.S.A., Art.No.0003 0.8% plus 0.5% NaCl) in 2.0 ml of soft agar. The soft agar was composed of: 100 ml of 0.6% agar solution (Agar purified, "Difco" certified) with 0.6% NaCl and 10 ml of a solution of L-histidine, 0.5 mM (Fluka, Buchs, Switzerland, Art.No.14400) and +biotin 0.5 mM (Fluka, Buchs, Switzerland, Art.No.53320). In the experiments in which the substance was metabolically activated, 0.5 ml of an activation mixture was added also[2,3]. 1 ml activation mixture contains: 0.3 ml S9 fraction of liver from rats induced with Aroclor 1254 (Analabs), 8 µmoles $MgCl_2$, 33 µmoles KCl, 5 µmoles glucose-6-phosphate, 4 µmoles NADP and 100 µmoles phosphate buffer, pH 7.4.

Positive control experiments were carried out simultaneously with the following substances: 1) for Strain TA 1535: N-methyl-N'-nitro-N-nitrosoguanidine (Fluka, Buchs, Switzerland Art.

No.68051), 3 and 5 µg/0.1 ml phosphate buffer; 2) for Strain TA 1537: 9(5)aminoacridine hydrochloride monohydrate (Fluka, Buchs, Switzerland, Art.No.06650), 25, 50, and 100 µg/0.1 ml DMSO; 3) for Strain TA 98: daunoblastin (Soc. Farmaceutici Italia, Milan, Italy), 2.5, 5, and 10 µg/0.1 ml phosphate buffer; 4) for Strain TA 100: 4-nitroquinoline-N-oxide (Fluka, Buchs, Switzerland, Art.No.73265), 0.0625, 0.125, and 0.25 µg/0.1 ml phosphate buffer. The activation mixture was tested with Strain TA 1535 and cyclophosphamide, 100 and 250 µg/0.1 ml phosphate buffer.

In the experiments with and without the addition of microsomal activation mixture three Petri dishes were prepared per strain and per group (i.e. per concentration or per control group). In the positive control experiments two Petri dishes were used per strain and per group.

The plates were incubated for about 48 hours at 37°C in darkness.

When the colonies had been counted, the arithmetic mean was calculated. The test substance was considered to be non-mutagenic if the colony count in relation to the negative control was not doubled at any concentration[3].

RESULTS

(see Tables 1 and 2)

In the experiments performed with and without microsomal activation some of the tested concentrations of TK 11 927 caused an increase in the frequency of histidine-prototrophic mutants in comparison with the controls.

After exposure to TK 11 927 in the concentrations of 225 µg/0.1 ml and above without microsomal activation, the number of colonies of histidine-prototrophic mutants in Strains TA 98, TA 1535 and TA 1537 was lower than that found in the controls, as a result of the inhibitory effect of the substance on the growth of the bacteria. This effect was also observed in the experiments with microsomal activation on Strains TA 98 and TA 1535 at the concentrations of 625 and 2025 µg/0.1 ml.

[1] AMES, B.N., F.D. LEE and W.E. DURSTON (1973), An Improved Bacterial Test System for the Detection and Classification of Mutagens and Carcinogens. Proc. Nat. Acad. Sci. USA 70, 782-786.

[2] AMES, B.N., W.E. DURSTON, E. YAMASAKI and F.D. LEE (1973), Carcinogens Are Mutagens: A Simple Test System Combining Liver Homogenates for Activation and Bacteria for Detection. Proc. Nat. Acad. Sci. USA 70, 2281-2285.

[3] AMES, B.N., J. McCANN and E. YAMASAKI (1975), Methods for Detecting Carcinogens and Mutagens with the Salmonella/Mammalian-Microsome Mutagenicity Test. Mutation Res. 31, 347-364.

Table 1

Salmonella/Mammalian-Microsome Mutagenicity Test
Experiments without microsomal activation
Number (arithmetic mean) of colonies of
histidine-prototrophic back-mutants

		Strain of S. typhimurium used			
		TA 98	TA 100	TA 1535	TA 1537
Test substance					
TK 11 927	Control	21	208	20	4
	25 µg/0.1 ml	30	206	20	5
	75 µg/0.1 ml	26	232	14	4
	225 µg/0.1 ml	17	199	0	0
	675 µg/0.1 ml*	6	162	0	0
	2025 µg/0.1 ml*	2	121	0	0
Positive controls					
Daunoblastin	Control	21			
	2.5 µg/0.1 ml	79			
	5.0 µg/0.1 ml	201			
	10.0 µg/0.1 ml	486			
4-Nitroquinoline-N-oxide	Control		216		
	0.0625 µg/0.1 ml		521		
	0.125 µg/0.1 ml		753		
	0.25 µg/0.1 ml		>1250		
N-Methyl-N'-nitro-N-nitroso-guanidine	Control			19	
	3 µg/0.1 ml			~100	
	5 µg/0.1 ml			>1000	
9(5)Aminoacridine hydrochloride	Control				7
	25 µg/0.1 ml				19
	50 µg/0.1 ml				166
	100 µg/0.1 ml				>1550

* At these concentrations the substance precipitated in soft agar.

Table 1

[illegible] Mutagenicity Test
[illegible] activation
[illegible] of colonies of
[illegible] mutants

		Strain of S. typhimurium used			
		TA 98	TA 100	TA 1535	TA 1537
Test substance					
TK 11 927	Control	28	176	13	9
	25 µg/0.1 ml	29	192	17	6
	75 µg/0.1 ml	31	200	13	5
	225 µg/0.1 ml	28	192	14	4
	675 µg/0.1 ml*	14	191	3	11
	2025 µg/0.1 ml*	4	163	3	3
Positive control of the microsomal activation					
Cyclophosphamide					
2.1.79	Control			22	
	100 µg/0.1 ml			478	
	250 µg/0.1 ml			897	
10.1.79	Control			11	
	100 µg/0.1 ml			58	
	250 µg/0.1 ml			141	
19.1.79	Control			16	
	100 µg/0.1 ml			262	
	250 µg/0.1 ml			528	

* At these concentrations the substance precipitated in soft agar.

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CONFIDENTIAL

79/CIA34B/251

HUMAN REPEAT INSULT PATCH TEST
TK 11927 IN POLYPROPYLENE (CARLONA HY P1v)

TINUVIN 144

Received by:
Date: 29. MAI 1979

To:
Ciba-Geigy Limited,
Rosental Facility,
4002 Basel,
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From:
P.C. Rofe,
J. Fincham,
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9 May 1979

LIFE SCIENCE RESEARCH

HUMAN REPEAT INSULT PATCH TEST
TK 11927 IN POLYPROPYLENE (CARLONA HY Plv)

LSR Report No : 79/CIA348/251

We, the undersigned, hereby declare that the report following constitutes a true and faithful account of the procedures adopted, and the results obtained, in the performance of this study.

P.C. Rofe, Ph.D.
(Associate Director)

Jill Fincham, Ph.D.
(Human studies Manager)

Jill Fincham

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SUMMARY

[illegible] occlusive plasters containing test preparations, [illegible] for three weeks. After an interval of [illegible] applications were made to both arms, followed by [illegible] and 48 hours.

[illegible] TK 11927, 0.5% and 5.0% in polypropylene [illegible] in 3% carboxymethylcellulose in water; [illegible] contained no TK 11927.

3. Irritation was observed during induction and after challenge according to a [illegible] reactive scale for erythema, with or without oedema.

4. No evidence of skin sensitization was seen.

5. The total numbers of erythema reactions of each grade were distributed as follows:

	Grade				
	0	1 + 1E	2 + 2E	3	4
Polypropylene (Carlona HY Plv)	943	96	1	Nil	Nil
TK 11927 0.5% in polypropylene (Carlona HY Plv)	894	145	1	Nil	Nil
TK 11927 5.0% in polypropylene (Carlona HY Plv)	764	273	3	Nil	Nil

METHOD

The test took place at the United Reformed Church, Danbury, Essex, England, from 5 February to 30 March 1979.

Eight-four subjects were recruited of whom 80 completed the programme. All volunteers signed a consent form, which is reproduced in Appendix 2. The age and sex of subjects are tabulated in Appendix 3.

The patch sites were scored by Mrs. Ann Town, and Dr. Jill Fincham was the trial supervisor.

The test materials were supplied as fine white powders labelled:

PP Carlona HY Plv without TK 11927

PP Carlona HY Plv 0.5% TK 11927

PP Carlona HY Plv 5.0% TK 11927

They were administered as 40% w/v or 50% w/v suspensions in 3% w/v carboxymethylcellulose in water. Sample volumes of 0.5 ml were dispensed on to a patch strip consisting of four 22 mm diameter circular undressed lint (Webril, Curity) pads located along the centre of 50 mm wide adhesive tape (Blenderm, 3M Company). The patch strip was applied to the dorsal surface of the upper arm of each subject, the position being marked by three spots of methyl violet stain.

To eliminate position bias, the test preparations and one other were applied in four different orders at random among the panel as follows (reading from the top of the arm):

1	2	3	4
2	3	4	1
3	4	1	2
4	1	2	3

The patch order was kept constant for each subject throughout the trial by using an identification card, colour-coded, and bearing the subject's details. The reverse side provided a record of patch location and attendance during the study.

Subjects were instructed to keep the patches dry, to remove and discard them after 24 hours, and to return after 48 hours.

[illegible] Wednesday and Friday of the three-week [illegible] were re-applied to the same site unless [illegible] the plaster adhesive necessitated a move, [illegible] was chosen. Subjects who were absent [illegible] received a make-up patch (MU) on the fourth [illegible]

[illegible] patch (i.e. five weeks after the [illegible] were made to both arms of each subject. The [illegible] original (Or.) or alternate (Alt.) and the results [illegible] after 48 and 96 hours.

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RESULTS

Skin erythema reactions are summarised below and tabulated in full in Appendix 4.

No evidence of sensitization was seen. The incidence of erythema, while low, appeared to be dose-related.

Carlona HY Plv: numbers of reactions to 40% suspension in 3% carboxymethylcellulose

Reaction	Session										Post-challenge 48 Hr.		Post-challenge 96 Hr.	
	2	3	4	5	6	7	8	9	10	MU	Or.	Alt.	Or.	Alt.
0	70	70	71	69	65	72	68	65	61	17	78	78	79	80
1	1	9	8	8	9	8	11	12	17	5	2	1	1	
1E								1	2			1		
2								1						
NP	9	1	1	3	6		1	1						

TK 11927 0.5% in Carlona HY Plv: numbers of reactions to 50% suspension in 3% carboxymethylcellulose

Reaction	Session										Post-challenge 48 Hr.		Post-challenge 96 Hr.	
	2	3	4	5	6	7	8	9	10	MU	Or.	Alt.	Or.	Alt.
0	66	68	71	64	55	68	67	58	54	17	70	79	77	80
1	5	11	8	13	18	12	11	20	26	4	10	1	3	
1E					1		1			1				
2E								1						
NP	9	1	1	3	6		1	1						

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TK 11927 5.0% in Carlona HY Plv: numbers of reactions to 50% suspension in 3% carboxymethylcellulose

Reaction	Session										Post-challenge 48 Hr.		Post-challenge 96 Hr.	
	2	3	4	5	6	7	8	9	10	MU	Or.	Alt.	Or.	Alt.
0	63	63	62	52	42	53	44	41	39	12	66	72	76	79
1	8	15	17	25	31	27	35	36	39	9	13	7	4	1
1E					1			1	1	1	1	1		
2									1					
2E		1						1						
NP	9	1	1	3	6		1	1						

APPENDIX 1

PATCH SCORING PROCEDURE

0	-	No visible reaction
1	-	Mild reaction, erythema
1E	-	Mild erythematous reaction with papules and/or oedema
2	-	Moderate reaction, erythema (a grade of 2 or higher during induction necessitates relocation of the patch)
2E	-	Moderate erythematous reaction with oedema and/or papules
3	-	Strong reaction, erythema
3E	-	Strong erythematous reaction with marked oedema, papules and/or vesicles
4	-	Severe reaction with erythema, oedema, papules and vesicles (may be evidence of weeping)
A	-	Marked reaction to adhesive (patch relocated)
L	-	Patch came off (lost) during first 12 hours
(-)	-	Subject absent
NP	-	In summary tables: total number not patched because of absence.

[illegible] - Notice to Volunteers and Consent Form

LIFE SCIENCE RESEARCH

SKIN PATCH TESTS

We are grateful to have your help in this trial of toiletry products/ detergents/plastics or their ingredients. The materials to be tested are, to the best of our knowledge, safe and should not cause troublesome skin reactions. Irritation may occur under some of the patches (redness, slight swelling, or itching), but this generally subsides quite soon. Very infrequently, an allergic response may occur which would take the form of marked redness, swelling and blistering, still confined to the area under the patch; in the unlikely event of your coming into contact with the same substance again in the future a similar reaction would occur. The main purpose of the test is to identify any substances which may do this, even though these are rare. If you have had psoriasis or eczema there is a risk of recurrence if such an allergic reaction should occur.

We are unable to accept people who have active skin conditions, who are pregnant, or who are taking drugs like cortisone or using cortisone creams or lotions.

Experience with about 800 patch test participants each year has been very satisfactory, and groups that have taken part in a test usually ask us to arrange another.

After reading the above, would you please sign the consent form.

Thank you for your co-operation, which is much appreciated.

Dr. P. C. Rofe

Participants in Patch Test at
The United Reformed Church, Danbury, Essex.

I have read and understand the notice "Skin Patch Tests" and I consent to participate. I have not taken part in a Patch Test during the last year.

No.	Signature	Date	No.	Signature	Date

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APPENDIX 3

Composition of Panel by Age and Sex

Age	Male	Female
21		1
24		1
25		1
26		1
27		1
29		2
30		5
31		5
32		3
33		5
34		1
35		3
36		4
37		4
38		2
39		1
40	1	3
41		1
42		3
43	1	2
44		2
46		1
47		1
48		2
49		1
51		1
53	1	1
55		2
56		2
58		2
59		1
61		1
62		1
63		1
64		2
65		3
68		1
70		2
78	1	
Total	4	76

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APPENDIX 4

Cartons BY 7Hz Intradermal responses to applications of 40% suspension in 3% carboxymethylcellulose

Subject number	Session 2	3	4	5	6	7	8	9	10	MU	Post-challenge 48 Hr. Or.	Alt.	96 Hr. Or.	Alt.
1	0	0	0	0	0	0	0	0	0		0	0	0	0
2	0	0	0	0	0	0	0	0	0		0	0	0	0
3	0	0	-	0	0	0	1	1	1	1	0	0	0	0
4	0	0	0	0	0	1	1A	1	1		0	0	0	0
5	0	1	1	1	-	1	1	1	0	0	0	0	0	0
6	0	0	0	0	0	0A	0	0	0		0	0	0	0
7	0	0	1	1	1	0	0	0	1		0	0	0	0
8	0	0	1	1	1	0	0	0	1		0	0	0	0
9	0	0	0	0	-	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0		0	0	0	0
11	0	0	0	0	0	0	0	0	0		0	0	0	0
12	0	0	0	0	0	0	0	0	0		0	0	0	0
13	0	0	0	0	-	0	0	0	0	0	0	0	0	0
14	0	0	0	-	0	0	0	0	1	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0		0	0	0	0
16	0	0	0	0	0	0	0	0	0		1	1E	0	0
17	0	0	0	0	0	0	0	0	0		0	0	0	0
18	0	0A	0	0A	0	0	0	1	0		0	0	0	0
19	0	0	0	0	1	0	1	1	0		0	0	0	0
20	0	0	0	0	0	0	0	0	0		0	0	0	0
21	0	0	0	0	0	0	1	0	0		0	0	0	0
22	0	0	0	0	0A	0	1	0	0		0	0	0	0
23	0	0	0	0	0	0	0	0	0		0	0	0	0
24	0	1A	0	0	0	0	0	0	0A		0	0	0	0
25	0	0	0	0	0	0	0	0	0		0	0	0	0
26	0	0	0	1	1	0	0	0	0		0	0	0	0
27	0	0	0	0	0	0	0	1E	1E		0	0	0	0
28	0	0	0	0	-	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0		0	0	0	0
30	0	0	0	0	0	0	0	0	0		0	0	0	0
31	0	0	0	0	0	0	0	0	0		0	0	0	0
32	0	1	0	0	0	0	0	0	0		0	0	0	0
33	0	0	0A	0	1	1	1A	1	1		0	0	0	0
34	0	0	0	0	0A	0	0	0	0		0	0	0	0
35	0	0	0	0	0	0	0	0	0		0	0	0	0
36	0	0	0	0	0	0	0	0	0		0	0	0	0
38	0	0	0	0	0	0	0	0	0		0	0	0	0
39	0	0	0	0	0	0	0	0	0		0	0	0	0
40	1	1	0	0	0	0	0	0	0		0	0	0	0
41	0	0	0	0	0	0A	0	0	0		0	0	0	0

APPENDIX 4 (Cont'd)

Carlona HY P1v: individual responses to applications of 40% suspension in 3% carboxymethylcellulose

Subject number	Session										Post-challenge 48 Hr.		Post-challenge 96 Hr.	
	2	3	4	5	6	7	8	9	10	MU	Or.	Alt.	Or.	Alt.
42	0	0	1	1	1	1	1	1A	1		0	0	0	0
44	0	0	0	0	0	0	0	0	1		0	0	0	0
46	0	0	0	0	0	0	0	0	0		0	0	0	0
47	0	-	0	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0		0	0	0	0
49	-	0	0	0	0	0	0	0	1	1	0	0	0	0
50	0	0	0	0	0	0	0	0	0		0	0	0	0
51	0	1	0	0	0	0	0	0	0		0	0	0	0
52	0	0	0	0	1	1	1	1	1		0	0	0	0
53	0	0	0	0	0	0	0	-	0	0	0	0	0	0
54	0	0	1	1	0	1	0	0	0		0	0	0	0
56	0	1A	0	0	0A	0	0	0	0		0	0	0	0
57	0	0	0	0	0	0	0	0	0		0	0	0	0
58	0	0	0	0	0	0	0	0A	0		0	0	0	0
59	0	1	1	-	0	0	0	1	1	1	0	0	0	0
60	-	0	1	1	1	1	1	2	11	0	0	0	0	0
61	-	0	0	0	0	0	0	0	0	0	0	0	0	0
62	0	0	0	0	0	0	0	0	0		0	0	0	0
63	0	0	0	0	-	0	0	0	0	0	0	0	0	0
64	0	0	0	0	0	0	0	0	0		0	0	0	0
65	0	0	0	-	0	0	0	1	1	1	1	1	1	0
66	0	0	0	0	0A	0A	0	0	0		0	0	0	0
67	0	0	0	0	0	0	0	0	0		0	0	0	0
68	0	0	0	0	0	0	0	0	1E		0	0	0	0
69	0	0	0	0	0	0	0	0	0		0	0	0	0
70	0	1	0	0	0	0	0	0	1		0	0	0	0
71	0	0	0	0	0	0	0	1A	0		0	0	0	0
72	0	0	0	0	0	0	0	0	0		0	0	0	0
73	0	0	0	0	0	0	0	0	1		0	0	0	0
74	0	0	0	0	-	0	0	0	0	0	0	0	0	0
75	0	0	0	0A	0	0	-	0	0	0	0	0	0	0
76	0	0	0	0	0	0	0	0	0		0	0	0	0
77	0	0	0	0	0	0	0	0	0		0	0	0	0
78	0	0	0	0	0	0	0	0	0		0	0	0	0
79	-	0	0	0	0	0	0	0	1	1	0	0	0	0
80	-	0	0	0	0	0	0	0	0	0	0	0	0	0
81	-	1	1	1	1A	1	1	1	1	0	0	0	0	0
82	-	0	0	0	0	0	0	0	0	0	0	0	0	0
83	-	0	0	0	0	0	0	0	0	0	0	0	0	0
84	-	0	0	0	0	0	0	0	0	0	0	0	0	0

A P P E N D I X 4 (Cont'd)

Tx. 1947 0.5% in carrier MPIVI individual responses
In application of PMI suspension in 3% carboxymethylcellulose

Animal Number	Days after Treatment 2	3	4	5	6	7	8	9	10	MU	Post-challenge 48 Hr. Or.	Alt.	96 Hr. Or.	Alt.
1	0	0	0	0	0	0	0	0	0		0	0	0	0
2	0	0	0	0	0	0	0	0	0		0	0	0	0
3	0	0	-	0	0	0	1	1	1	1	0	0	0	0
4	0	0	0	1	1	1	1A	1	1		0	0	0	0
5	0	1	0	0	-	1	1	1	0	0	1	0	0	0
6	0	0	0	0	0	0	0	0	0		0	0	0	0
7	1	1	1	1	1	1	1	0	1		0	0	0	0
8	1	1	1	1	1	1	1	0	1		0	0	0	0
9	0	0	0	0	-	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0		0	0	0	0
11	0	0	0	0	0	0	0	0	0		0	0	0	0
12	0	0	0	1	1	0	0	1	1		1	0	0	0
13	0	0	0	0	-	0	0	1	0	0	1	0	0	0
14	0	0	0	-	0	0	0	1	1	0	0	0	0	0
15	0	0	0	0	0	0	0	0A	0		0	0	0	0
16	0	0	0	1	1	1	1	1	0		1	0	0	0
17	0	0	0	0	0	0	0	0	0		0	0	0	0
18	0	0A	0	0A	0	0	0	1	0		0	0	0	0
19	0	0	1	1	1	1	1	1	1		0	0	0	0
20	0	0	0	1	1	1	1	1	1		0	0	0	0
21	0	0	0	0	0	1	1	1	1		0	0	0	0
22	0	0	0	0	0A	0	0	0	1		0	0	0	0
23	0	0	0	0	0	0	0	0	0		0	0	0	0
24	1	1A	0	0	0	0	1	1	0		0	0	0	0
25	0	0	0	0	0	0	0	0	1		0	0	0	0
26	0	0	0	1	1	0	0	1	1		0	0	0	0
27	0	0	0	0	0	0	0	0	0		1	1	1	0
28	0	0	0	0	-	0	0	1	1	0	1	0	1	0
29	0	0	0	0	0	0	0	0	0		0	0	0	0
30	0	0	0	0	0	0	0	0	0		0	0	0	0
31	0	0	0	0	0	0	0	0	0		0	0	0	0
32	0	1	0	1	1	0	0	0	0		0	0	0	0
33	0	0	0	0	0	0	0A	1	1		0	0	0	0
34	0	0	0	0	0A	0	0	0	0		0	0	0	0
35	0	0	0	0	0	0	0	0	0		1	0	1	0
36	0	0	0	0	0	0	0	0	0		0	0	0	0
38	0	0	0	0	0	0	0	0	0		0	0	0	0
39	0	0	0	0	0	0	0	0	0		1	0	0	0
40	0	0	0	0	0	0	0	0	0		0	0	0	0
41	0	0	0	0	0	0	0	0	0		0	0	0	0

APPENDIX 4 (Cont'd)

TK 11927 0.5% in Carlona HY Plv: individual responses to applications of 50% suspension in 3% carboxymethylcellulose

Subject number	Session										Post-challenge 48 Hr.		96 Hr.	
	2	3	4	5	6	7	8	9	10	MU	Or.	Alt.	Or.	Alt.
42	0	1	1	1	1	1	1	1A	1		0	0	0	0
44	0	0	0	0	0	0	0	1	1		0	0	0	0
46	0	0	0	0	0	0	0	0	0		0	0	0	0
47	0	-	0	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0		0	0	0	0
49	-	1	0	0	1	0	0	0	1	1	0	0	0	0
50	0	0	0	0	0	0	0	0	0		0	0	0	0
51	0	0	0	1	0A	0	0	0	0		0	0	0	0
52	0	0	0	0	0	0	0	0	0		1	0	0	0
53	0	0	0	0	0	0	0	-	0	0	0	0	0	0
54	1	0	0	0	0	0	0	0	0		0	0	0	0
56	0	1A	0	0	1A	0	0	0	1		0	0	0	0
57	0	0	0	0	0	0	0	0	0		0	0	0	0
58	0	0	0	0	0	0	0	0A	0		0	0	0	0
59	1	1	1	-	0	0	0	1	1	1E	0	0	0	0
60	-	1	1	1	1	1	0	1	1	0	0	0	0	0
61	-	0	0	0	1	0	0	0	0	0	0	0	0	0
62	0	0	0	0	0	0	0	0	0		0	0	0	0
63	0	0	0	0	-	0	0	0	0	0	0	0	0	0
64	0	0	0	0	0	0	0	0	0		0	0	0	0
65	0	0	1	-	0	0	0	1	1	1	1	0	1	0
66	0	0	0	0	0A	0	0	0	0		0	0	0	0
67	0	0	0	0	0	0	0	0	0		0	0	0	0
68	0	0	0	0	0	0	0	0	1		0	0	0	0
69	0	0	0	0	0	0	0	0	1		0	0	0	0
70	0	0	0	0	0	0	0	0	0		0	0	0	0
71	0	0	0	0	1	0	0	1A	0		0	0	0	0
72	0	0	0	0	1	0	0	0	1		0	0	0	0
73	0	0	0	0	0	0	0	0	1		0	0	0	0
74	0	0	0	0	-	0	0	0	0	0	0	0	0	0
75	0	0	0	0A	0	0	-	0	0	0	0	0	0	0
76	0	0	0	0	0	1	0	0	0		0	0	0	0
77	0	0	0	0	0	0	0	0	1		0	0	0	0
78	0	0	0	0	0	0	0	0	0		0	0	0	0
79	-	0	0	0	0	0	0	0	1	1	0	0	0	0
80	-	0	0	0	0	0	0	0	0	0	0	0	0	0
81	-	1	1	1	1E	0	1E	2E	01	0	1	0	0	0
82	-	0	0	0	0	0	0	0	0	0	0	0	0	0
83	-	0	0	0	0	1	0	0	0	0	1	0	0	0
84	-	0	0	0	1	0	0	0	0	0	0	0	0	0

APPENDIX 4 (Cont'd)

[illegible] in Guinea [illegible] five individual responses [illegible] suspension in 5% carboxymethylcellulose

[illegible]	Reaction										Post-challenge 48 Hr.		96 Hr.	
	2	3	4	5	6	7	8	9	10	MU	Or.	Alt.	Or.	Alt.
1	0	0	1	1	1	1	1	1	1		0	0	0	0
2	0	0	0	0	1	1	1	1	1		0	0	0	0
3	0	0	[illegible]	0	0	0	1	1	0	0	0	0	0	0
4	0	2	1E	1	1A	0	1A	1A	1		0	0	0	0
5	0	1	1	1	-	1	1	1	0	0	1	1	0	0
6	0	0	0	0	0	0	0	0	0		0	0	0	0
7	0	0	1	1	1	1	1	0	1		0	0	0	0
8	1	1	1	1	1	1	1	1	1		0	1	0	0
9	0	0	0	0	-	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0		0	0	0	0
11	0	0	0	0	0	0	0	0	0		0	0	0	0
12	0	0	0	1	1	0	0	1	1		0	0	0	0
13	0	0	0	1	-	0	0	1	1	0	0	0	0	0
14	0	0	0	-	0	0	1	1	1	1	0	0	0	0
15	0	0	0	0	1	0	1	1	1		0	0	0	0
16	0	0	1	1	1EA	1	1	1	1		1	1	0	0
17	0	0	1	1	0	0	1	1	1		0	0	0	0
18	0	0A	1	1A	0	0	1	1	1		1	0	1	0
19	0	0	1	1	1	1	1	1	1		1	1	0	0
20	0	0	1	1	1	1	1	1	1		1	0	0	0
21	0	0	1	1	1	1	1	1	1		1	0	0	0
22	0	0	1	1	1A	1	1	1	1		0	0	0	0
23	0	0	1	0	0	0	1	0	1		0	0	0	0
24	0	1A	0	0	0	1A	1	0	0		0	0	0	0
25	0	0	0	0	0	0	0	0	1		0	0	0	0
26	0	0	0	1	1	0	0	0	0		0	0	0	0
27	0	0	0	1	1	1	1	1E	1E		1E	1E	1	0
28	0	0	0	0	-	0	0	0	0	0	0	0	0	0
29	0	0	1	0	0	0	0	0	0		0	0	0	0
30	0	0	0	0	0	0	1	1	1		0	0	0	0
31	0	1	0	0	0	0	1	1	1		0	0	0	0
32	0	1	0	1	1	0	1	1	1		0	0	0	0
33	0	0	0	1	1	1	1A	1	2		0	0	0	0
34	0	0	0	0	0A	0	0	0	1		0	0	0	0
35	0	0	0	0	0	0	0	1	0		0	0	0	0
36	0	0	0	0	0	0	0	1	0		0	0	0	0
38	0	0	0	0	1	1	1	1	1		0	0	0	0
39	1	1	0	0	1	1	0	0	0		1	0	0	0
40	1	1	1	1	1	1	1	1	1		0	0	0	0
41	0	0	0	0	0	1A	1	1	1		0	0	0	0

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APPENDIX 4 (Cont'd)

TK 11927 5.0% in Carlona HY Plv: individual responses to applications of 50% suspension in 3% carboxymethylcellulose

Subject number	Session										Post-challenge 48 Hr.		Post-challenge 96 Hr.	
	2	3	4	5	6	7	8	9	10	MU	Or.	Alt.	Or.	Alt.
42	1	1	1	1	1	1	1	1A	1		0	1	0	0
44	0	0	0	0	0	0	0	0	1		0	0	0	0
46	1	0	1	1	1	1	1	1	0		0	0	0	0
47	0	-	0	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0		0	0	0	0
49	-	1	0	1	1	0	1	1	1	1	0	0	0	0
50	0	0	0	0	0	0	0	0	0		0	0	0	0
51	0	0	0	0	0	0	0	0	0		0	0	0	0
52	0	0	0	1	1	1	1	1	1		1	0	0	0
53	0	0	0	0	0	0	0	-	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0		0	0	0	0
56	1	1A	0	1	1A	0	0	0	1		0	0	0	0
57	1	0	0	0	0	0	0	0	0		0	0	0	0
58	0	0	0	0	0	0	0	0A	0		0	0	0	0
59	0	1	1	-	0	0	1	1	1	1	1	0	1	0
60	-	1	1	1	1	1	1	1	1	1	0	0	0	0
61	-	0	0	0	1	1	1	1	1	1	0	0	0	0
62	0	0	0	0	1	0	1	1	1		0	0	0	0
63	0	0	0	0	-	0	0	0	1	1	0	0	0	0
64	0	0	0	0	0	0	0	0	0		0	0	0	0
65	0	1	1	-	0	1	0	1	1	1	1	1	1	1
66	0	0	0	0	0A	1A	0	0	0		0	0	0	0
67	0	0	0	0	0	0	0	0	0		0	0	0	0
68	0	0	0	1	1	1	1	1	1		1	0	0	0
69	1	0	1	1	1	0	1	1	1		1	0	0	0
70	0	0	0	0	0	1	0	0	0		0	1	0	0
71	0	0	0	0	0	1	1	1A	0		0	0	0	0
72	0	1	0	0	1	0	0	0	1		0	0	0	0
73	0	0	0	1	0	0	0	0	1		0	0	0	0
74	0	0	0	0	-	0	0	0	0	0	0	0	0	0
75	0	0	0	0A	0	0	-	0	0	0	0	0	0	0
76	0	0	0	0	0	0	0	0	0		0	0	0	0
77	0	0	0	0	0	0	0	0	1		0	0	0	0
78	0	0	0	0	0	0	0	1	1		0	0	0	0
79	-	0	0	0	0	0	0	0	1	1	0	0	0	0
80	-	0	0	0	0	0	1	1	0	1	0	0	0	0
81	-	1	1	1	1	1	1	2E	01	1E	1	0	0	0
82	-	0	0	0	0	0	0	0	1	0	0	0	0	0
83	-	0	0	0	0	0	0	0	0	0	1	0	0	0
84	-	0	0	0	1	0	0	0	0	0	0	0	0	0

00077

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May 24, 1978/wu
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[illegible] - TINUVIN 144

ACUTE TOXICITY TO RAINBOW TROUT, CARP, CATFISH AND BLUEGILL OF TK 11927

[illegible]

Project No.: [illegible] - Sins 6626

1. Summary and Conclusion

The LC 50 for a 96 hour exposure is for the

Rainbow trout	-	1.03 (0.74-1.69)* ppm**
Carp	-	0.38 (0.33-0.43) ppm
Catfish	-	0.25 (0.20-0.31) ppm
Bluegill	-	0.77 (0.62-1.01) ppm

The test material has a high acute toxicity to carp and catfish and a medium acute toxicity to trout and bluegill when tested and evaluated according to the procedure of Bathe et al. (1974)***.

2. Material and Method

TK 11927 was tested in accordance with the method reported by Bathe et al. (1974)*** which is a modification of the procedure proposed by the United States Department of the Interior Fish and Wildlife Service, reported in "Procedure for Evaluation of Acute Toxicity of Pesticides to Fish and Wildlife" of December 14, 1964.

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* LC 50 including 95 % confidence limits were calculated by the logit model.

** Concentrations were expressed as weight of substance per volume of water, in parts per million (ppm). These values based upon nominal concentrations of TK 11927.

*** R. Bathe, K. Sachsse, L. Ullmann, W.D. Hörmann, F. Zäk and R. Hess: The evaluation of fish toxicity in the laboratory. In: Proceedings of the Europ. Soc. of Toxicology. Vol. XVI, pp. 113-124, Carlsbad, June 1974

a) Fish

Fish toxicity was tested in four species.

1. Rainbow trout (Salmo gairdneri), supplied by "Mändli" Liestal, Switzerland, fish breeding station.

   Average Weight: 11 g
   Average Length: 100 mm

2. Carp (Cyprinus carpio), supplied by "Riegger", Ettenheim, W.Germany, fish breeding station.

   Average Weight: 3 g
   Average Length: 63 mm

3. Catfish (Ictalurus melas), supplied by "Weber", Wohlen Switzerland.

   Average Weight: 3 g
   Average Length: 60 mm

4. Bluegill (Lepomis macrochirus), supplied by "Exotarium Stubenvoll", Allschwil, Switzerland.

   Average Weight: 5 g
   Average Length: 70 mm

Prior to testing, the fish were adapted to laboratory conditions for a minimum of 10 days. They were kept in 250 lit. glass tanks containing normal drinking water which was aerated and filtered continuously through a filter bed of activated charcoal. The fish were fed daily. Prior to testing the food was withdrawn for 3 days.

Overall mortalities in stocks were well below 10 % and no deaths occurred during the 10 days prior to testing. All fish were in good condition and free from disease.

b) Testing Procedures:

The fish were tested in glass tanks, of 12 and 15 litre capacity. Testing was performed in reconstituted water prepared of deionised water to which salts were added in the following amount per litre:

30 mg calcium sulphate
30 mg magnesium sulphate
48 mg sodium bicarbonate
3 mg potassium chloride

[illegible] $\pm 2^{\circ}$ C (trout, bluegill) and at 21 $\pm$ 1° C [illegible] exception of experiments on trout [illegible] during testing. Two to five fish [illegible]

[illegible] of TX 11927 were prepared by [illegible] diluted in acetone (stock solution) at the appropriate amount ensuring that the total volume in each vessel remained the same.

A [illegible] was formed in all concentrations immediately after the introduction of the acetone diluted toxicant into the aerated test water.

Oxygen dissolved in the water and pH were monitored at 24 hour intervalls throughout the 96 hour testing period.

3. <u>Results</u>

Page 4 lists oxygen content and pH values.

Pages 5 to 8 contain data on the time course for occurrence of deaths, toxic signs and symptoms for each particular species.

K. Sachsse D.V.M.

R. Bathe D.V.M.

Oxygen content (mean values in mg O_2/litre H_2O) in particular fish tanks

Time hrs	Deionised Water without fish	Rainbow trout**	Carp	Catfish	Bluegill
0*	11.3		8.8	8.9	9.6
24	11.3	NOT	4.4	3.8	8.2
48	11.3	DETER-	1.4	1.8	6.9
72	11.3	MINED	1.4	2.2	6.9
96	11.3		1.5	2.3	4.7

* Prior to addition of test substance.

** Continuous aeration throughout treatment.

pH (mean values) in particular fish tanks

Time hrs	Deionised Water without fish	Rainbow trout**	Carp	Catfish	Bluegill
0*	7.5	7.7	7.8	7.6	7.7
24	7.5	7.7	7.1	7.0	7.3
48	7.5	7.7	6.9	6.9	7.2
72	7.5	7.6	6.9	7.0	7.1
96	7.5	7.6	6.9	7.0	7.0

* Prior to addition of test substance.

** Continuous aeration throughout treatment.

Rate of deaths for rainbow trout

Concentration ppm	Number of fish tested	Deaths after 24 hrs	48 hrs	72 hrs	96 hrs	% Mortality after 96 hours
0.21	10	0	0	0	0	0
0.65	10	0	0	0	1	10
1.0	10	0	1	1	4	40
2.1	10	0	9	10	10	100

Symptoms	Concentration (ppm)				
	0.21	0.65	1.0	2.1	
Mucous secretion					
Localized hemorrhagie					
Discolorations	+	+	+	+	
Hypersensitivity	+	+	+	+	
Diminished sensitivity					
Remaining on the bottom					
Remaining under the surface					
Fins spread					
Fins adiacent					
Hyperactivity	+	+	+	+	
Retarded movements					
Hyperventilation	+	+	+	+	
Decreased respiratory rate					
Upright vertical position					
Downright vertical position					
Loss of equilibrium					
Convulsions		+	+	+	
Spasms with rotatory movements				+	
Paralytic scoliosis					
Body paralysis					
Unconsciousness					

Key: + = slight, ++ = moderate, +++ = severe

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Rate of deaths for carp

Concentration ppm	Number of fish tested	Deaths after 24 hrs	48 hrs	72 hrs	96 hrs	% Mortality after 96 hours
0.28	10	0	0	0	0	0
0.37	10	2	4	5	5	50
0.49	10	4	10	10	10	100
0.65	10	9	10	10	10	100

Symptoms	Concentration (ppm)				
	0.28	0.37	0.49	0.65	
Mucous secretion					
Localized hemorrhagie					
Discolorations	+	+	+	+	
Hypersensitivity	+	+	+	+	
Diminished sensitivity					
Remaining on the bottom					
Remaining under the surface					
Fins spread					
Fins adjacent	+				
Hyperactivity	+	+	+	+	
Retarded movements					
Hyperventilation	+	++	++	++	
Decreased respiratory rate					
Upright vertical position					
Downright vertical position					
Loss of equilibrium	+	+	+	+	
Convulsions	+	+	+	+	
Spasms with rotatory movements				+	
Paralytic scoliosis					
Body paralysis					
Unconsciousness		+	+	+	

Key: + = slight, ++ = moderate, +++ = severe

Rate of deaths for catfish

Concentration ppm	Number of fish tested	Deaths after 24 hrs	48 hrs	72 hrs	96 hrs	% Mortality after 96 hours
0.1	10	0	0	0	0	0
0.21	10	0	1	2	2	20
0.37	10	1	6	8	9	90
0.49	10	0	9	10	10	100

Symptoms	Concentration (ppm)				
	0.1	0.21	0.37	0.49	
Mucous secretion					
Localized hemorrhagie					
Discolorations	+	+	+	+	
Hypersensitivity	+	+	+	+	
Diminished sensitivity					
Remaining on the bottom					
Remaining under the surface					
Fins spread					
Fins adjacent					
Hyperactivity				+1)	
Retarded movements	+	++	++	++2)	
Hyperventilation	+	++	+++	+++	
Decreased respiratory rate					
Upright vertical position				+	
Downright vertical position					
Loss of equilibrium		+	++	++	
Convulsions		+	+	+	
Spasms with rotatory movements				+	
Paralytic scoliosis					
Body paralysis					
Unconsciousness		+	+	+	

Key: + = slight, ++ = moderate, +++ = severe
1) Within 5 hours 2) After 24 hours

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Rate of deaths for bluegill

Concentration ppm	Number of fish tested	Deaths after 24 hrs	48 hrs	72 hrs	96 hrs	% Mortality after 96 hours
0.28	10	0	0	0	0	0
0.49	10	0	0	0	1	10
0.65	10	0	0	0	2	20
0.87	10	1	1	4	8	80
2.1	10	3	9	9	10	100

Symptoms	Concentration (ppm)				
	0.28	0.49	0.65	0.87	2.1
Mucous secretion					
Localized hemorrhagie					
Discolorations					
Hypersensitivity	+				
Diminished sensitivity		+	+	+	+
Remaining on the bottom					
Remaining under the surface					
Fins spread					
Fins adjacent					
Hyperactivity					
Retarded movements	+	+	+	+	++
Hyperventilation		+	+	+	+
Decreased respiratory rate					
Upright vertical position					
Downright vertical position					
Loss of equilibrium		+	+	+	+
Convulsions					
Spasms with rotatory movements					
Paralytic scoliosis					
Body paralysis					
Unconsciousness			+	+	+

Key: + = slight, ++ = moderate, +++ = severe

[illegible] TINUVIN 144

[illegible]

[illegible] (using C^{14}-sample)

At [illegible]

days	A B	Outrage concentration (dpm/g)	Outrage accumulation factors	A B	Residue concentration (dpm/g)	Residue accumulation factors	Total Accumulation factors
2	A	31069	63.5	A	525	1.1	64.6
	B	23794	48.7	B	310	0.6	49.3
5	A	49306	100.8	A	511	1.0	101.9
	B	60183	123.1	B	2256	4.6	127.7
10	A	78803	161.2	A	1722	3.5	164.7
	B	81941	167.6	B	3817	7.8	175.4
15	A	134550	275.2	A	3088	6.3	281.5
	B	144700	295.9	B	10454	21.3	317.3
20	A	174992	357.9	A	3483	7.1	365.0
	B	155049	317.1	B	4380	10.2	327.3
30	A	8286	16.9	A	3396	6.9	23.9*
	B	198947	406.8	B	4083	8.4	415.2
40	A	59307	121.3	A	3343	6.8	128.1
	B	91053	186.2	B	3645	7.5	193.7
50	A	116460	238.2	A	6083	12.4	250.6
	B	208830	427.1	B	4920	10.1	437.1
60	A	58740	120.1	A	9122	18.7	138.8
	B	137899	282.0	B	6556	13.4	295.4

Note: It was determined that the radioactivity was due to TINUVIN 144 itself.

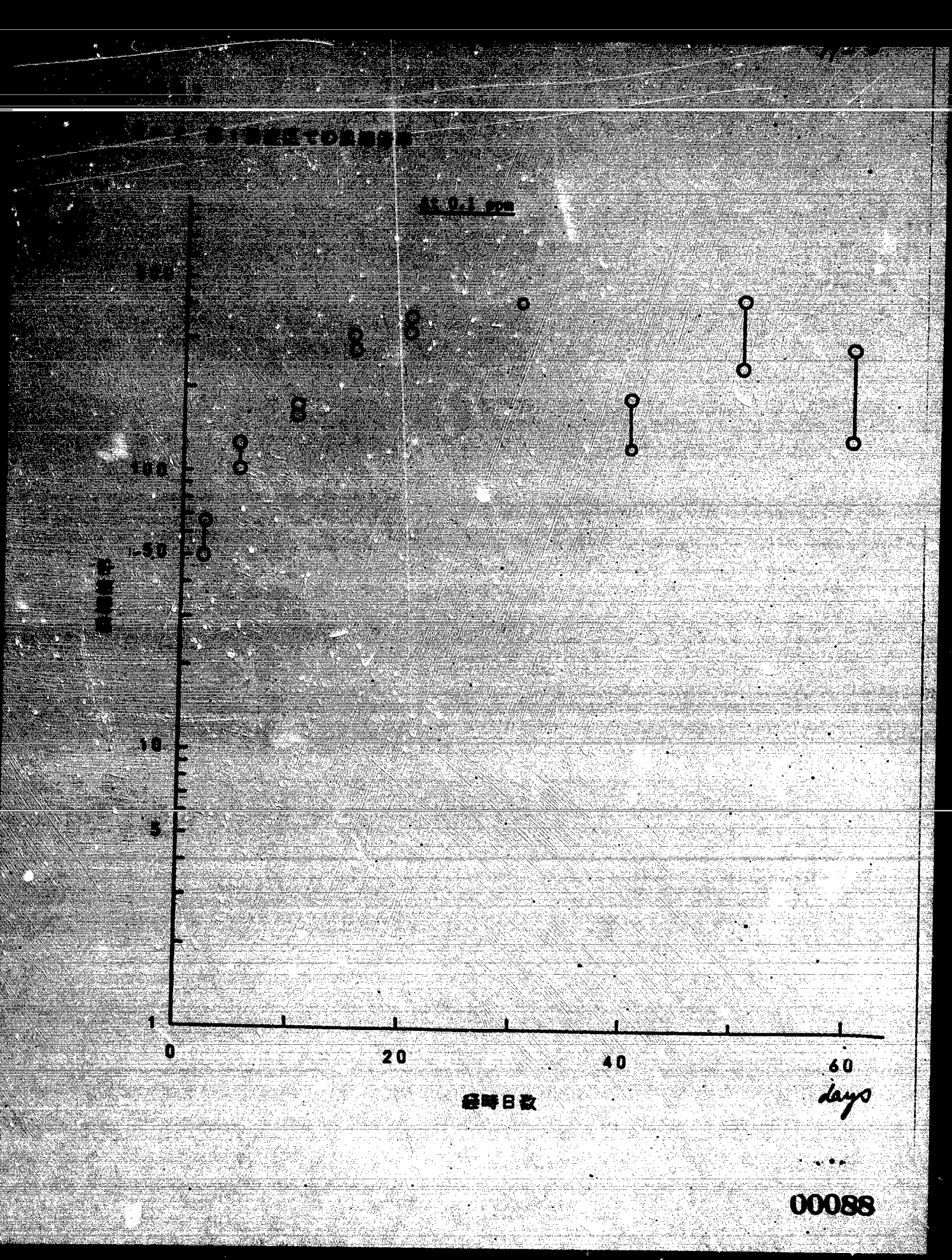
* abnormal value

Test result

Accumulation factors (using C^{14}-sample)

At 0.01 ppm

days		Extract concentration (dpm/g)	Extract accumulation factors		Residue concentration (dpm/g)	Residue accumulation factors	Total Accumulation factors
2	A′	14958	26.5	A′	180	0.3	26.8
	B′	12879	22.8	B′	835	1.5	24.3
5	A′	79580	140.8	A′	4115	7.3	148.1
	B′	42558	75.3	B′	1807	3.2	78.5
10	A′	72090	127.6	A′	1753	3.1	130.7
	B′	45246	80.1	B′	1630	2.9	83.0
15	A′	65952	116.7	A′	2609	4.6	121.3
	B′	56719	100.4	B′	3449	6.1	106.5
20	A′	118546	209.8	A′	1892	3.3	213.2
	B′	150702	266.7	B′	2363	4.2	270.9
30	A′	88878	157.3	A′	2226	3.9	161.2
	B′	131915	233.5	B′	3576	6.3	239.8
40	A′	187984	332.7	A′	4103	7.3	340.0
	B′	175146	310.0	B′	6314	11.2	321.2
50	A′	133996	237.2	A′	5719	10.1	247.3
	B′	156005	276.1	B′	10238	18.1	293.3
60	A′	75183	133.1	A′	7915	14.0	147.1
	B′	41203	72.9	B′	3834	6.8	79.7



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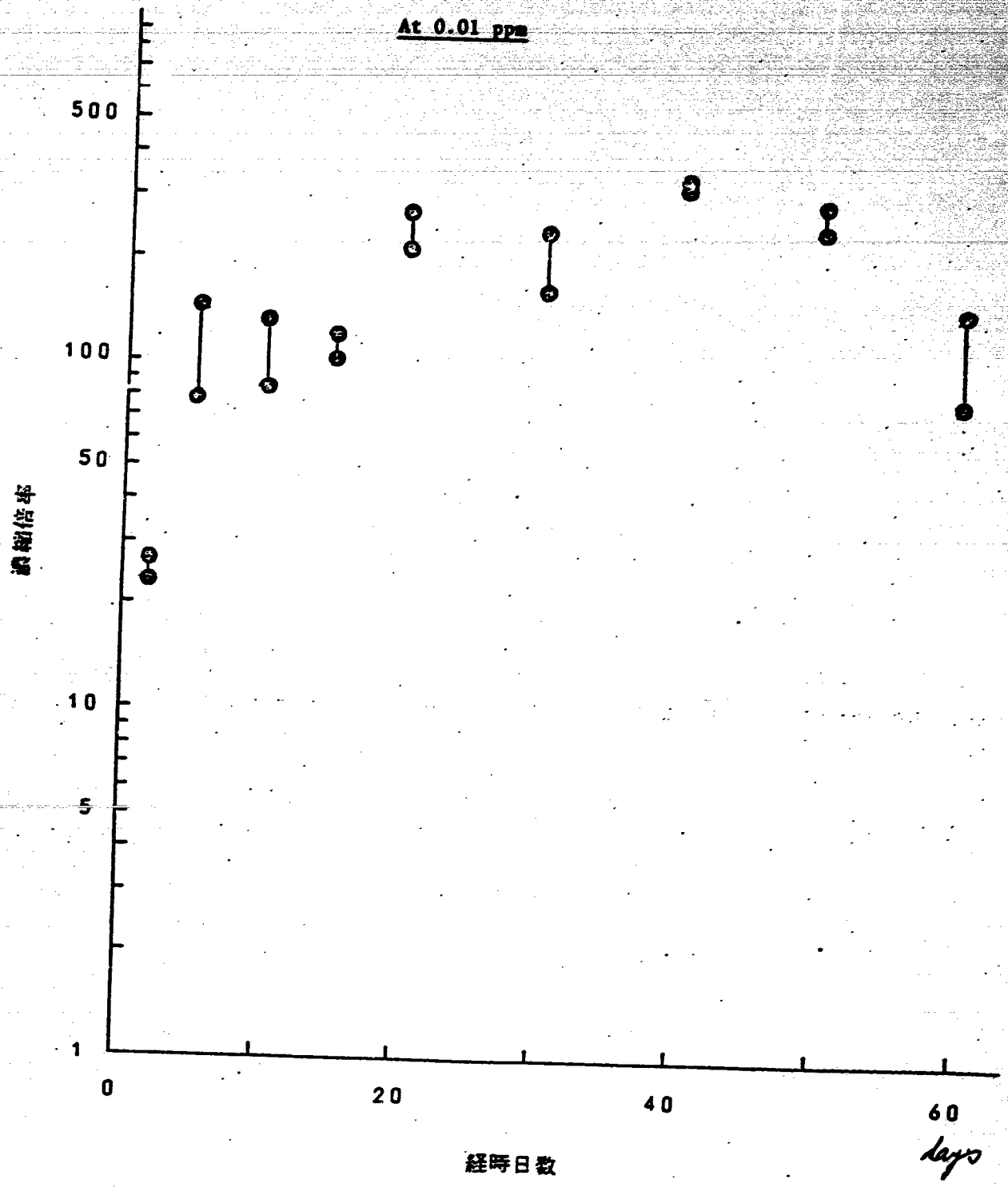
2－2 第2試験区での濃縮倍率



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