



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

SEP 27 1994

C11248

SEP 27 1994

MEMORANDUM

#497AB

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: IMAZALIL: Review of Submitted Acute Toxicity Studies
Performed with Imazalil Technical (MRIDs 416061-04,
416061-05, and 417187-01).

D170446

S405920

Tox Chem No. 497AB

PCCode 111901

TO: Barbara Briscoe
PM 51
Reregistration Division (H7505)

FROM: Henry Spencer, Ph.D. *Henry Spencer 9/22/94*
Review Section 3
Toxicology Branch I
Health Effects Division (H7509)

THRU: Karen Hamernik, Ph.D.
Section Head
Review Section 3
Toxicology Branch I
Health Effects Division (H7409)

K. Hamernik 9/22/94
KB 9/23/94

CONCLUSIONS:

The following study reviews have been completed for Imazalil technical (a.i. of approximately 98% purity) and are attached:

1. Acute Dermal Toxicity in Rabbits, MRID 416061-04.

The study is Acceptable and fulfills Guideline requirement (81-2) as a limit dose study and demonstrates a dermal LD 50 of greater than 2000 mg/kg for both sexes. The Toxicity category is III for acute dermal toxicity.



2. Primary Eye Irritation in Rabbits, MRID 416061-05.

The study is Acceptable and fulfills the Guideline requirement (81-4). The Irritation Score (IS) is 28.9. In addition, the test material caused moderate eye irritation and corneal opacity occurred that was not completely reversible in 2 of 3 animals within 21 days. The test material is placed in Toxicity Category I for primary eye irritation.

3. Dermal Sensitization Study in Guinea Pigs, MRID 417187-01.

The study is Acceptable and fulfills the Guideline requirement (81-6). The test material produced a weak sensitizing reaction in the test animals and is classified as a positive sensitizer in this study.

Another review, for MRID 418898-02, (addendum to MRID 152439, Gdln 81-3 is for another test material (Clinifarm Smoke) and follows under a separate bean.

DOC 920157
FINAL

DATA EVALUATION REPORT

IMAZALIL

Study Type: Acute Dermal Toxicity in Rabbits

Study Title: Evaluation of the Acute Dermal Toxicity of Imazalil - R 23979
(Technical Grade) in New Zealand White Rabbits

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer

Jessica Kidwell
Jessica Kidwell, M.S.

9/11/92
Date

Independent Reviewer

John Liccione
John Liccione, Ph.D.

9/11/92
Date

QA/QC Manager

Sharon Segal
Sharon Segal, Ph.D.

9/11/92
Date

Contract Number: 68D10075
Work Assignment Number: 1-52
Clement Number: 91-170
Project Officer: James E. Scott

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EPA Reviewer: Dr. Henry Spencer
Review Section III, Toxicology Branch I/HED

Henry Spencer
Signature

10/20/92
Date

Acting Section Head: Dr. Karen Hamernick
Review Section III, Toxicology Branch I/HED

Karen Hamernick
Signature

9/22/94
Date

DATA EVALUATION REPORT

STUDY TYPE: Acute dermal toxicity in rabbits

EPA IDENTIFICATION NUMBERS:

Tox. Chem. Number: 497AB

MRID Number: 416061-04

TEST MATERIAL: Imazalil

SYNONYMS: Fungaflor

SPONSOR: Janssen Pharmaceutica, N.V., 2340 Beerse, Belgium

STUDY NUMBER: 2344

TESTING FACILITY: Department of Toxicology, Janssen Research Foundation,
2340 Beerse, Belgium

TITLE OF REPORT: Evaluation of the Acute Dermal Toxicity of Imazalil -
R 23979 (Technical Grade) in New Zealand White Rabbits.

AUTHORS: G. Teuns and R. Marsboom

STUDY COMPLETED: July 6, 1990

CONCLUSIONS: The acute dermal LD₅₀ of imazalil was greater than 2000 mg/kg
for male and female rabbits.

CORE CLASSIFICATION: Acceptable. This study is in conformity with acute
dermal Guideline Series 81-2 as a limit dose study.

TOXICITY CATEGORY: III--Caution

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A. MATERIALS

1. Test Material

Test material: Imazalil
Code Number: R 23979 technical grade
Purity: 97.6%
Physical description: Slightly yellow to brown crystalline mass
(solidified oil)
Lot number: ZR023979 BEB191
Storage conditions: Room temperature in closed containers
Vehicle: None

2. Controls

Animals: Rabbits
Test Substance: None

3. Test Animals

Species: Rabbit
Strain: Albino New Zealand White
Sex: Male and female
Source: Buyens, Lichtaart, Belgium
Receipt date: Not reported
Numbers: 10 males and 10 females
Housing: Individual
Age: Young
Weight: 2.35-2.85 kg (initial body weights)
Feeding: Feed and water provided ad libitum
Selection: Randomization procedure based on sex and body weight

4. Exposure

Route of administration: Dermal
Dose level: 2000 mg/kg

B. TEST PERFORMANCE

Approximately 24 hours prior to testing, fur was clipped from the back of each test animal. The test substance was administered dermally (2000 mg/kg) to the backs of 5 males and 5 females and held in contact with the skin for 24 hours under occlusive patch. At least 10% of the body surface area was treated with the test article. Control group animals did not receive a control article but were only kept for 24 hours under occlusive patch. The application site was covered with a porous gauze dressing and non-irritating tape for the 24-hour exposure period to retain the test article and to prevent ingestion of the test material. After the 24-hour exposure period, the residual test article was removed with water. All animals were observed and scored daily for erythema and edema on the treated and untreated skin areas according to the Draize method (see CBI Appendix), for other toxic signs, and for mortality. Individual body weights were recorded prior to the study and on days 7 and 14. After the 14-day observation period, gross necropsy was performed on all animals.

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C. RESULTS AND STUDY AUTHORS' CONCLUSIONS

Tables were provided for mortality, clinical observations, Draize scores, and body weights.

During the 14-day observation period, no mortalities occurred. All 20 rabbits, control or imazalil-treated, survived. Since all treated rabbits survived the 2000-mg/kg limit test, no other dose level was tested. Based on these results, the acute dermal LD₅₀ of imazalil was greater than 2000 mg/kg for male and female rabbits.

In the imazalil-dosed group, 3 males and 3 females showed slight sedation on day 1 postexposure. The sedation was completely reversible after day 1.

The dermal irritation index according to the Draize test showed a barely perceptible irritation for the dosed group. The irritation index was calculated incorrectly. It should be 0.28 (11/40), not 0.55, as reported on pages 21 and 26 (see CBI Appendix). No dermal irritation was seen in the control group (index: 0.00). From day 4 through day 13, all dosed animals developed slight to moderate scaling. During this period, thickened skin was palpable in 6 of these rabbits. At the end of the study, no visible skin changes were seen.

No dermal irritation or visible skin changes were seen in the unexposed skin in both the control and the dosed groups.

All animals gained weight during the study. Body weight and body weight gain were comparable between groups.

At necropsy, no macroscopic lesions were noted in the control group. In the dosed group, slightly thickened skin at the exposed area or slightly swollen and pale liver with pronounced lobulation were noted in 2 females. The study author considered the latter lesion to be of no relevance since this change was noted as an isolated case in control rabbits.

D. REVIEWERS' COMMENTS

The estimated acute dermal LD₅₀ of imazalil is greater than 2000 mg/kg. Based on this result, the Toxicity Category is III--Caution. This study is classified as acceptable (81-2).

The study authors did not indicate how the test material was applied, i.e., as a pulverized and moistened solid or undiluted. The test material is a solidified oil.

E. QUALITY ASSURANCE MEASURE

A signed Quality Assurance Statement, dated 07/06/90, was presented. A Good Laboratory Practice compliance statement was included.

F. CBI APPENDIX

CBI Draize scoring system, p. 17
CBI Results, p. 21
CBI Table 3a, p. 26

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Imazalil Tox Review

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Pages 7 through 9 are not included.

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- ☐ Identity of product impurities.
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DOC 920158
FINAL

DATA EVALUATION REPORT

IMAZALIL

Study Type: Primary Eye Irritation in Rabbits

Study Title: Evaluation of Eye Irritation of Imazalil - R 23979 Technical
Grade - in NZW Rabbits

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

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Jessica Kidwell
Jessica Kidwell, M.S.

9/8/92
Date

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John Liccione, Ph.D.

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Sharon A. Segal
Sharon Segal, Ph.D.

9/8/92
Date

Contract Number: 68D10075
Work Assignment Number: 1-52
Clement Number: 91-171
Project Officer: James E. Scott

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EPA Reviewer: Dr. Henry Spencer
Review Section III, Toxicology Branch I/HED

Henry Spencer
Signature

Date

10/20/92

Acting Section Head: Dr. Karen Hamernik
Review Section III, Toxicology Branch I/HED

KH
Signature

Date

9/22/94

DATA EVALUATION REPORT

STUDY TYPE: Primary eye irritation in rabbits

EPA IDENTIFICATION NUMBERS:

Tox. Chem. Number: 497AB
MRID Number: 416061-05

TEST MATERIAL: Imazalil

SYNONYMS: Fungaflor

SPONSOR: Janssen Pharmaceutica, N.V., 2340 Beerse, Belgium

STUDY NUMBER: 2253

TESTING FACILITY: Department of Toxicology, Janssen Research Foundation,
2340 Beerse, Belgium

TITLE OF REPORT: Evaluation of Eye Irritation of Imazalil - R 23979 Technical
Grade - in NZW Rabbits.

AUTHORS: G. Teuns and R. Marsboom

STUDY COMPLETED: June 19, 1990

CONCLUSIONS: An average group eye irritation score of 28.9 was recorded
indicating a moderate eye irritation.

CORE CLASSIFICATION: Core minimum (Acceptable). This study was classified as core minimum
because only 3 animals (instead of a required minimum of 6) were used.

TOXICITY CATEGORY: I--Danger. Corneal opacity was not completely reversible
within 21 days.

A. MATERIALS

1. Test Material

Test material: Imazalil
 Code number: R 23979 technical grade
 Purity: 98.1% (sponsor analysis)
 Physical description: Slightly yellow to brown crystalline mass
 (solidified oil)
 Lot number: ZR023979BEB191
 Storage conditions: Room temperature in closed containers
 Vehicle: None
 Stability: Not reported

2. Controls

Animals: None
 Test Substance: None

3. Test Animals

Species: Rabbit
 Strain: New Zealand White
 Sex: Male and female
 Source: Supplied by an established stock farm, but source was not
 specified
 Receipt date: Not reported
 Numbers: Three females
 Housing: Individual
 Age: Young
 Weight: 2.030-2.550 kg (initial body weights)
 Feeding: Feed ("Huybrechts" pelleted rabbit food) and water provided
ad libitum
 Selection: Not reported

4. Exposure

Route of administration: Ocular
 Dose levels: 0.1 g

B. TEST PERFORMANCE

Imazalil (technical grade) was ground to a fine dust and administered once (0.1 g/rabbit) in the conjunctival sac of the left eye of 3 rabbits. The eyes of all rabbits remained unwashed for at least 24 hours. All animals were observed daily for clinical behavior and mortality and were scored for ocular reactions according to the Draize method at 1, 2, 3, 4, 7, 10, 14, and 21 days after instillation. Individual body weights were recorded prior to the study and on days 7, 14, and 21.

The individual values for each animal at each interval were converted to a score using the following formulas:

Cornea weighted score = density score $\times$ area score $\times$ 5
 Iris weighted score = iris score $\times$ 5

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Conjunctivae weighted score = (redness score + chemosis score + discharge score) x 2

The resulting scores for the cornea, iris, and conjunctivae were summed to give a total weighted score per animal, and the average daily score was then calculated to give a mean for each animal and for all 3 animals combined. The average score for all 3 animals was then rated for the severity of irritation. The severity of overall eye irritation was rated as follows: 0-10 - minimal; 11-25 - slight; 26-56 - moderate; 57-84 - marked; above 84 - extreme.

C. RESULTS AND STUDY AUTHORS' CONCLUSIONS

Tables were provided for mortality, clinical observations, Draize scores, and body weights.

Corneal opacity (Grades 1 and 2) was observed in all 3 animals through day 14 and persisted in 2 of 3 animals (Grade 1) through day 21 (Table 1). Iritis (Grade 1) was observed in all 3 animals by day 3 and persisted in 2 of 3 animals through day 7 and 1 animal through day 10. Conjunctival irritation was observed in all 3 animals and persisted in 1 animal through day 10. Twenty-four hours postdose, redness (Grade 1) was seen in all 3 animals and persisted in 1 animal through day 4. Chemosis (Grades 1 and 2) was seen in all 3 animals by 24 hours, in 2 animals at 48 hours, and persisted in 1 animal (Grade 1) through day 10. Discharge (Grade 1) was seen in one animal from 48 hours through day 4. An average group eye irritation score of 28.9 was recorded indicating a moderate eye irritation.

TABLE 1: Summary of Incidence of Positive Ocular Effects

	Observation Intervals								
	Hour				Day				
	1	24	48	72	4	7	10	14	21
<u>Cornea</u>									
Opacity	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3	2/3
<u>Iris</u>									
Iritis	0/3	1/3	3/3	2/3	2/3	2/3	1/3	0/3	0/3
<u>Conjunctivae</u>									
Redness	2/3	3/3	2/3	1/3	1/3	0/3	0/3	0/3	0/3
Chemosis	3/3	3/3	2/3	1/3	1/3	1/3	1/3	0/3	0/3
Discharge	0/3	0/3	1/3	1/3	1/3	0/3	0/3	0/3	0/3

D. REVIEWERS' COMMENTS

The reviewers conclude that imazalil causes moderate eye irritation.

The toxicity category for this chemical is I--Danger because corneal opacity was not reversible within 21 days, however, some signs of reversibility were seen by day 21.

This study was classified as core minimum because only 3 animals were used for this study, instead of at least 6 as indicated in the guidelines. The actual source where the rabbits were obtained was not reported. The study report did not indicate if an illustrated guide was used for grading eye irritation.

It was not reported whether or not the lids were gently held together for about 1 second to prevent loss of the material following application. It was reported that body weight remained normal, except for a slight body weight loss in rabbits 2 and 3 during week 2; however, examination of individual body weight loss revealed only a very slight body weight loss in rabbit No. 3 at week 2. A discrepancy was noted in the reporting of the group score. The group score is reported as 28.9 in CBI Table 3 and 29.1 in the results section on page 19 and on page 8. The correct score is 28.9.

E. QUALITY ASSURANCE MEASURE

A signed Quality Assurance Statement, dated 06/19/90, was presented. A Good Laboratory Practice compliance statement was included.

F. CBI APPENDIX

CBI Draize scoring system, pp. 16-17

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RW 1067-98

Imazalil Tox Review

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Pages 15 through 16 are not included.

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DOC 920156
FINAL

DATA EVALUATION REPORT

IMAZALIL

Study Type: Dermal Sensitization in the Guinea Pig

Study Title: Evaluation of the Sensitization Potential of Imazalil Technical Grade (R 23979) in Guinea Pigs

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
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Sharon Segal, Ph.D.

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Date

Contract Number: 68D10075
Work Assignment Number: 1-52
Clement Number: 91-169
Project Officer: James E. Scott

17

EPA Reviewer: Dr. Henry Spencer
Review Section III, Toxicology Branch I/HED

Henry Spencer
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10/20/92
Date
[Signature]
Signature
9/20/94
Date

Acting Section Head: Dr. Karen Hamernick
Review Section III, Toxicology Branch I/HED

DATA EVALUATION REPORT

STUDY TYPE: Guideline 81-6: Dermal sensitization study

EPA IDENTIFICATION NUMBERS:

011248

Tox. Chem. Number: 497AB
MRID Number: 417187-01

TEST MATERIAL: Imazalil

011248

SYNONYMS: Fungaflor

SPONSOR: Janssen Pharmaceutica, N.V., B-2340 Beerse, Belgium

STUDY NUMBER: 2417

TESTING FACILITY: Department of Toxicology, Janssen Research Foundation,
2340 Beerse, Belgium

TITLE OF REPORT: Evaluation of the Sensitization Potential of Imazalil
Technical Grade (R 23979) in Guinea Pigs

AUTHORS: G. Teuns, R. Marsboom, W. Coussement, and H. Van Cauteren

STUDY COMPLETED: November 15, 1990

CONCLUSIONS: Delayed contact hypersensitivity was observed upon challenge in guinea pigs exposed to imazalil. Imazalil technical grade was classified as a weak sensitizer based on the incidence of positives in the test group.

CORE CLASSIFICATION: Acceptable. This study was in conformity with Guideline Series 81-6.

TOXICITY CATEGORY: Not applicable

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A. MATERIALS

1. Test Material

Test material: Imazalil
 Code Number: R 23979 technical grade
 Batch No.: G3A561
 Purity: 98.1%
 Physical description: Slightly yellow to brown crystalline mass
 (can occur as an oily liquid)
 Lot number: ZR023979G3A561
 Storage conditions: Room temperature in closed containers
 Stability: Not reported
 Homogeneity: Not reported
 Vehicle: Sesam oil or petrolatum

2. Controls

(a) Intradermal induction phase (day 0)

Solutions used: vehicle (sesam oil)

(b) Epicutaneous induction (day 7)

Solutions used: vehicle (petrolatum)

(c) Challenge phase (day 21)

Route of administration: epicutaneous

Solutions used: 5% test article powder in petrolatum

3. Test Animals

Species: Guinea pig
 Strain: Pirbright
 Sex: Male
 Source: Supplied by in-house non-inbred laboratory colony
 (established 1956)
 Receipt date: Not reported
 Numbers: 40
 Housing: Individual
 Age: Adult
 Weight: 300-400 g
 Feeding: Feed ("Hope-farms" standardized pellets) and water provided
ad libitum
 Selection: Randomization

4. Test Material

(a) Intradermal induction phase (day 0)

Solutions used: 1% solution of test article in sesam oil

(b) Epicutaneous induction phase (day 7)

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Solutions used: 10% test article in petrolatum (powder)

(c) Challenge phase (day 21)

Route of administration: epicutaneous

Solutions used: 5% test article in petrolatum (powder)

The formulations used were chosen based upon a screen test which indicated that the 1% solution in sesam oil alone produced no necrosis at the injection site. The 10% powder in petrolatum produced a slight erythema at the application site, whereas the 5% powder in petrolatum did not result in erythema when applied to the skin of guinea pigs during 24 hours under occlusive patch.

B. TEST PERFORMANCE

The potential of imazalil to produce delayed contact hypersensitivity in guinea pigs was evaluated using the maximization test of Magnusson and Kligman.

There were two main groups, imazalil-induced and vehicle-induced, each consisting of 20 guinea pigs.

Intradermal induction (day 0)

The test article formulation (1% in sesam oil) was injected in the depilated nuchal area (nape of neck) as follows:

- Two injections of 0.1 mL of Freund's complete adjuvant blended with an equal amount of water
- Two injections of 0.1 mL of the test article formulation (1% in sesam oil) close to the first two injections
- Two injections of 0.1 mL of the test article formulation emulsified with Freund's complete adjuvant.

In the vehicle-induced group, the injections were given in a similar way, with replacement of the test article by the vehicle.

Epicutaneous induction (day 7)

The test article formulation (10% in petrolatum) was administered epicutaneously on the nuchal area. For the vehicle-induced group, the vehicle formulation was applied. The test article and vehicle formulations were held in contact with the skin under an occlusive patch for 48 hours. Scoring of the skin reaction (erythema, edema) was performed 24 hours later.

Challenge (day 21)

Two weeks after the epicutaneous induction, both imazalil- and vehicle-induced groups were challenged with the test article formulation (5% in petrolatum) applied epicutaneously on the left shaved flank under occlusive patch for 24 hours. Scoring was performed 48 and 72 hours after challenge.

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Observations

Body weights were determined prior to and at the end of the study.

Evaluation of reaction: The minimum criterion of an allergic reaction is redness (erythema) all or no accompanied by swelling (edema). The reactions are classified according to a 4-point scale: no reaction - 0; scattered, mild redness - 1; moderate and diffuse redness - 2; intense redness and swelling - 3. Scoring was performed on days 10, 23, and 24.

Determination of positivity: The individual animal scores after challenge of the vehicle-induced group and the group induced with the test article formulation were compared. Subsequently, the sensitization potential of the test article was classified according to the number of positive animals:

<u>Sensitization rate (%)</u>	<u>Grade</u>	<u>Classification</u>
0-8	I	weak
9-28	II	mild
29-64	III	moderate
65-80	IV	strong
81-100	V	extreme

Statistics

Body weight and scores for erythema and edema were analyzed to detect any possible test article-related effect using the Mann-Whitney U test (Siegel S., Nonparametric Statistics, McGraw Hill, New York, 1956).

C. RESULTS AND STUDY AUTHORS' CONCLUSIONS

All guinea pigs survived the study. The first intradermal induction produced slight necrosis (Grade 1) at the injection site of all animals in both the vehicle-induced and test article-induced groups. The epicutaneous induction produced slight erythema (Grade 1) in 13 of 20 vehicle-induced animals and in 15 of 20 test article-induced animals. Forty-eight and 72 hours after challenge, all vehicle-induced animals were normal (sensitization rate = 0%) and 1 out of 20 test article-induced animals had slight erythema (sensitization rate = 5%). A known positive sensitizer, 2,4-dinitro-1-chlorobenzene (DNCB), was additionally evaluated in a separate study (Exp. No. 2216). After comparing these results with the results of the positive control study with DNCB, in which 100% sensitization rate was obtained 48 and 72 hours after challenge, it was concluded that imazalil technical grade can be classified as a weak sensitizer (grade I).

D. REVIEWERS' COMMENTS

The reviewers conclude that imazalil is a weak sensitizer.

E. QUALITY ASSURANCE MEASURE

A signed Quality Assurance Statement, dated 11/15/90, was presented. A Good Laboratory Practice compliance statement was included.

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