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INITIAL SUB- MISSION

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TSCA HEALTH & SAFETY STUDY COVER SHEET

TSCA CBI STATUS: -CHECK IF THIS PAGE CONTAINS CONFIDENTIAL BUSINESS INFORMATION (CBI) Clearly mark the confidential information with bracketing and check the box in the appropriate section (If Contains CBI) Submit a sanitized cover sheet with CBI deleted. Mark the sanitized copy, "Public Display Copy" in the heading.

RECEIVED OPT M/C 11/18/99

1.0 SUBMISSION TYPE - Contains CBI
 8(d) 8(e) FYI 4 OTHER: Specify _____
 Initial Submission Follow-up Submission Final Report Submission
 Previous EPA Submission Number or Title if update or follow-up: _____
 continuation sheet attached Docket Number, if any: # _____

2.1 SUMMARY/ABSTRACT ATTACHED (may be required for 8(e); optional for §4, 8(d) & FYI)
 X - YES NO

2.2 SUBMITTER TRACKING NUMBER OR INTERNAL ID
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 (99-276)

2.3 FOR EPA USE ONLY

3.0 CHEMICAL/TEST SUBSTANCE IDENTITY - Contains CBI
 CAS# 13475-82-6 Reported Chemical Name (specify nomenclature if other than CAS name): _____
 Purity _____ %
 Single Ingredient
 Commercial/Tech Grade
 Mixture Trade Name: Modedecine Common Name: _____

4.0 REPORT/STUDY TITLE - Contains CBI
 Subchronic (13-Week) Inhalation Toxicity Study in Rats, Report # V82.275/212294
 Continuation sheet attached

5.1 STUDY/TSCATS INDEXING TERMS (CHECK ONE)
 HEALTH EFFECTS (HE): ENVIRONMENTAL EFFECTS (EE): _____ ENVIRONMENTAL FATE (EF): _____

5.2 STUDY/TSCATS INDEXING TERMS (see instructions for 4 digit codes)
 STUDY SUBJECT ROUTE OF EXPOSURE (HE only): _____ VEHICLE OF EXPOSURE (HE only): _____
 TYPE: STOX ORGANISM (HE, EE only): RATS Other: _____ Other: _____
 Other: _____ Other: _____ Other: _____

6.0 REPORT/STUDY INFORMATION Contains CBI Study is GLP
 Laboratory: CIVO Institutes Tno, Netherlands Report/Study Date: 10/82
 Source of Data/Study Sponsor (if different than submitter): Bayer AG Number of pages: 19
 continuation sheet attached

7.0 SUBMITTER INFORMATION Contains CBI
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 Technical Contact: Donald W. Lamb, Ph.D Submitter Address (if different): _____
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8.0 ADDITIONAL/OPTIONAL STUDY COMMENTS Contains CBI
 continuation sheet attached



RECEIVED OPT M/C 11/18/99

Submitter Signature: Donald W. Lamb Date: 11/18/99



Contains No CBI

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9.0 CONTINUATION SHEET
Submitter Tracking Number/Internal ID

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CONTINUED FROM COVER SHEET SECTION # 2.1

TSCA 8(e) Evaluation:

The reporting is based on the kidney nephrosis which was observed in this subchronic inhalation rat study with isododecane.

Abstract

1. A subchronic inhalation toxicity study with isododecane in rats was conducted to establish a no-toxic-effect level. Five groups of rats, consisting of 20 males and 20 females each, were exposed to atmospheres containing 0, 12.5, 50, 100, and 200 ppm isododecane respectively, for 6 hours a day, 5 days a week, for a period of 13 weeks. Observations were made for general appearance, growth, hematology, biochemistry of the blood, composition of the urine, organ weights, gross pathology, and microscopic pathology of the kidneys.
2. The actual mean concentrations of isododecane in the various test atmospheres were 12.5, 50.2, 99.9, and 201.1 ppm.
3. The health and behavior of the rats were not visibly affected by exposure to isododecane.
4. There were no changes in hematological, blood chemistry, or urinary values, or in organ weights, which could be unequivocally attributed to the isododecane.
5. An increased incidence of minimal to slight tubular nephrosis was found in the kidneys of males at dose levels of 50 ppm and above. There was a positive dose-response relationship.
6. It was concluded that under the experimental conditions of the present study, the no-toxic-effect level of isododecane in rats was 12.5 ppm. However, the actual no-toxic-effect level in rats may be only slightly lower than 50 ppm.

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netherlands organization
for applied scientific
research



division for nutrition and
food research tno

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netherlands

*Start der Studie: 13.1.1982
Ende der Studie: 16.4.1982*

Report no. V 82.275/212294

SUBCHRONIC (13-WEEK) INHALATION
TOXICITY STUDY WITH ISODODECANE
IN RATS v. Oktober 1982

Authors: Drs L.M. Appelman, Drs M.C.
Bosland and J.P. Bruyntjes

At the request of: EC. Erdölchemie GmbH, Cologne,
Federal Republic of Germany

Project number: B 81-2294

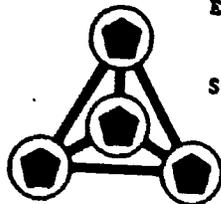
Date: October, 1982

Approved by: Dr V.J. Feron

Start of the study: 13 January 1982

End of the study: 16 April 1982

Study director: Drs L.M. Appelman



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23a-10 000-0181

19 pages

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SUMMARY

1. A subchronic inhalation toxicity study with isododecane in rats was conducted to establish a no-toxic-effect level. Five groups of rats, consisting of 20 males and 20 females each, were exposed to atmospheres containing 0, 12.5, 50, 100 and 200 ppm isododecane respectively, for 6 hours a day, 5 days a week, for a period of 13 weeks. Observations were made of general appearance, growth, haematology, biochemistry of the blood, composition of the urine, organ weights, gross pathology and microscopic pathology of the kidneys.
2. The actual overall mean concentrations of isododecane in the various test atmospheres were 12.5, 50.2, 99.9 and 201.1 ppm.
3. Health condition and behaviour of the rats were not visibly affected by exposure to isododecane.
4. There were no changes in haematological, blood chemical or urinary values, or in organ weights, which could be unequivocally attributed to the test article.
5. An increased incidence of minimal to slight tubular nephrosis was found in the kidneys of males at levels of 50 ppm and above. There was a positive dose-response relationship.
6. It was concluded that under the experimental conditions of the present study the no-toxic-effect level of isododecane in rats was 12.5 ppm. However, the actual no-toxic-effect level in rats may be only slightly lower than 50 ppm.

7)

$$1 \text{ ppm} = 7 \text{ mg/m}^3$$

$$\text{Actual}^2 = 1.542 \text{ ppm (... 2)}$$

SUBCHRONIC (13-WEEK) INHALATION TOXICITY STUDY WITH ISODODECANE IN RATS

1. INTRODUCTION

At the request of EC. Erdölchemie GmbH, Cologne, Germany, a subchronic (13-week) inhalation toxicity study with isododecane in rats was carried out. The exposure levels (0, 12.5, 50, 100 and 200 ppm) were selected on the basis of the results of a previous subchronic toxicity study (Appelman et al., 1981).

This previous study, in which male and female rats were exposed by inhalation to 0, 200, 600 or 1,800 ppm isododecane, 6 hours a day, 5 days a week for a period of 13 weeks, showed that the kidneys were the organs primarily affected by isododecane. The renal effects consisted of tubular nephrosis and were limited to the males. The no-toxic-effect level appeared to be lower than 200 ppm.

The present 13-week study was conducted in order to verify the renal effects observed in the previous study and to assess the no-toxic-effect level in rats.

2. MATERIAL AND METHODS

2.1 Material

The test material (50 1) was received from the principal in October 1981. It was a colourless liquid, having a boiling point range from 160 °C to 170 °C, with the following composition as reported by the principal (see annex 1):

- total C ₄ hydrocarbons	< 2 ppm
- total C ₈ hydrocarbons	0.3 % (w/w)
- total C ₁₂ hydrocarbons	97.7 % (w/w)
consisting of: 82 % 2.2.4.6.6. pentamethylheptane and	
	17.7 % other C ₁₂ hydrocarbons
- total C ₁₆ hydrocarbons	< 0.1 % (w/w)
- aromatics content	< 10 ppm
- water content	10 ppm
- bromium index	2 mg Br ₂ /100 g

2.2 Animals

One hundred male and 100 female weanling SPF-bred rats (Cpb:WU; Wistar random) were obtained from the Central Institute for the Breeding of Laboratory Animals TNO, Zeist, The Netherlands. On arrival the rats weighed 35-50 g. They were divided into five groups of 20 males and 20 females each by computer randomization according to a program provided by the computer manufacturer. Each group was coded by a letter and a colour. Within each group the individual rats were identified by sex, earmark and computer reference number.

2.3 Maintenance

During exposure as well as during non-exposure periods all rats were housed individually in wire-mesh stainless steel cages. The temperature inside the chambers was 19.5 ± 0.5 °C. The relative humidity in the exposure chambers varied from 40 to 60 %.

During exposure the animals were deprived of food and water. During the non-exposure periods the animals were fed the Institute's stock diet and tap water ad libitum. The levels of nutrients in stock diet and of contaminants in stock diet and in tap water are determined periodically (annexes 2-6).

2.4 Exposure chambers

H 1000 multitiered inhalation chambers manufactured by Hazleton systems Inc., U.S.A., were used. The chambers have been constructed of stainless steel with glass doors on two sides. This allows observation of the animals during exposure. The capacity of the chambers is about 2.5 m^3 .

2.5 Generation of the test atmospheres

The test atmospheres are obtained as follows: filtered and dried air from the compressed-air line was passed through a glass evaporator, filled with isododecane. To obtain the desired isododecane concentration in the test atmosphere the airflow laden with isododecane was mixed in the proper ratio with the main airflow passed through the exposure chambers.

2.6 Analysis of the test atmospheres

The analysis of test atmospheres to monitor the isododecane concentration was carried out by gaschromatography. Samples were taken automatically at regular intervals by means of a timer-controlled 7-port gas-sampling valve. The sample loop was calibrated by comparing the area of the isododecane peak obtained from a loop sample with the area of the isododecane peak obtained from a sample taken simultaneously with a gas-tight syringe. The detector response to isododecane was calibrated by injecting known amounts of a standard solution of isododecane in diethylether.

The gaschromatograph - an Intersmat GC 120 instrument, equipped with a flame ionisation detector - was operated under the following conditions:
column: 3 m x 0.4 cm stainless steel, packed with 5 % Carbowax 20 M on Chromosorb MAW, 60-80 mesh.

temperature: column: 110 °C

injection port: 110 °C

detector: 150 °C

carrier gas: nitrogen, 65 ml/min.

2.7 Experimental design and conduct

After an acclimatization period of one week the experiment (Assay No. 378) was started on 13 January 1982. The last day of exposure was 16 April 1982. A table showing the group code, colour code, exposure level and number of animals per group is given on the next page.

Group code		exposure level (ppm)	number of animals	
letter code	colour code		males	females
A	white	0	20	20
B	blue	12.5	20	20
C	green	50	20	20
D	red	100	20	20
E	yellow	200	20	20

Each rat was identified by a six digit computer reference number, which was even for males and odd for females. The rats were individually identified by sex and by different V-shaped earmarks according to the following code:

Z = without earmark
 R_1 = one right
 R_2 = two right
 L_1 = one left
 L_2 = two left
 R_1L_1 = one right, one left
 R_1L_2 = one right, two left
 R_2L_1 = two right, one left
 R_2L_2 = two right, two left
 R_3 = three right

The rats were exposed to atmospheres containing the test substance for six hours a day. Usually the exposure to isododecane was started between 08.30 and 10.30 a.m.

The following observations were made:

a. Exposure levels

At regular time-intervals samples of the test atmospheres were analysed and from the results the mean concentration of isododecane to which each test group was exposed each day, was calculated.

b. Clinical signs

The general condition and behaviour of the animals was checked daily. All signs of ill health and reaction to treatment were recorded.

c. Body weight

The individual body weight of each animal was recorded just before the start of the first exposure to the test substance, and once every week thereafter.

d. Haematology and clinical chemistry

- Haematology

Blood samples from the tip of the tail of 10 animals per sex of each group were collected in week 6 (days 36 and 37) and 12 (days 82 and 83). All blood samples were examined for the following parameters:

1. Haemoglobin concentration by cyanmethaemoglobin method using Zap Oglobin[®] of Coulter Electronics.
2. Packed cell volume as micro-haematocrit.
3. Red blood cell count by Coulter Counter, Model ZF.
4. White blood cell count by Coulter Counter, Model ZF.
5. Differential white blood cell count by direct visual count of smear after Pappenheim staining, according to Gorter and De Graaff (1955).

- Blood chemistry

In week 6 (days 36 and 37) and 12 (days 82 and 83) after a 24 h period of deprivation of food and water, samples of tail-tip blood were collected from 10 rats/sex/group for the determination of glucose.

Also in week 6 (days 42 and 43) blood samples - of 10 rats/sex/group - were collected by orbital puncture. Just like blood samples taken at autopsy from the sorts of 10 rats/sex/group, whilst the animals were under ether anaesthesia, these samples were collected in plastic tubes containing two drops of heparine. The samples were centrifuged at 2000 rpm for 15 minutes using Sure-Sep[®] from General Diagnostics for good separation of the plasma. Subsequently the following determinations were carried out by means of a Coulter KEM-O-LAB, using Coulter test methods.

1. Urea
2. Plasma glutamic-oxalacetic transaminase
3. Plasma glutamic-pyruvic transaminase
4. Plasma alkaline phosphatase
5. Total plasma protein
6. Plasma albumin
7. Creatinine

- Urine analysis

Individual urine samples were collected from 10 rats/sex/group during the last 16 hours of a 24-hour period of deprivation of food and water in week 6 (day 40) and 12 (day 84). The following measurements were made:

1. Density by refractometry
2. Volume by calibrated tube
3. pH)
4. Protein)
5. Glucose) using test strips (L-Combur 5 test[®],
Boehringer)
6. Occult blood)
7. Ketones)
8. Appearance
9. Microscopical examination of the sediment - after centrifuging the urine at 2,000 rpm for 3 min. - for: erythrocytes, leucocytes, epithelial cells, amorph material, crystals, casts, bacteria and sperm cells.

e. Autopsy

In week 14 the animals were sacrificed on 4 successive working days, in such a way that, on the average, time of sacrifice was about the same for each group. The rats were killed by exsanguination from the abdominal aorta under ether anaesthesia, and then examined grossly for pathological changes.

The following organs were weighed:

adrenals	lungs with trachea and larynx
brain	pituitary
heart	spleen
kidneys	testes/ovaries
liver	thymus
	thyroid (with parathyroid)

Samples of the organs weighed and of the following tissues and organs were preserved in a neutral aqueous phosphate-buffered 4 X formaldehyde solution.

aorta	pancreas
axillary lymph nodes	parotid salivary glands
caecum	prostate
coagulating glands	sciatic nerve
colon	seminal vesicles
duodenum	skeletal muscle (thigh)
epididymides	skin (flank)
exorbital lachrymal glands	spinal cord
eyes	sternum (with bone marrow)
ileum	stomach
jejunum	submaxillary salivary glands
mesenteric lymph nodes	sublingual salivary glands
nose (sections at 4 levels)	urinary bladder
oesophagus	uterus (with cervix)
	all gross lesions

The lungs were fixed (after weighing) by intratracheal infusion of the fixative under 10 cm water pressure.

The kidneys of all rats were embedded in paraffin wax, sectioned at 5 μ m, stained with haematoxylin and eosin, and examined by light microscopy.

2.8 Statistical analysis

Statistical analyses of body weights and organ to-body weight ratios were carried out using analysis of co-variance followed by the Dunnetts Test, whereas the haematological and biochemical data were evaluated by means of the Mann/Whitney U-test. For statistical analysis of the histopathological data, chi-square analysis was used according to the limitations outlined by Siegel (1956).

2.9 Contributors

Major contributions to this study were made by:

Animal handling	: F. Hendriksma
Diet preparation	: J.M. Blom
Clinical chemistry	: Dr H.E. Falke
	J.F. Catsburg
Pathology	: Drs M.C. Bosland
	J.P. Bruyntjes
Histology	: Ms. N. Hagemeyer
Study director/Toxicologist	: Drs L.M. Appelman
Study supervisor	: Dr V.J. Feron

2.10 Deviations from the protocol

- The thyroid (with parathyroid) was weighed because this organ is weighed routinely in subchronic studies.
- The food intake was not measured, because the Hazleton chambers were not equipped for individual measurements of the amount of food consumed.

3. RESULTS

3.1 Exposure levels

The mean actual concentrations of isododecane, to which the rats in the different groups were exposed, were 0, 12.5, 50.2, 99.9 and 201.1 ppm, the standard error of the mean being 0, 0.08, 0.37, 0.40 and 1.1 ppm respectively.

The mean daily concentrations are summarized in table 1.

3.2 Symptomatology

Health and behaviour of the rats of the test groups were not visibly affected by exposure to the test material.

3.3 Body weights

The mean body weights are summarized in table 2. The animals, both males and females, of all test groups gained weight at a rate similar to that of the controls.

3.4 haematology and clinical chemistry

- Haematology

Mean haematologic values are summarized in the tables 3-10 and include values obtained from rats in week 6 and 13. A few statistically significant differences occurred between test animals and controls. All values were increased with respect to the corresponding items of the control group. The differences occurred haphazardly among the exposure groups. Moreover, all values were within the range of "biological variability", or expected values for rats of this strain and age (see the table below), and there never was a clear dose-response relationship for any of the criteria concerned. Therefore, these findings are considered to be of no toxicological significance.

Normal values for haematologic criteria, which showed statistically significant differences between test and control animals in the present study

criterion	ranges at week:			
	6		13	
	♂	♀	♂	♀
HB(μmol/l)	8.5-10.9	8.4-10.8	9-10.2	8.6-10.2
PCV (l/l)	0.470-0.510	0.443-0.543	0.463-0.523	0.438-0.518
WBC ($\times 10^9/l$)	12-24	10-20	11.4-21.8	10-19

- Blood chemistry

The results of blood chemistry determinations are presented in the tables 11-14.

Statistically significant differences between test animals and controls were found in parameters determined in week 7 and 13, most of them in week 13. However, some were increased and other decreased; they occurred arbitrarily among the test groups; all were within the normal range found in rats of this strain and age (see the table below), and moreover, in all cases there was no indication of a dose-response relationship for any of the criteria concerned. Therefore, no toxicological significance is attached to these findings.

Normal values for blood chemistry criteria, which showed statistically significant differences between test and control animals in the present study

criterion	range at week 13:	
	♂	♀
GPT (U/l)	36-64	n.r. 1)
GOT (U/l)	47-81	n.r.
urea (mmol/l)	n.r.	5.1-9.4
albumin (g/l)	n.r.	37-49
glucose (mmol/l)	n.r.	3.3-4.9

1) n.r. = not relevant.

- Urine analysis

The results of the urine analysis findings are presented in the tables 15-20. No exposure-related alterations were observed for any of the parameters in any of the groups exposed to 12.5, 50, 100 or 200 ppm isododecane. The few statistically significant differences in specific gravity and in volume between males exposed to 50 or 200 ppm and control males in week 13, could not be correlated with the exposure levels and were within the range of normal values for rats of this strain and age.

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3.5 Organ weights

Absolute and relative organ weights of the rats are presented in the tables 21-28.

Absolute brain weight and lung-to-body weight ratio of males of the 100 ppm groups were statistically significantly different from those of the controls. Because these effects were observed in one of the intermediate dose groups only and because the differences were only marginal, no toxicological significance is attached to these findings.

3.6 Pathology

- Macroscopical examination

Macroscopical examination at autopsy did not reveal any gross lesions that could be attributed to the treatment. All lesions observed were either about equally distributed among the various groups or they occurred in one animal or in a few animals only.

- Microscopical examination of the kidneys (table 29)

Microscopical examination of the kidneys revealed a dose-related increase in incidence of tubular nephrosis. These lesions were characterized by a loss of cytoplasmatic eosinophilia and striation, a loss of the brush border, and an increased cellular and nuclear size of epithelium of mainly the proximal tubules. These changes were occasionally accompanied by very small to small aggregates of mononuclear inflammatory cells.

In males, statistical analysis of the data, comparing the various treatment groups with controls revealed a significant increase of the number of animals showing tubular nephrosis at the 50, 100 and 200 ppm exposure levels. In line with these findings a slight increase was found in the incidence of inflammatory cell infiltrates.

Other changes observed in the kidneys, such as hydronephrosis and calcareous deposits occurred in one or two animals only, without any apparent relation to the treatment.

4. DISCUSSION

The findings in the present study were well in line with the results of a previous subchronic inhalation study with isododecane in rats (Appelman et al., 1981). In both studies the kidney lesions were similar. The extent of the lesions observed in the control and 200 ppm groups used in both studies was comparable.

A clear positive relation between the exposure levels and the renal effects was found.

In the present study a statistically significant increase in incidence of tubular nephrosis was still observed at 50 ppm level, but it was, however, fully absent at the 12.5 ppm level.

From the results of the present study it appears that the no-toxic-effect level of isododecane in rats is 12.5 ppm. However, it is not unlikely, actually, that the no-toxic-effect level is only slightly lower than 50 ppm, as can be easily deduced from the data on tubular nephrosis given in table 29.

1) $42,5 \text{ ppm (}\mu\text{l/m}^3\text{)} = 87,5 \text{ }\mu\text{g/m}^3$

5. REFERENCES

Appelman, L.H., M.C. Bosland and J.P. Bruyntjes.
Subchronic (13-week) inhalation toxicity study with isododecane in rats.
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Siegel, S.
Non parametric statistics for the behavioural sciences.
McGraw-Hill, Tokyo, 1956.

1 ppm = 7 mg/m³
A unclear? = 6.442 ppm (approx.?)

B 08

AUTHENTICATION

We, the undersigned, hereby declare that the work described in this report was performed under our supervision, in accordance with the agreed protocol, and that the report provides a true and accurate record of the results obtained.



Drs L.M. Appelman
Inhalation toxicologist/
Study director

date: 12/10/1982



Drs M.C. Bosland
Pathologist

date: 14-10-82



Dr V.J. Feron
Deputy Head Dept. of
Biological Toxicology.

date: 13/10/1982

All raw data and specimens and the master copy of the final report are filed in the archives of the department of Biological Toxicology under the reference:
"Erdölchemie, isododecane, inhalation toxicity in rats".

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QUALITY ASSURANCE UNIT TNO - P.O. Box 360, 3700 AJ ZEIST, Netherlands

STATEMENT OF GLP COMPLIANCE

On : Subchronic (13-wk) inhalation toxicity study with isododecane
in rats
Report no.: V 82.275/212294
Date : September, 1982

The study was carried out under conditions of good laboratory practice.
Within reason there have been no circumstances that might have affected
the quality and integrity of the results obtained.

Dates and number of inspections:	Dates of reports to management:
11 September 1981 (1)	14 September 1981
6 January 1982 (2)	6 January 1982
14 January 1982 (1)	15 January 1982
10 March 1982 (1)	10 March 1982
19 March 1982 (1)	22 March 1982
16 April 1982 (1)	16 April 1982
23 June 1982 (2)	24 June 1982
7 July 1982 (1)	7 July 1982
22 July 1982 (1)	22 July 1982
Final report audit: 20-22 September 1982	23 September 1982


Mr. W.C. Wijnands
Quality Assurance Manager i/c

date: 13 October 1982

CERTIFICATE OF AUTHENTICITY

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