N, O-Di(hydroxyethyl)-2-amino-5-nitrophenol: Human health tier II assessment

27 October 2017

CAS Number: 59820-43-8

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted

and published separately, using information available at the time, and may be undertaken at different tiers.

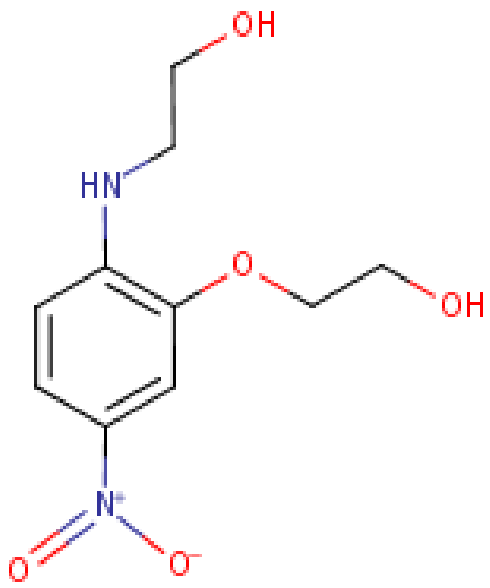
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:www.nicnas.gov.au

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	HC Yellow No 4 ethanol, 2-((2-(2-hydroxyethoxy)-4-nitrophenyl)amino)-
Structural Formula	
Molecular Formula	C10H14N2O5
Molecular Weight (g/mol)	242.23
Appearance and Odour (where available)	bright yellow/green solid
SMILES	c1(NCCO)c(OCCO)cc(N(=O)=O)cc1

Import, Manufacture and Use

Australian

The chemical is on the 'List of chemicals used in dyes in permanent and semi-permanent hair dyes in Australia' (NICNAS, 2007).

The chemical has reported cosmetic use in permanent and semi-permanent dye preparations.

International

The following international uses have been identified through Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); the International Agency for Research on Cancer (IARC, 1993); the Cosmetic Ingredient Review report (CIR, 2012) and the Scientific Committee on Consumer Products (SCCS, 2009).

The chemical has reported cosmetic use as a hair dye ingredient in oxidative and non-oxidative hair dye products at a maximum concentration of 1.5 % (SCCS, 2009).

Restrictions

Australian

No known restrictions have been identified.

International

The chemical is listed on the following (Galleria Chemica):

- EU Cosmetics Regulation 1223/2009 Annex III—List of substances which cosmetic products must not contain except subject to the restrictions laid down; and
- Association of South East Asian Nations (ASEAN) Cosmetic Directive Annex III—Part 1: List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down.

Under these restrictions, this chemical may be used in non-oxidative hair dye products at a maximum final concentration applied to hair of 1.5 %. The following restrictions also apply: 'Do not use with nitrosating agents; Maximum nitrosamine content: 50 µg/kg; and; Keep in nitrite-free containers' (CosIng; Galleria Chemica).

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not listed on the Hazardous Chemical Information System (HCIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Toxicokinetics

The dermal absorption of the chemical in hair dye formulations was investigated in vitro and low percutaneous absorption was found.

In an in vitro percutaneous study, an oxidative hair dye formulation containing the chemical at 1.5 % was tested using 12 human skin samples from three donors. A mean amount of 0.034 % (0.102 $\mu g/cm^2$) of applied dose was found in the receptor fluid within 30 min post-exposure. The majority of the applied dose (~92 %) was rinsed off the skin surface (SCCS, 2009; CIR, 2012).

Acute Toxicity

Oral

The chemical has low to moderate acute toxicity based on results from animal tests following oral exposure. The median lethal dose (LD50) in rats is between 500 to 5000 mg/kg bw. A hazard classification is recommended (see **Recommendation** section).

Sprague-Dawley (SD) rats (n=20/sex/dose) were orally administered the chemical at 500 or 2000 mg/kg bw in 0.5 % aqueous carboxymethylcellulose, and observed for 14 days. At 2000 mg/kg bw, all animals were killed in extremis. Sublethal effects included piloerection, soiled coat, reduced activity, ataxia, subdued behaviour, prostration, yellow discolouration of urine and extremities, hunched appearance and laboured breathing in all treated rats on the day of dosing. The LD50 was reported to be between 500 to 2000 mg/kg bw (CIR, 1998; SCCS, 2009).

In a study conducted according to OECD Test Guideline (TG) 401, Wistar rats (n=5/sex/dose) were administered a 10 % suspension of the chemical in 3 % acacia in water, by gavage at 1250 or 5000 mg/kg bw, and to a group of female rats at 2500 mg/kg bw. No mortalities were recorded at 1250 mg/kg bw, but all animals died at 5000 mg/kg bw. At 2500 mg/kg bw, 3/5 female rats died within 24 hours of dosing. An LD50 between 1250 to 5000 mg/kg bw was reported (CIR, 1998; SCCS, 2009).

Dermal

No data are available for the chemical.

Inhalation

No data are available for the chemical.

Corrosion / Irritation

Skin Irritation

The chemical is not a skin irritant.

In a skin irritation study, four male and two female rabbits were topically treated with 500 mg of an aqueous slurry of the chemical to intact skin for 24 hours under non-occlusive conditions. Observations were recorded at days 1 and 3, post application. No signs of dermal irritation were observed (CIR, 1998; SCCS, 2009).

Eye Irritation

The chemical is slightly irritating to eyes.

The chemical was reported to slightly irritate the eyes when tested in four New Zealand White (NZW) rabbits at 100 mg. Conjunctival redness, mild eyelid swelling and discharge were reported one hour after dosing. All effects were reversible within three days (CIR, 1998; SCCS, 2009).

Sensitisation

Skin Sensitisation

The chemical is not considered to be a skin sensitiser.

In a Buehler dermal sensitisation study, the chemical (0.5 mL in 75 % in corn oil) in 0.5 % aqueous carboxymethylcellulose was applied to the back of 20 Dunkin Hartley guinea pigs, once per week for three weeks (induction phase). Two weeks after the induction phase, a challenge concentration of 0.5 mL of the chemical (75 % in corn oil (0.5 % aqueous carboxymethylcellulose) was applied to the test site. No signs of local irritation or skin sensitisation were observed at 24 or 48 hours after patch removal (CIR, 1998; SCCS, 2009).

In another Buehler assay in guinea pigs, the chemical (10 % in propylene glycol) did not induce any reaction on challenge at 2.5, 5.0 or 10 % (CIR, 2012).

In a local lymph node assay (LLNA) in CBA/CaJ female mice (n=5), the chemical was not a sensitiser at concentrations of 0.25, 0.5, 1.0 or 2.0 % (CIR, 1998; SCCS, 2009).

Repeated Dose Toxicity

Oral

Based on the available data, the chemical is not expected to be harmful to health following repeated oral exposure.

In a 14-day repeated dose toxicity study, Fischer 344 (F344/N) rats and B6C3F1 mice (n=5/sex/dose) were orally administered the chemical at concentrations of 0, 5000, 10000, 20000, 40000 or 80000 ppm in rats (equivalent to 0, 250, 500, 1000, 2000 and 4000 mg/kg bw/day) and 0, 1250, 2500, 5000, 10000 or 20000 ppm in mice (equivalent to 0, 250, 500, 750, 1500 and 3000 mg/kg bw/day). No mortalities were recorded in rats or mice. Significantly decreased final mean body weights and mean body weight changes were observed in male rats at ≥20000 ppm and in female rats at ≥10000 ppm. Significant changes in absolute and relative organ weights were also observed, but these were likely to be secondary to decreases in body weights. In mice, significantly lower final mean body weights and mean body weight changes in females, and lower mean body weights in males

at 20000 ppm were reported. No significant changes in absolute and relative organ weights were observed (CIR, 1998; NTP, 1992; SCCS, 2009).

In a four-week study, groups of SD rats (n=50/sex/dose) were orally administered the chemical at 0, 0.5, 1.0, 1.25 or 1.5 % in the diet (equivalent to 0, 5000, 10000, 12500 and 15000 mg/kg bw/day). No mortalities were recorded. All animals were euthanised at four weeks. Significant decreases in the mean body weights were recorded in males at week 1 (0.5 % dose); weeks 1–3 (1.0 % dose); and weeks 1–4 (1.25 % and 1.5 % doses), and in all treated females at week four. A significant increase in relative liver weight in all treated male groups and at 1.5 % in females, was reported. Males at 1.25 and 1.5 % and all treated females showed a significant decrease in absolute kidney weights (CIR, 1998; SCCS, 2009).

In a 13-week study, groups of F344/N rats and B6C3F1 mice (n=10/sex/dose) were administered the chemical in diet at 0, 2500, 5000, 10000, 20000 or 40000 ppm (rats; equivalent to 150 to 3200 mg/kg bw/day) and 0, 5000, 10000, 20000, 40000 or 80000 ppm (mice; equivalent to 500 to 10600 mg/kg bw/day). No mortality was reported for rats. Final mean body weights of male rats at ≥10000 ppm and female rats at 20000 or 40000 ppm were significantly lower than controls. All male rats at 40000 ppm showed mineralisation of the renal papilla, and all male and female rats at this dose showed thyroid pigmentation. Uterine atrophy was observed in female rats at 20000 and 40000 ppm. Eight male mice and seven female mice in the highest dose group (80000 ppm) and one male in the 40000 ppm group died during treatment. Thyroid pigmentation in male mice at 5000 ppm, and a dose-related increase in the incidence of thyroid pigmentation in female mice from 5000 ppm were reported. Female mice at 40000 and 80000 ppm showed uterine atrophy. Male mice at 40000 and 80000 ppm and female mice at 80000 ppm had lymphoid depletion and atrophy of the spleen. All mice at 40000 and 80000 ppm showed atrophy of the thymus. No observed adverse effect levels (NOAELs) of 5000 ppm (250 mg/kg bw/day) for male rats; 10000 ppm (500 mg/kg bw/day) for female rats and 5000 ppm (750 mg/kg bw/day) for mice were determined (CIR, 1998; NTP, 1992; SCCS, 2009).

In a 6-month feeding study, SD rats (n=10/sex/dose) were orally administered the chemical at concentrations of 0, 0.1, 0.3 or 1.0 % (equivalent to 0, 1000, 3000 and 10000 mg/kg bw/day). Significant reduction in the weight of female rats at 0.1 and 0.3 % was reported. Males in the 0.1 and 0.3 % groups had significantly increased body weights during week 14–27. All treated groups showed a significant increase in the relative weight of the liver, and males in the 1.0 % dose group showed a significant decrease in the absolute and relative testes weights (CIR, 1998; SCCS, 2009).

Dermal

Based on the available data, the chemical is not expected to be harmful to health following repeated dermal exposure.

In a 13-week non-guideline dermal toxicity study, NZW rabbits (n=12/sex/group) were treated with dermal application of 1 mL/kg of the chemical as a 0.4 % solution, twice weekly for 13 weeks. One hour post-application, the test sites were shampooed and dried. Observations were made at 0, 3, 7 and 13 weeks. Significant increases in white blood cells in male rabbits, and in blood urea nitrogen in both the sexes were reported. No other treatment-related signs of toxicity were observed (CIR, 1998; SCCS, 2009).

Inhalation

No data are available for the chemical.

Genotoxicity

Based on the weight of evidence from the available in vitro and in vivo genotoxicity studies, the chemical is not considered to be genotoxic. Some in vitro genotoxicity tests indicated positive results, but all in vivo tests were negative.

In vitro studies

The available in vitro studies gave both positive and negative results for the chemical (CIR, 1998; CIR, 2012; NTP, 1992; SCCS, 2009).

In a bacterial reverse mutation assay conducted according to OECD Test Guideline (TG) 471, the chemical gave positive results in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537, at concentrations up to 5000 μg/plate, with and without

metabolic activation (SCCS, 2009).

In another bacterial reverse mutation assay, the chemical produced concentration dependent increases in the number of revertant colonies with and without activation, (rat and hamster microsomes) at concentrations up to 10000 μg/plate (CIR, 1998; SCCS, 2009).

In a mammalian cell gene mutation assay (OECD TG 476), the chemical was tested in mouse lymphoma cell line L5178Y (thymidine kinase (*tk*) locus) at concentrations up to 1100 μg/mL. The chemical did not induce forward mutations with or without metabolic activation (CIR, 2012; SCCS, 2009).

In an in vitro mammalian chromosome aberration test conducted according to OECD TG 473, the chemical gave positive results for inducing numerical and structural chromosomal aberrations in Chinese hamster ovary (CHO) cells without metabolic activation (CIR, 2012; SCCS, 2009).

In vivo studies

The available in vivo studies had negative results (CIR, 1998; CIR, 2012; NTP, 1992; SCCS, 2009).

In an in vivo mammalian erythrocyte micronucleus test, the chemical was not clastogenic at a single dose of 300 mg/kg bw in mice (n=70/sex) (SCCS, 2009).

In an unscheduled DNA synthesis (UDS) test, the chemical was orally administered in male F344/N rats (n=18) at doses of 0, 100, 250, 500 or 1000 mg/kg bw. No DNA damage was reported in any of the doses tested (SCCS, 2009).

In a dominant lethal study in male SD rats (n=60), the chemical had no dominant lethal effects or infertility effects on male rats at concentrations up to 0.1% (SCCS, 2009).

Carcinogenicity

Based on the available data, the chemical is not expected to be carcinogenic. The International Agency for Research on Cancer (IARC) has classified the chemical as ‘not classifiable as to its carcinogenicity to humans’ (Group 3), based on inadequate evidence for carcinogenicity in humans and in experimental animals.

In a 104-week study in rats, groups of F344/N (n=50/sex/dose) were administered the chemical (>93 % purity) in diet at 0, 2500 or 5000 ppm (males; equivalent to 0, 100 or 200 mg/kg bw/day) and 0, 5000 or 10000 ppm (females; equivalent to 0, 150 and 300 mg/kg bw/day). All animals were euthanised at 110–111 weeks. Survival rate was reported in males as: 29/50 (2500 ppm) and 28/50 (5000 ppm), and females: 31/50 (5000 ppm) and 34/50 (10000 ppm). In males, marginal increases in the adenomas of the pituitary glands [20/49 (2500 ppm) and 28/49 (5000 ppm)]; and a dose-related increase in the incidence of hyperplasia [13/49 (2500 ppm) and 18/49 (5000 ppm)] were observed. In females, no increases in the incidence of pituitary gland adenomas or carcinomas were reported. The US National Toxicology Program (NTP) concluded that there was equivocal evidence of carcinogenic activity of the chemical, based on the increase in pituitary gland adenomas and hyperplasia being observed only in males and not in females (CIR, 1998; CIR, 2012; NTP, 1992; SCCS, 2009).

In a mouse carcinogenicity study, groups of B6C3F1 mice (n=50/sex/dose) were orally administered the chemical (>93 % purity) in diet at 0, 5000 or 10000 ppm. Survival rate was recorded in males as: 29/50 (5000 ppm) and 35/50 (10000 ppm) and in females as: 38/50 (5000 ppm) and 43/50 (10000 ppm). It was reported that there was no evidence of carcinogenicity (CIR, 1998; NTP, 1992; SCCS, 2009).

Reproductive and Developmental Toxicity

The chemical does not show specific reproductive or developmental toxicity. Any reproductive and developmental effects were only observed secondary to maternal toxicity.

In a prenatal developmental study conducted according to OECD TG 414, female Crl:CD (SD) rats (n=40/dose) were administered the chemical by gavage at doses of 0, 50, 200, 500 or 1000 mg/kg bw, once daily on gestation days (GD) 6–20. All treated animals were euthanised on day 21. Animals in all treatment groups had yellow or orange discolouration of the urine, black faeces, and yellow or red fur. Two rats in the 500 mg/kg bw/day group and one in the 1000 mg/kg bw/day group had

yellow skin and yellow perioral colouration. Reduction in the mean absolute and relative feed consumption was reported. At 1000 mg/kg bw/day, brown stained abdominal fur in three rats, and dehydration and brown skin in all rats were observed. All treated animals in this group had reduced mean body weights throughout gestation. At 500 and 1000 mg/kg bw/day, gravid uterine weight and corrected maternal body weights were reduced on gestation day 21. The number of resorptions and percent of resorbed conceptuses per litter were increased. Decreased foetal body weights were observed at 1000 mg/kg bw/day. Whole body oedema (anasarca) was observed in 13 foetuses from five litters. Reduced mean litter sizes and number of live foetuses were also reported. A maternal NOAEL of 50 mg/kg bw/day and a developmental NOAEL of 500 mg/kg bw/day were reported (CIR, 1998; CIR, 2012; NTP, 1992; SCCS, 2009).

In a prenatal developmental study (OECD TG 414), 5 mL of the chemical was orally administered to groups of 100 pregnant female Crl:CD (SD)IGS BR VAF/Plus rats (n=25/group), once daily from GD 6–20 at doses of 0, 50, 150 or 300 mg/kg bw/day. Dams were euthanised on day 21. At 300 mg/kg bw/day, one animal died on day 19. Significant increases in the discolouration of urine, fur, skin and perivaginal area was reported in all treated animals. Significantly reduced body weight gains on days 15 to 18, and significantly reduced corrected maternal body weights were reported. However, foetal body weight was significantly increased. At 150 and 300 mg/kg bw/day, significantly reduced absolute feed consumption on days 15 to 18 were reported. No differences in the number of corpora lutea, implantations or resorptions were observed in all treated rats. No significant differences in the number of live foetuses, dead or resorbed foetuses, or foetal abnormalities in any treated groups were reported. A maternal NOAEL of 50 mg/kg bw/day and a developmental NOAEL of 300 mg/kg bw/day were determined (CIR, 1998; CIR, 2012; SCCS, 2009).

In a teratology study, female SD rats (n=25/group) were administered the chemical in the diet at doses of 0, 0.03 or 0.1 % (equivalent to 0, 300 and 1000 mg/kg bw/day) for a period of six weeks prior to mating. During mating all dams were maintained on basal laboratory chow. All females were euthanised on day 20. No reduction in the body weight gain was seen. The number of pregnancies, pre-implantation and post-implantation loss, and live pups were similar among all groups (SCCS, 2009).

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation is acute oral toxicity.

Public Risk Characterisation

The characterised critical health effect (systemic acute) is not likely to pose an unreasonable risk under the identified uses.

Occupational Risk Characterisation

During product formulation, oral and dermal exposure may occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemicals at lower concentrations could also occur while using formulated products containing the chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic acute health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise oral and dermal exposure are implemented. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

The data available support a new entry to the hazard classification in the HCIS (Safe Work Australia) (see **Recommendation** section).

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Work Health and Safety

The chemical is recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Not Applicable	Harmful if swallowed - Cat. 4 (H302)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing the chemical should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral and dermal exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemicals are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

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