# COSMETIC SAFETY ASSESSMENT REPORT
# No.Zav 007/2018

Product Name

# ORGANIC TOOTHPASTE 0- 36 MONTHS STRABERRY

Product code AB044

## 1.0 Qualitative and Quantitative Composition of Cosmetic Product

| ORGANIC TOOTHPASTE 0- 36 MONTHS STRABERRY | |
|---|---|
| Cod. | AB044 |

**Composition with raw materials and ingredients**

| | Raw material | % | Ingredients | CAS# | % composition | % total | Functions |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| 1. | **PURIFIED WATER** | 54,8100 | Aqua | 7732-18-5 | 100,0000 | 54,81000 | Solvent |
| 2. | **SORBITOL 70%** | 20,0000 | Sorbitol | 50-70-4 | 70,0000 | 14,00000 | Humectant, Plasticiser, Skin conditioning |
| | | | Aqua | 7732-18-5 | 30,0000 | 6,00000 | Solvent |
| 3. | **GLYCERYN** | 18,0000 | Glycerin | 56-81-5 | 100,0000 | 18,00000 | Denaturant, Humectant, Perfuming, Solvent |
| 4. | **XANTAN GUM** | 2,3000 | Xanthan gum | 11138-66-2 | 100,0000 | 2,30000 | Binding, Emulsifying, Emulsion stabilising, Gel forming, Skin conditioning, Surfactant, Viscosity controlling |
| 5. | **SIDENT 9** | 1,5000 | Hydrated silica | 10279-57-9; 1343-98-2; 7631-86-9; 112926-00-8; 63231-67-4 | 100,0000 | 1,50000 | Abrasive, Absorbent, Anticaking, Bulking, Opacifying, Viscosity controlling |
| 6. | **SODIUM SACCHARIN** | 1,1000 | Sodium saccharin | 128-44-9; 6155-57-3 | 100,0000 | 1,10000 | Flavouring, Masking, Oral care |
| 7. | **SENSIVA PA 20** | 0,8000 | Phenethyl alcohol | 60-12-8 | 90,0000 | 0,72000 | Masking |
| | | | Ethylhexylglycerin | 70445-33-9 | 10,0000 | 0,08000 | Skin conditioning |
| 8. | **XYLITOL** | 0,7000 | Xylitol | 87-99-0 | 100,0000 | 0,70000 | Humectant, Skin conditioning |
| 9. | **AROMA STRAWBERRY 70697** | 0,6000 | Aroma | | 100,0000 | 0,60000 | Flavouring |
| | | | Benzyl alcohol | 100-51-6 | 4,9402 | 0,02964 | Masking, Preservative, Solvent |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | Linalool | 78-70-6 | 0,2218 | 0,00133 | Deodorant, Perfuming |
| | | | Geraniol | 106-24-1 | 0,0850 | 0,00051 | Perfuming, Tonic |
| | | | d-Limonene | 5989-27-5 | 0,0054 | 0,00003 | Denaturant, Perfuming, Solvent |
| | | | Benzyl benzoate | 120-51-4 | 0,0040 | 0,00002 | Antimicrobial, Perfuming, Solvent |
| | | | Eugenol | 97-53-0 | 0,0008 | 0,00000 | Denaturant, Perfuming, Tonic |
| 10. | **SYMBIO SOLV XC** | 0,1800 | Caprylyl/capryl wheat bran/straw glycosides | | 50,0000 | 0,09000 | Cleansing, Emulsifying, Emulsion stabilising, Foam boosting, Surfactant |
| | | | Fusel wheat bran/straw glycosides | | 20,0000 | 0,03600 | Antifoaming, Emulsifying, Hydrotrope, Solvent, Surfactant |
| | | | Aqua | 7732-18-5 | 15,0000 | 0,02700 | Solvent |
| | | | Sodium cocoyl glutamate | 68187-32-6 | 5,0000 | 0,00900 | Cleansing, Surfactant |
| | | | Polyglyceryl-5 oleate | 86529-98-8 | 5,0000 | 0,00900 | Emulsifying |
| | | | Glyceryl caprylate | 26402-26-6 | 5,0000 | 0,00900 | Emollient, Emulsifying |
| 11. | **ALOE EXTRACT BIO** | 0,0100 | Glycerin | 56-81-5 | 59,5000 | 0,00595 | Denaturant, Humectant, Perfuming, Solvent |
| | | | Aloe barbadensis leaf extract | 85507-69-3; 94349-62-9 | 29,9000 | 0,00299 | Emollient, Humectant, Oral care, Skin conditioning |
| | | | Aqua | 7732-18-5 | 9,7000 | 0,00097 | Solvent |
| | | | Benzyl alcohol | 100-51-6 | 0,6000 | 0,00006 | Masking, Preservative, Solvent |
| | | | Sodium benzoate | 532-32-1 | 0,1800 | 0,00002 | Anticorrosive, Masking, Preservative |
| | | | Potassium sorbate | 24634-61-5; 590-00-1 | 0,1200 | 0,00001 | Preservative |
| **Tot.** | | **100,000** | | | | | |

## 2.0 PHYSICAL CHEMICAL CHARACTERISTICS and STABILITY

## 2.1 PHYSICAL CHEMICAL CHARACTERISTICS

**Product information**

Physical and chemical characteristics and stability

| Chemical-physical characteristics | | |
|---|---|---|
| General informations | | |
| Tecnical Form | Toothpaste | |
| Appearance | Gel | Visual |
| Colour | Off-white / yellow | Visual |
| Odor | Caracteristic | Olfactory |
| Physical characteristics | | |
| Density | (20°C): 0,970-1,100 g/cm3 | Densimeter |
| Viscosity | (20°C): 22000 - 75000 mPas | Spindle Iv64, RPM 12, Twinsting 62% |
| Chemical characteristics | | |
| pH | 5,7 - 6,5 (50 g/l H2O) | pH-Metro |
| Centrifugal stability | Stable | 3000 RPM for 1 hour |
| Microbiological characteristics | | |
| Microbiological specifications | | |
| Bacteria | <= 100 | USP Pharmacopea |
| Yeasts and molds | <= 10 | USP Pharmacopea |
| Staphilococcus Aureus | Absent | USP Pharmacopea |
| Candida Albicans | Absent | USP Pharmacopea |
| Pseudomonas Aeruginosa | Absent | USP Pharmacopea |
| | | |

## 2.2 STABILITY

## ACCELERATED STABILITY TEST on ORGANIC TOOTHPASTE 0-36 MONTH STRAWBERRY RESULTS SUMMARIES

Start Analysis 15/12/2016
End Analysis 15/02/2017

| Conservation | TEST | METHOD | SPECIFICATION | Check points (months) and Analytical Results | | |
|---|---|---|---|---|---|---|
| | | | | T0 | T2 | T3 |
| 40°C/ 75 % RH | Appearance | IO PIT 005 | Gel with characteristic odor | conforms | conforms | Conforms |
| | pH | Ph.Eur 8.0 2.2.3 | 5,7 - 6,5 | Conforms | Conforms | Conforms |
| | TYMC | Ph.Eur. 2.6.12 | < 10 UFC/ml | Conforms | Conforms | Conforms |
| | TAMC | Ph.Eur. 2.6.12 | < 100 UFC/ml | Conforms | Conforms | Conforms |
| 4-5°C/ 75 % RH | Appearance | IO PIT 005 | Gel with characteristic odor | conforms | conforms | Conforms |
| | pH | Ph.Eur 8.0 2.2.3 | 5,7 - 6,5 | Conforms | Conforms | Conforms |
| | TYMC | Ph.Eur. 2.6.12 | < 10 UFC/ml | Conforms | Conforms | Conforms |
| | TAMC | Ph.Eur. 2.6.12 | < 100 UFC/ml | Conforms | Conforms | Conforms |
| Room Temperature | Appearance | IO PIT 005 | Gel with characteristic odor | conforms | conforms | Conforms |
| | pH | Ph.Eur 8.0 2.2.3 | 5,7 - 6,5 | Conforms | Conforms | Conforms |
| | TYMC | Ph.Eur. 2.6.12 | < 10 UFC/ml | Conforms | Conforms | Conforms |
| | TAMC | Ph.Eur. 2.6.12 | < 100 UFC/ml | Conforms | Conforms | Conforms |
| Room Temperature | Efficacy of antimicrobial preservation | Ph.Eur. 8.0 5.1.3 | 2 Log10 reduction after 30 hours | Conforms | Conforms | Conforms |
| | Patch test on sensitive and reactive skin | Guidelines for Assessment of Skin Tolerance of Potentially Irritant Cosmetic Ingredients, 199 | Non Irritating | Conforms | | |

Date: 15/02/17
Study Monitor: Marvel 80 snc

**3.0 Microbiological Purity**

Ingredients microbiological purity raise no concerns. Microbiological quality control is not necessary for low microbiological risk substances. Furthermore, justified cases, materials fulfil the microbiological criteria for cosmetic ingredients, both qualitatively and quantitatively.

**Attached challenge test method ISO 11930: 2012 COD. LAB 1801255**

**4.0 Information for Packaging Material**

The product is packaged in 50 ml Micro Round airless in high density PE with high density PE pump.
The plastic PE that makes up the bottle and the pump are compliant

• D.M. of 21/03/73 published on the G.U. of 20/04/1973 with D.M. 220 of 26/04/1993 and subsequent updates (for materials intended to come into contact with food and drugs);

• Directive 94/62 / EEC, implemented by D.L. N ° 152/2006 dated 03/04/2006 Art. 226 C 3 on the content of heavy metals.

• Directive 2023/2006 / EC, Regulation
1935/2004 / CE Regulation 10/2011 UE (Materials and objects intended to come into contact with food products);

• Regulation1907 / 2006CE (Reach- SVHC);

• Regulation282 / 2008 / EU (Recycle material);

• Directive 2007/19 / EC (Fhathalates)

- Substances Bisphenol-A and Nitrites: it is certified that during production it is not used or intentionally incorporated;

- Recycle it: the material is recyclable. The prevailing operation is the mechanical recovery of the material. The components of the packaging are, for the most part, separable to allow separate collection.

**5.0 Intended use and reasonably foreseeable**

| Information on the use of the product | |
|---|---|
| Proper use of the product | |
| Description of the normal use | The teeth of kids are particularly sensible to dental caries since the enamel is not strong as adult's enamel. Furthermore, the dental caries in kids' teeth have a direct impact on permanent teeth that, in turn, are weakened. |
| Indications | It's gentle formulation respects the gums and dental enamel. It contains an amount of xylitol which is slightly lower than the amount contained in our baby toothpaste in order to be less sweet and more suitable to their age. It protects the dental enamel. Xylitol is a not cariogenic substance, it means that it is not fermented by mouth acids and consequently it prevents the enamel corrosion. |
| Mode of use | Brush the teeth twice a day. |
| Area of application and surface involved | teeth |
| Quantity, duration and normal frequency of application | 1 - 2 times a day |
| Other product usage | |
| Assumptions about a misuse | Non-dangerous product: Do not use if you have known allergies to any component contained. |
| Assessments of the consequences of any misuse | Non-dangerous product: Keep it away from children. It is advisable to keep it in room temperature at closed It is. |

**6.0 COSMETIC PRODUCT EXPOSURE**

| | |
|---|---|
| Formulation type: | Toothpaste (oral hygiene products) |
| Product category: | Toothpaste for bay |
| Main product properties: | cleaning and care of teeth |
| Target group: general population | 1 years old |
| Normal amount of application in grams | 0,5 gr (estimated for children's teeth) |
| Contact time | Rinse after application. |
| Retention | 5% |

**7.0 RAW MATERIAL EXPOSURE IN FORMULA**

7.1 PURIFIED WATER

INCI NAME aqua

CAS N. 7732-18-1

| TEST | METHOD | Lower Lim. - Upper Lim. | u.m. |
|---|---|---|---|
| Apperance | | Clear liquid colourles odourles | |
| Chloride/Nitrate | | Conform Ph. Eur. | |
| Calcium and Magnesium | | < 0.2 | ppm |
| Sulphate | | Conform Ph. Eur. | |
| Ammonium | | Confrom Ph. Eur. | |
| Residue on evaporation | EP | < 0.2 | ppm |
| Heavy metals | | < 0.001 | % |
| Acidity and alcalinity | EP | < 0.1 | ppm |
| Oxydable substances | | Confom Ph. Eur. | |
| Conducibility | | Conform Ph. Eur. | |
| Total viable count | | <4,3 | microS.c |
| | | <= 100 | cfu/ml |

7.2 GLYCERIN

INCI NAME: Glycerin

CAS N.. 56-81-5 EINECS / ELINCS 200-289-5

FORMULA C3 H8 O3

PESO MOLECOLARE 92,0

| SPECIFICATION | METHOD | Lower Lim. - Upper Lim. | u.m. |
|---|---|---|---|
| Identification A: Refractive | Ph.Eur. | Conform | |
| indetification B: IR | Ph.Eur. | Conform | |
| Heavy metals | Ph.Eur. | <=5 | ppm |
| Chloride | Ph.Eur. | <=10 | ml HCl 0.1 |
| Impurity A- | Ph.Eur. | <=0,10 | % |
| Other impurity- | Ph.Eur. | <=0,10 | % |
| Total impurity | Ph.Eur. | <=0,50 | % |
| Assay (EP) | Ph.Eur. | 98,00 - 101,00 | % |
| Alogenad Compund | | <=35 | ppm |

LD 50 12600 mg/Kg

NOAEL 2000 mg/Kg/die

Information on toxicological effects: Eye irritation (rabb): not irritation. Skin irrtation (rabb): not irritation. sensitization (patch-test, man): negative. Mutagenicity (Ames test): negative. (From MSDS)

7.3 XANTAN GUM

INCI NAME Xanthan gum

CAS N. 11138-66-2

EINECS / ELINCS 234-394-2

| SPECIFICATION | METHOD | Lower Lim. - Upper Lim. | Um |
|---|---|---|---|
| Identificazion IR | FT-IR | Conform | |
| Loss on dryng | Ph.Eur. | max. 15 | % |
| Ash | Ph.Eur. | max. 16 | % |
| Lead | Ph.Eur. | max. 2 | ppm |
| Assay | Ph.Eur. | 91.0 -108.0 | % |
| Total viable count | Ph.Eur | Conform | |
| Yeast and mould | | Conform | |
| Pathogens | | Absen | |

LD 50 5000 mg/Kg

NOAEL 500 mg/Kg/die

Information on toxicological effects: Eye irritation (rabb): not irritation. Skin irrtation (rabb): not irritation. sensitization (patch-test, man): negative. Mutagenicity (Ames test): negative. (From MSDS)

7.4 SENSIVA PA 20

INCI NAME: Phenethyl Alcohol & Ethylhexylglycerin

Phenethyl Alcohol Cas N. 60-12-8 EINECS 200-456-2

Ethylhexylglycerin Cas N. 70445-33-9 EINECS 408-080-2

| Physico-chemical properties | |
|---|---|
| Colour | nearly colourless - light yellow |
| Form | liquid |
| Odour | characteristic |
| Density (20 °C) | 1.006 - 1.020 g/ml |
| Refractive index (20 °C) | 1.517 - 1.531 |

LD 50 2000 mg/Kg

Information on toxicological effects: Eye irritation (rabb): not irritation. Skin irrtation (rabb): not irritation. sensitization (patch-test, man): negative. Mutagenicity (Ames test): negative. (From MSDS)

7.5 SODIUM SACCARIN

INCI NAME SODIUM SACCARIN

CAS N. 6155-57-3

EINECS / ELINCS 204-886-1

| SPECIFICATION | METHOD | Lower Lim. - Upper Lim. | U.M. |
|---|---|---|---|
| Aspect | | White or almost white, crystalline powder or colourless crystals, efflorescent in dry air. | |
| Solubility | | Freely soluble in water, slightly soluble in alcohol, practically insoluble in ether | |
| Melting point | | 226,0 - 230,0 | ° C |
| Water | | <=15,00 | % |
| Arsenic | | <=3,0 | ppm |
| Selenium | | <=30 | ppm |
| Lead | | <=1,00 | ppm |
| Assay | | 99,00 - 101,00 | % |

LD 50 14200 mg/Kg

NOAEL 500 mg/Kg/die

Information on toxicological effects: Eye irritation (rabb): not irritation. Skin irrtation (rabb): not irritation. sensitization (patch-test, man): negative. Mutagenicity (Ames test): negative. (From MSDS)

7.6 AROMA STRAWBERRY 70697

INCI NAME: AROMA

CAS N. //

EINECS N. //

| | |
|---|---|
| Appearance | Colourless to light yellow |
| Odour | Characteristic |
| Solubility | 1,025-1,050 g/ml |
| Water Solubility | soluble |
| Refractive index | 1.500-1.515 |

1 Aromatic composition (Regulation 1334/2008 / EC) :Aroma

2 Limited active substances Reg. 1334/2008 / EC, Annex III): nobody

3 Limited flavoring agents (D.M. n. 107/1992 annex VI / VII): nobody

All flavoring substances or aromatic preparations contained in this product are classified GRAS (generaly Recognized as safe) from the FDA and / or FEMA.

ATE(mix) oral = 12.386,8 mg/kg
ATE(mix) dermal = 84.615,4 mg/kg
ATE(mix) inhal = 222,7 mg/l/4 h

ACUTE RISKS / SYMPTOMS

INHALATION Cough. Vertigo. Headache.

CUTE Redness.

EYES Redness.

INGESTION Abdominal pain. Diarrhea. Drowsiness. Nausea. Vomiting.

LD50 Oral (rat) (mg / kg body weight) = 3100

LD50 Dermal (rat or rabbit) (mg / kg body weight) = 200

7.7 ORGANIC ALOE EXTRACT 1:2

INCI NAME : Aloe Barbadensis Leaf Extract, Glycerin, Aqua

CAS N. 85507-69-3 /94349-62-9, 56-81-5

EINECS N. 287-390-8 /305-181-2, 200-289-5

| | |
|---|---|
| Density (20° C) | 1, 150 ± 1,170 |
| pH | 4,0 ± 5, 5 |
| DRY RESIDUE | 1.5 ± 2.5 % |
| APPEARANCE | Clear liquid or light. Opalescent |
| COLOUR | From pale yellow to light pink |
| ODOUR | Mild |
| REFRACTIVE INDEX | 1,400 – 1,420 |
| TOTAL VIABLE COUNT | < 100 UFC/ ml |

LD 50 > 5000 mg/Kg

Information on toxicological effects: Eye irritation (rabb): not irritation. Skin irrtation (rabb): not irritation. sensitization (patch-test, man): negative. Mutagenicity (Ames test): negative. (From MSDS)

7.8 SYMBIO SOLV XC

INCI NAME Caprylyl/Capryl Wheat Bran/Straw Glycosides; Aqua; Fusel Wheat Bran/Straw Glycosides; Polyglyceryl-5 Oleate; Sodium Cocoyl Glutamate; Glyceryl Caprylate

CAS N. 1235391-18-0; 161074-97-1; 7732-18-5; 1235390-87-0; 9007-48-1; 68187-32-6; 26402-26-6

EINECS N. 484-390-1; 231-791-2; 484-370-2; Polymer; 269-087-2; 247-668-1

| | |
|---|---|
| Assay | 65 - 75% |
| Water | 25 - 35% |
| Aditive | None |
| Impurities | |
| 1,4-Dioxan | not to be expected |
| Ethylenoxide | not to be expected |
| Residual Solvent | not to be expected |
| Monomers | not to be expected |
| Free Amines | not to be expected |
| Nitrosamines | not to be expected |
| Heavy Metals | < 10 ppm |
| Pesticides | not known |
| Polyaromatic Hydrocarbons | not known |
| Other Impurities | not known |
| Total Viable Count | < 100 cfu/g |

LD 50 > 2000 mg/Kg

Information on toxicological effects: Eye irritation (rabb): not irritation. Skin irrtation (rabb): not irritation. sensitization (patch-test, man): negative. Mutagenicity (Ames test): negative. (From MSDS)

7.9 SIDENT 9

INCI NAME Hydrated silica

CAS N. 112926-00-8, 7631-86-9

EINECS N. 215-683-2; 231-545-4

| SPECIFICATION | METHOD | Lower Lim. - Upper Lim. | U.M. |
|---|---|---|---|
| Appearance | | White powder | |
| Loss on dryng | ISO 787-2 | <= 7 | % |
| pH | ISO 787-9 | 6,2 – 7,6 | |
| Particular Size | ISO 13330 | 7 – 11 | micron |
| Surface BET | ISO 92700 | 30 – 60 | m2/g |

LD 50 > 10000 mg/Kg

NOAEL 8980 mg/Kg/die

Information on toxicological effects: Eye irritation (rabb): not irritation. Skin irrtation (rabb): not irritation. sensitization (patch-test, man): negative. Mutagenicity (Ames test): negative. (From MSDS)

7.10 SORBITOL 70%

INCI NAME Sorbitol, Aqua

CAS N. 50-70-4, 7732-18-5

EINECS N. 200-061-5, 231-791-2

| SPECIFICATION | METHOD | Lower Lim. - Upper Lim. | U.M. |
|---|---|---|---|
| Dry Substances | On d.b. | 69.8 – 70.9 | % |
| Mannitol | On d.b. | 2.0 – 7.0 | % |
| Reducing Sugar | Ph.Eur. | <= 0.2 | % |
| Lead | Ph.Eur. | <= 0.5 | Ppm |
| Nickel | Ph.Eur. | <= 1 | ppm |

LD 50 > 5000 mg/Kg

NOAEL 15400 mg/Kg/die

Information on toxicological effects: Eye irritation (rabb): not irritation. Skin irrtation (rabb): not irritation. sensitization (patch-test, man): negative. Mutagenicity (Ames test): negative. (From MSDS)

**8.0 Authorized substances with Reg.1223/2009**

**Sodium Benzoate -** annex V, no 1: benzoic acid and its sodium salt are preservatives allowed for use with max. concentration in ready for use preparation:
o rinse-off products, except oral products - 2,5%(asacid)
o oral products -1,7% (acid)
o leave-on product - 0,5%(acid)
**in formula used: 0,00002%**

**Potassium Sorbate -** annex V, no 4: preservative - max. concentration in ready for use preparation: 0,6%(as acid)

**in formula used: 0,00001%**

**Benzyl Alcohol** annex V, no 34: preservative - max. concentration in ready for use preparation: 1.0%

**in formula used: 0,00306%**

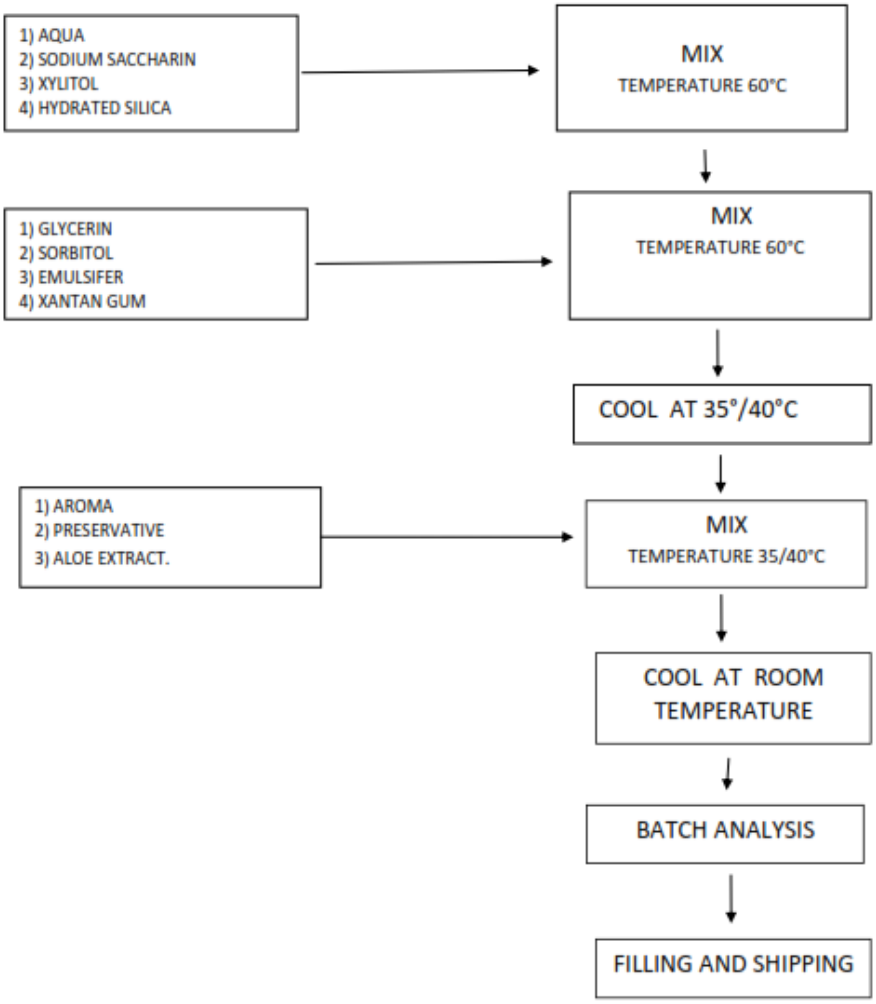
## 9.0 METHOD OF PRODUCTION

| production method | |
|---|---|
| production method | |
| Description of operations | The necessary equipment is prepared: stainless steel turboemulsor (with opening for top loading, discharge cock, rotating shaft), stainless steel fuser, containers (plastic or glass, depending on quantities) for picking and dosage of the ingredients, drum for the storage of the semi-finished product, all previously sanitized. |
| ... | The ingredients are measured in identified containers and inserted into the turboemulsifier according to the following method: |
| ... | |
| ... | 1) AQUA (60°C)<br>2) SODIUM SACCHARIN<br>3) XYLITOL<br>4) HYDRATED SILICA |
| ... | Mix for 10 minutes |
| | |
| ... | After 10 minutes add |
| ... | 1) GLYCERIN<br>2) SORBITOL<br>3) EMULSIFER<br>4) XANTAN GUM |
| ... | Mix for 60 minutes |
| ... | Cool at 35/40°C an add. |
| ... | 1) AROMA<br>2) PRESERVATIVE<br>3) ALOE EXTRACT. |
| ... | Mix for 30 minutes |
| ... | Cool at Room Temperature |
| ... | |
| ... | Batch Analysis |
| ... | Filling and Shipping |
| ... | |
| ... | |

**9.1 FLOW CHARD PRODUCTION**

## 033-000-126 TOOTHPASTE BABY STRAWBERRY

## FLOW CHART



## 10.0 EXPOSURE TO COSMETIC COMPONENT COMPONENTS

| Final Evaluation on Product Safety | |
|---|---|
| Considerations on the ingredients | |
| Considerations related to the toxicological profile of the ingredients | The quality and the toxicological/irritation profile of the raw materials used have been evaluated through the technical documentation provided by the suppliers and the data available in literature.<br>The exposure level of the raw materials that are part of the formulation has been carefully evaluated in order to guarantee that the finished product has not undesired effects.<br>These data were taken from the documentation provided by the suppliers, safety data sheets and toxicological information of raw materials.<br><br>***IN ATTACHMENT OCCLUSIVE PATCH TEST PERFORMED BY UNIVERSITY OF FERRARA*** |
| Considerations on product safety | |
| Considerations on product safety | The margin of safety (MoS) it is calculated as: -<br>MoS = NOAEL/ SED<br>where MoS - margin of safety<br>NOAEL - "No Observed Adverse Effect Level"<br>SED= Systemic Exposure Dose<br>**Based on the obtained results, the systemic absorption dose of product's components (SED) during the regular use of the product is very low. The product formulation does not contain any ingredients with carcinogenic, mutagenic and teratogenic effects (CMR). The MoS values of the ingredients, calculated using the NOAEL values, is higher than 230.**<br>**Therefore, the use of the product is safe and suitable for consumer from 0 to 6 months of age.**<br>Table margin of security:<br>230: at birth<br>180: Up to 6 months<br>160: Up to 12 months<br>150: until 5 years<br>130: until 10 years,<br>were more than 230 or were ingredients known for their safety<br>It is therefore unlikely that there will be no systemic effects for the product in object |
| ... | Possible tests and experiments carried out in order to test the safety of the product.<br>No experiments have been carried out since the product used in the recommended doses, also considering the low retention index per COLIPA directives and the almost immediate rinsing of product after its application, can be considered safe.<br>See the exposure tables. |
| Possible considerations related to the use of the product on children under the age of three | Even if the product is intended for children under 3 years of age, it is to be considered safe.<br>In any case, the raw materials used in the preparation and the production methods guarantee the safety of the product |
| Possible considerations related to the use of the product for external intimate hygiene | The product is not intended for external intimate hygiene |

## 10 Exposure levels of the ingredients

| | |
|---|---|
| Cosmetic category | Oral hygiene products |
| type of product | Toothpaste children |
| Normal amount of application in grams | 0,5 |
| Retention % | 5 |

| | Ingredients | % In the product | Absorbiment % | Absorbiment in mg/Kg/die (SED) (60 Kg) | Assorbiment in mg/Kg/die (SED) for baby (10 Kg) | LD50 | NOAEL/LOAEL | Safety margin MoS (NOAEL/SED 60 Kg) | Safety margin MoS (NOAEL/SED 10 Kg) |
|---|---|---|---|---|---|---|---|---|---|
| 1. | Aqua | 60,83797 | 100,00 | 0,50698 | 3,04190 | 100.000 mg/Kg | 100.000,000 mg/Kg/die | 197.245,20 | 32.874,21 |
| 2. | Glycerin | 18,00595 | 100,00 | 0,15005 | 0,90030 | 12.060 mg/Kg | 2.000,000 mg/Kg/die | 13.328,93 | 2.221,49 |
| 3. | Sorbitol | 14,00000 | 100,00 | 0,11667 | 0,70000 | 17.800 mg/Kg | 15.400,000 mg/Kg/die | 132.000,00 | 22.000,00 |
| 4. | Xanthan gum | 2,30000 | 100,00 | 0,01917 | 0,11500 | 5.000 mg/Kg | 500,000 mg/Kg/die | 26.086,96 | 4.347,83 |
| 5. | Hydrated silica | 1,50000 | 100,00 | 0,01250 | 0,07500 | 5.620 mg/Kg | 8.980,000 mg/Kg/die | 718.400,00 | 119.733,30 |
| 6. | Sodium saccharin | 1,10000 | 100,00 | 0,00917 | 0,05500 | 14.200 mg/Kg | 500,000 mg/Kg/die | 54.545,46 | 9.090,91 |
| | ^ NOAEL Note: EUROPEAN COMMISSION<br>DIRECTORATE-GENERAL III INDUSTRY<br>Industrial affairs III: Consumer goods industries<br>Foodstuffs - Legislation and scientific and technical aspects<br>ANNEX III TO DOCUMENT III/5157/97<br>SCIENTIFIC COMMITTEE FOR FOOD CS/ADD/EDUL/148-FINAL<br>February 1997 | | | | | | | | |
| 7. | Phenethyl alcohol | 0,72000 | 100,00 | 0,00600 | 0,03600 | 5.000 mg/Kg | 120,000 mg/Kg/die | 20.000,00 | 3.333,33 |
| | ^ NOAEL Note: The EFSA Journal (2009) 930, 1-53 | | | | | | | | |
| 8. | Xylitol | 0,70000 | 100,00 | 0,00583 | 0,03500 | 5.000 mg/Kg | 2.000,000 mg/Kg/die | 342.857,20 | 57.142,86 |
| | ^ NOAEL Note: https://echa.europa.eu/registration-dossier/-/registered-dossier/13631/1 | | | | | | | | |
| 9. | Aroma | 0,60000 | 100,00 | 0,00500 | 0,03000 | - | - | - | - |
| 10. | Caprylyl/capryl wheat bran/straw glycosides | 0,09000 | 100,00 | 0,00075 | 0,00450 | 4.000 mg/Kg | 75,000 mg/Kg/die | 100.000,00 | 16.666,67 |
| | ^ NOAEL Note: Regulatory Toxicology and Pharmacology<br>Acute and repeated doses (28 days) oral toxicity study of Vicenin-1, a-favonoid glycoside isolated from fenugreek seeds in laboratory mice<br>Amit D. Kandhare<br>, Subhash L. Bodhankar a, *, V. Mohan b , Prasad A. Thakurdesai Department of Pharmacology, Poona College of Pharmacy, Bharati Vidyapeeth Deemed University, Erandwane, Paud Road, Pune, 411 038, India<br>Indus Biotech Private Limited, 1, Rahul Residency, Off Salunke Vihar Road, Kondhwa, Pune, 411 048, India | | | | | | | | |
| 11. | Ethylhexylglycerin | 0,08000 | 100,00 | 0,00067 | 0,00400 | 2.000 mg/Kg | 50,000 mg/Kg/die | 75.000,00 | 12.500,00 |
| 12. | Fusel wheat bran/straw glycosides | 0,03600 | 100,00 | 0,00030 | 0,00180 | 4.000 mg/Kg | 75,000 mg/Kg/die | 250.000,00 | 41.666,67 |
| | ^ NOAEL Note: Regulatory Toxicology and Pharmacology<br>Acute and repeated doses (28 days) oral toxicity study of Vicenin-1, a-favonoid glycoside isolated from fenugreek seeds in laboratory mice | | | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Amit D. Kandhare<br>, Subhash L. Bodhankar a, *, V. Mohan b , Prasad A. Thakurdesai Department of Pharmacology, Poona College of Pharmacy, Bharati Vidyapeeth Deemed University, Erandwane, Paud Road, Pune, 411 038, India<br>Indus Biotech Private Limited, 1, Rahul Residency, Off Salunke Vihar Road, Kondhwa, Pune, 411 048, India | | | | | | | | |
| 13. | Glyceryl caprylate | 0,00900 | 100,00 | 0,00008 | 0,00045 | 5.000 mg/Kg | 1.000,000 mg/Kg/die | 13.333.330,00 | 2.222.222,00 |
| | ^ NOAEL Note: Amended Safety Assessment of Monoglyceryl Monoesters as Used in Cosmetics CIR (Cosmetic index Rewiew) | | | | | | | | |
| 14. | Polyglyceryl-5 oleate | 0,00900 | 100,00 | 0,00008 | 0,00045 | 5.000 mg/Kg | 2.000,000 mg/Kg/die | 26.666.670,00 | 4.444.445,00 |
| | ^ NOAEL Note: Polyglyceryl Fatty Acid Esters<br>The Panel issued a tentative report for public comment with the conclusion that the following 274 polyglyceryl fatty acid esters are safe as used in cosmetics when formulated to be non-irritating. Cosmetic Ingredient Review Expert Panel<br>138th Meeting (March 31-April 1, 2016) - Findings | | | | | | | | |
| 15. | Sodium cocoyl glutamate | 0,00900 | 100,00 | 0,00008 | 0,00045 | 6.000 mg/Kg | 3.200,000 mg/Kg/die | 42.666.660,00 | 7.111.111,00 |
| | ^ NOAEL Note: Safety Assessment of Amino Acid Alkyl Amides as Used in Cosmetics (Cosmetic Ingredient Review) | | | | | | | | |
| 16. | Benzyl alcohol | 0,00306 | 100,00 | 0,00003 | 0,00015 | 1.620 mg/Kg | 400,000 mg/Kg/die | 15.686.280,00 | 2.614.379,00 |
| | ^ NOAEL Note: EUROPEAN COMMISSION<br>HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL<br>Directorate C - Scientific Opinions<br>C2 - Management of scientific committees II; scientific co-operation and networks<br>Scientific Committee on Food SCF/CS/ADD/FLAV/78 Final | | | | | | | | |
| 17. | Aloe barbadensis leaf extract | 0,00299 | 100,00 | 0,00002 | 0,00015 | 5.000 mg/Kg | 2.000,000 mg/Kg/die | 80.267.560,00 | 13.377.930,00 |
| | ^ NOAEL Note: Safety studies conducted o a , George A. Burdock<br>Eunju Shin b , Seunghyun Kim , Kenneth N. Jones<br>, Ray A. Matulka Burdock Group, 801 N. Orange Ave., Suite 710, Orlando, FL 32801, USA<br>Univera, Inc., ECONET Center 302-4, Sungsu-dong 2 Ga, Sungdong-gu, Seoul 133-120, Republic of Korea<br>ECONET CTO Of?ce, ECONET Center 302-4, Sungsu-dong 2 Ga, Sungdong-gu, Seoul 133-120, Republic of Korea<br>Aloecorp, Inc., 100 Lee Lane, Lyford, TX 78569, USA | | | | | | | | |
| 18. | Geraniol | 0,00007 | 100,00 | 0,00001 | 0,00000 | 2.000 mg/Kg | 558,000 mg/Kg/die | 956.571.400,00 | 159.428.600,00 |
| 19. | Citronellol | 0,00006 | 100,00 | 0,00001 | 0,00000 | 3.450 mg/Kg | 300,000 mg/Kg/die | 600.000.000,00 | 100.000.000,00 |
| 20. | Sodium benzoate | 0,00002 | 100,00 | 0,00001 | 0,00000 | 2.000 mg/Kg | 500,000 mg/Kg/die | 3.000.000.000,00 | 500.000.000,00 |
| | ^ NOAEL Note: EUROPEAN COMMISSION<br>HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL<br>Directorate C - Scientific Opinions<br>C2 - Management of scientific committees II; scientific co-operation and networks Scientific Committee on Food SCF/CS/ADD/CONS/48 Final 17 Sept 2002 | | | | | | | | |
| 21. | Potassium sorbate | 0,00001 | 100,00 | 0,00001 | 0,00000 | 4.920 mg/Kg | 2.500,000 mg/Kg/die | 30.000.000.000,00 | 5.000.000.000,00 |
| | ^ NOAEL Note: Joint FAO/WHO Expert Committee on Food Additives | | | | | | | | |
| 22. | Linalool | 0,00001 | 100,00 | 0,00001 | 0,00000 | 3.000 mg/Kg | 100,000 mg/Kg/die | 1.200.000.000,00 | 200.000.000,00 |
| 23. | Citral | 0,00000 | 100,00 | 0,00000 | 0,00000 | 1.000 mg/Kg | 200,000 mg/Kg/die | | |

## SECTION-B: SECURITY EVALUATION FINAL REPORT

| | |
|---|---|
| Final Assessment | After reviewing the physical, safety and toxicological information of the raw materials and the product itself, the examination of the formula, the expected exposure to the consumer, the warnings and the method of use, we believe that, in the current state of knowledge, the product placed on the market should not cause harms to human health if applied under normal or reasonably foreseeable conditions of use.<br>In the event that significant cases of adverse reactions on the customers caused by this product are reported (eg an abnormal number of side effects), the undersigned must be informed and a re-evaluation must be considered. |
| Warnings and instructions for use on the label | |
| Special warnings for the use of the product | There are not particular warnings to the use of the product. |
| Special instructions for the use of the product | There are not particular warnings to the use of the product. |
| Final Motivation | |
| Final Motivation and Reasoning on the security | The product is considered safe since the quality of the raw materials used and their level of use has been carefully assessed. The working and sanitizing methods comply with the cosmetic GMP UNI EN ISO 22716. |
| **Credentials of the safety assessor** | |
| Name and surname: | Nicolò Gatti |
| Address of residence: | Via Gramsci N. 45 - 26865 San Rocco al Porto (LO) -Italy- |
| Telephone number: | +393406846569 |
| Other contact details: | gatti_nicolo@virgilio.it |
| Employment relationship with the responsible person: | Occasional consultancy |
| Studies and specific experiences: | Master degree in Chemistry and Pharmaceutical Technologies<br>Specific training and experiences: Experimental thesis title: Characterization of the molecular mechanism of action of drugs associated to allergic reactions, Supervisor: Prof. Emanuela Corsini<br>-Pharmaceutical technologies and legislation<br>-Pharmacology<br>-Pharmaceutical chemistry<br>-Toxicology<br>-Organic chemistry |
| Publications: | Toxicology in Vitro<br>Title: OPTIMIZATION OF THE THP-1 ACTIVATION ASSAY TO DETECT PHARMACEUTICALS WITH POTENTIAL TO CAUSE IMMUNE MEDIATED DRUG REACTIONS<br>Authors: Daniele Corti; Valentina Galbiati, Pharmacy; Nicolò Gatti; Marina Marinovich; Corrado L Galli; Emanuela Corsini<br>Article Type: Research Paper |
| ... | |
| - Approval of the safety assessment - | |
| Concluding Declaration on the safety of the cosmetic product: | The undersigned Dr. Nicolò Gatti has carefully verified and evaluated the information received on the documentation provided to me by Zavagli S.a.s., which includes the chemical, physical, safety and toxicological characteristics of the raw materials used in the production of the following cosmetic product.<br>After a careful analysis and evaluation of the formulation of the cosmetic in question, production steps included, and the evaluation of the exposure foreseen by the regulation 1223/2009 for the final consumer and his use I believe that, in the current state of knowledge acquired, the following product placed on the market is to be considered safe and should not cause harm to human health if applied under normal or reasonably foreseeable conditions of use. |

| | |
|---|---|
| | In the event that significant cases of adverse reactions on the customers caused by this product are reported (eg an abnormal number of side effects), the undersigned must be informed and a re-evaluation must be considered. |
| … | The following evaluation is based on the information acquired from the documentation provided to me by Zavagli S.a.s for the drafting of the following documentation.<br>We decline all liability from the wrong information received.<br>The author of the assessment does not assume any risk for the updating, accuracy, completeness or quality of the information made available by Zavagli S.a.s. |
| | **The oral exposure values of the non-organic ingredients contained in the toothpaste are safe and have no negative effects if ingested** |
| Signature |  <br>Dr. Gatti Nicolò |

**N.B. attached**

**1) Patch test**

**2) Challenge test**

**3) GMP Certification**

**CENTRO DI COSMETOLOGIA**
**UNIVERSITA' DI FERRARA**
**Direttore: prof. Michele Simonato**

**Via Fossato di Mortara 17/19 – 44122 Ferrara**
**Tel.: 0532.455.295 – Fax: 0532.455.344**
**sito: www.unife.it/centro/cosmetologia**
**e-mail: cosm@unife.it**

**PATCH TEST OCCLUSIVO** ***(Occlusive Patch Test / Patch Test Occlusif)***

**RISULTATI** ***/RESULTS/RESULTATS*** (Serie: 415/ 54)

Il campione è contraddistinto dalla sigla:
*The sample carries the name / l'èchantillon se distingue par le sigle:*

# ZAVA.GLI S.a.s. di Gollinucci Gianni & C.

**Via Piave, 374 47023 Cesena (FC)**

**(Committente: MARVEL 80 s.r.l.)**

## Codice Articolo: Z033K11010 Dentifricio BIMBI FRAGOLA

Lotto: **FR001**

Il test è stato eseguito utilizzando il prodotto:
*The test was performed by using the product / le test a été executé utilisant le produit:*

**tal quale/** ***as it is/ tel quel*** **(X)** **diluito** ***/diluted/ dilué*** **1:10** **( )**

Ulteriori informazioni gentilmente fornite dal cliente:
*Further information kindly provided by the costumer:*
*Ulterieures informations gentilement fournies par le client:*

_dichiarazione che il prodotto cosmetico sottoposto a test non contiene alcuna sostanza di cui è proibito l'uso in prodotti cosmetici e di igiene corporale (legislazione CEE), che gli agenti conservanti introdotti nella formula del prodotto figurano nella lista positiva approvata dalla CEE, che essi sono utilizzati ad una concentrazione conforme all'uso previsto da questa legge

*_declaration that the tested cosmetic product does not contain any substance which is forbidden by the EEC legislation as far as the use of cosmetic and personal hygiene products is concerned, that the preservatives in the formula are in the list of the accepted components approved by the EEC and are used in a concentration provided for by the law*

*_déclaration que les produit cosmetique soumis à test ne contient aucune substance don't est interdit l'usage dans les produits cosmetiques et dans l'hygiéne corporelle (legislation CEE), que les élements conservants introduit dans la formule du produit figurent sur la liste positive approuvée par la CEE, que ceux-ci sont utilisés à une concentration conforme aux disposition de la loi*

**ZAVA.GLI S.a.s. di Gollinucci Gianni & C.**

(Committente: MARVEL 80 s.r.l.)

**Codice Articolo: Z033K11010 Dentifricio BIMBI FRAGOLA**

Lotto: **FR001**

**Tabella 3 (Table 3/Tableau 3)**

| Volont. n° | Eta' *(Age)* | Sesso *(Sex)* | ERITEMA *(erythema/erythéme)* | | EDEMA *(oedema/oedéme)* | | VESCICOLE *(blisters/vesicles)* | |
|---|---|---|---|---|---|---|---|---|
| | | | 15' | 24h | 15' | 24h | 15' | 24h |
| **1** | 29 | M | 0 | 0 | 0 | 0 | - | - |
| **2** | 30 | M | 0 | 0 | 0 | 0 | - | - |
| **3** | 25 | F | 0 | 0 | 0 | 0 | - | - |
| **4** | 20 | F | 0 | 0 | 0 | 0 | - | - |
| **5** | 42 | F | 0 | 0 | 0 | 0 | - | - |
| **6** | 33 | F | 0 | 0 | 0 | 0 | - | - |
| **7** | 21 | F | 0 | 0 | 0 | 0 | - | - |
| **8** | 32 | F | 0 | 0 | 0 | 0 | - | - |
| **9** | 26 | M | 0 | 0 | 0 | 0 | - | - |
| **10** | 54 | M | 0 | 0 | 0 | 0 | - | - |
| **11** | 36 | M | 0 | 0 | 0 | 0 | - | - |
| **12** | 33 | M | 0 | 0 | 0 | 0 | - | - |
| **13** | 27 | F | 0 | 0 | 0 | 0 | - | - |
| **14** | 21 | F | 0 | 0 | 0 | 0 | - | - |
| **15** | 48 | M | 0 | 0 | 0 | 0 | - | - |
| **16** | 45 | F | 0 | 0 | 0 | 0 | - | - |
| **17** | 26 | F | 0 | 0 | 0 | 0 | - | - |
| **18** | 25 | F | 0 | 0 | 0 | 0 | - | - |
| **19** | 23 | M | 0 | 0 | 0 | 0 | - | - |
| **20** | 26 | F | 0 | 0 | 0 | 0 | - | - |

**Tabella 3** Riassunto dei risultati del patch test

***Table 3 / Tableau 3*** *Summary of the patch test results / Resumé des resultats du patch test*

**Figura 1 (Figure 1)**

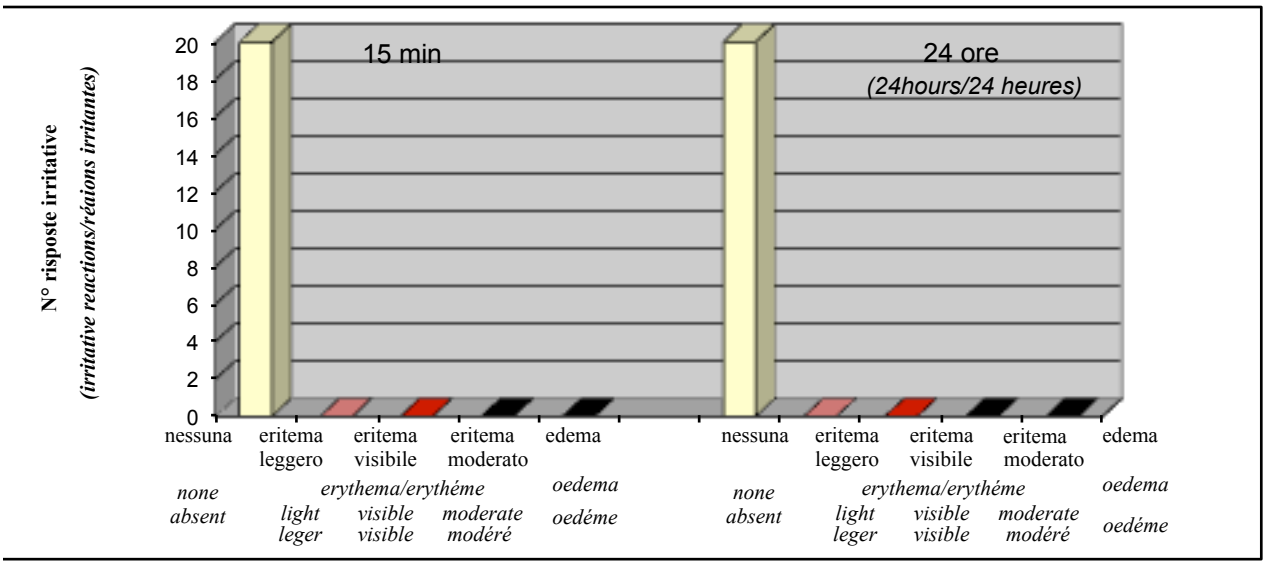



**Figura 1** Numero di risposte irritative (eritematose e/o edematose) riscontrate a 15 minuti e a 24 ore dalla rimozione del patch. Le reazioni eritematose sono state suddivise in tre gruppi in base al grado dell'eritema: leggero, ben visibile o moderato/grave.

***Figure 1*** *Number of irritative reactions (erythematous and/or oedematous) encountered at 15 minutes and at 24 hours after the removal of the patch. Erythematous reactions have been sorted out into three groups according to the reaction degree: light, clearly visible and moderate/serious erythema.*

***Figure 1*** *Nombre de réactions irritantes (erythemateuses et/ou oedemateuses) rencontrées à 15 minutes et 24 heures du deplacement du patch. Les reactions erythemateuses ont été sous divisées en 3 groupes sur la base du niveau de la réaction: leger bien visible ou modéré/grave.*

**Figura 2 (Figure 2)**

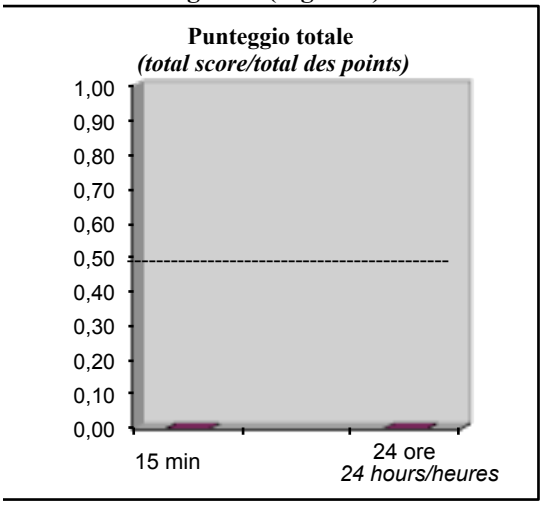



**Figure 2** Indice medio di irritazione (punteggio totale). I punteggi relativi a risposte eritematose leggere, ben visibili e moderate/gravi (incluso l'eventuale edema associato) sono indicati rispettivamente in blu, rosso e nero. La linea tratteggiata indica il limite oltre il quale il prodotto testato è lievemente irritante

***Figure 2*** *Mean index of irritation (total score). The scores due to light, clearly visible and moderate/serious erythematous reactions (including the associated oedema) are shown in blue, purple and black, respectively. The dashed line indicates the treshold above which the product is to be classified as slightly irritating*

***Figure 2*** *L'indice moyen d'irritation (total des points). Les points dus aux reactions erythemateuses legeres, bien visibles, modérées/graves sont indiqués respectivement en bleu, rouge sombre et noir. La ligne hachurée indique le seuil au-delà duquel le produit testé est classifié comme legerement irritant*

Il prodotto dermatologicamente testato, applicato tal quale in condizioni occlusive alla cute sana di 20 volontari, ha ottenuto un indice medio di irritazione pari a

**0,00** (zero,zero) dopo 15 minuti dalla rimozione della Finn Chamber
**0,00** (zero,zero) dopo 24 ore dalla rimozione della Finn Chamber

In base alla scala utilizzata (Tabella 2), il prodotto può essere classificato come:

*The dermatologically tested product, applied as it is under occlusive condition on the healthy skin of 20 volunteers, resulted in a mean index of irritation of*

***0,00*** *(zero,zero) 15 minutes after the removal of the Finn Chamber*
***0,00*** *(zero,zero) 24 hours after the removal of the Finn Chamber*

*According to the evaluation scale used (Table 2), the product can be classified as:*

*Le produit testé dermatologiquement, appliqué tel quel dans les conditions occlusives sur les peaux saines de 20 volontaires a obtenu un indice moyen d'irritation égal à:*

***0,00*** *(zero,zero) aprés 15 minutes du deplacement du Finn Chamber*
***0,00*** *(zero,zero) aprés 24 heures du deplacement du Finn Chamber*

*Sur la base de l'echelle utilisée (Tableau 2), le produit peut etre classifié comme:*

# ZAVA.GLI S.a.s. di Gollinucci Gianni & C.

**Via Piave, 374 47023 Cesena (FC)**

**(Committente: MARVEL 80 s.r.l.)**

## Codice Articolo: Z033K11010 Dentifricio BIMBI FRAGOLA

Lotto: **FR001**

**NON IRRITANTE** se applicato su cute umana

***NOT IRRITATING*** *if applied to human skin*

***NON IRRITANT*** *s'applique sur la peau humaine*

**Data:** **29/01/18**

**Coordinatore**
Dott.ssa Leda Montesi (Farmacista Cosmetologa)

**Sperimentatore**
Dott. Simone Sbrenna (Medico Farmacologo)

**Responsabile delle prove**
Prof. Michele Simonato (Medico Tossicologo)

**Supervisione**
Dott. Alex Gezzi (Medico Dermatologo)

CONSORZIO FUTURO IN RICERCA

# REPORT CHALLENGE TEST
# METODO ISO 11930:2012

| |
|---|
| COD. LAB.: 1801255 |
| Data emissione: 28/02/2018 |
| Rev. 0 |
| Challenge test |

Valutazione "*in vitro*" del sistema preservante di un prodotto cosmetico in base al metodo ISO 11930:2012, secondo il Regolamento 1223/2009

*According the European Regulation 1223/2009 the "in vitro" evaluation of the preservative system in cosmetic products by the method ISO 11930:2012.*

**Committente /** *Customer:*

**ZAVA.GLI SAS di GOLLINUCCI GIANNI & C.**
Via Piave, 374
47023 CESENA (FC) - ITALY

Prodotto /*Product:*
**COD. ART. Z033K11002-3-4-5-9-10-11 DENTIFRICIO BABY – L.25012018-005**

Data ricevimento campione / *Reception date*: 29/01/2018

Periodo di analisi: *Period of analysis:*

Data inizio analisi / *Date of testing:* 29/01/2018
Data fine analisi / *End Date test*: 26/02/2018

CONSORZIO FUTURO IN RICERCA

## CHALLENGE TEST: METODO ISO 11930:2012 DELL'EFFICACIA PRESERVANTE

### 1-SCOPO

Verificare *"in vitro"* l'efficacia del sistema di conservazione e, quindi, la stabilità microbiologica di formulazioni cosmetiche entro un determinato intervallo di tempo, in base al Regolamento Europeo 1223/2009.
Il Challenge test è eseguito secondo il metodo *ISO* (International Organization for Standardization) 11930:2012.

La valutazione complessiva della protezione antimicrobica comprende le caratteristiche chimiche del sistema conservante, ma anche la tipologia della formulazione, il packaging e il processo di fabbricazione (norme GMP).

### 2-CRITERI DI ACCETTABILITÀ: CRITERIO A e B METODO ISO 11930:2012

Il campione in esame deve presentare attività inibente nei confronti dei microrganismi utilizzati secondo i criteri di accettabilità secondo i criteri di accettabilità del metodo ISO come riportato nella tabella B.1:

## *CHALLENGE TEST: ISO 11930 Method : 2012 OF THE EFFICACY PRESERVATIVE*

### *1-SCOPE*

*According to the European Regulation 1223/2009 the "in vitro" evaluation of the effectiveness of the preservative system and, therefore, the microbiological stability of the cosmetics formulation.*
*The Challenge test is performed by ISO (International Organization for Standardization) method 11930:2012.*

*This evaluation of the antimicrobial protection comprises chemical preservation, but also the characteristics of the formulation, the packaging and the manufacturing process (GMP).*

### *2-ACCEPTANCE CRITERIA: A and B CRITERION METHOD ISO 11930: 2012*

*According to the criteria of acceptability of the ISO method the specimen was tested for the preservative efficacy testing against the microorganisms as described in the following table B.1:*

**Table B.1 — Evaluation criteria**

| Log reduction values ($R_x = \lg N_0 - \lg N_x$) required[a] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Micro-organisms | Bacteria | | | *C. albicans* | | | *A. brasiliensis* | |
| Sampling time | T7 | T14 | T28 | T7 | T14 | T28 | T14 | T28 |
| Criteria A | ≥3 | ≥3 and NI[b] | ≥3 and NI | ≥1 | ≥1 and NI | ≥1 and NI | ≥0[c] | ≥1 |
| Criteria B | Not performed | ≥3 | ≥3 and NI | Not performed | ≥1 | ≥1 and NI | ≥0 | ≥0 and NI |

[a] In this test, an acceptable range of deviation of 0,5 log is accepted (see 5.7).
[b] NI: no increase in the count from the previous contact time.
[c] $R_x = 0$ when $\lg N_0 = \lg N_x$ (no increase from the initial count).

**Microrganismi utilizzati ATCC***
*ATCC* microorganisms for antibacterial testing*: **ATCC (American Type Collection Control)*

| | | | | |
|---|---|---|---|---|
| *Staphylococcus aureus* | ATCC* 6538 | G + bacteria | Microbiologics Lotto 485-707-1 Exp. 03/2018 | $6.2 \times 10^6$ cfu/g |
| *Pseudomonas aeruginosa* | ATCC* 9027 | G - bacteria | Microbiologics Lotto 484-715-1 Exp. 04/2018 | $6.6 \times 10^6$ cfu/g |
| *Escherichia coli* | ATCC* 8739 | G - bacteria | Microbiologics Lotto 483-582-1 Exp. 07/2018 | $4.7 \times 10^6$ cfu/g |
| *Candida albicans* | ATCC*10231 | Lievito / Yeast | Microbiologics Lotto 392-705-1 Exp. 03/2018 | $6.5 \times 10^5$ cfu/g |
| *Aspergillus brasiliensis* | ATCC*16404 | Muffa/ *Molds* | Microbiologics Lotto 392-505-1 Exp. 02/2018 | $6.0 \times 10^5$ cfu/g |

*Customer:* Microbiologics (BIOLIFE):
Fornitura di ceppi titolati per l'inoculum al tempo 0 / Delivery of titrated strains for inoculation at time 0.

CONSORZIO FUTURO IN RICERCA

## RISULTATI / *RESULTS*

**Prodotto** / *Product:*
**ZAVA.GLI SAS**
**COD. ART. Z033K11002-3-4-5-9-10-11 DENTIFRICIO BABY – L.25012018-005**

Tabella 1: Conta microbica totale per ogni microrganismo di prova Metodo ISO

*Table 1: Total viable count for each test microorganisms Method ISO*

| **Microrganismi/** *Microorganisms test* | ATCC | **$T_0$** ***inoculum*** | **$T_{7\ gg.}$** | **$T_{14\ gg.}$** | **$T_{28\ gg.}$** |
|---|---|---|---|---|---|
| *Stafilococcus aureus* | 6538 | $6.2x10^6$ cfu/g | <10 | <10 | <10 |
| *Pseudomonas aeruginosa* | 9027 | $6.6x10^6$ cfu/g | $7,0x10^3$ | <10 | <10 |
| *Escherichia coli* | 8739 | $4.7x10^6$ cfu/g | $2,8x10^3$ | <10 | <10 |
| *Candida albicans* | 10231 | $6.5x10^5$ cfu/g | <10 | <10 | <10 |
| *Aspergillus brasiliensis* | 16404 | $6.0x10^5$ cfu/g | $3,0x10^3$ | <10 | <10 |

I dati esprimono le unità formanti colonia (CFU) relative ad 1 grammo di prodotto.
T= intervallo di tempo di analisi.
Conta microbica totale prima dell'esecuzione del Challenge test: <10 cfu/g.

*The data express the colony forming units (CFU) relative to 1 gram of product.*
*T= time of analysis.*
*Total Vital Count before the execution of the test: <10 cfu/g.*

Tabella 2: **Riduzione microbica in logaritmo ($Log_{10}$) in funzione del tempo (T)/**

*Table 2: Microbial reduction expressed in logarithm ($Log_{10}$) in function of time (T):*

| **Microrganismi/** *Microorganisms test* ATCC | **RIDUZIONE $LOG_{10}$** / *$LOG_{10}$ REDUCTION* | | | |
|---|---|---|---|---|
| | **$T_{7\ gg.}$** | **$T_{14\ gg.}$** | **$T_{28\ gg.}$** | ***CRITERIO DI ACCETTABILITÀ: Acceptance criterion A ISO*** |
| *Stafilococcus aureus* 6538 | ≥6 Log | NI | NI | ACCETTABILE / *ACCEPTABLE* |
| *Pseudomonas aeruginosa* 9027 | ≥3 Log | 6 Log | NI | ACCETTABILE /*ACCEPTABLE* |
| *Escherichia coli* 8739 | ≥3 Log | 6 Log | NI | ACCETTABILE / *ACCEPTABLE* |
| *Candida albicans* 10231 | ≥5 Log | NI | NI | ACCETTABILE / *ACCEPTABLE* |
| *Aspergillus brasiliensis* 16404 | ≥2 Log | 5 Log | NI | ACCETTABILE / *ACCEPTABLE* |

I dati esprimono la riduzione microbica in $LOG_{10}$ in funzione del tempo. NI: nessun incremento

*The data express the $LOG_{10}$ reduction of inoculated germs relative to established control intervals. NI: No Increase.*

Convalida del Metodo di analisi per il Challenge test / Validation of the *Method of the challenge test*:

Diluizione – neutralizzazione e tecnica in superficie su Tryptic Soy Agar-Tween-Lecitine /
*Dilution-neutralization method and spread plate technique on Tryptic Soy Agar-Tween-Lecitin (LTHT).*
TSA LTHT per i batteri: Oxoid REF. BO0330V Lotto/ Lot. 001168 Exp. Date: 2018Apr02.
SDA LTHT: Sauboraud Agar per i miceti: Oxoid REF. BO1155T Lotto/ Lot. 001239
Exp. Date: 2018Mar21.

Quality control: Sterility Test: incubation 48 hours at 37°C and 48 hours at 25°C: no growth:
RESULT: Satisfactory
Fertility Test (Microbiological quality criteria according to European Pharmacopoeia):
aerobiosis incubation 48 hours at 37°C. Reading at 18-72 hours: growth. RESULT: Satisfactory.

CONSORZIO FUTURO IN RICERCA

## GRAFICI

In ogni grafico è riportato la riduzione della carica microbica in funzione del tempo per ogni ceppo microbico di prova.

## *CHARTS*

*In eac graph is shown microbial reduction a function of time for each test microbial strain.*

PRODOTTO / *PRODUCT:*

**ZAVA.GLI SAS**
**COD. ART. Z033K11002-3-4-5-9-10-11 DENTIFRICIO BABY – L.25012018-005**

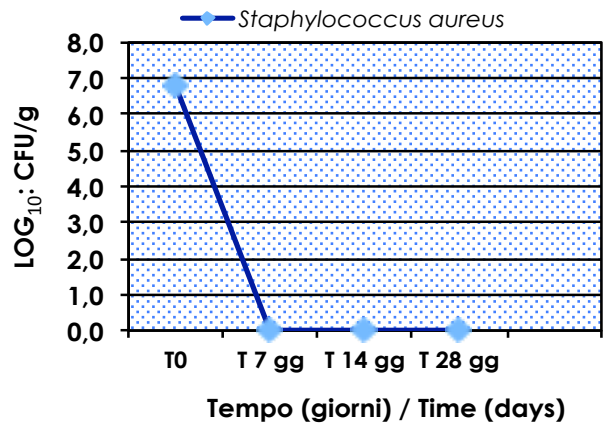



Figura 1: Batteri Gram positivi: *Stafilococcus aureus*

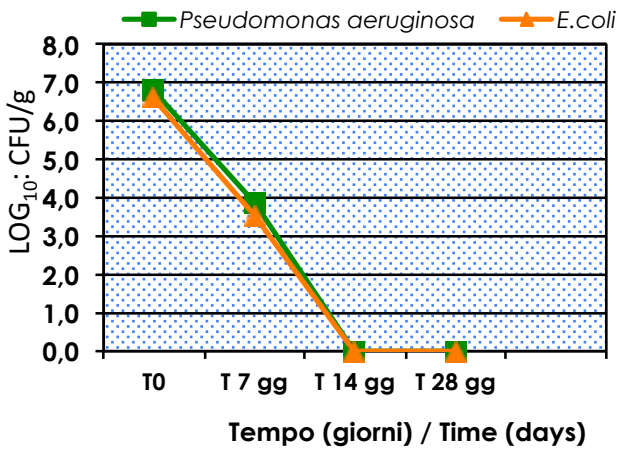



Figura 2_Batteri Gram negativi: *Escherichia coli* (enterobatteri) e *Pseudomonas aeruginosa* (ambientale)

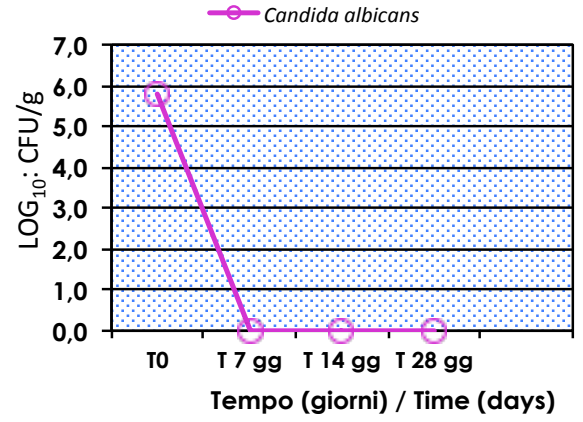



Figura 3: Lieviti *Candida albicans*

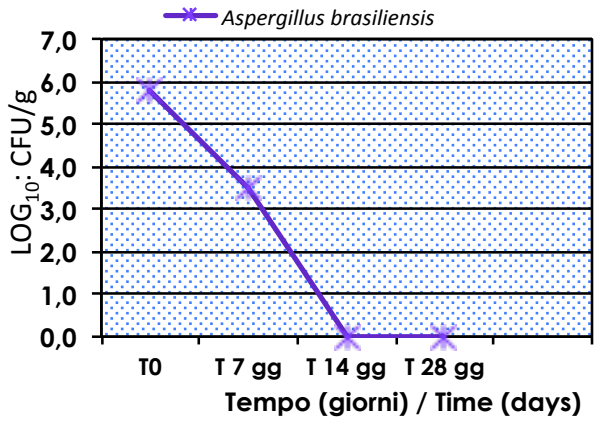



Figura 4: Muffe *Aspergillus brasiliensis*

**Legenda: $LOG_{10}$:** valore logaritmo dei risultati
**CFU/g:** unità formanti colonia relative ad 1 grammo (g) di campione analizzato.

***Explanation:* $LOG_{10}$:** *logaritm value of the results.*
**CFU/g:** *colony forming units relative to 1 gram (g) of test product.*

CONSORZIO FUTURO IN RICERCA

## CONCLUSIONE

In base ai criteri di valutazione raccomandati dal ISO 11930:2012 il sistema preservante è accettabile.

Il prodotto denominato:

## *CONCLUSION*

*According to the assessment criteria recommended by the ISO Method 11930:2012 the preservative system is acceptable.*

*The results obtained by testing the product called:*

**ZAVA.GLI SAS**

**COD. ART. Z033K11002-3-4-5-9-10-11 DENTIFRICIO BABY – L.25012018-005**

i risultati ottenuti del Challenge test sono accettabili secondo il criterio A:
il rischio microbiologico è **ACCETTABILE**.

*the results of the Challenge test are acceptable according to criterion A:*
*the microbiological risk is ACCEPTABLE.*

Il prodotto è considerato protetto contro la proliferazione microbica durante il suo utilizzo.
É necessario considerare i fattori di controllo che non sono collegati con la formulazione, quali le modalità di produzione e di confezionamento in conformità alle Norme di Buona Fabbricazione (GMP) per la sicurezza microbiologica del cosmetico.

*The product is considered protected against the microbial proliferation when using it.*
*It is necessary to consider the control factors not related to the formulation, such as the system of production and packaging in accordance with Good Manufacturing Practice (GMP) for the microbiological quality of the cosmetic product.*

Data report : 28/02/2018

(Firma / *Signature*) Dr.ssa Alberta Vandini
n. AA_039993 O.N.B.)

in collaborazione con il CENTRO DI COSMETOLOGIA UNIVERSITÀ DI FERRA

Bibliografia / *References*:

I. Regulation (EC) No 1223/2009 (the “Cosmetic Products Regulation”), replaced the European Union (EU) Cosmetics Directive 76/768/EEC, which harmonizes and simplifies the cosmetics regulations across the EU member states by Product Information File (PIF).
II. COLIPA Guidelines “Product Information File (PIF)”- December 15th 2011.
III. ISO (International Organization for Standardization) 11930:2012.

Certificate IT16/0277

The management system of

# MARVEL 80 S.r.l.

Via dell'Industria, 21/23 - 60031 Castelplanio (AN) - Italy

Has been assessed and certified as meeting the requirements of

## ISO 22716
## Cosmetics – Guidelines on Good Manufacturing Practices (GMP)
**(First edition 2007-11-15)**

For the following activities

**Production of creams, emulsions, lotions, fluids, gels and oils for the skin (hands, face, body), bath and shower preparation, hair care products water, oil alcohol, silicone based (hot/cold preparation); shaving, teeth and mouth care, tanning products.**

The responsibility for the quality of the individual batches of the cosmetic products labelled, packed and stored lies with the organization

This certificate is valid from 19/05/2016 until 19/05/2019
and remains valid subject to satisfactory surveillance audits.
Issue 1. Certified since 19/05/2016.

Authorised by

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Certification Manager
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