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Functional Chemicals Division

Taking care of
your customers'
hair

Antidandruff Active Ingredient Octopirox®

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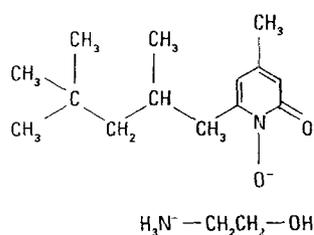
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Product data

Structural Formula Octopirox®



Antidandruff active ingredient

Chemical name

1-Hydroxy-4-methyl-6-(2,4,4-trimethyl-pentyl)-2(1H)-pyridone;
combination with 2-aminoethanol (1:1)

International nonproprietary name

(USAN, WHO, INCI): Piroctone Olamine

Molar mass

298.4 g/mol

Appearance

white to faintly yellowish-white
crystalline powder

Odour

Faint characteristic odour

Chemical and Physical Data

Active ingredient content (I)

min. 98.0 %

Loss on drying (II)

max. 0.3 %

Sulphate ash (III)

max. 0.2 %

Melting range

133 – 136 °C (with decomposition)

pH (IV)

(1 % aqueous suspension, 20 °C)

8.5 – 10.0

Solubility

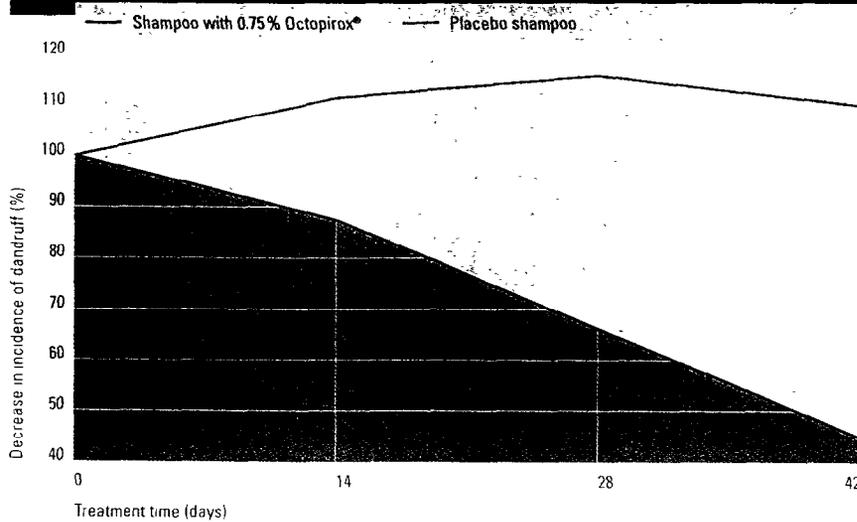
readily soluble in alcohol (10 %),
soluble in aqueous surfactant solutions
and water/alcohol mixtures (1–10 %),
slightly soluble in water (ca. 0.05 %)
and oils (0.05 – 0.1 %)

Analytical Methods of Determination

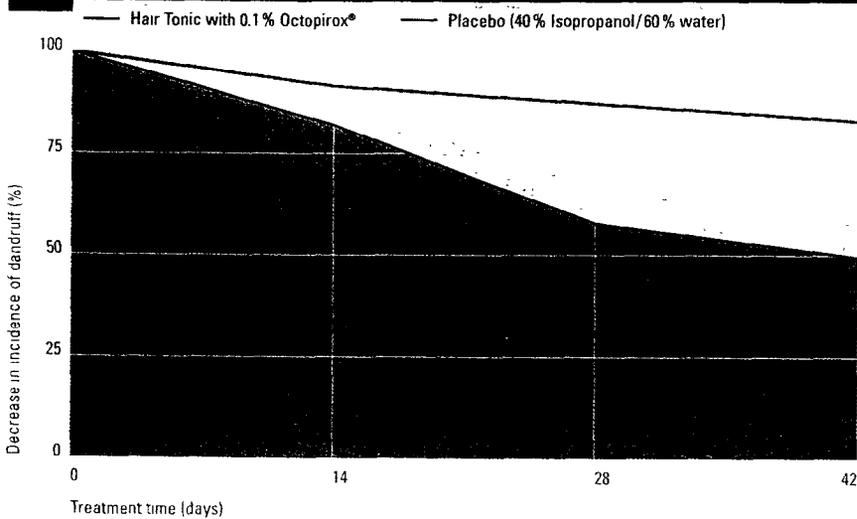
- (I) Determination of the active ingredient content is done by potentiometric titration with sodium hydroxide solution. (This method of determination is available on request).
- (II) Drying in vacuum at room temperature for six hours.
- (III) The sulphate ash is determined from 2.0 g substance.
- (IV) DGF standard method H – III 1.

Action

1 Antidandruff action (shampoo)



2 Antidandruff action (hair tonic)



Antidandruff action

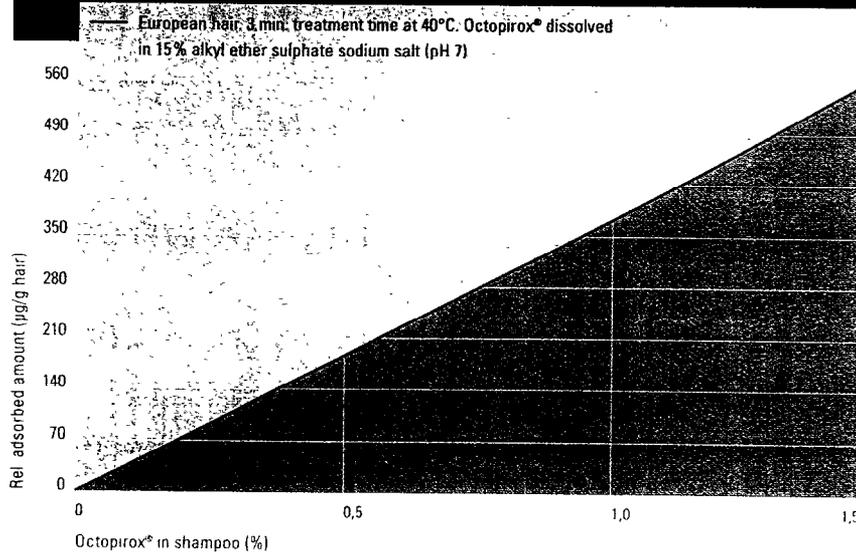
Octopirox® is an effective, practically nontoxic antidandruff active ingredient which is particularly suitable for the manufacture of antidandruff shampoos and hair care products such as hair tonics and cream rinses with an antidandruff action.

The concentrations used should be between 0.1 and 1.0%, depending on the type of finished product. The concentration can be reduced even further for preparations that remain on the hair or the scalp. In these cases a concentration between 0.05 and 0.1% is sufficient. Because of its solubility in aqueous surfactant solutions and alcohol-water mixtures Octopirox® is highly suitable for the manufacture of clear finished products.

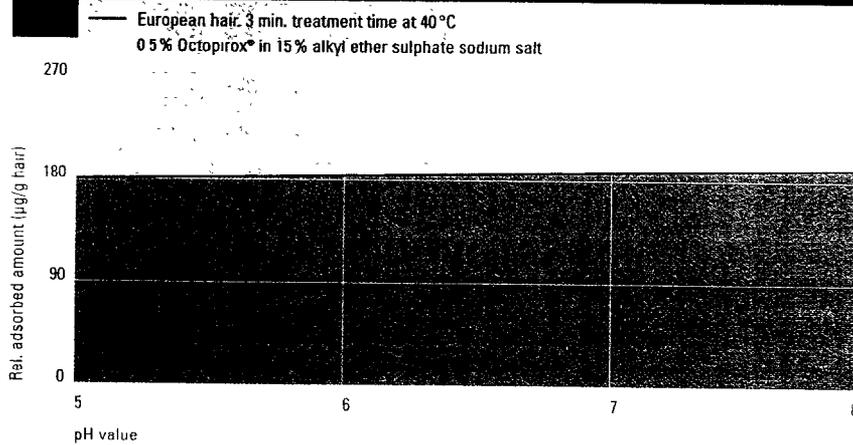
The effectiveness of antidandruff preparations containing Octopirox®, especially antidandruff shampoos and hair tonics, has been investigated and described in numerous studies. Their excellent efficacy has also been substantiated in various clinical trials.¹⁻⁸ Figs. 1 and 2 show the antidandruff action, i.e. the incidence of dandruff as a function of the treatment time, when the treatment is applied once weekly. Fig. 1 shows the effect of a shampoo with 0.75% Octopirox® compared to a shampoo without this active ingredient.²

Fig. 2 shows the efficacy of a hair tonic with 0.1% Octopirox®.

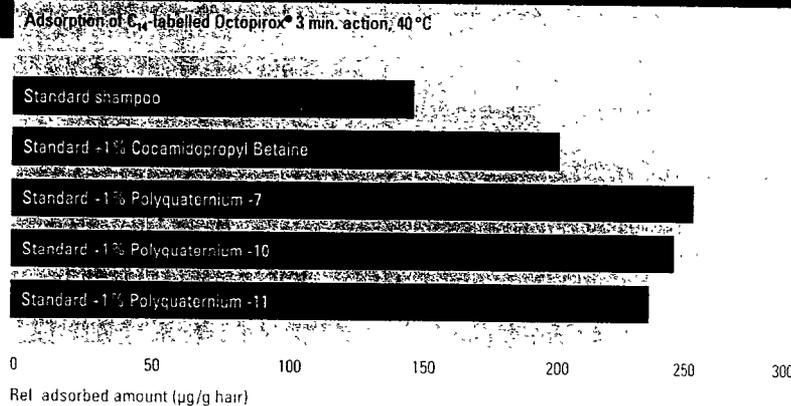
3 Substantivity of Octopirox® as a function concentration used



4a Substantivity of Octopirox® as a function of the pH



4b Substantivity of Octopirox® on human hair



Substantivity

The substantivity of Octopirox® was determined by adsorption measurements of C₁₄-labelled active ingredient on keratin (human hair).⁹

Figs. 3 and 4a show the adsorbed amount Octopirox® per g hair as a function of the active ingredient concentration in the shampoo and of the pH respectively.

Whereas a marked increase in the amount adsorbed takes place as the concentration rises, the pH has only a slight effect on substantivity.

As shown in fig. 4b the substantivity of Octopirox® on human hair can be increased considerably by the addition of 1% cationic polymer and 1% amphoteric surfactant, respectively, to the shampoo formulation. Standard shampoo consists of 0.5% Octopirox® in 15% alkyl ether sulphate sodium salt (pH 7).

Antimicrobial action

The antibacterial action, expressed by the minimum inhibitory concentration (MIC), was determined in the serial dilution test in a Mueller Hinton medium at pH 7 (Difco Laboratories, Detroit, Michigan, USA). Aceton/water was used as the solvent. The MIC values of Octopirox® for the most familiar gram-positive and gram-negative bacteria can be found in fig. 5.

The effect on fungi and yeasts, similarly expressed by the minimum inhibitory concentration (MIC), was tested in a Sabouraud dextrose test medium at pH 6.5. The Octopirox® being tested was dissolved in an ethanol/ water mixture.

The results presented in fig. 6 show that the MIC for the most important species of fungi lies between 0.5 and 4.0 µg/ml.

5 Antibacterial spectrum of action of Octopirox® (pH 7)

Bacteria	No. of strains investigated	Minimum inhibitory concentration (µg/ml)								
		4	8	16	31	63	125	250	500	1000
Gram-positive										
Staph aureus					■	■				
Micrococcus luteus	1					■				
Streptoc pyogenes	2					■				
Bac subtilis	1					■				
Gram-negative										
Escherichia coli	9					■	■			
Salmonella var. species	6						■	■		
Proteus var species	9						■	■	■	
Klebsiella var species	3						■	■		
Enterobacter var species	4							■	■	
Shigella flexneri	1					■				
Pseudomonas aeruginosa	8					■	■	■	■	
Haemophilus influenzae	1					■				
Corynebact var species	2					■				
Past multocida	1				■					

6 Antifungal spectrum of action of Octopirox® (pH 6.5)

Species of fungus	No. of strains investigated	Minimum inhibitory concentration (µg/ml)											
		0.1	0.2	0.3	0.5	1	2	4	8	16	31	64	125
Trichophyton rubrum	5				■	■	■						
Trichophyton mentagrophytes	4					■	■						
Other Trichophyton-species	1						■						
Microsporium canis	1						■						
Other Microsporium-species	2				■	■							
Epidermophyton floccosum	1						■						
Candida albicans	5					■							
Candida tropicalis	3					■							
Other yeastlike fungi	3					■							
Aspergillus niger	1						■						
Aspergillus fumigatus	2					■	■	■					
Other moulds	4					■	■						

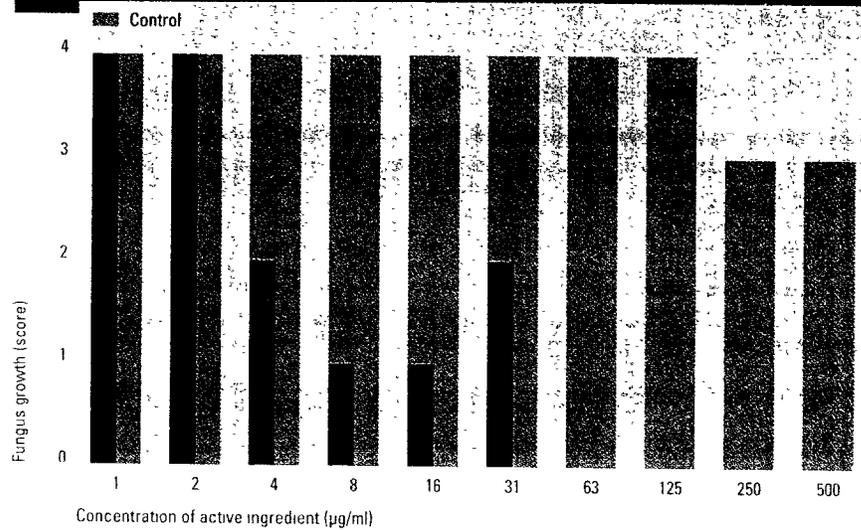
Mechanism

According to Prof. Bonadeo (1975) and Prof. Lübke (1979) the increased formation of dandruff can be explained by the mechanism shown in fig. 8.^{10, 12}

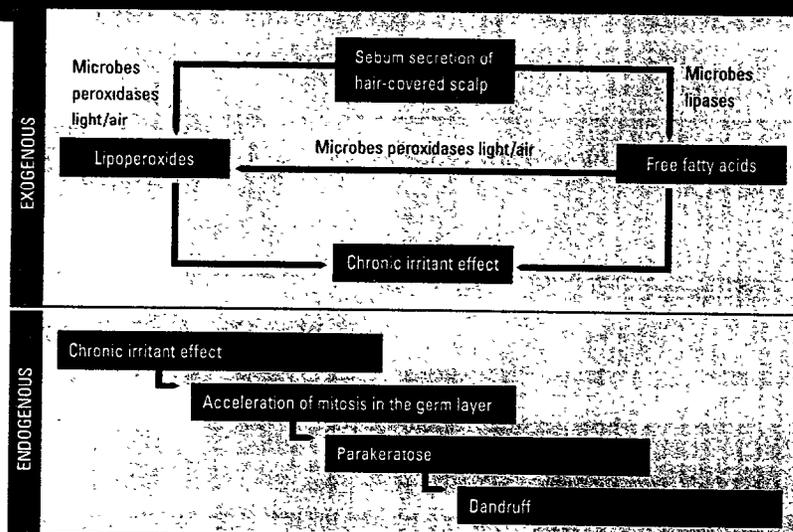
The action of Octopirox® within this mechanism is attributed both to its antimicrobial and its antioxidative action."

As outlined in fig. 7 Octopirox® is also highly effective against malassezia species (formerly called Pityrospirium ovale or orbiculare), which are considered to be the main causes of dandruff.

7 In vitro activity of Piroctone Olamine towards Malassezia species



8 Mechanism according to Bonadeo and Lüpke



General Properties

Solubility

The solubility of Octopirox® is greatly dependent on the pH. Generally speaking, its solubility in aqueous formulations is greater in the neutral and weakly alkaline ranges than in the acid range (formation of free acid).

Octopirox® does however have adequate solubility in the usual pH range (pH 5 – 8) in commercial surfactant solutions and alcohol-water mixtures.

The solubility of Octopirox® in ethanol-water mixtures at pH 7 and 20°C is shown in fig. 9.

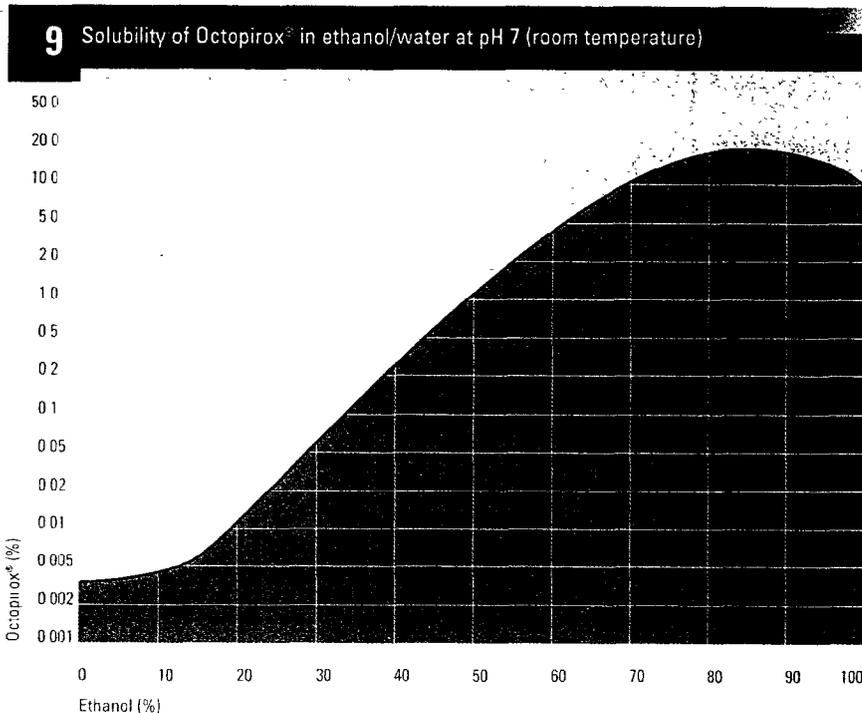
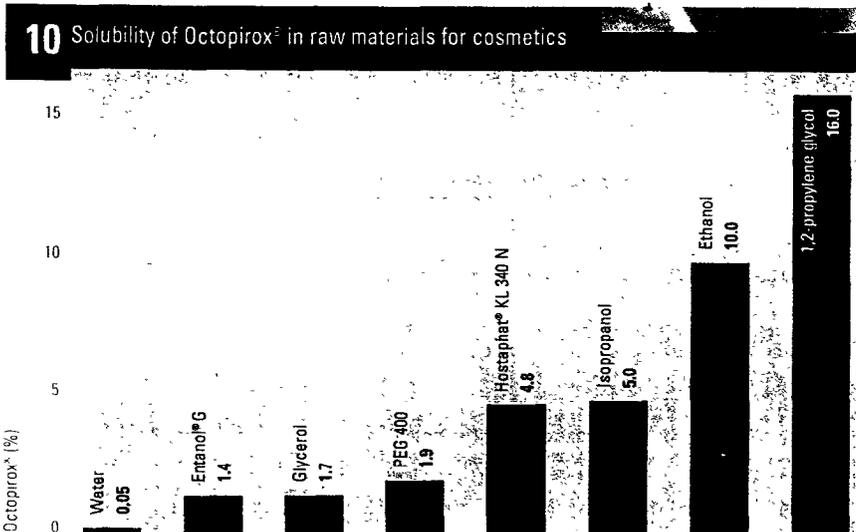


Fig. 10 shows the solubility of Octopirox® in various solvents and important additives such as emulsifiers and solubilisers. Particularly remarkable is the product's good solubility in 1,2-propylene glycol.



Solubility of Octopirox® in various surfactants

(15% active detergent, pH 7, room temperature)

- Alkyl ether sulphate sodium salt 1.1 – 1.4 %
- Lauryl sulphate sodium salt approx. 2.8 %
- Sec. alkane sulphonate sodium salt approx. 1.4 %
- α-olefin sulphonate sodium salt approx. 2.3 %
- Alkyl amidopropyl betaine approx. 1.9 %

Fig. 11 shows the solubility of Octopirox® in three important basic surfactants as a function of the surfactant concentration.

The pH has a very great influence on the product's solubility in surfactants. Solubility in most surfactants increases between pH 5 and 8.

Influence of the pH value

At a neutral pH a substantial part of the Octopirox® exists in the form of free acid. The pKa value is about 7.4. Octopirox® is chemically stable over a wide pH range. In the range that is important for practical purposes, namely between pH 3 and 9, neither deterioration of the active ingredient nor impairment of its efficacy was observed even after prolonged storage.

Thermal stability

Octopirox® is noted for good thermal stability. The high temperatures (up to 80°C) occasionally occurring in the manufacture of cosmetic preparations do not cause deterioration of the product or loss of efficacy. Still, prolonged heating to high temperatures should be avoided if possible. No decrease in the active ingredient content of an Octopirox® shampoo (pH 5.5 and 7.0) was observed after storage for 12 months at +40°C.

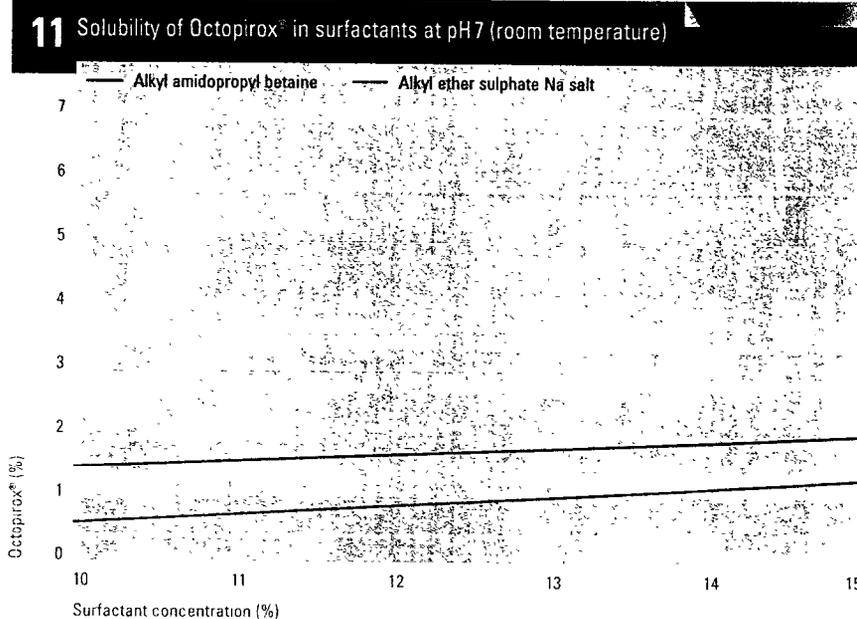
Light stability

Storage of Octopirox®-containing preparations in daylight can cause a deterioration of the active ingredient, depending on the amount of UV light. It is therefore advisable to use colored or opaque packaging materials. Stability tests should be carried out if transparent packaging materials are used.

Compatibility with cosmetic raw materials

Octopirox® is compatible with most surfactants, additives and active ingredients used in cosmetics. Concerning compatibility with perfume oils, those with aldehyde and keto groups may cause problems.

Despite the anionic character of the active ingredient molecule, Octopirox® can be combined without any problems with most cationic surfactants (quaternary ammonium compounds) and cationic active ingredients. In some cases the solubility of Octopirox® in water is increased even further. Nevertheless it is advisable to carry out compatibility and stability tests when using these substances.

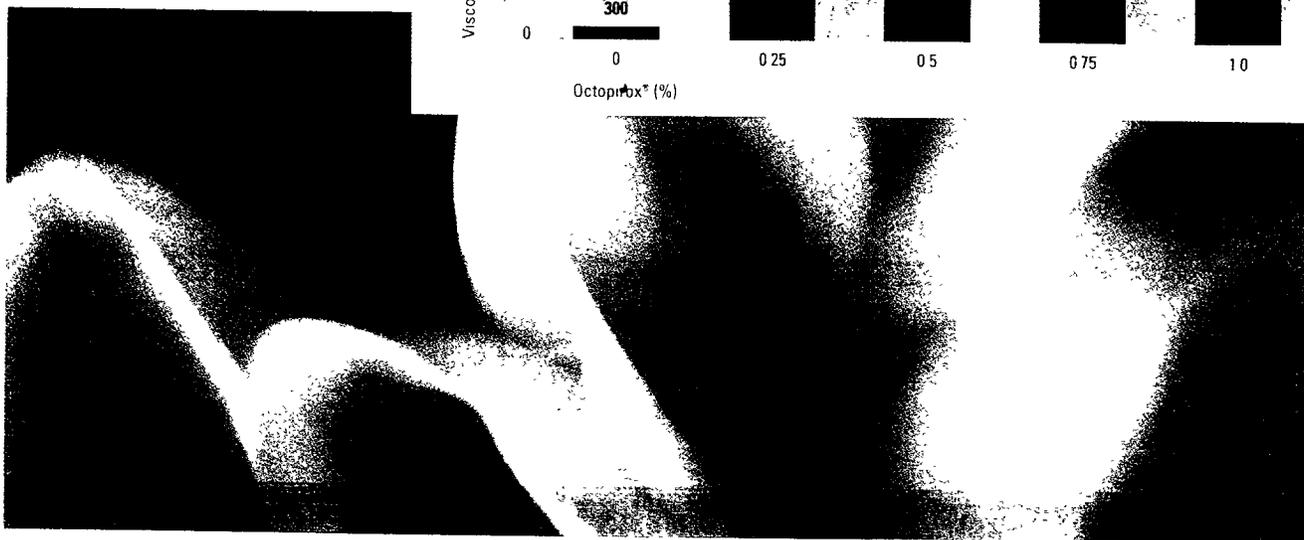
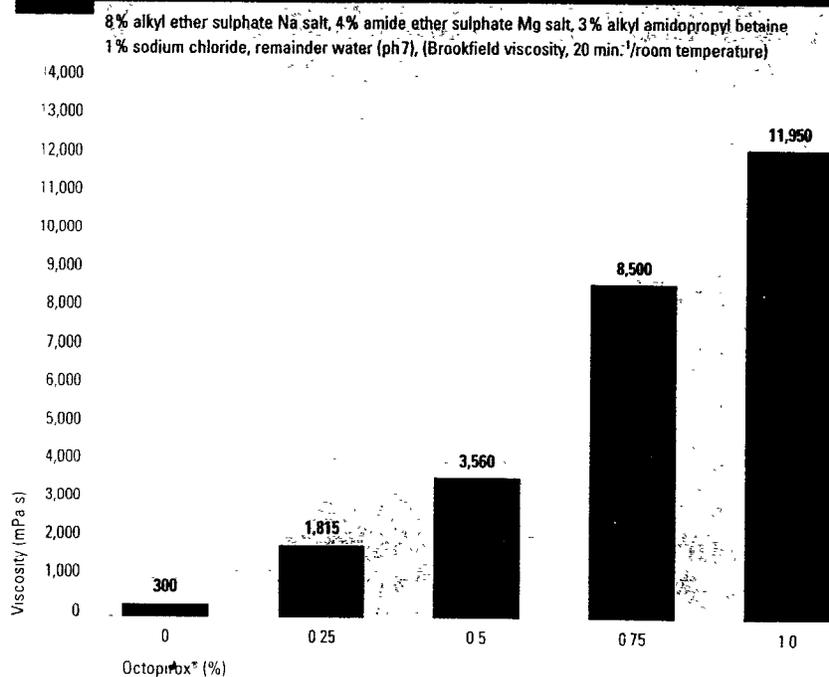


Attention must be drawn to the product's property of forming complexes with metal ions, especially iron and copper ions. For example, with mere traces of iron (1 ppm Fe) a clearly visible yellow iron complex is formed. Formation of the complex is not prevented by adding the usual complexing agents (see section on processing information).

Influence on viscosity in surfactant systems

Studies have shown that Octopirox® increases the viscosity of numerous surfactant systems. Fig. 12 shows the viscosity-increasing effect of Octopirox® at concentrations of up to 1.0%, using the example of a commercial surfactant combination (pH 7). This generally very beneficial property (economising on consistency modifiers) should be taken into consideration when developing corresponding formulations.

12 Viscosity-increasing effect of Octopirox® at pH 7



Toxicological and Dermatological Properties

Acute toxicity

1. Oral administration

The acute oral toxicity tests were carried out on rats, mice and dogs. The following results were obtained:

- Rat
LD₅₀ = 8100 mg/kg body weight.
- Mouse
LD₅₀ = 4300 mg/kg body weight.
Doses up to 1000 mg/kg body weight were tolerated by all test animals, which showed normal behaviour.
- Dog
LD₅₀ = >4000 mg/kg body weight.
Thus Octopirox® possesses no significant potential regarding acute oral toxicity.

2. Dermal administration

The percutaneous toxicity was tested with an almost saturated solution in 1,2-propylene glycol by means of a covered patch test for 24 hours on rats. Doses of 2000 mg/kg body weight (pH 9.3 – unadjusted) and 750 mg/kg (pH 7.0 – adjusted) gave no indication of a toxic reaction.

The dermal LD₅₀ of the undiluted substance, tested on rats, is >2000 mg/kg body weight.

Therefore Octopirox® provides no significant risk concerning acute dermal toxicity.

3. Skin compatibility

Primary skin irritation was tested in the patch test on rabbits over 24 hours.

The test substance used was a solution of 0.5% Octopirox® and 5% of a lauryl polyglycol ether sulphosuccinate disodium salt in water (pH7 adjusted with citric acid). The test was carried out on intact and abraded skin. Only slight irritation was observed. A 5% solution of the same surfactant without the addition of Octopirox® showed the same degree of irritation. Thus, under the test conditions described, Octopirox® does not cause an increase in the irritation potential.

1% solutions in 1,2-propylene glycol or PEG 400 adjusted to pH 7 proved to be slightly irritant. The irritation symptoms had largely disappeared after 72 hours

4 Mucous membrane compatibility

The acute eye irritation was carried out on rabbits. The test substance used was a 1:1 shampoo formulation diluted with water, consisting of 15% of a sodium lauryl ether sulphate and 1% Octopirox® (pH 7 adjusted with citric acid); the control used was a corresponding formulation without Octopirox®. Both preparations proved to be moderately irritant.

In similar trials commercial shampoo formulations with 0.3% or 0.5% Octopirox®, hair tonics based on isopropanol/ water with 0.2% Octopirox® and the corresponding placebo preparations proved to be slightly irritant.

5. Sensitisation

Studies on guinea pigs using the methods of Buehler and Tanaka et al. and the methods of Morikawa gave no indication of a sensitising or photosensitising effect.

Subacute and subchronic toxicity

- Rat
When Octopirox® was administered in daily doses of up to 800 mg/kg body weight by means of a stomach tube for 30 and 90 days the maximum nontoxic dose was 100 mg/kg weight. No organic damage was observed with any dose.
- Dog
When Octopirox® was administered in daily doses of up to 100 mg/kg body weight with the food for 30 and 90 days no toxic findings were recorded.
- Rabbit
The epidermal application to 30 rabbits of a shampoo with 0.5% Octopirox® (dose: 0.5 mg Octopirox® per animal) or of a hair tonic with 0.1% Octopirox® (dose: 0.1 mg Octopirox® per animal) caused no toxic reactions or substance-induced changes in organs, including the skin.

Chronic toxicity

The daily epidermal application of 0.5 and 1.0% Octopirox® in 1,2-propylene glycol to rats (dose: 0.1 or 2 mg per animal) for six and 12 months caused rapidly reversible changes to the area of skin affected. A systemic effect was not observed.

Pharmacokinetics

The pharmacokinetic studies were carried out after dermal, oral, subcutaneous, intraperitoneal and intravenous administration of C₁₄-labelled Octopirox® to rats and dogs.

The active ingredient administered was eliminated in unchanged form largely in the faeces and in small amounts in the urine. The blood values reached their maximum between three and eight hours after oral administration of Octopirox® (dose: 0.24 mg/kg body weight).

Only very low values were recorded in the cellular tissue. The maximum values were determined in the liver six hours after administration. After topical application of a 1% solution of Octopirox® (dose: 15.4 mg/kg body weight) without rinsing (under occlusive conditions) a concentration of 0.32 µg/ml in the blood was reached after six hours. With the same test procedure, but after rinsing the treated skin after five minutes, greatly reduced concentrations in the blood were recorded with a maximum after one hour (0.02 µg/ml).

The skin penetration of Octopirox® depends on the treatment time. A significant increase in penetration was determined between 2.5 and 10 minutes contact time. No further increase in the penetration rate was recorded with a longer contact time of up to 20 minutes. The pharmacokinetic studies and subchronic tests (90-day test) carried out indicate a safety factor of about 30,000.¹³

Pharmacological studies

Studies of the effect of Octopirox® in a dose of 5 mg/kg body weight on the central nervous system and vegetative functions (isolated organs, cardiovascular parameters and specific metabolic functions) of mice, guinea pigs, cats and rats gave no indication of acute pharmacological effect.

Reproductive toxicology studies

Octopirox® proved to be neither embryotoxic nor teratogenic in studies on rabbits after oral administration of up to 63 mg/kg body weight and on rats after subcutaneous administration of up to 2000 mg/kg body weight whilst the animals were pregnant. Even after subcutaneous application of up to 500 mg/kg body weight to rats before mating and until the early stage of

pregnancy or during the last stage of pregnancy and the lactation period no impairment of the fertility of the test animals or their progeny or teratogenic effects on the foetuses of the first and second generation were observed.

Mutagenicity testing

The mutagenicity was investigated in several in-vitro and in-vivo studies such as point mutation tests (AMES test, mouse lymphoma test), chromosome aberration tests (micronucleus test, cytogenetic in-vivo test) and a DNA binding study on the rat with a very low detection limit.

None of the in-vivo studies gave any indication of a mutagenic effect.

Octopirox® was not mutagenic in the AMES test.



Skin compatibility on humans

The application of a 20% aqueous lauryl polyglycol ether sulphosuccinate disodium salt solution with 0.5% Octopirox® caused no primary skin irritation in the repeated Shelansky & Shelansky patch test on 50 test subjects and gave no indication of a sensitising effect.

The epidermal application of a solution of 0.1% Octopirox® in aqueous isopropanol to 10 test subjects with subsequent exposure to UV-A or UV-B light gave no indication of a phototoxic effect.

In consumer tests with Octopirox®-containing shampoos (0.2 – 1.0%) on more than 300 people with severe

dandruff (18 of the test subjects had psoriasis) no skin incompatibility was observed after seven applications within four weeks.

Processing Information

Aqueous or alcoholic-aqueous solutions of Octopirox® have a pH of 9 – 10. Organic acids such as citric acid or lactic acid are highly suitable for adjusting the pH to the commercially required range between 5 and 7. It should be borne in mind that the solubility of Octopirox® is somewhat reduced in the acid range, particularly with an extremely low active ingredient content.

In the manufacture of antidandruff shampoos the viscosity can be adjusted readily with any of the commonly employed consistency modifiers. In some cases when Octopirox® is used, however, an additional and in some instances very great increase in viscosity is observed (see fig. 12). In the manufacture of shampoos or hair conditioners with Octopirox® a temperature of 80 °C should not be exceeded if possible.

Similarly, interactions with cationic surfactants can occur in a number of instances.

In each case the compatibility should be checked by storage trials. In selecting dyes for colouring the preparations it should be borne in mind that in the presence of traces of iron (due to the formation of an intensely yellow iron complex) the formulation has an inherent yellow colour.

It is advisable to carry out preliminary trials for colour change in the case of preparations to be coloured blue or pale green.

Yellow, orange or red dyes are highly suitable. If blue or green dyes are used, the raw materials should if possible be free from traces of iron.

The following concentrations are used for the various cosmetic preparations:

▪ Hair shampoos	0.3 – 1.0%
▪ Hair tonics	0.05 – 0.1%
▪ Hair conditioners	0.1 – 0.3%
▪ Setting lotions/hair gels	0.05 – 0.2%
▪ Hair creams	0.1 – 0.3%
▪ Deodorants	0.1 – 0.3%

Formulations

- Antidandruff Shampoo
- Antidandruff Cream rinse
- Antidandruff Hair treatment
- Antidandruff Setting lotion
- Antidandruff Hair tonic
- Antidandruff Hair gel
- Antidandruff Hair cream
- Antidandruff Hair oil
- Deodorants
- Anti acne products

Guide recipes for the above mentioned product types are available on request.

Analytical Determination in Preparations

The quantitative determination of Octopirox® in finished cosmetic formulations, e.g. at the production control stage, can be carried out by the colorimetric method described below.

Colorimetric determination of Octopirox® in finished cosmetic formulations

18–22 mg Octopirox®, weighed accurately (= ms), are dissolved in 80 % acetic acid in a 100-ml graduated flask, which is then filled to the mark (standard solution).

Dissolve about 1.5g finished product (with an expected Octopirox® content between 0.5 and 1.0 %; weigh in less or more if the concentration is higher or lower), weighed accurately (= mp), in 80 % acetic acid in a 50-ml graduated flask and fill the flask to the mark (sample solution).

If the formulation has undissolved particles (e.g. pearl lustre agents), the solution must be filtered through a folded filter.

Preparation of the iron reagent solution

0.3g iron (II) sulphate ($\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$) are dissolved in about 5 ml water in a graduated flask, 0.3ml acetic acid 99 % in a 50-ml flask are added, and the flask is filled to the mark with methanol (iron reagent solution).

Production of the standard solutions

10.0 ml of the Octopirox® standard solution are transferred to a 25-ml graduated flask and 10.0 ml of the sample solution being investigated are transferred to a second 25-ml graduated flask.

1 ml iron reagent solution is added to each of these solutions (standard solution and sample solution), and the flasks are filled to the mark with 80 % acetic acid. For the blank value 1 ml iron reagent solution is diluted with 80 % acetic acid to 25 ml. The samples are then kept in a dark place for one hour.

The extinction of the Octopirox® standard solution (=E_s) and of the sample solution (=E_p) is then measured against the blank value at a wavelength of 440 nm in a spectrophotometer.

$$\% \text{ Octopirox}^{\circledast} = \frac{E_p \cdot m_s \text{ (mg)}}{E_s \cdot m_p \text{ (g)} \cdot 20}$$

Problems in carrying out this method can be caused by intense yellow preparations or by the presence of substances that form yellow complexes with Fe²⁺ ions. In these cases the determination should be carried out by the HPLC method. This method is available on request.

Storage

Octopirox® should if possible be stored in its original container at normal room temperature protected from moisture. If stored correctly in its original container Octopirox® can be kept for at least five years. A safety data sheet is available on request.



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Clariant GmbH
Functional Chemicals Division
BU II Personal Care
D-65840 Sulzbach/Ts.
Germany

Marketing
T +49 61 96 757 78 50
F +49 61 96 757 69 33

Research & Development
T +49 69 30 51 81 00
F +49 69 31 84 35