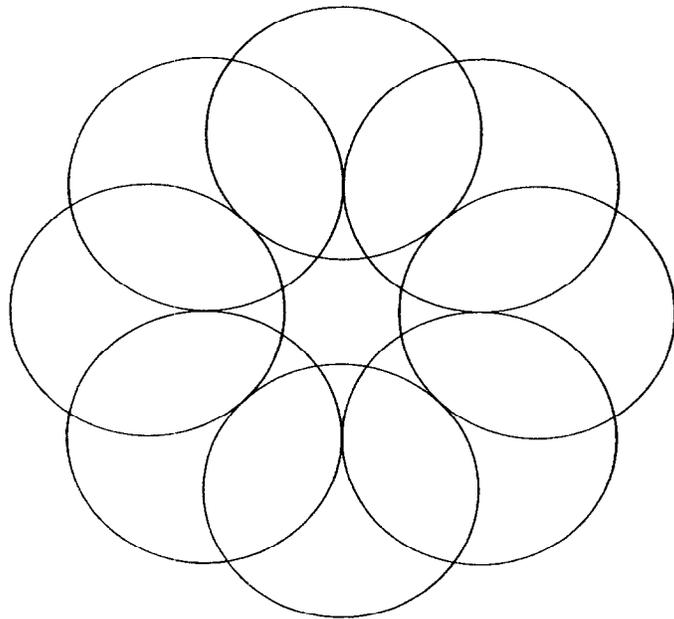




# Octopirox<sup>®</sup>



# Octopirox<sup>®</sup>

## Antidandruff active ingredient

### Chemical name

1-Hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2(1H)-pyridone; combination with 2-amino-ethanol (1:1)

### International nonproprietary name (USAN, WHO)

Piroctone Olamine

### Molar mass

298.4 g/mol

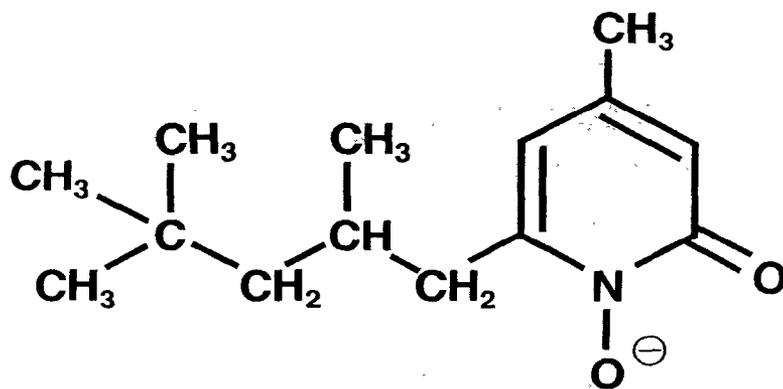
### Appearance

White to faintly yellowish-white crystalline powder

### Odour

Faint characteristic odour

### Structural formula



# Chemical and Physical Data

**Active ingredient content (1)**

min. 98.0 %

**Loss on drying (2)**

max. 2.0 %

**Sulphate ash (3)**

max. 0.2 %

**Melting range**

130–135 °C (with decomposition)

**pH (4)**

(1 % aqueous suspension, 20 °C)

8.5–10.0

**Solubility**

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

# Analytical Methods of Determination

- (1) Determination of the active ingredient content is done by titration with lithium methylate solution against thymol blue as indicator. (This method of determination is available on request).
- (2) Drying in a vacuum at room temperature for 6 hours
- (3) The sulphate ash is determined from 1.5 g substance
- (4) DGF standard method H-III 1.

# Action

## 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 Octopirox-containing antidandruff preparations, 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 0.1 % Octopirox-containing hair tonic (5).

## Substantivity

The substantivity of Octopirox was determined by adsorption measurements of <sup>14</sup>C-labelled active ingredient on keratin (human hair) (9).

Figs. 3 and 4 show the relative adsorbed amount 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.

## 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). Acetone/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.

## Mechanism

According to Prof. Bonadeo (1975) and Prof. Lüpke (1979) the increased formation of dandruff can be explained by the mechanism shown in fig. 7 (10, 11).

The action of Octopirox within this mechanism is attributed both to its antimicrobial and its antioxidative action (11).

Fig. 1: Antidandruff action (shampoo)

— = Placebo shampoo  
— = Shampoo with 0.75% Octopirox

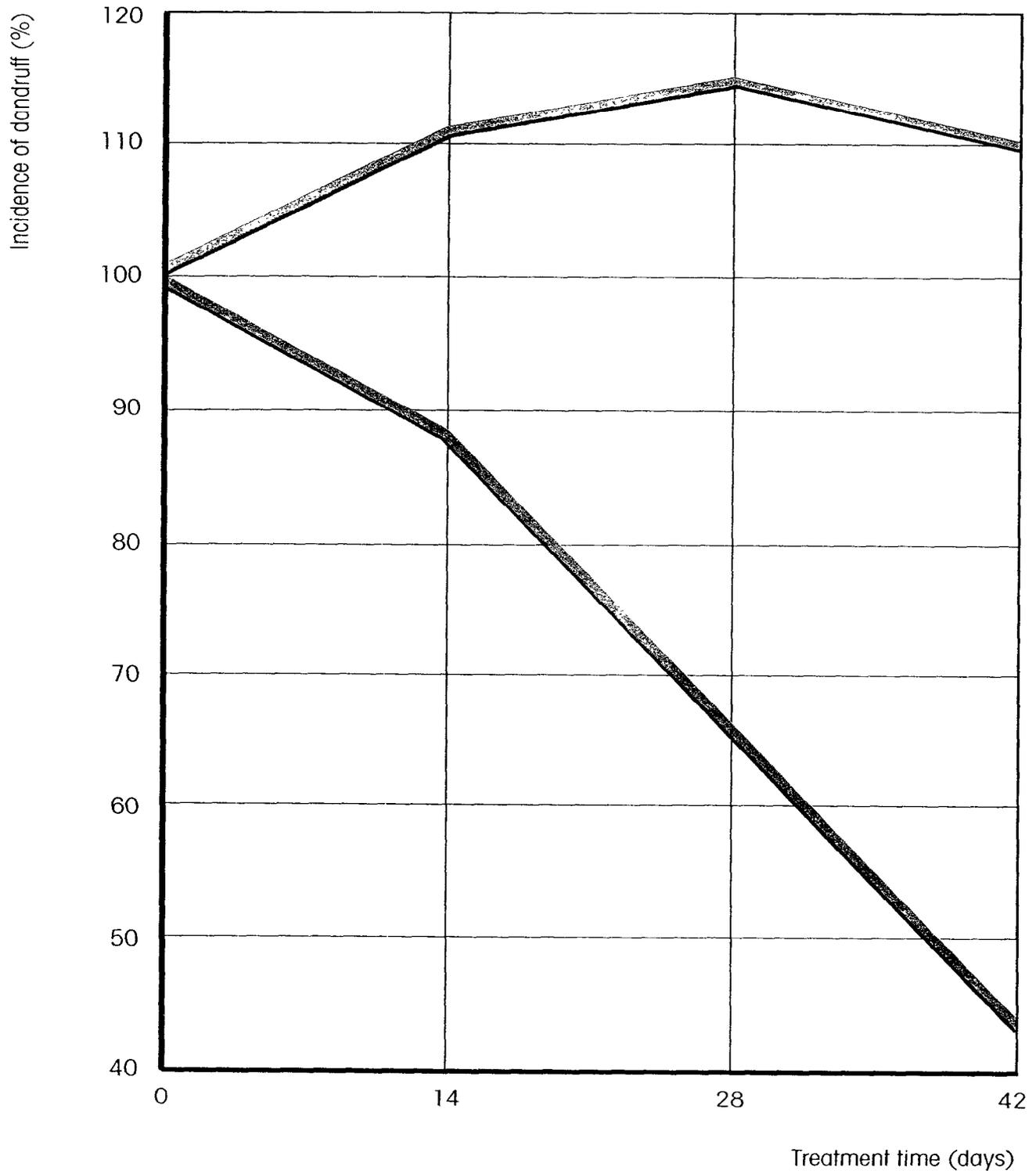


Fig. 2: Antidandruff action (hair tonic)

— = Placebo (40 % Isopropanol / 60 % water)  
— = 0.1 % Octopirox (hair tonic)

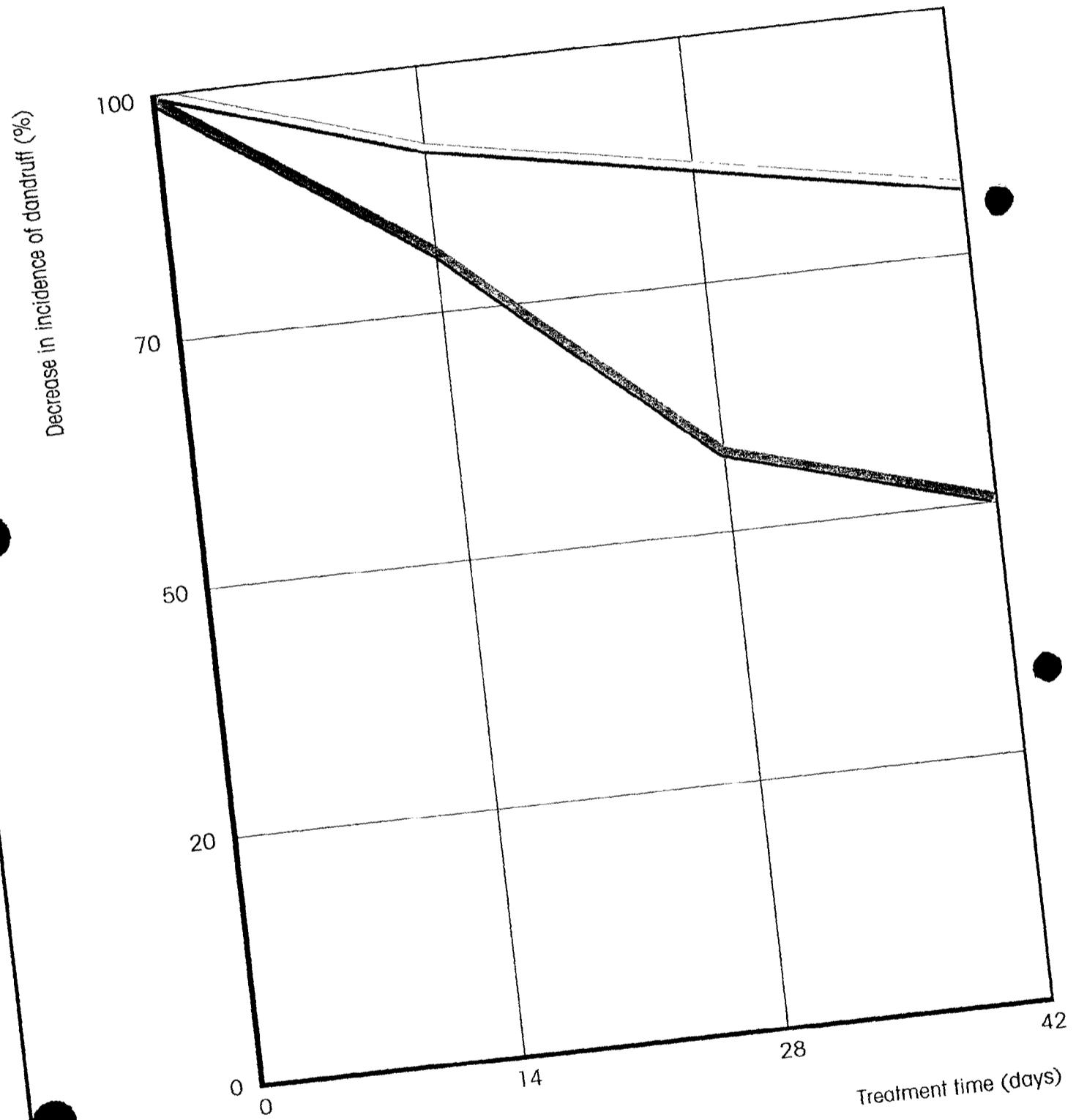


Fig. 3: **Substantivity of Octopirox as a function of the concentration used**

— = European hair. 3 min treatment time at 40°C.  
Octopirox dissolved in 15% alkyl ether sulfate sodium salt (pH 7)

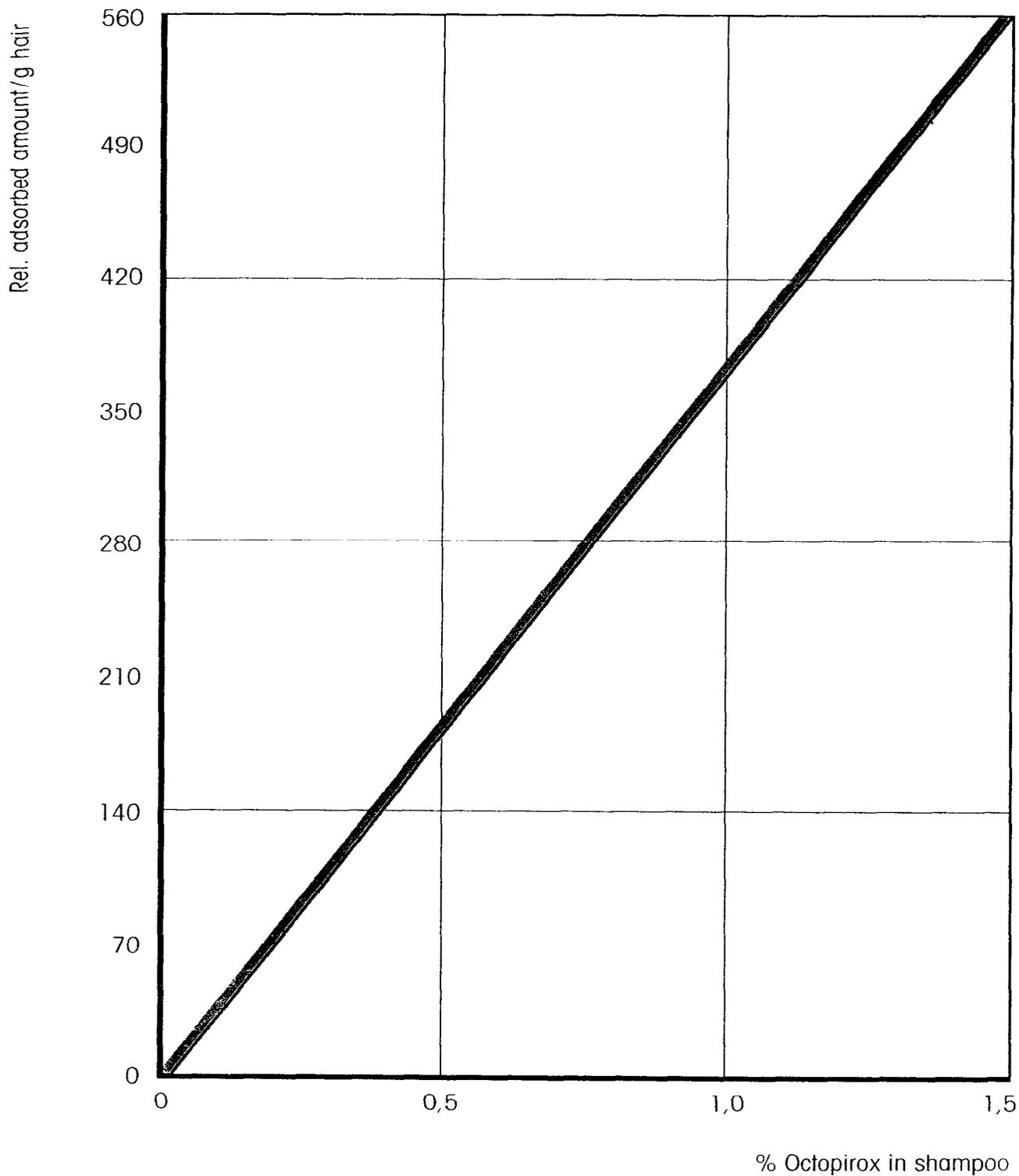


Fig. 4: **Substantivity of Octopirox as a function of the pH**

█ = European hair. 3 min treatment time at 40°C.  
0.5% Octopirox in 15% alkyl ether sulphate sodium salt

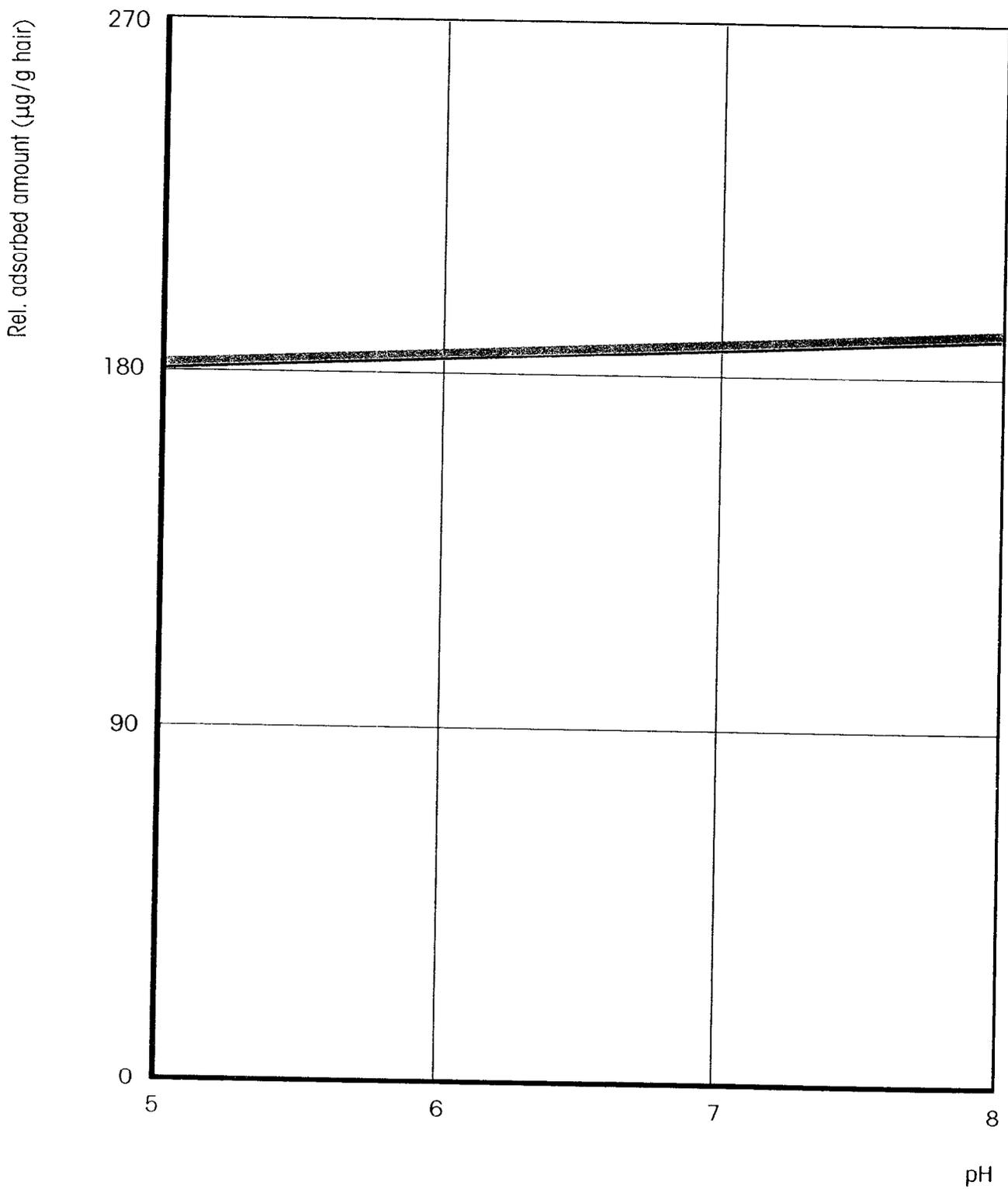


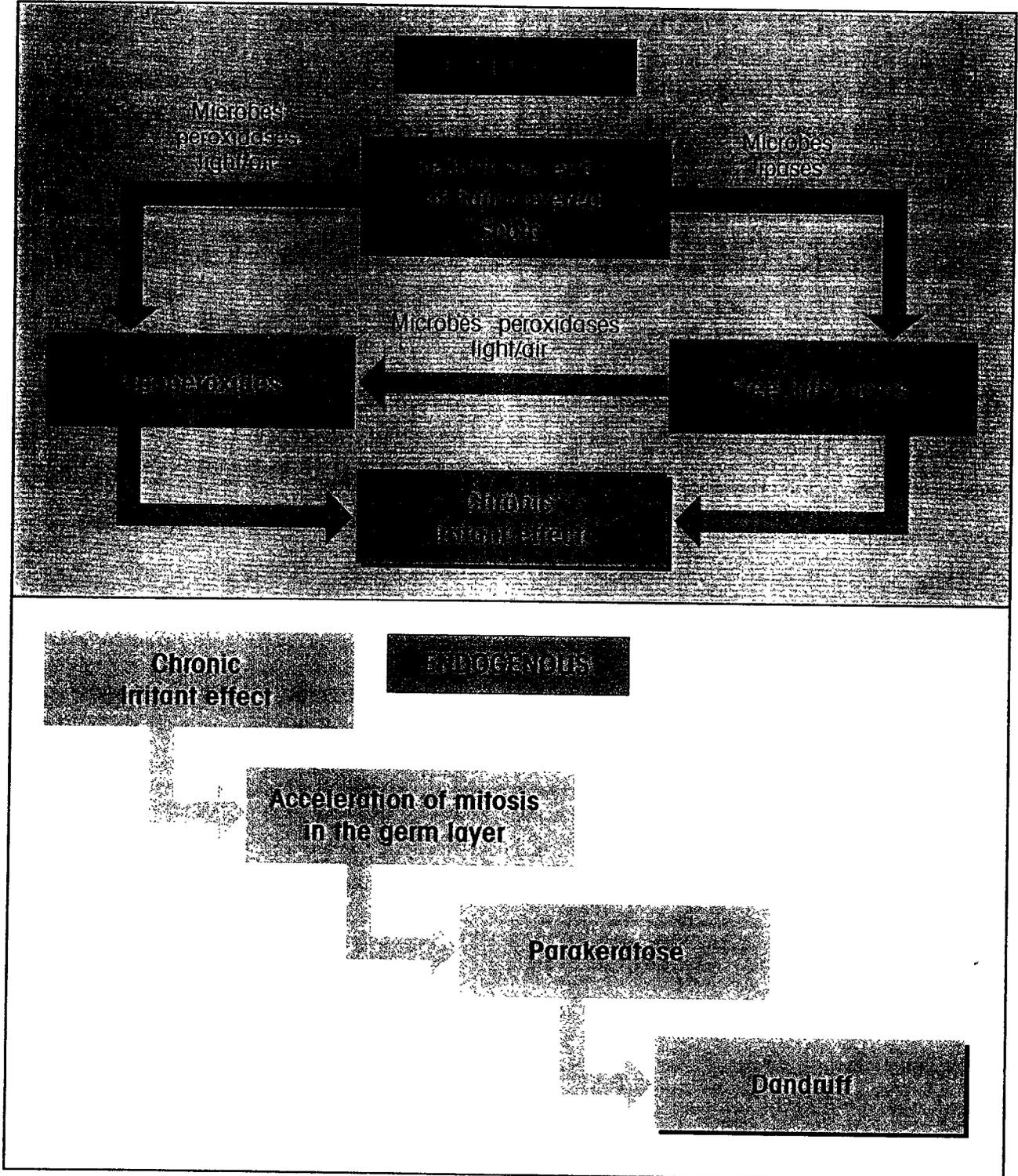
Fig. 5: Antibacterial spectrum of action of Octopirox (pH 7)

|               | Bacteria                  | No. of strains investigated | Minimum inhibitory concentration ( $\mu\text{g/ml}$ ) |   |    |    |    |     |     |     |      |
|---------------|---------------------------|-----------------------------|---|---|----|----|----|-----|-----|-----|------|
|               |                           |                             | 4   | 8 | 16 | 31 | 63 | 125 | 250 | 500 | 1000 |
| Gram-positive | Staph. aureus             | 5                           |   |   |    |    |    |     |     |     |      |
|               | 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                           | ■   | ■ | ■  | ■  | ■  | ■   | ■   | ■   | ■    |

Fig. 6: Antifungal spectrum of action of Octopirox (pH 6,5)

| Species of fungus           | No. of strains investigated | Minimum inhibitory concentration ( $\mu\text{g/ml}$ ) |     |     |     |     |     |     |    |    |    |     |
|-----------------------------|-----------------------------|---|-----|-----|-----|-----|-----|-----|----|----|----|-----|
|                             |                             | 0,1   | 0,2 | 0,5 | 1,0 | 2,0 | 4,0 | 8,0 | 16 | 31 | 63 | 125 |
| Trichophyton rubrum         | 5                           |   |     |     | ■   | ■   |     |     |    |    |    |     |
| Trichophyton mentagrophytes | 4                           |   |     |     | ■   | ■   |     |     |    |    |    |     |
| Other Trichophyton-spec.    | 1                           |   |     |     |     | ■   |     |     |    |    |    |     |
| Microsporum canis           | 1                           |   |     |     |     | ■   |     |     |    |    |    |     |
| Other Microsporum-spec.     | 2                           |   |     |     | ■   |     |     |     |    |    |    |     |
| Epidermophyton floccosum    | 1                           |   |     |     |     | ■   |     |     |    |    |    |     |
| Candida albicans            | 5                           |   |     |     | ■   | ■   |     |     |    |    |    |     |
| Candida tropicalis          | 3                           |   |     |     | ■   |     |     |     |    |    |    |     |
| Other yeastlike fungi       | 3                           |   |     |     | ■   |     |     |     |    |    |    |     |
| Aspergillus niger           | 1                           |   |     |     |     | ■   |     |     |    |    |    |     |
| Aspergillus fumigatus       | 2                           |   |     |     | ■   |     |     |     |    |    |    |     |
| Other moulds                | 4                           |   |     |     | ■   | ■   |     |     |    |    |    |     |

Fig. 7: 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 normal 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. 8.

Fig. 9 shows the solubility of Octopirox in various solvents and important additives such as emulsifiers and solubilizers. Particularly worth noting is the product's extremely good solubility in 1,2-propylene glycol.

The solubility of Octopirox in the most important surfactants varies greatly, as the table shows. Its good solubility in amide ether sulphate magnesium salt (®Genapol AMG) deserves special mention.

## Solubility of Octopirox in various surfactants (15 % active detergent, pH 7, room temperature)

|   |             |
|---|-------------|
| Alkyl ether sulphate sodium salt        | 1.1–1.4 %   |
| Amide ether sulphate magnesium salt     | about 6.2 % |
| Lauryl sulphate sodium salt             | about 2.8 % |
| Sec. alkane sulphonate sodium salt      | about 1.4 % |
| $\alpha$ -olefin sulphonate sodium salt | about 2.3 % |
| Alkyl amidopropyl betaine               | about 1.9 % |

Fig. 10 shows the solubility of Octopirox in three important basic surfactants as a function of the surfactants concentration.

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

Fig. 11 shows that maximum solubility in an amide ether sulphate magnesium salt is observed at pH 5.8. Even with amphoteric surfactants special effects can be established as a function of the pH.

## Influence of the pH

At a neutral pH a substantial part of the Octopirox is in the form of free acid. The  $pK_a$  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 3 and 9, no deterioration of the active ingredient or 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.

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).

Prolonged heating to high temperatures should be avoided if possible.

### **Light stability**

Storage of Octopirox-containing preparations in daylight can cause a deterioration in the active ingredient, depending on the amount of UV light. It is therefore advisable to use 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.

As regards 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 (economizing on consistency modifiers) should be taken into consideration in developing corresponding formulations.

Fig. 8: Solubility of Octopirox in ethanol/water at pH 7 (room temperature)

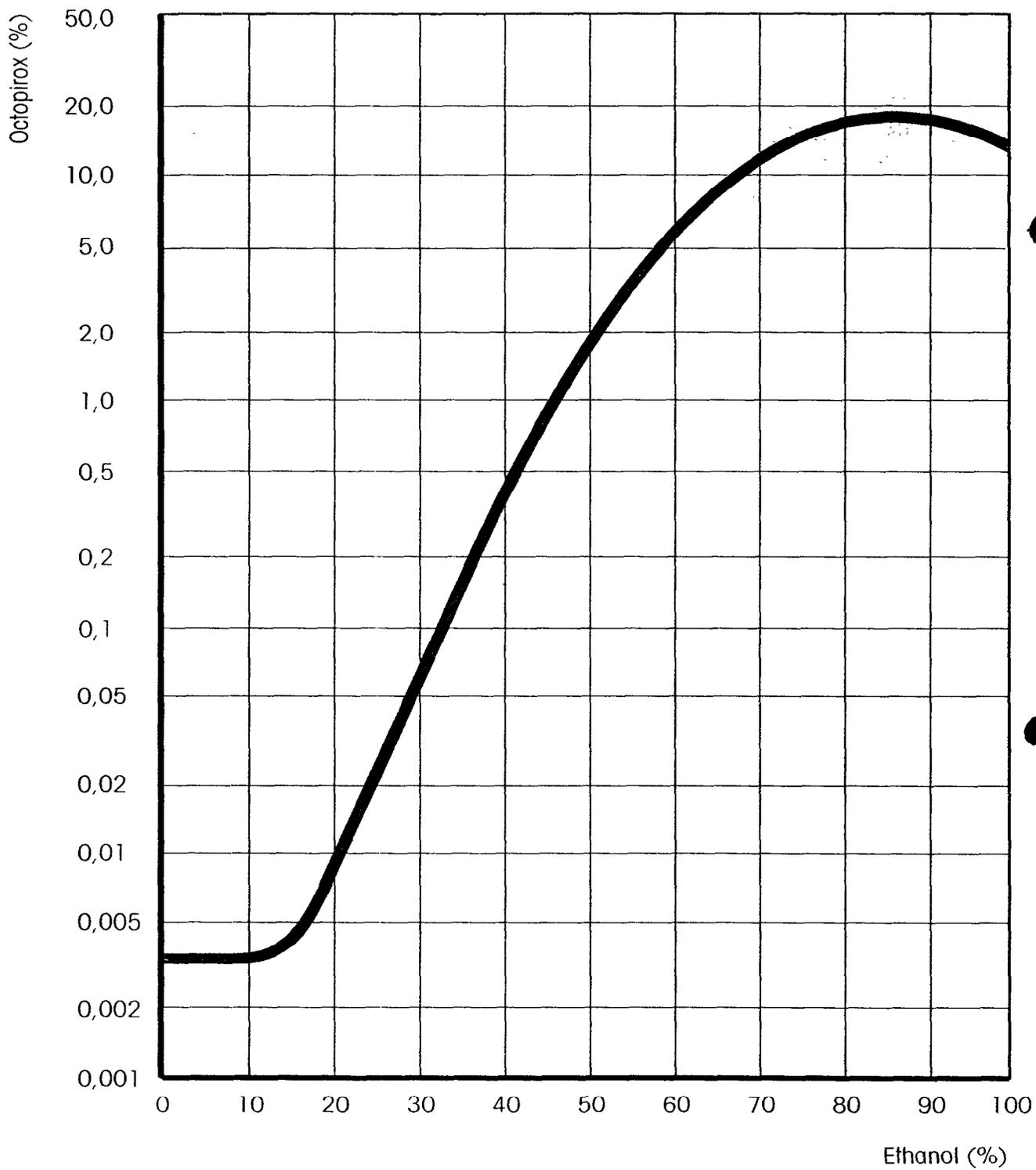


Fig. 9: Solubility of Octopirox in raw materials for cosmetics

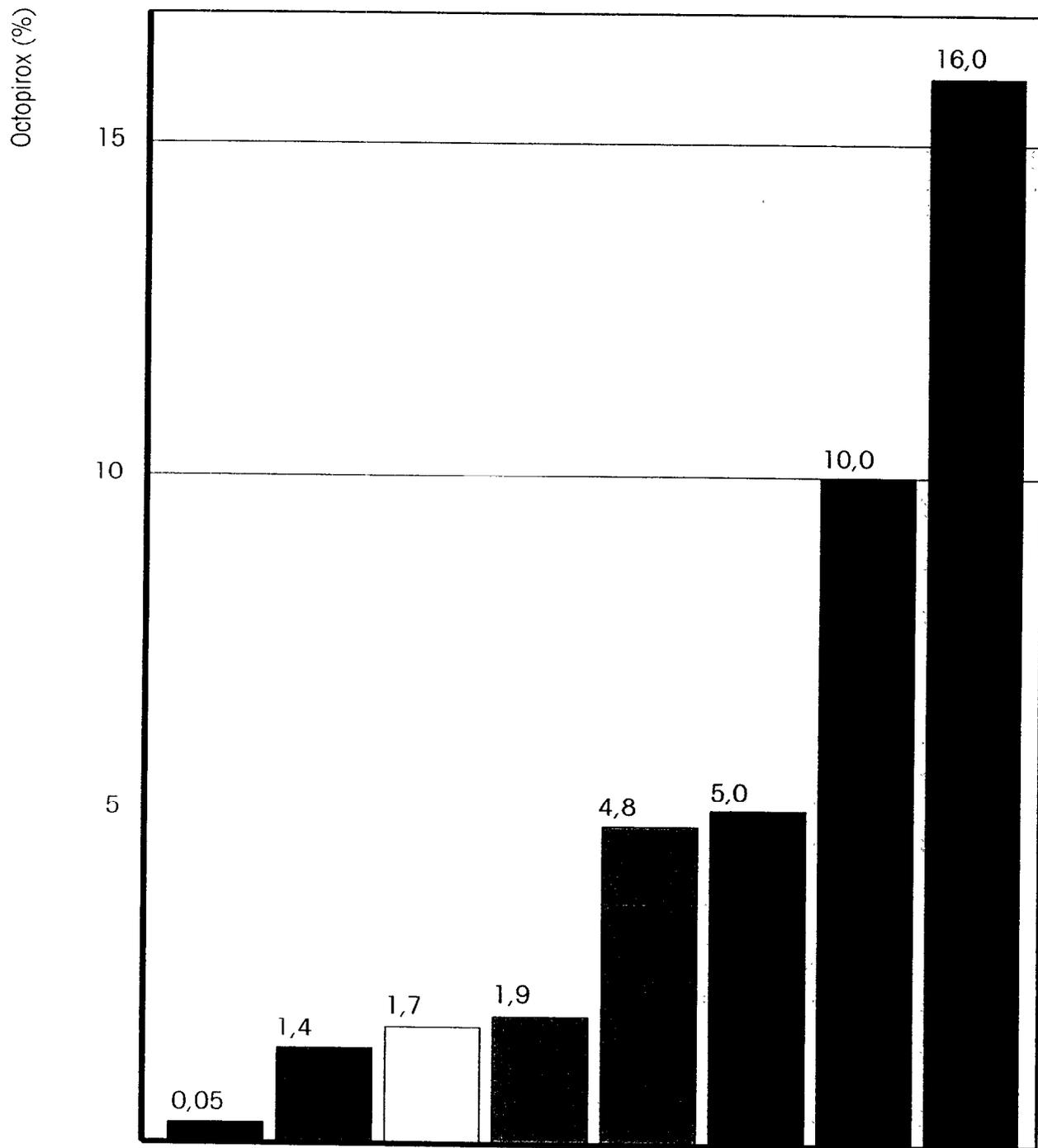
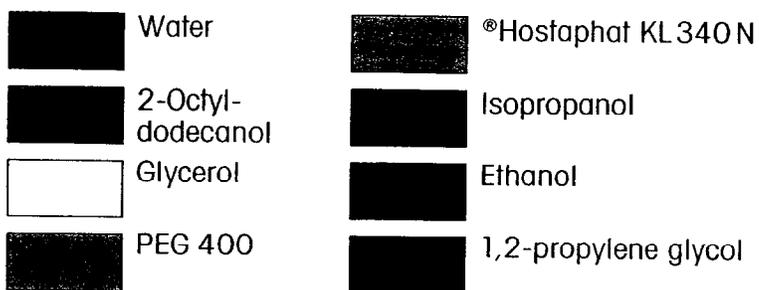


Fig. 10: Solubility of Octopirox in surfactans at pH 7 (room temp.)

-  = amide ether sulphate Mg salt
-  = alkyl amidopropyl betaine
-  = alkyl ether sulphate Na salt

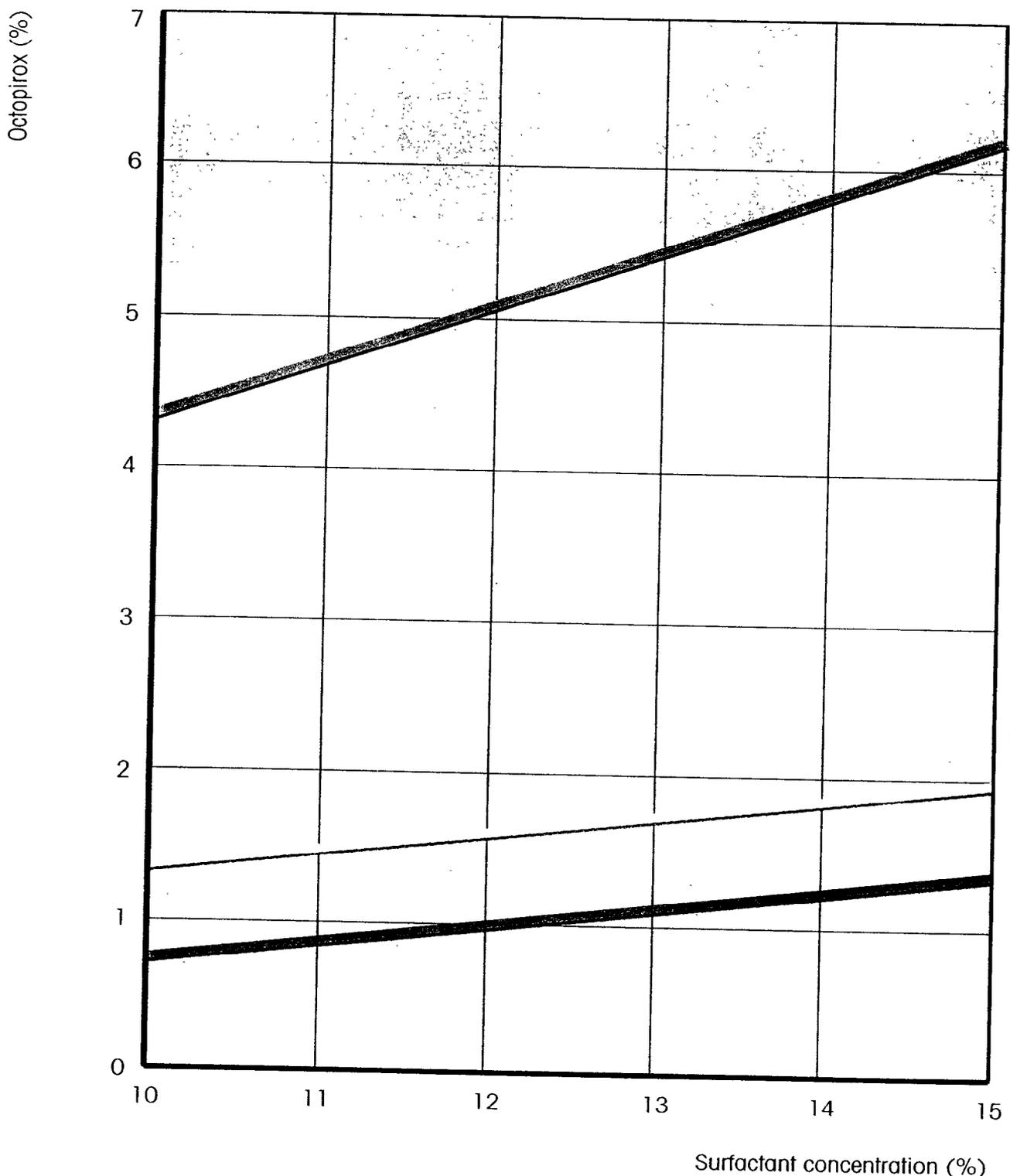


Fig. 11: Solubility of Octopirox as a function of the pH (10% active detergent, room temp.)

— = amide ether sulphate Mg salt  
— = alkyl ether sulphate Na salt

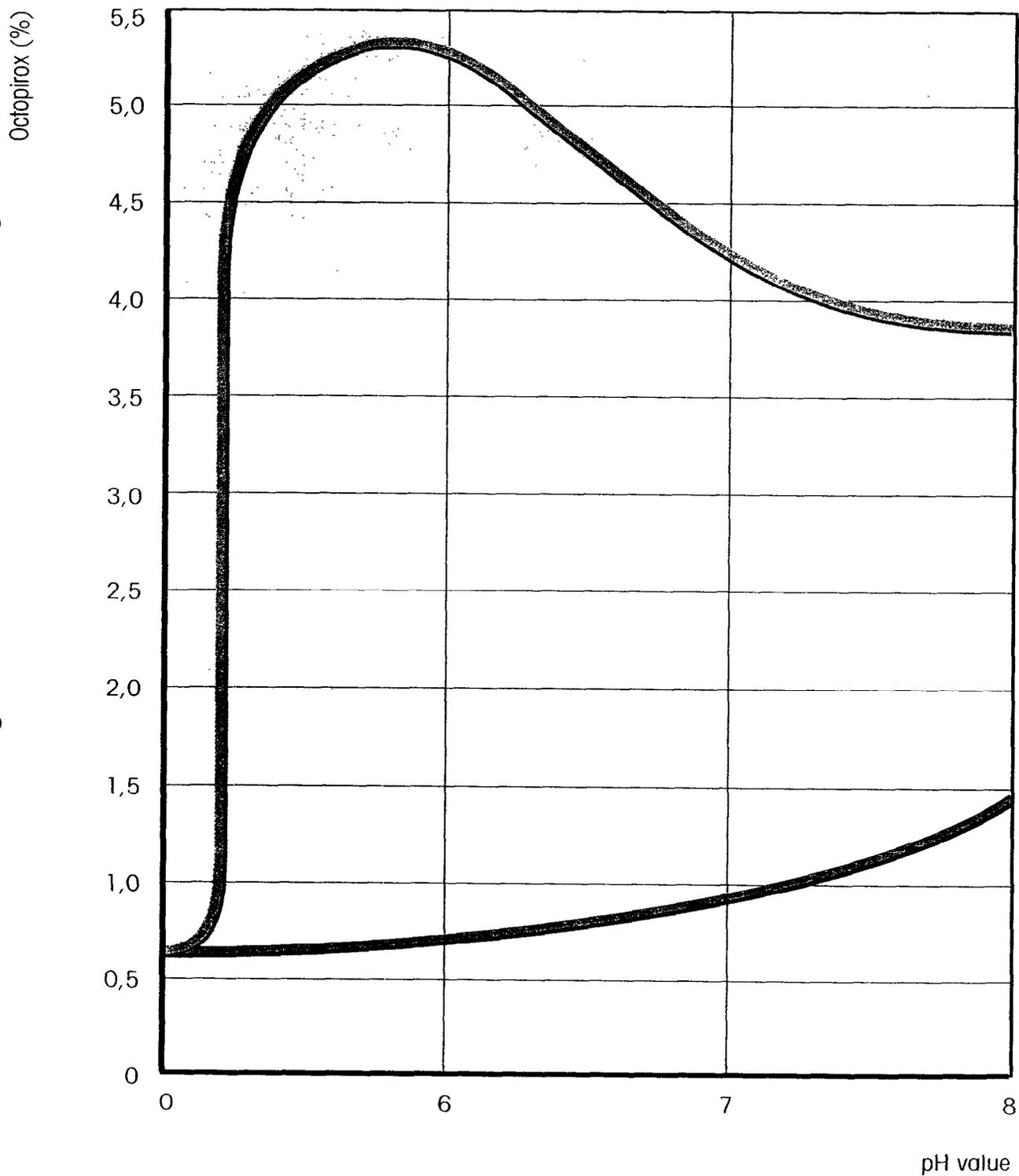
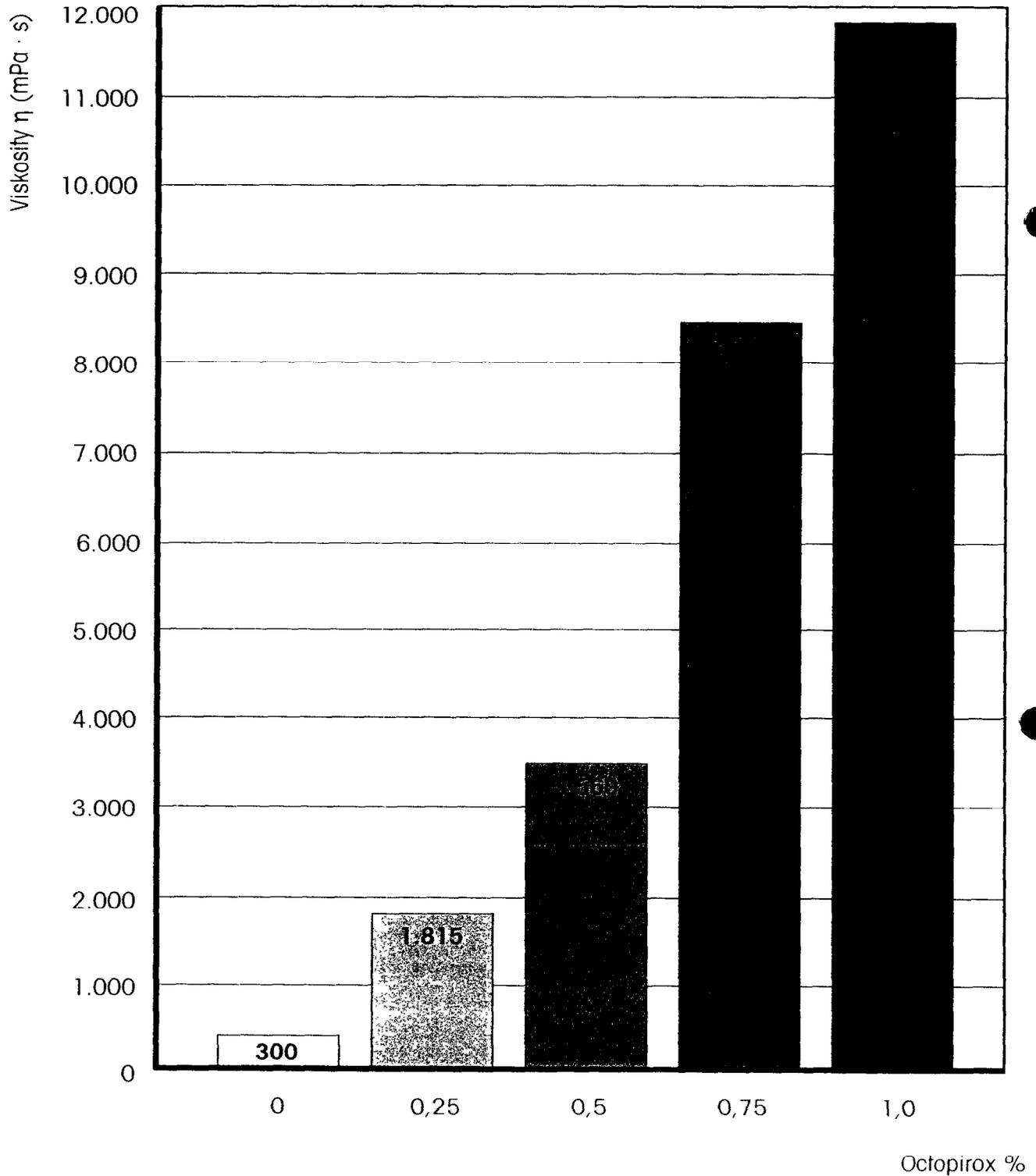


Fig. 12: Viscosity-Increasing effect of Octopirox

8% alkyl ether sulphate Na salt  
4% amide ether sulphate Mg salt  
3% alkyl amidopropyl betaine  
1% sodium chloride  
remainder water (pH 7)  
(Brookfield viscosity 20 min/room temp )



# 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:  $LD_{50} = 8100$  mg/kg body weight

Mouse:  $LD_{50} = 4300$  mg/kg body weight  
Doses up to 1000 mg/kg body weight were tolerated by all test animals, which showed normal behaviour.

Dog:  $LD_{50} = > 4000$  mg/kg body weight

### 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  $LD_{50}$  of the undiluted substance, tested on rats, is  $> 2000$  mg/kg body weight.

### 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 (pH 7 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 test 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. Sensitization

Studies on guinea pigs using the methods of Buehler and Tanaka et al and of Morikawa gave no indication of a sensitizing or photosensitizing 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 non-toxic dose was 100 mg/kg body 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, 0.5 or 1.0% Octopirox in 1,2-propylene glycol to rats (dose: 0.1 or 2 mg per animal) for 6 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 <sup>14</sup>C-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 3 and 8 hours after oral administration of Octopirox (dose: 0.24 mg/kg body weight).

Only very low values were recorded in the tissue. The maximum values were determined in the liver 6 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 6 hours. With the same test procedure, but after rinsing the treated skin after 5 minutes, greatly reduced concentrations in the blood were recorded with a maximum after 1 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 1st and 2nd 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 sensitizing 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 7 applications within 4 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. 9).

In the manufacture of shampoos or hair conditioners with Octopirox a temperature of 80°C should if possible not be exceeded.

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             | 0.5 –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                       | BI/6112   |
| Antidandruff shampoo                       | BI/6115   |
| Antidandruff shampoo                       | BI/6116   |
| Antidandruff shampoo                       | BI/6117   |
| Cream rinse with<br>antidandruff action    | BII/1045  |
| Antidandruff hair tonic                    | BIII/3006 |
| Setting lotion with<br>antidandruff action | BV/5001   |
| Hair cream with<br>antidandruff action     | BIII/1019 |

# 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 rapid colorimetric method described below.

## Colorimetric determination of Octopirox in finished cosmetic formulations

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

Dissolve about 1.5 g 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 ( $= m_p$ ), 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

0.3 g iron (II) sulphate ( $\text{FeSO}_4 \cdot 7 \text{H}_2\text{O}$ ) are dissolved in about 5 ml water in a graduated flask, 0.3 ml acetic acid 99 % 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 1 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.

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

Problems in carrying out this method can be caused by intense yellow preparations or by the presence of substances that form yellow complexes with  $\text{Fe}^{++}$  ions. In these cases the determination should be carried out by the line elution 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 2 years.

A safety data sheet is available on request.

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