ICHTHYOL® PALE

ICHTHYOL-GESELLSCHAFT manufactures unique raw materials from highly sulfuric and organic matter rich limestone in GMP compliant production under the umbrella term of Ichthyol substances. Fascinated by the numerous inclusions of prehistoric scale fish in the rock Greek “Ichthys” was combined with latin “Oleum” to the illustrious name of “ICHTHYOL®”.

Chemically regarded Ichthyol substances are sulfonated shale oils of highest purity. Their uniquely high content of organically combined sulphur is indispensable for their therapeutic efficacy.

The Ichthyol substances belong to the best documented active ingredients from nature today. Their versatile actions and their good tolerance are substantiated by clinical and toxicological studies, respectively.

Under the name of ICHTHYOL® PALE a pale Ichthyol substance specially developed for cosmetic application is offered. In hair and skin care the cosmetic agent with the official INCI-name “sodium shale oil sulfonate” has gained importance worldwide because of its broad action profile. Its benefits in control of severe dandruff and skin blemishes could be proven in a variety of clinical studies. ICHTHYOL® PALE is distinguished by versatile cosmetic formulation possibilities. Manufacture and quality are adapted to the ever-growing legal requirements in order to provide users of our raw material certainty for future utilization.

Convince yourself on the following pages about quality and action mechanisms of a unique raw material.

Thank you for your interest.

Sincerely yours,
ICHTHYOL GESELLSCHAFT

You can find more information under www.ichthyol.com
Advantages at a glance

:: Natural origin (from organic matter rich limestone)
:: High purity
:: Good tolerance
:: Large safety factor (MoS)
:: Broad spectrum of efficacy
:: GMP-controlled manufacture
:: Reliable Processing
:: Versatile formulations (water soluble)
:: Comprehensive documentation
:: Fully REACH compatible

REACH Substance Identification:
ICHTHYOLIC ACID, SODIUM SALT

TRADE MARK
ICHTHYOL® PALE

CAS NO.
1340-06-03

EINECS NO.
215-671-7

INCI

SODIUM SHALE OIL SULFONATE
ICHTHYOL-GESELLSCHAFT: A story to tell

Founded back in 1884 ICHTHYOL-GESELLSCHAFT today is a renowned address in the dermatological field. For more than 130 years the family-run company is based mainly on its unique active ingredient Ichthyol that gave the company its name.

Bringing together tradition and progress as well as science and service ICHTHYOL-GESELLSCHAFT offers comprehensive solutions for dermatological needs.

Laboratories and pilot plant capabilities give the company extensive possibilities for research and development. From the river Rhone in France via the mountains of Austria to Hamburg the substance ICHTHYOL® PALE develops in a multinational cooperation.

The well-tolerated substance of natural origin can be used in hair care products (e.g. for treatment of dandruff) and for skin care as well (e.g. for treatment of blemishes) due to its broad spectrum of efficacy.
ICHTHYOL® PALE Research - Hair Care/Dandruff
A complex condition requires an inspired answer

**Characteristics of Dandruff**
- Colonization with bacteria and fungi
- Skin redness, itching
- Greasy scalp and hair

**ICHTHYOL® PALE takes action**
- Antibacterial and antifungal action
- Soothing, anti-inflammatory action
- Antiseborrhoic action

**ICHTHYOL® PALE**
Take advantage of its broad spectrum of efficacy & compatibility with a variety of substances. **Exemplary shampoo formulation:**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>69.9 %</td>
</tr>
<tr>
<td>Sodium Laureth Sulfate &amp; Lauryl Glucosid</td>
<td>15.0 %</td>
</tr>
<tr>
<td>Cocamidopropyl-Betaine</td>
<td>6.0 %</td>
</tr>
<tr>
<td>Disodium Cocoamidopropionate</td>
<td>5.0 %</td>
</tr>
<tr>
<td>Coco-Glucoside &amp; Glyceryl Oleate</td>
<td>2.5 %</td>
</tr>
<tr>
<td>Sodium Shale Oil Sulfonate</td>
<td>1.0 %</td>
</tr>
<tr>
<td>Parfum</td>
<td>0.5 %</td>
</tr>
<tr>
<td>Phenoxyethanol</td>
<td>0.1 %</td>
</tr>
</tbody>
</table>

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2. Gayko, G.: Sodium shale oil sulfonate against dandruff, Parfums Cosmétiques Actualités, No. 170, Avril/mai 2003
Dandruff most often comes along with unpleasant concomitant symptoms as skin redness, itching and greasy scalp and hair. **ICHTHYOL® PALE** is suitable for an all-embracing treatment. This could be proved in studies in which it was compared with the well known synthetic antidandruff agents Zinc Pyrithione and Piroctone Olamine. All findings reflect: **ICHTHYOL® PALE** is superior due to multifunctionality, good tolerance and long-term safety.

Combination with established anti-dandruff agents

In combination shampoos with potent anti-fungal agents **ICHTHYOL® PALE** provides valuable additional actions for an exceptional antidandruff performance. Faster and broader effects are observed and symptoms concomitant to dandruff are successfully countered.

**ICHTHYOL® PALE** Research - Effect/Dandruff
Comparison with established anti-dandruff agents

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**Fig. 1.** Excerpt from studies of **ICHTHYOL® PALE** vs. Zinc Pyrithione and Piroctone Olamine. **ICHTHYOL® PALE** is superior in improving dandruff and itching due to its multifunctionality.
Coal Tar, clinically beneficial in the treatment of dandruff without doubt, is known to contain carcinogens.

On account of safety reasons, therefore, Coal Tar has already been banned from uncontrolled use in cosmetics in the European Union.

It could be proved that a safe, well-tolerated and, above all, similarly effective and ‘broad spectrum’ alternative of natural origin is available with ICHTHYOL® PALE to substitute Coal Tar in dandruff shampoos. It could be proved that a safe, well-tolerated and, above all, similarly effective and ‘broad spectrum’ alternative of natural origin is available with ICHTHYOL® PALE to substitute Coal Tar in dandruff shampoos. In Europe, this exchange has already been done successfully.

ICHTHYOL® PALE Research - Effect/Dandruff

Comparison with Coal Tar

ICHTHYOL® PALE - well tolerated Coal Tar substitute for reformulation

**Fig. 2.** Excerpt from the comparison study ICHTHYOL® PALE vs. Coal Tar: ICHTHYOL® PALE is as effective as Coal Tar in the reduction of dandruff, however, in contrast to Coal Tar it is safe in long-term treatment.

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4 Gayko, G. et al.: Antidandruff Efficacy of Sodium Shale Oil Sulfonate versus Coal Tar, Cosmetics & Toiletries 120 (3), (2005) 83-92
ICHTHYOL® PALE makes no concessions: Threefold action in one ingredient for modern treatment of skin blemishes and pimples. In a study on 101 humans after a treatment period of 6 weeks great improvements in elimination of skin impurities could be observed in nearly 80% of the cases using a cream containing 1 % of ICHTHYOL® PALE (see exemplary formulation below).

Exemplary cream formulation:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aqua</td>
<td>25-50 %</td>
</tr>
<tr>
<td>Propylene Glycol</td>
<td>5-10 %</td>
</tr>
<tr>
<td>PEG-20 Glyceryl Stearate</td>
<td>5-10 %</td>
</tr>
<tr>
<td>Titanium Dioxide</td>
<td>1-5 %</td>
</tr>
<tr>
<td>Sodium Shale Oil Sulfonate*</td>
<td>1.0 %</td>
</tr>
<tr>
<td>Petrolatum</td>
<td>10-25 %</td>
</tr>
<tr>
<td>Caprylic/Capric Triglyceride</td>
<td>5-10 %</td>
</tr>
<tr>
<td>Cetyl Alcohol</td>
<td>1-5 %</td>
</tr>
<tr>
<td>Glyceryl Stearate</td>
<td>1-5 %</td>
</tr>
</tbody>
</table>

*ICHTHYOL® PALE is added to the water phase containing the hydrophilic compounds.

FORMULATIONS:
Clarifying creams, Cleansing milks, Alcoholic-aqueous solutions
**ICHTHYOL® PALE Research - Skin irritations like redness and itching**

Inflammatory processes like redness and itching of the skin can be countered excellently by **ICHTHYOL® PALE**. The antinflammatory action was confirmed recently by means of the UVB erythema test. In the study a cream with 4 % of **ICHTHYOL® PALE** was compared with the active ingredient-free vehicle and a reference product containing 0.5 % of hydrocortisone as active substance.

**ICHTHYOL® PALE** in a concentration of 4 % exerts an anti-inflammatory action equivalent to 0.5% hydrocortisone:

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**COMPARISON OF SKIN COLOUR 24H AFTER UVB-IRRADIATION**

- 4% **ICHTHYOL® PALE**
- reference 0.5% Hydrocortisone
- active ingredient-free vehicle

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The anti-bacterial and anti-mycetic actions of ICHTHYOL® PALE, expressed by the minimal inhibitory concentration (MIC) and inhibiting zone diameters, were determined in dilution and plate diffusion tests.

## EFFECT OF SODIUM SHALE OIL SULFONATE

<table>
<thead>
<tr>
<th>Micro-organism</th>
<th>MIC*(%)</th>
<th>Inhibiting zone Aqueous solution of 1% ICHTHYOL® PALE</th>
<th>diameter (mm) Aqueous solution of 5% ICHTHYOL® PALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>0.039</td>
<td>1.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>0.039</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Pityrosporum spec.</td>
<td>-</td>
<td>2.0</td>
<td>11.0</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>0.2-5.1</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Dermatophytes</td>
<td>0.05-0.1</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Propionibacterium acnes</td>
<td>0.039</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* MIC / Minimum inhibitory concentration

**ICHTHYOL® PALE** exhibits anti-microbial actions in all micro-organisms relevant in cosmetically significant skin conditions.
ICHTHYOL® PALE Research - Safety evaluation

The good tolerance of ICHTHYOL® PALE has been verified in numerous toxicological studies. ICHTHYOL® PALE showed itself to be well-tolerated both in short-term as well as long-term administration. There was no evidence of any teratogenic, mutagenic or cancerogenic properties. The safety of a raw material such as ICHTHYOL® PALE is best illustrated by calculating the „margin of safety“. With hair shampoo (rinse-off) and body lotion (leave-on) as formulation examples, safety factors clearly above the required minimum value of 100 result for ICHTHYOL® PALE.

ICHTHYOL® PALE can, therefore, be classified as a safe substance in accordance with the European Regulation on Cosmetic Products.

ON THE SAFE SIDE
ICHTHYOL® PALE is well tolerated

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Safety Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shampoo (rinse-off)</td>
<td>230769</td>
</tr>
<tr>
<td>Body Lotion (leave-on)</td>
<td>1730</td>
</tr>
</tbody>
</table>

ICHTHYOL® PALE can, therefore, be classified as a safe substance in accordance with the European Regulation on Cosmetic Products.

7 Cholcha, W. et al.: Experimental Studies on the Tolerance of Pale Sulfonated Shale Oil Following Local and Systemic Application, Arzneim. – Forsch./Drug Res. 44(I), 2 (1994) 170
There are still some reports in the scientific literature in which sulfonated shale oils, such as ICHTHYOL® PALE, are grouped with tars because of their related efficacy and characteristic odour. This classification, however, is wrong. ICHTHYOL® PALE and tars differ in terms of:

<table>
<thead>
<tr>
<th>ICHTHYOL® PALE</th>
<th>COAL TAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>From nature</td>
<td>From nature</td>
</tr>
<tr>
<td>Raw material: oil shale</td>
<td>Raw material: coal</td>
</tr>
<tr>
<td>Processing temperature: &lt;480 °C</td>
<td>Processing temperature: 1000 °C</td>
</tr>
<tr>
<td>Rich in sulphur (11-13.5 %)</td>
<td>Low in sulphur (&lt;1 %)</td>
</tr>
<tr>
<td>Water-soluble</td>
<td>Non-water-soluble</td>
</tr>
<tr>
<td>Surface-active</td>
<td>Non-surface-active</td>
</tr>
<tr>
<td>High purity (&lt;0.1 ppb BaP*)</td>
<td>Severely PAH-contaminated (&gt;5,000,000 ppb BaP*)</td>
</tr>
<tr>
<td>Non-mutagenic, Non-cancerogenic</td>
<td></td>
</tr>
</tbody>
</table>

The high purity of ICHTHYOL® PALE is also confirmed by PAH analyses. It can be demonstrated with gas chromatography/mass spectrometry that ICHTHYOL® PALE contains only hardly detectable traces of polycyclic aromatic hydrocarbons (regularly less than 0.1 ppb benzo[a]pyrene). These findings coincide with the good tolerance of ICHTHYOL® PALE. In addition, if one considers the active ingredient concentration to be applied, i.e. 0.5 - 5 %, this means that the content of benzo[a]pyrene as leading substance is below the analytical detection limit in the finished cosmetic product.
ICHTHYOL® PALE Manufacture -
Origin and GMP-controlled manufacture

OIL SHALE
ICHTHYOL® PALE has an an extremely interesting history of development.

In geoscientific terms its origin goes back to deposits of microscopically small algae (phytoplankton) in a special lagoon milieu in the alpine region of the mesozoic era.

Under certain conditions large quantities of organically combined sulphur could be formed in the biomass during biological (anaerobic) degradation of the marine phytoplankton by sulphate reducing bacteria.

By diagenetic processes the periodic deposits developed into schist-like sedimentary rocks (oil shale) that contain the marine biomass in a solidified form today.

The extraction of suitable shale rock from deposits inside the mountain and the further manufacture of ICHTHYOL® PALE are very complex and challenging technically. At the end of geological processes qualitatively appropriate, highly sulphuric deposits of oil shale are hidden hardly accessible inside the mountains and have to be exploited in a complicated system of underground chambers.

In the dry distillation process following underground mining the oil shale rock is gently heated under exclusion of air.

Thereby, biomass present in the rock is decomposed only to such an extent that it can be converted from a solid into a liquid form. The resulting shale oil is distinguished by a high content of organically combined sulphur (up to 15 %) which is unequalled world-wide.

Distillative Refinement
The shale oil is purified before undergoing further processing. A distillation treatment is carried out in order to remove finely distributed solid particles and high-molecular substances (e.g. polycyclic aromatic hydrocarbons, PAH).

Thereby, one obtains a special, low-boiling shale oil fraction.

ICHTHYOL® PALE
The low-boiling shale oil fraction is allowed to react with concentrated sulphuric acid in a gentle sulfonation reaction and is then neutralized with sodium.
hydroxide solution. The non-polar oil is thereby converted into the water-soluble and surface-active ICHTHYOL® PALE.

Quality Assurance
To obtain a constantly good quality of ICHTHYOL® PALE, it is absolutely necessary to carry out the manufacturing process under exactly defined and controlled conditions in accordance with the Guidelines for Good Manufacturing Practice, GMP. Our manufacturing site is regularly inspected by health authorities. A corresponding GMP-Certificate is available.