



InuMax Advanced Retinol Cosmetic Active

**Maximum Retinol Stability,
Bioavailability and Lower
Irritation Potential**

Retinol: Functions in the Skin

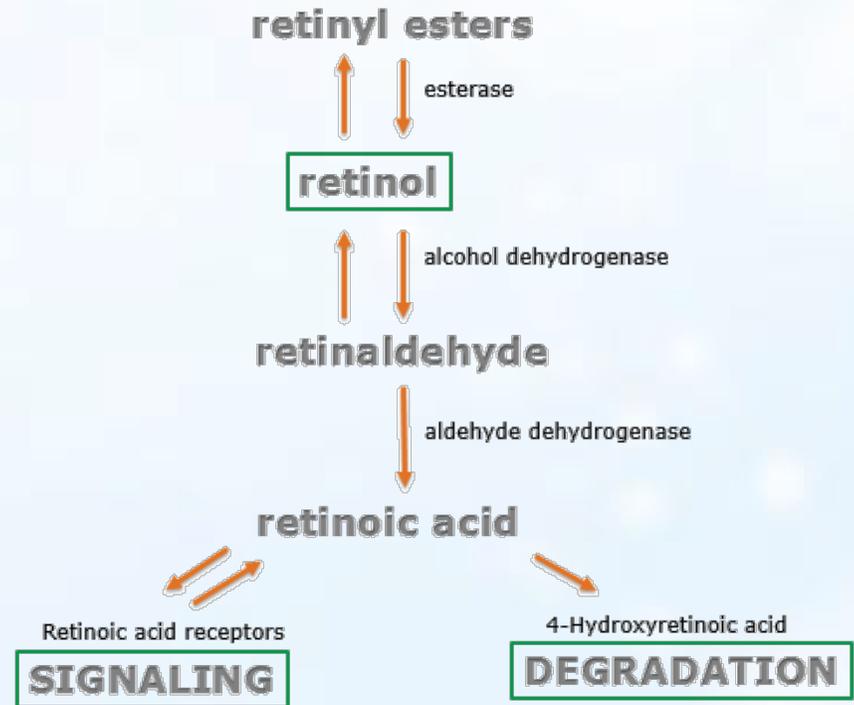
Essential for the formation and maintenance of the skin:

- A precursor for synthesis of endogenous retinaldehyde and retinoic acid
- **Anti-aging effect** of topical retinol is mainly linked to the receptor-mediated **gene activation** induced by the ligand retinoic acid in the skin cells⁽¹⁾, modulating:
 - Mitosis and thickening of epidermis
 - UV induction of extracellular matrix metalloproteinase
 - Stimulation of collagen synthesis
 - Regulation of keratinocytes terminal differentiation

Critical age-dependent changes in the skin may be reverted by topical application⁽²⁾

- Improvement of **coarse wrinkling**
- Increased **smoothness**

Conversion of Retinol into Retinoic Acid ⁽³⁾



Topical retinol has to be metabolised to retinoic acid in the skin to exert the genomic effects

Retinol: Uses in Personal Care



Among the most well-known and well-studied cosmetic ingredient used in a large variety of cosmetic preparations to provide specific abilities to ⁽⁴⁾:

- Counteract **skin aging** by inducing the biosynthesis of collagen in the skin
- Counteract **photoaging** by impeding the UV-induced synthesis of collagen-reducing enzymes
- Prevent **oxidative stress**
- Control **cutaneous bacterial flora**



(4) SCCS/1576/16 European Commission. Health and Food Safety, cited from Serri and Iorizzo, 2008

* Retinol not used in sunscreen products and not used on baby skin-care products in the EU

Retinol: Global Market Drivers



A steadily growing market: CAGR 6,6%* by 2020

Demographic drivers

- Increasing in life expectancy of a rapidly **aging world population**
- Social media rising **consciousness of the benefits of Retinol** in anti-aging routines
- Rise in stress caused by hectic lifestyles and pollution, driving a growing demand of retinoids in **Developing Countries**

Industry drivers

- **„Supercharged Retinol“** and **„Fortified Retinol“** extensively claimed by so called „hard-working“ anti-aging products
- Increasing demand of **professional-grade and OTC cosmetics**

**High strength
retinol claims
in Skin Care**

* Estimated based on Global Industry Analytics

Challenges Affecting Retinol-based Products



Regulatory status of Retinol limits usage levels



- Health Canada (Hotlist): cosmetic products < 1.0% RE



- In many cases 1% is the conventional maximum concentration that formulators use

California's Safe Cosmetics Program and Proposition 65: daily dosage < 10,000 IU or 3,000 RE



- Health agency ANVISA: > 1.0% RE are classified as Drugs



SCCS Opinion Adopted (EU Commission) ⁽⁴⁾

| Product Category | Retinol Equivalents (RE) |
|--|--------------------------|
| Face and hand creams and other leave-on products | 0,3% |
| Rinse-off products | 0,3% |
| Body lotions | 0,05% |



- Permitted Cosmetic Ingredient



- Amended the Japanese Standards of Quasi-drug Ingredients testing methods of Retinol esters



- Ongoing regulatory updates currently for public consultation

Challenges Affecting Retinol-based Products

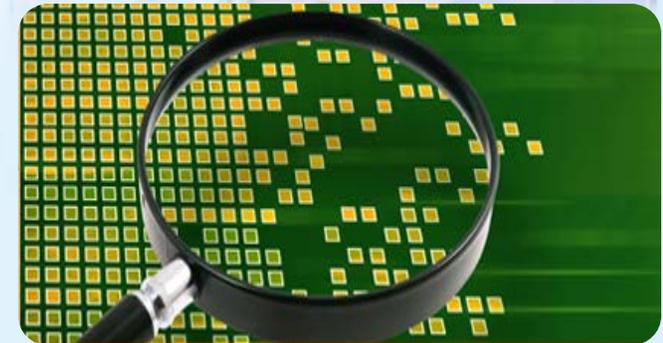


Consumer experiences and expectations impact opinion

- ❑ Beneficial effects of **low strength retinol-based products** are seen slowly and over a long period of time, which often leads to discontinuation of use.
- ❑ Preference for **prescription-like or OTC products**, believed to be highly effective for anti-aging skin.
- ❑ Related **adverse side-effects**, like irritation, erythema, and scaling of the skin.

Effectiveness for formulators can be challenging

- ❑ Maximize **potency** and minimize **degradation**



Benefits of Encapsulated Retinol

Cosmetic active delivery technologies can improve the performance of specific ingredients in meaningful ways. For Retinol, some key benefits include:

1. Improve Stability of Retinol

2. Improve Bioavailability

3. Reduce Irritation Potential on the Skin



Benefits of Encapsulated Retinol



1. Improve Stability of Retinol

SCCS general comments on Stability of *Unencapsulated* Retinol ⁽⁵⁾:

*„Retinol is unstable and easily gets **degraded to biological inactive forms** when exposed to oxygen, heat, light and heavy metals“, and „is unstable to acids and to alkali in the presence of oxygen“*

Encapsulation technologies can enhance the stability of retinol by safeguarding it from environmental and intrinsic factors

(5) Mukherjee *et al.*, 2006 as referred by the SCCS/1576/16 European Commission.

Benefits of Encapsulated Retinol



2. Improve Bioavailability

SCCS general comments on Skin Bioavailability of *Unencapsulated* Retinol ⁽⁴⁾:

*„Recent in vitro skin penetration data....observed some skin penetration, although most found that the vast majority of the test material was **absorbed by the stratum corneum** and was, thereby, considered **non-bioavailable**.“*

Encapsulation technologies can improve the epidermal bioavailability of retinol by delivering the ingredient into deep skin layers

Benefits of Encapsulated Retinol



3. Reduce Irritation Potential on the Skin

Norwegian Scientific Committee for Food Safety (VKM) Comments on Skin Irritation of *Unencapsulated* Retinol ⁽⁶⁾:

*„the retinoids used in cosmetics **may also induce local irritation**. The concentrations of these retinoids in cosmetic products are to a high degree determined and limited by these immediate adverse effects“*

Encapsulation technologies can reduce the irritation potential of Retinol by modulating the release of retinol

(6) VKM Norwegian Scientific Committee for Food Safety (2012)



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Maximum Retinol Stability, Bioavailability and Lower Irritation Potential

InuMax Advanced Retinol Cosmetic Active



Description

- » A cosmetic active with 8% retinol encapsulated with Air Products' patent pending **InuMax** technology

✓ **Maximum Stability**

✓ **Bioavailability**

✓ **Lower Irritation**

Key Benefits

- » Enables **high-load retinol** use-level claims
- » Proven to significantly enhance the **stability of retinol over 28 weeks**
- » Provides notably **lower skin irritation potential** from retinol
- » Uses an advanced delivery technology to enhance the **epidermal bioavailability of retinol**
- » Offers **cost-effective use of retinol** in final product formulations

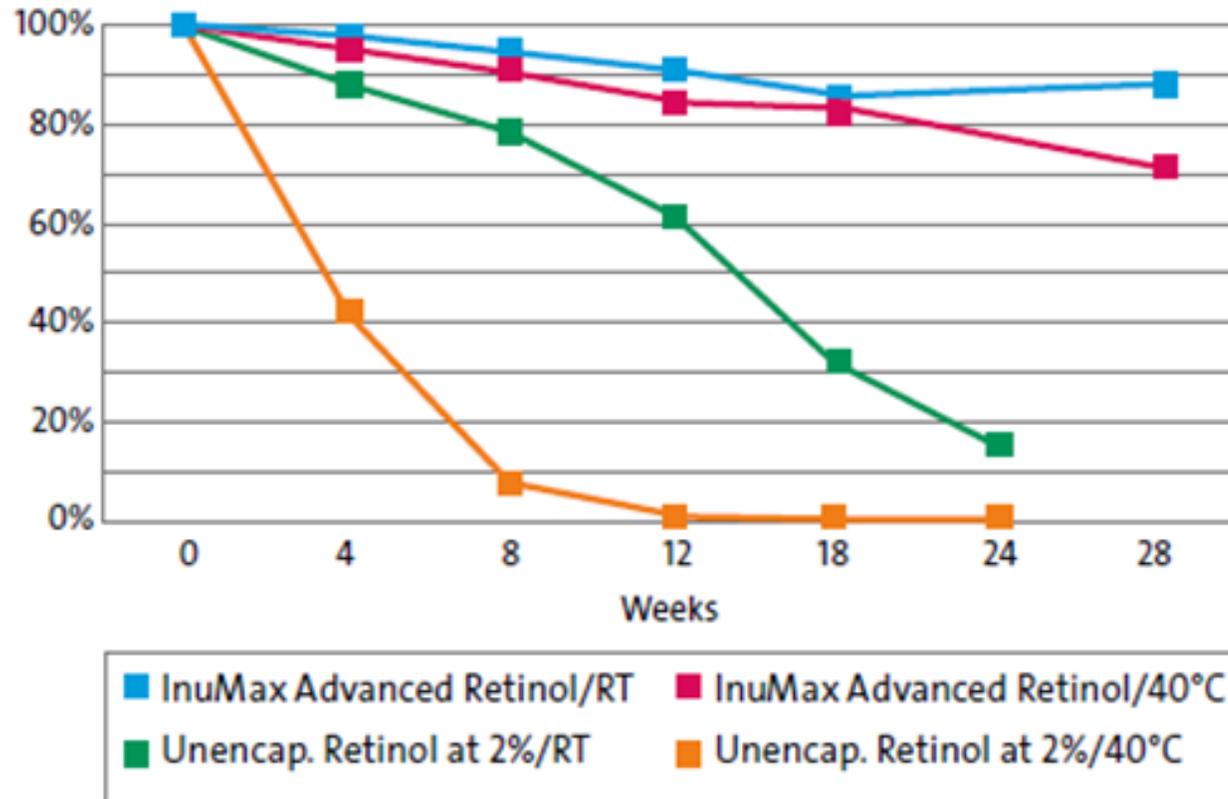
InuMax Advanced Retinol Cosmetic Active

Provides a high degree of Retinol stability



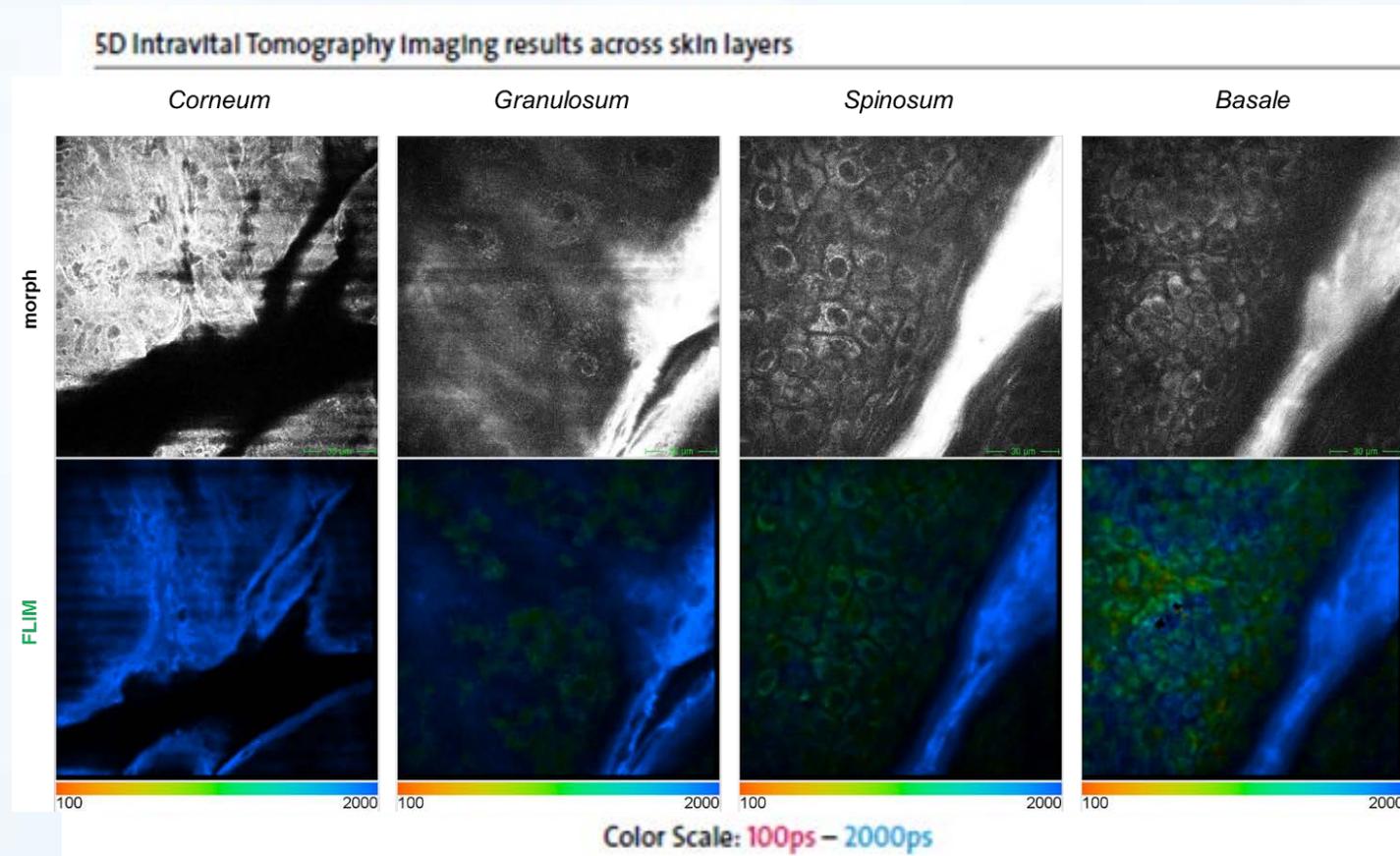
In vitro study – enhanced retinol stability

Retinol stability of InuMax Advanced Retinol Cosmetic Active upon storage for 28 weeks (HPLC method)



InuMax Advanced Retinol Cosmetic Active

Delivers a high load of Retinol into the skin



Channel 2 (Retinol) Excitation:
 $\lambda_{ex} = 710 \text{ nm}$

Retinol, which appears with a blue fluorescence is seen to have penetrated into the Stratum Basale layer after 5 h

InuMax Advanced Retinol Cosmetic Active



Enables low skin irritation from Retinol

Human Patch Test of InuMax delivery technology with encapsulated Retinol – in vivo

| | |
|----------------------------|--|
| Method | Epicutaneous Human Patch Test (in vivo) 50 Test persons, in accordance with the Colipa Guidelines. Assessment of the primary skin irritation potential |
| Concentration | InuMax delivery technology, encapsulating retinol, used at a use level to delivery 0.3% active Retinol in aqueous solution |
| Site and Incubation | Back skin. 48 h incubation period |
| Assessment Period | 48 h and 72 h |

**Classified as
“Harmless“ in
a concentration
of 4%**

InuMax Advanced Retinol Cosmetic Active

Enables low skin irritation from Retinol



In vivo study – lower skin irritation potential ⁽⁷⁾

Irritation profile of InuMax Retinol Cosmetic Active compared to free retinol at skin's stratum spinosum

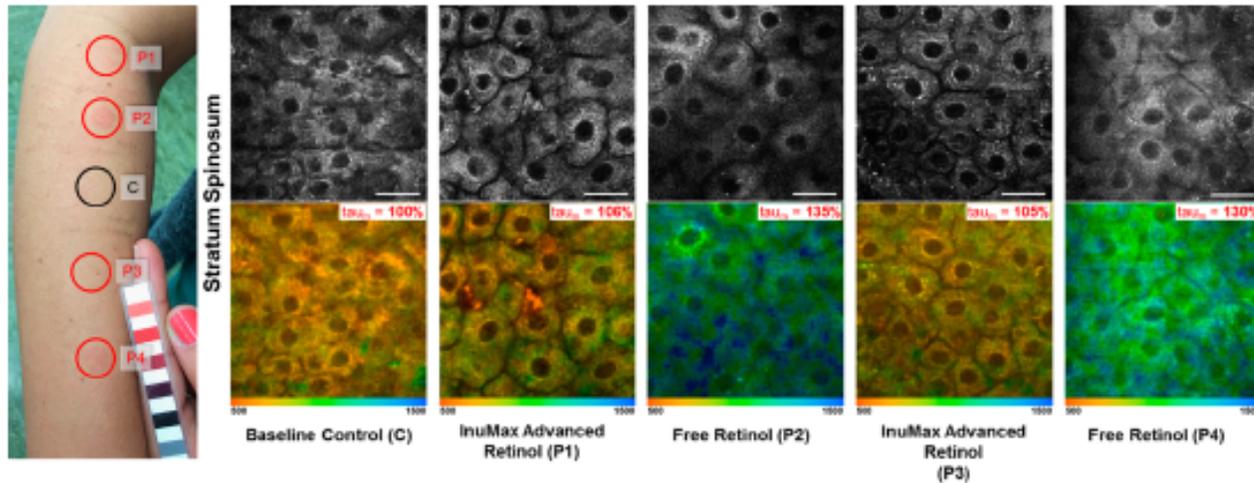
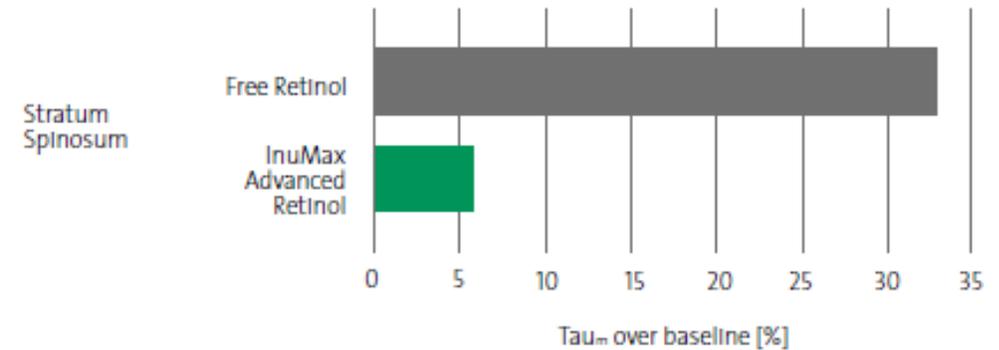


Figure 3: Quantification of skin irritation profile of InuMax Retinol compared to free retinol relative to baseline conditions for Stratum Spinosum



- **InuMax Retinol** = InuMax Advanced Retinol Cosmetic Active at 4% in an aqueous dilution (represents ~ 0.3 % of active Retinol)
- **Free Retinol** = 4 % of a corresponding solution containing the same ingredients with the exception of the vesicle forming ingredients in an aqueous dilution (represents ~ 0.3% of active Retinol)

(7) Volker Huck et al. From morphology to biochemical state – intravital multiphoton fluorescence lifetime imaging of inflamed human skin; Sci. Rep. Published: <http://www.nature.com/articles/srep22789>



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Product summary

- » Enables high-load retinol use-level claims
- » Is proven to significantly enhance the stability of retinol over 28 weeks
- » Uses an advanced delivery technology to enhance the epidermal bioavailability of retinol
- » Provides notably lower skin irritation potential from retinol
- » Enables cost-effective use of retinol in final product formulations



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