Scientific Committee on Consumer Safety

SCCS

OPINION ON

Polidocanol

ADDENDUM to the SCCP opinion on polidocanol (SCCP/1130/07)

The SCCS adopted this opinion at its 13th plenary meeting

of 13-14 December 2011

About the Scientific Committees

Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

They are: the Scientific Committee on Consumer Safety (SCCS), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) and are made up of external experts.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Agency (EMA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCCS

The Committee shall provide opinions on questions concerning all types of health and safety risks (notably chemical, biological, mechanical and other physical risks) of non-food consumer products (for example: cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products such as detergents, etc.) and services (for example: tattooing, artificial sun tanning, etc.).

Scientific Committee members

Contact
European Commission
Health & Consumers
Directorate D: Health Systems and Products
Unit D5 - Risk Assessment
Office: B232 B-1049 Brussels
Sanco-SCCS-Secretariat@ec.europa.eu

ISSN 1831-4767 ISBN 978-92-79-30727-0
Doi:10.2772/22389 ND-AQ-11-020-EN-N

ACKNOWLEDGMENTS

Prof. J. Angerer
Dr. U. Bernauer
Dr. C. Chambers
Prof. G. Degen (rapporteur)
Dr. W. Lilienblum (associated Scientific Advisor)
Dr. S.C. Rastogi
Dr. E. Nielsen
Prof. V. Rogiers
Prof. T. Sanner (chairman)
Dr. J. van Engelen
Prof. R. Waring
Dr. I.R. White

Keywords: SCCS, scientific opinion, polidocanol, laureth-9, directive 76/768/ECC, CAS 3055-99-0, EC 221-284-4

Opinion to be cited as: SCCS (Scientific Committee on Consumer Safety), Opinion on polidocanol. Addendum to the SCCP opinion on polidocanol (SCCP/1130/07), 13-14 December 2011

TABLE OF CONTENTS

ACKNOWLEDGMENTS 3

1. BACKGROUND 5

2. TERMS OF REFERENCE 5

3. OPINION 6

   3.1. Local anaesthetic properties of polidocanol when applied topically 6

   3.2. Antipruritogenic effects of polidocanol containing products 7

   3.3. Use of polidocanol in sunscreens 8

   3.4. Sensitisation potential of topically applied polidocanol 8

   3.5. Bradycardia/hypotension side effects 8

   3.6. Safety of Laureth-7 8

4. CONCLUSIONS 9

1. BACKGROUND

Polidocanol (CAS 3055-99-0) with the INCI-name laureth-9 is a polyethylene glycol ether of lauryl alcohol, where the average value of ethylene oxide units is 9. The chemical name of polidocanol is 3,6,9,12,15,18,21,24,27-nonaoxanonatriacontan-1-ol according to ECB [1].

The first opinion (SCCP/1130/07) on the substance was adopted by the SCCP the 2nd October 2007 with the conclusion:

"The data included in this dossier demonstrate that polidocanol is of low toxicity and does not pose a risk to the health of the consumer when used up to 3% in leave-on and up to 4% in rinse-off cosmetic products.

Recent scientific evidence does not confirm the assumed local-anaesthetic effect of polidocanol. Thus, its presence in cosmetics and skin care products will not affect cutaneous sensation".

According to the applicant the substance is used in rinse-off products as a non-ionic emulsifier and co-surfactant, particularly in shampoos and hair conditioners in concentrations from 1 to 4%. It is also used in leave-on products, such as body and face creams, up to a concentration of 3%.

At least one Member State has authorized polidocanol for use in a topical drug formulation at a concentration of 2%. A drug for injection has been approved in concentrations as from 0.5%.

Meanwhile more data was submitted by Member States in order to ensure that all available documentation of the inherent local anaesthetic effects and the ability to curb pruritus that polidocanol possesses have been properly assessed by the Scientific Committee, and especially the use of polidocanol in leave-on products should be revisited.

Furthermore, Member States are asking whether adverse effects have been considered like bradycardia/hypotension and sensitisation reactions.

At the same time, the Commission was asked to request the SCCS to evaluate the homologue substance Laureth-7 together with polidocanol, as this substance is considered to be even more potent than polidocanol with respect to the local anaesthetic properties. However, not much data was submitted to support that purpose.

2. TERMS OF REFERENCE

1. *Does the SCCS see it necessary to change its conclusion on the safe use of polidocanol, especially its safe use in leave-on products or other use conditions taken into account the documentation provided?*

2. *And/or does the SCCS have any further concerns regarding the use of polidocanol in cosmetic products?*

3. *On the available data provided can the SCCS express an opinion on the safe use of laureth-7 in cosmetic products?*

[1] ECB – European Chemicals Bureau (ECB)

3. Opinion

The mandate is based on a document from the Norwegian Food Safety Authority, which the Commission received after the proposal to implement the earlier polidocanol opinion, i.e. inclusion in Annex III of Directive 76/768/EEC with a concentration limit of 3% in cosmetic products. In this addendum to its previous opinion SCCP/1130/07 the SCCS identified and addressed the issues and questions raised in this document.

Concerns were raised in particular about possible local anaesthetic effects and an anti-pruritic effect of polidocanol (Laureth-9) when applied topically. This exposure situation is relevant for use of cosmetic products as well as application of medicinal products for treatment of dermatological conditions such as dry and itchy skin. This scenario differs considerably from uses for medical treatments such as sclerotherapy, treatment of varicosities, etc., where polidocanol is injected intravenously. Nonetheless, the SCCS has also considered literature on this particular use of polidocanol in its re-evaluation of possible adverse side effects from the use in cosmetic products.

3.1. Local anaesthetic properties of polidocanol when applied topically

Numerous studies, mostly old ones, clearly document anaesthetic properties of polidocanol. However, the data were obtained in animals (and volunteers) with injection of the test agents (intracutaneous, subcutaneous, intravenous, peridural, paravertrebral [Soehring et al. 1952; Siems & Soehring 1952; Zipf et al. 1957].

Two papers describe also local anaesthesia in the rabbit cornea reflex test with polidocanol [Zipf & Dittmann 1964; Ansmann et al. 1997]. The latter, a patent document without any methodological descriptions, states shorter chain alkoxyethylates (Laureth-7) to be more potent than polidocanol (Laureth-9).

The above data document anaesthetic properties, but the application modes clearly differ from topical application of polidocanol containing consumer products. In this situation the efficacy of any local anaesthetic will strongly depend upon its dermal penetration. According to human studies, dermal penetration of polidocanol is rather limited with about 2% [opinion SCCP/1130/07; BfR 2003; Drotman et al. 1980].

When local anaesthetic drugs are applied, various effects may be observed, such as a decrease in pricking pain and a change in burning, itch, and thermal sensations. These effects occur after skin penetration and may be attributed to the action of the anaesthetics on nociceptors and thermoreceptors, i.e., on C and A-delta nerve fibres respectively [Leopold & Maibach 1999].

It is worth noting that well established local anaesthetics do not penetrate readily through human skin. EMLA® cream (a 1:1 mixture of lidocaine and prilocaine), widely used as analgesic to decrease venipuncture pain in children, is applied under occlusive dressing to facilitate absorption [Rogers & Ostrow 2004].

Indeed, local anaesthetic drugs differ considerably in percutaneous absorption as measured *in vitro* and also in efficacy when assessed in human volunteers by suitable methods such as pin pricking [McCafferty et al. 1988; McCafferty et al. 1989] or thermal sensory analysis [Leopold & Maibach 1999; 2004]. For instance, in line with their higher permeability in vitro, local anaesthesia was demonstrated in pinpricking tests for amethocaine, lignocaine, amylocaine, fomocaine and benzocaine whereas bupivacaine, cinchocaine and mepivacaine (with low apparent permeability *in vitro*) were not active *in vivo* [McCafferty et al. 1988; McCafferty et al. 1989]. In principal similar results were reported by Leopold and Maibach (1999) who assessed percutaneous penetration of local anaesthetics and thermal thresholds over time (3 hours) with a thermal sensory analyzer in human volunteers. In this study, lidocaine, prilocaine, their 1:1 mixture (EMLA) as well as a triple mixture of lidocaine,

prilocaine and tetracaine (1:1:1) clearly affected the threshold for cold and warm sensation whilst bupivacaine and mepivacaine were inactive in this respect.

A recent study with topic application of polidocanol, some other non-ionic surfactants and five conventional local anaesthetics [Leopold & Maibach 2004] confirmed that lidocaine, prilocaine, the 1:1 mixture and the triple mixture of lidocaine, prilocaine and tetracaine are potent local anaesthetics. In contrast, none of the investigated surfactants nor bupivacaine and mepivacaine affected thermal thresholds under the same conditions.

The lack of an anaesthetic effect for topically applied polidocanol is a relevant finding for the overall evaluation, since results for active and inactive local anaesthetics (bupivacaine and mepivacaine) in the thermal sensory analysis [Leopold & Maibach 1999 and 2004] are in accord with negative results for these agents in previous studies with pinpricking [McCafferty et al. 1988; McCafferty et al. 1989].

In the SCCP opinion (SCCP/1130/07), the study by Leopold and Maibach (2004) has been considered as evidence for the absence of local anaesthetic effects with topical application of polidocanol. The SCCS in its re-evaluation endorses this position.

The SCCS sees no need to supplement the study of Leopold and Maibach with additional studies, as there are no scientific arguments against thermal threshold analysis when compared to other methodology, e.g. pin pricking (see above).

3.2. Antipruritogenic effects of polidocanol containing products

With regard to possible antipruritic effects, the SCCP has quoted Weisshaar et al. (1996), a well controlled clinical study: The effects of a polidocanol containing medicinal product (Optiderm with 5% urea and 3% polidocanol) and of other creams (EMLA® and xylocaine) were evaluated in volunteers who received a focal histamine stimulus. The results were compared to pre-treatment with the corresponding placebo creams. Itching was significantly reduced by all active substances, including the placebo cream corresponding to Optiderm. Therefore it was concluded that antipruritogenic effects may be due to the presence of urea.

As urea-containing products improve moisture in the skin and can reduce itch, such products are highly regarded in dermatological practice as basic and intermittent therapies for topical treatment of dry skin diseases [Freitag & Hoppner, 1997; Twycross et al. 2003; Weisshaar 2010]. Although polidocanol is often called a 'local anaesthetic' in the literature [e.g. Ring & Frohlich 1985; Ständer et al. 2005], the exact mechanism of an antipruritic effect remains to be defined. It is worth noting that alleviation of symptoms such as itch by means of creams and emollient bath products with polidocanol is not necessarily related to a local anaesthetic effect, but rather to additives such as oils and urea which improve skin conditions.

This view based on the results of Weisshaar et al. (1996) is supported by further experimental studies in humans. Fearfield et al. (2000) investigated whether the use of topical polidocanol containing products could influence cutaneous innervation: They compared in randomized double-blind studies the effects of Balneum® and Balneum Plus® bath oils as well as Optiderm® cream and placebo cream (i.e. the same formulations without and with polidocanol) with regard to treatment differences in weal, flare and blood flow (measured by laser Doppler flowmetry) following challenge with histamine, calcitonin-related peptide (CRGP) and other stimuli. In study I which compared Balneum® and Balneum Plus® bath oils, a significantly smaller mean flare size was observed following challenge with CRPG, not with the other stimuli. In study II which compared Optiderm® and placebo cream, the only treatment difference that achieved statistical significance was a reduced flare size in favour of placebo after intradermal injection of one stimulus (compound 48/80, provokes histamine release). Thus, the authors conclude that the

antipruritic effect claimed for Optiderm® does not appear to be due to cutaneous neuronal or microvasculature influences [Fearfield et al. 2000].

Thereby, this study confirms the findings of Weisshaar et al. (1996) who observed also no superior effects for polidocanol containing creams versus cream base.

3.3. Use of polidocanol in sunscreens

According to the Norwegian document [Enclosure Talberg; Appendix 1 on a search in the EWG database] there are 131 products containing Laureth-9 (polidocanol) none of which are sun protection products. Laureth-7 is used in many more (1702) products, also in several (78) sun protection products. Although this is based on the US market, there are no indications that polidocanol has a widespread use in sun protection products in Europe.

The SCCS has no concerns about possible anaesthetic effects of polidocanol containing products applied with leave-on products to skin that is exposed to UV radiation from the sun. Local increased blood flow to the skin enhances *systemic* delivery but decreases *local* availability of a topically applied drug [Hull 2002]. Under conditions of UV-induced erythema the expectation for polidocanol is that rapid clearance occurs.

3.4. Sensitisation potential of topically applied polidocanol

Human studies listed in the SCCP opinion and reviews on topically applied products with polidocanol – mostly for treatment of pruritus – do not indicate sensitization as an issue of concern [Fruitjer-Pölloth 2005; Twycross et al. 2003; Weisshaar 1996, 2010; Ständer et al. 2006]. In a large survey of clinical patch test populations, patients with atopic dermatitis (which is often treated with polidocanol-containing emollients) was not a significant risk factor for contact allergy to polidocanol [Uter et al. 2000] whilst elderly patients with lower leg dermatitis were at risk, a phenomenon well known for a number of other topical drugs and cosmetic ingredients also.

When polidocanol is injected, mainly for sclerotherapy, allergic and anaphylactic reactions are infrequent with a reported incidence of 0.01 to 0.3 % [Conrad et al. 1995; Feied et al. 1994; Goldman & Bergan 2001; Mimura et al. 2009].

Serious allergic reactions are rare upon injection of polidocanol, and the SCCS sees no risk of sensitisation from topical application of cosmetic products containing it.

3.5. Bradycardia/hypotension side effects

There are only rare reports on bradycardia/hypotension as side effect when polidocanol is injected for medicinal reasons, mainly sclerotherapy [Marrocco-Trishitta et al. 2002; Mimura et al. 2009]. This may occur if maximum doses are exceeded, due to intrinsic negative ionotropic effects of polidocanol [Oexle et al. 1988]. Rather large studies [Conrad et al. 1995] report complications such as "fainting on injection" only in 4 of 16,804 treated legs.

This side effect of polidocanol is only seen at high systemic doses, and thus not a relevant issue with topical application. According to literature [e.g. Hyodoh et al. 2005] and the information from Norway, the maximum recommended daily dose for injection of polidocanol is 2 mg/kg bw, while the SCCS calculated a systemic exposure dose from cosmetic use of 0.132 mg/kg bw/day.

3.6. Safety of Laureth-7

According to the limited information available, Laureth-7 seems to have stronger local anaesthetic effects than polidocanol. At least on the US market, it is used more widely, and also in sun protection products. As no data on the pharmacological and toxicological

properties of Laureth-7 is available, the SCCS is presently not in the position to evaluate its safe use in cosmetic products. For the assessment of Laureth-7, a complete safety dossier, including data on dermal penetration and anaesthetic properties, would be required.

4. Conclusions

1. *Does SCCS foresees it necessary to change its conclusion on the safe use of polidocanol, especially its safe use in leave-on products or other use conditions taken into account the documentation provided?*

The SCCS, in a re-evaluation of the earlier SCCP opinion (SCCP/1130/07), taking into account the documentation provided, does not find it necessary to change its conclusions on the safe use of polidocanol in consumer products.

2. And/or does the SCCS have any further concerns regarding the use of polidocanol in cosmetic products?

The SCCS has no further concerns regarding the topical use of polidocanol in cosmetic products.

3. On the available data provided can the SCCS express an opinion on the safe use of laureth-7 in cosmetic products?

The data presently available indicate that Laureth-7 is used in numerous cosmetic products and in sun protection products. Laureth-7 seems to have stronger local anaesthetic effects than polidocanol. As no other data on the pharmacological and toxicological properties of Laureth-7 is available, the SCCS is presently not in the position to evaluate its safe use in cosmetic products.

References

Ansmann et al. Local Anesthetic in United States Patent Nr. 5,676,955 of oct 14, 1997; available at http://www.freepatentsonline.com/5676955.html

BfR (2003). German Federal Institute for risk evaluation. Polidocanol in cosmetic products

Conrad P, Malouf GM, Stacey MC (1995) The Australian Polidocanol (aethoxasklerol) study. Dermatol Surg. 21: 334-336, discussion 337-8

Drotman, RB (1980). The absorption, distribution and excretion of alkyl polyethoxylates by rats and humans. Tox. Appl. Pharm. 52:38-44

Fearfield LA et al. (2000) Topical lauromacragols and cutaneous neural function. J Dermatological Treatment 11: 69-72

Feied CF, Jackson JJ, Bren TS et al (1994) Allergic reactions to polidocanol for vein sclerosis. Two case reports. J Dermatol Surg Oncol 20:466–468

Freitag G, Hoppner T (1997) Results of a postmarketing drug monitoring survey with a polidocanol-urea preparation for dry, itching skin. Curr Med Res Opin. 13: 529-537.

Fruijtier-Poelloth C (2005) Safety assessment on polyethylene glycols (PEGs) and their derivatives as used in cosmetic products. Toxicology 214 (1-2): 1-38

Goldman MP, Bergan JJ (2001) Sclerotherapy: Treatment of Varicose and Telangiectic Leg Veins.; Third Edition, St. Louis, Mosby; Chapter 8 (p.217-218)

Guex JJ (2010) Complications of Sclerotherapy: An Update Dermatologic Surgery 36 Suppl 2: 1056-1063

Hull W (2002) Heat-Enhanced Transdermal Drug Delivery: A Survey Paper. Journal of Applied Research, Volume 2, Number 1 Winter 2002 (8pp)

Hyodoh H, Hori M, Akiba H, et al. (2005) Peripheral Vascular Malformations: Imaging, Treatment Approaches, and Therapeutic Issues. RadioGraphics 25, S159-S171

Leopold CS, Maibach HI (1999) Percutaneous Penetration of Local Anesthetic Bases: Pharmacodynamic Measurements. The Society for Investigative Dermatology. 304-307

Leopold CS. (2003) Effect of cutaneously applied non-ionic surfactants and local anesthetic bases on thermal sensations. Pharmaziz 59: 50-54 (2004)

Leopold CS, Maibach HI (2004) Effect of cutaneously applied nonionic surfactants and local anesthetic bases on thermal sensations. Pharmazie 59: 50–54

Marrocco-Trischitta MM, Guerrini P, Abeni D et al (2002) Reversible cardiac arrest after polidocanol sclerotherapy of peripheral venous malformation. Dermatol Surg 28:153–155

McCafferty DF, Woolfson AD, Boston V et al. (1989) *In vivo* assessment of percutaneous local anaesthetic preparations. Br. J. Anaesth. 62, 17-21

McCafferty DF, Woolfson AD, McClelland KH, Boston V (1988) Comparative *in vivo* and *in vitro* assessment of the percutaneous absorption of local anaesthetics. Br J Anaesth. 60:64-9.

Mimura H, Fujiwara H, Hiraki T, Gobara H, Mukai T et al. (2009) Polidocanol sclerotherapy for painful venous malformations: evaluation of safety and efficacy in pain relief. Eur Radiol. 19:2474-2480

Oexle B, Weirich J, Haverkamf K, Antoni H (1988) Effects of polidocanol as a constituent of a venous sclerosing agant on cardiac electrical activity. Arzneim.-Forsch./Drug Res.38: 1578-1582

Rogers TL, Ostrow CL (2004) The use of EMLA cream to decrease venipuncture pain in children. J Pediatr Nurs. 19(1):33-39.

SCCP (Scientific Committee on Consumer Products) (2007) Opinion on Polidocanol (Laureth-7), adopted on 2 October 2007 (SCCP/1130/07)

Siems KJ, Soehring K (1952) Die Ausschaltung sensibler Nerven durch peridurale und paravertrebrale Injektion von Alkylpolyäthylenoxydäthern bei Meerschweinchen. Arzneimittelforschung/Drug Research 2: 109-111

Soehring K, Frahm M, Miletzko K (1951) Beiträge zur Pharmakologie der Alkylpolyäthylenoxidderivate. I: Untersuchungen über die acute und subchronische Toxizität bei verschiedenen Tierarten. Arch Int Pharmacodyn 87: 301-320

Soehring K, Frahm M, Miletzko K (1952) Beiträge zur Pharmakologie der Alkylpolyäthylenoxidderivate. IV: Lokalanalgetische Wirkungen und Anmerkungen zur vergleichenden Auswertung. Arch Int Pharmacodyn 91: 112-130

Ständer R, Streit M, Darsow U et al. (2006) Leitlinie: Diagnostisches und therapeutisches Vorgehen bei chronischem Pruritus. J Dtsch Dermatol Ges 4: 350-370

Twycross R, Greaves MW, Handwerker H, Jones EA, Libretto SE, Szepietowski JC, Zylicz Z. (2003) Itch: scratching more than the surface. Q. J. Med 96: 7-26.

Uter W, Geier J, Fuchs T (2000) Contact allergy to polidocanol, 1992 to 1999. J Allergy Clin Immunol 106(6), 1203-1204

Weisshaar E (2009) Pruritus im Alter. Ursachen und Therapiemöglichkeiten. Ars Medici 1, 10-14

Weisshaar E, Heyer G, Forster C, Hornstein OP, Handwerker HO (1996) Antipruritogener Effekt antihistaminerger und lokalanästhestischer Externa nach iontophoretischem Histaminreiz. (Effects of a topical antihistamine maleate and topical anaesthetics on iontophoretically induced itch). Hautarzt 47: 355–360.

Zipf HF, Dittmann ECh (1964) Beziehungen zwischen Alkylkettenlänge, Lipiphilie, local-anaestheischer und endoanaesthetischer Wirksamkeit bei homologen Alkylpolyglykoläthern. Naunyn-Schmiedebergs Arch exp Path Pharmak 247:544-557

Zipf HF, Wetzels E, Ludwig H, Friedrich M (1957) Allgemeine und lokal toxische Wirkungen von Dodecyl-polyaethoxyenoxyd-aethern. Arzneimittelforschung/Drug Research 7: 162-166

In addition to the above listed references cited in this opinion, the following documents were submitted to and reviewed by SCCS regarding their relevance for inclusion in this addendum.

Akomeah et al.: Effect of heat on the percutaneous absorption and skin retention of three model penetrants. European Journal of Pharmaceutical Sciences 21 (2004) 337-345

Arildsson et al.: Skin Capillary Appearance and Skin Microvascular Perfusion Due to Topical Application of Analgesia Cream. Microvascular Research 59, 14-23 (2000)

Benke et al. (1977) Safety testing of alkyl polyethoxylate non-ionic surfactancs. I. Acute effects. Fd Cosm Toxicol. Vol 15, pp. 309-318

Benson et al.: Influence of anatomical site and topical formulation on skin penetration of sunscreens. 2005. Ther Clin Risk Manag. 1(3): 209-218

Bopp BA et al. (1978) Local anesthetic activity and acute toxicity of N-heptyl-1,2,3,4-tetra-6-methoxy-1-naphthylamine methanesulfonate. J. Pharm. Sciences vol 67 n° 6 pp. 882-884

Bronaugh RL. (1985) Methods for in vitro percutaneous absorption studies V: permeation through damaged skin. J. Pharm. Sciences vol. 74, n° 10 pp. 1062-64

Caselli et al. (2003) Local anesthesia reduces the maximal skin vasodilation during iontophoresis of sodium nitroprusside and heating. Microvascular Research Vol 66, issue 2, pp 134-139

Chandrasekaran SK et al. (1978) Factors influencing the percutaneous absorption of drugs. Curr. Probl. Dermatol., vol 7, pp 142-155

Clarys et al.: *In vitro* percutaneous penetration through hairless rat skin: influence of temperature, vehicle and penetration enhancers. European Journal of Pharmaceutics and Biopharmaceutics. Vol 46, issue 3 November 1998. pp 279-283/

Communication from the Federal German Government. Health-risk evaluation of a cosmetic product constituent. (2004) 04/ENTR/COS/32

Cordero et al.: *In vitro* based index of topical anti-inflammatory activity to compare a series of NSAIDs. European Journal of Pharmaceutics and Biopharmaceutics. Vol 51, issue 2 March 2001. pp 135-142

Covino B. G.: Pharmacology of Local Anaesthetic Agents. Br. J. Anaesth. (1986), 58-701-716

Craig F. Feied. Mechanism of action of sclerosing agents and rationale for selection of a sclerosing solution. American Vein & Aesthetic Institute. 9pp

Cross et al.: Human Skin Penetration of Sunscreen Nanoparticles: In-vitro Assessment of a Novel Micronized Zinc Oxide Formulation. Skin Pharmacol Physiol 2007; 20: 148-154

Dahse T. (2007) Synthese, pharmakodynamik und biotransformation des fomocain-derivats Oe 9000. Dissertation. Friedrich-Schiller-Universitat Jena

Draize et al. (1944) Methods for the study of irritation and toxiciyu of substances applied topically to the skin and mucous membranes. Pp. 377-390

DSM (2007) Safety data sheet

DSA (2008) Nutritional Products

EFSA. Opinion of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics of the Norwegian Scientific Committee for Food Safety. 2007. Risk assessment related to solar radiation and the use of sun protection products

Filipe P. et al. (2009) Stratum corneum is an effective barrier to TiO2 and ZnO nanoparticle percutaneous absorption. Skin Paharmacol Physiol 2009;22:266-275

Gamer et al.: The *in vitro* absorption of microfine zinc oxide and titanium dioxide through porcine skin. Toxicology in Vitro, Volume 20, issue 3, 2006, pages 301-307

Ghelardini C. et al. (2001) Local anesthetic activity of beta-caryophyllene. Il Farmaco 56 (2001) 387-389

Ghosh TK. et al. Penetration enhancement by thermal energy. Temperature effects on drug diffusion. Transdermal and topical drug delivery systems. Interpharm Press INC, Illinois. ISBN 1-57491-041-8

Goldman MP. et al (1987) Treatment of telangiectasia: a review. J American Academy of Dermatology. Vol 17 n° 2, part 1 pp 167-182

Hartwig R. et al. (2006) Transdermal drug delivery of polar derivativezs of ketoprofen free acid through human cadaver skin. Noven Pharmaceuticals Inc. Miami, Florida

HERA (2005) Human & Environmental Risk Assessment on ingredients of European household cleaning products. Alcohol ethoxylates.

Henkel (1997) US patent n° 5,676,955 on lauryl polyglycol ethers

Herkenne et al.: Ibuprofen Transport into and through Skin from Topical Formulations: *In Vitro - in Vivo* Comparison. Journal of Investigative Dermatology (2007) 127, 135-142

Lamaud E. et al (1984) Influence of UV radiation on penetration of hydrocortisone. In vivo study in hairless rat skin. British Journal of Dermatology (1984) III, Suppl 27, 152-157

Lautenschläger H: Polyethylene glycols & Co – On effects and side effects, published in: Kosmetische Praxis 2009 (1), 12-15

Lim S.H. et al. (2007) Change of biophysical properties of the skin caused by ultraviolet radiation-induced photodamage in Koreans. Skin Research and Technology 2008; 14:93-102

Lipkind and Fozzard. Molecular Modeling of Local Anesthetic Drug Binding by Voltage-Gated Sodium Channels.

Luduena et al.: The Pharmacology and Toxicology of Mepivacaine, a New Local Anesthetic. Toxicology and Applied Pharmacology 2, 295-315 (1960)

Mc Coy et al.: Sclerotherapy for Leg Telangiectasisa – A Blinded Comparative Trial of Polidocanol and Hypertonic Saline. Dermatol Surg 1999, 25:381-386

Mortensen L.J. et al. (2008) In vivo skin penetration of quantum dot nanoparticles in the murine model: the effect of UVR. Nano Letters 2008 vol. 8, n° 9, 2779-2787

Muermann (1986) Akute orale toxizitat von marlipal 24/60 fur ratten. Huls AG. Bericht n° 0802

Muermann (1986) Prufung der akuten hautreizwirkung von MARLIPAL 013/60 (alt). Huls AG. Bericht n° 0629

Muermann (1986) Prufung der akuten hautreizwirkung von MARLIPAL 24/60. Huls AG. Bericht n° 0803

Muermann (1986) Prufung der akuten augen- und schleimhautreizwirkung von MARLIPAL 013/60 (alt). Huls AG. Bericht n° 0630

Nishiyama et al.: *In vivo* percutaneous absorption of polyoxyethylene lauryl ether surfactants in hairless mice. J. Soc. Cosmet. Chem., 34, 263-271 (1983)

Peltola et al.: Microemulsions for topical delivery of estradiol. International Journal of Pharmaceutics 254 (2003) 99-107

Permanent Representation of the Federal Republic of Germany to the European Union (2004) polydocanol in cosmetics. Ref.: BMVEL 316-451-1/10

Pershing et al.: Effects of vehicle on the uptake and elimination kinetics of capsaicinoids in human skin *in vivo.* Toxicology and Applied Pharmacology 200 (2004) 73-81

Puschmann M. et al. (2003) Extensive treatment of itching, dry dermatoses with a polidocanol-urea-combination. Akt Dermatol 2003; 29:77-91

Ring J. et al. (1985) Allgemeine juckreizstillende massnahmen. Wirkstoffe in der Dermatologischen Therapie. 2nd ed Springer Verlag. Berlin. p. 181

Roman FJ et al. (1999) pharmacological properties of trimebutine and N-monodesmethyltrimebutine. JEPT 289:1391-1397, 1999

Staender et al. (2005) Diagnostisches und therapeutisches Vorgehen bei chronischem Pruritus. 2005 pp 53

Thibault PK. (2010) Sclerotherapy of Varicose Veins and Telangiectasias: A 2-year Experience with Sodium Tetradecyl Sulphate. 6 pages. Central Vein and Cosmetic Medical Centre. Broadmeadow, Australia

Thibault PK. Sclerosing agents. 4 pages Central Vein and Cosmetic Medical Centre. Broadmeadow, Australia

Thiele J.J. et al (2003) Impact of ultraviolet Radiation and ozone on the transepidermal water loss as a function of skin temperature in hairless mice. Skin Pharmacol Appl Skin Physiol 2003; 16:283-290

VKM – Norwegian Scientific Committee for Food Safety (2007) Opinion of the panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics of the Norwegian Scientific Committee For Food Safety. Adopted 6 June 2007. Risk assessment related to salar radiation and the use of sun protection products

Wade Hull: Heat-Enhanced Transdermal Drug Delivery: A Survey Paper. Journal of Applied Research, Volume 2, Number 1 Winter 2002

Wasik F. et al. (1996) Relief of ureamic pruritus after balneological therapy with a bath oil containing polidocanol (Balneum Hermal Plus). An open clinical study. J. of Dermatol Treatm. (1996) 7, 231-233

Wu et al.: Toxicity and penetration of TiO_2 nanoparticles in hairless mice and porcine skin after subchronic dermal exposure. Toxicology Letters. 191 (2009) 1-8

Yarov-Yarovoy V. et al. (2002) Role of amino acid residues in transmembrane segments IS6 and IIS6 of the Na+ channel alpha subunit in voltage-dependent gating and drug block. The Journal of Biological Chemistry. Vol 27 n° 38 pp. 35393-35401