

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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**JEFE DE DIVISIÓN DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**

E. S. D.

REF: Expediente No. 03 050 565 – solicitud de patente de invención a favor
de PATRICK FRANKE

Respuesta al oficio No. 05288 del 23 de abril de 2010

JUAN PABLO CADENA SARMIENTO, portador de la tarjeta profesional No. 57.492 del C.S.J., obrando como apoderado de la sociedad COLGATE PALMOLIVE COMPANY, según lo acredita el documento de poder presentado ante esa División me permito dar respuesta a las observaciones de carácter técnico y jurídico, relacionadas con la patentabilidad, para la concesión de la patente de acuerdo con la Decisión 486 según el concepto técnico No. 267 notificado por fijación en lista de fecha 23 de abril de 2010 y cuyo término fue prorrogado el 14 de julio de 2010.

En primer lugar, adjuntamos un nuevo capítulo reivindicatorio de 1-13 reivindicaciones que subsana las objeciones realizadas por el Señor Examinador, sin ampliar en ningún momento la materia divulgada inicialmente y encontrando entero sustento en la descripción. En particular, haciendo referencia a las objeciones a la claridad de la solicitud, se ha eliminado la característica relacionada con el número de ingredientes presentes en la composición de la reivindicación 1, con el fin de garantizar la concisión de la solicitud. De igual manera, la antigua reivindicación 5 ha sido eliminada, dado que el ingrediente allí mencionado estaba ya incluido en la reivindicación 3, siguiendo las recomendaciones del Señor Examinador.

De acuerdo a la discusión sostenida durante nuestra entrevista, el solicitante ha decidido sostener la característica bajo el numeral (a), donde se especifican los componentes que no están presentes dentro de la formulación reclamada. Esto porque consideramos que en este caso particular, dado el problema técnico resuelto y el concepto inventivo en que se centra la solicitud, esta forma de descripción es la única que permite definir adecuadamente la invención de manera que el aporte realizado al estado del arte quede completamente claro. De esta manera, es imprescindible tener en cuenta el siguiente aparte de la descripción para definir adecuadamente el problema técnico resuelto por la presente invención.

“La técnica anterior no ha podido proporcionar una formulación del cuidado de la piel que evite ingredientes irritantes y alergénicos, pero que retengan las propiedades favorables, en particular en el campo médico del cuidado de la piel. Esto puede atribuirse al hecho que el evitar estrictamente tales ingredientes afecta otras propiedades deseadas tal como humedad efectiva de la piel seca, estabilidad de la formulación y atributos sensoriales favorables desde el punto de vista del paciente/consumidor” (Página 6, párrafo 2).

De acuerdo con la información aquí contenida puede establecerse entonces que el problema técnico no es únicamente obtener una composición hipoalergénica y no irritante para el cuidado de la piel, como lo menciona el Señor Examinador, sino además obtener una composición con estas características que no contenga ningún ingrediente irritante y/o alergénico, conservando al mismo tiempo una estabilidad física y microbiológica adecuada. En particular, como puede observarse en la descripción de la solicitud y en la reivindicación 1, los ingredientes que pueden llegar a causar este tipo de reacciones adversas en la piel son fragancias, conservantes, colorantes, extractos vegetales, PEGs (polietilen glicoles), alcohol cetilestearílico, alcoholes bajos y proteínas. Por esta razón, resulta imprescindible incluir en las reivindicaciones la ausencia de estos ingredientes para definir adecuadamente la invención y demostrar la novedad e inventiva de la misma. De acuerdo con esto, respetuosamente solicitamos

al Señor Examinador la aceptación de este tipo de lenguaje dentro de las reivindicaciones, ya que no es posible definir la invención únicamente por los ingredientes contenidos en la composición, sin comprometer la adecuada especificación del aporte realizado al estado de la técnica por la presente invención.

Ahora en referencia a las objeciones al nivel inventivo, en vista de los documentos EP0847750 (D1), WO1998/017246 (D4), US4832858 (D5) y US5017605 (D6), presentamos los siguientes comentarios.

El Señor Examinador objeta el nivel inventivo de las reivindicaciones 1-12 (nuevas reivindicaciones 1-11) teniendo en cuenta a D1, como arte previo más cercano, y a D2 como complemento que permite a un técnico entrenado en la materia derivar la presente invención de manera obvia. En este sentido, es preciso señalar que D1 describe composiciones que contienen un filtro ultravioleta, mono y/o oligoésteres de glicerina, fragancias y preservativos. Por otra parte, D4 se refiere a una formulación hipoalergénica que comprende un extracto vegetal de Ginkgo biloba y un β -Glucano o uno de sus derivados. De esta forma, estos dos documentos se alejan sustancialmente del concepto inventivo de la presente solicitud, ya que ambos sugieren que las propiedades adecuadas de las composiciones para el cuidado de la piel solo se alcanzan mediante la inclusión de varios ingredientes que no se encuentran presentes dentro de la composición reclamada. Incluso cuando D4 se refiere a una composición hipoalergénica, este efecto se alcanza solamente mediante la inclusión de un extracto vegetal dentro de la misma, por lo que las enseñanzas de este documento, en complemento con D1, no llevarían en ningún momento al técnico a prescindir de las fragancias, conservantes y extractos vegetales para lograr una composición hipoalergénica estable física y microbiológicamente asimismo agradable para el usuario.

De acuerdo con lo anterior, los inventores encontraron de manera sorprendente que al omitir ingredientes específicos, como conservantes, fragancias, PEG y alcohol cetilestearílico, se obtiene una composición que es estable y al mismo tiempo un humectante eficiente. Esta efectividad fue

especialmente sorprendente ya que el alcohol cetilestearílico y el PEG son usados normalmente como emulsificantes y compuestos grasos que mejoran la capacidad de esparcir la composición sobre la piel. Además, la estabilidad de la emulsión de agua en aceite (w/o), como se reivindica, fue lograda sin la necesidad de incluir los parabenos, que son conservantes comúnmente usados para este fin. Vale la pena resaltar que la estabilidad fue lograda entonces exclusivamente por el sistema amortiguador o buffer compuesto de ácido láctico y lactato de sodio. De acuerdo con esto, ninguno de los documentos citados contiene enseñanza alguna acerca de la efectividad de tal sistema amortiguador ni de la posibilidad de omitir tales ingredientes, por lo que la composición reivindicada no resulta obvia en ningún momento.

El Señor Examinador, en relación a la no inclusión de ciertos ingredientes dentro de la composición, afirma que era de esperarse que si la composición de la invención no incluye ninguno de los componentes que potencialmente dan origen a una alergia o irritación, esta mostraría un bajo nivel de irritación y sensibilidad. A este respecto, consideramos que el Señor Examinador tiene razón, sin embargo en caso que una de las composiciones del arte previo prescindiera de estos ingredientes, aunque no tendría potencial alguno de generar alguna alergia o irritación, perdería completamente su estabilidad y su capacidad de perdurar en el tiempo. Para soportar esto, adjuntamos a este memorial tres artículos que ilustran la importancia de incluir ingredientes como conservantes, fragancias y PEG dentro de formulaciones cosméticas así como su potencial demostrado de generar alguna reacción alérgica en la piel. Este material soporta entonces la necesidad de proporcionar composiciones, como la reivindicada, que omitan la inclusión de estos ingredientes. Las referencias bibliográficas son:

- Artículo 1: Wolf Ronni, Wolf Danny, Tüzün Binnur, Tüzün Yalcin, Contact dermatitis to cosmetics, Clinics in Dermatology, 2001; 19: 502-515.
- Artículo 2: Hostynek J.J., Magee, P.S., Fragrance allergens: Classification and ranking by QSAR, Toxicology in vitro 11 (1997) 377-384.

- Artículo 3: Fruijtier-Pölloth Claudia, Safety assessment on polyethylene glycols (PEGs) and their derivatives as used in cosmetic products.

En cuanto al artículo 1, se establece en este documento que los cosméticos son en general seguros y tolerados adecuadamente ya que las compañías dedicadas a esta actividad prueban sus productos en un gran número de sujetos voluntarios antes de salir al mercado. Sin embargo, a pesar de estas precauciones, se siguen presentando efectos secundarios por lo que se espera que aún cuando haya mejoras en seguridad, tolerancia y compatibilidad en la piel, esto no previene los efectos secundarios debido a los constantes objetivos de intensificar su actividad biológica y eficacia terapéutica (ver artículo 1, página 502, párrafos 1-2). Además, este artículo menciona como los agentes que causan mayor cantidad de casos de Dermatitis de Contacto Alérgico a las fragancias (ver página 503) y los conservantes o preservativos (ver página 504), los cuales son necesarios dentro de la gran mayoría de composiciones cosméticas.

De acuerdo con esto, se puede deducir de este artículo que el uso de este tipo de ingredientes es generalizado dentro de las composiciones cosméticas y, dado el potencial de presentar efectos secundarios, sería entonces deseable formular una composición estable que omita dichos ingredientes, manteniendo su estabilidad y eficacia tal como se reivindica.

En complemento a lo anterior, el artículo 2 profundiza en las reacciones alérgicas causadas por las fragancias y establece que, incrementalmente, los datos disponibles muestran evidencia que una parte importante de la intolerancia cutánea a los cosméticos se debe a sus componentes de fragancia (ver artículo 2, página 377, párrafo 1). Por esta razón, se puede reafirmar que el formular una composición que omita estos compuestos es un aporte al estado del arte ya que soluciona efectivamente cualquier inconveniente alergénico que pueda llegar a presentarse.

Finalmente el artículo 3, que se refiere a los compuestos PEG, menciona que se ha demostrado un efecto irritante para la mayoría de compuestos de este tipo, donde la magnitud de este efecto depende de su peso molecular, del

periodo de aplicación y de la condición de la piel (ver artículo 3, página 32, párrafo 3). Además, este artículo hace referencia al uso común de estos compuestos dentro de la industria cosmética (ver resumen). Por esta razón, se puede deducir entonces que los efectos no deseados de estos compuestos son recurrentes, por lo que la solución planteada por los inventores que logra una composición estable que prescinde de estos ingredientes resulta adecuada y elimina cualquier riesgo potencial existente.

En conclusión, consideramos que en vista de lo expuesto anteriormente se ha demostrado adecuadamente que la presente invención cumple con los requisitos de claridad, concisión y nivel inventivo. En particular, se ha demostrado que el describir la composición reclamada por medio de los componentes que no contiene es adecuada en este caso, dado el problema técnico resuelto y el concepto inventivo de la solicitud, que hacen necesario el uso de este lenguaje para lograr una definición adecuada y completa. Además, se han aportado argumentos y pruebas suficientes que permiten observar que la presente invención no es una derivación obvia del arte previo, y que resuelve problemas de alergenidad y toxicidad recurrentes en el campo de la cosmética. Aún cuando todos los ingredientes que contiene la composición se describen en el arte previo, tuvo que realizarse una selección inventiva que permitiera proporcionar una composición sin ningún compuesto potencial alergénico o irritante, ya que como se demostró, son compuestos generalmente necesarios en este tipo de formulaciones y que son imprescindibles en los documentos citados por el Señor Examinador. Por esta razón, las reivindicaciones 1-11 cumplen con el requisito de nivel inventivo.

Ahora en cuanto a las reivindicaciones 13-14 (nuevas reivindicaciones 12-13) que describen un proceso, el Señor Examinador objeta el nivel inventivo con los documentos D5 y D6. Sin embargo, dado que las reivindicaciones de composición son inventivas, como se mencionó anteriormente, el proceso para elaborarlas resulta en consecuencia inventivo, en concordancia con todos los requerimientos de patentabilidad establecidos.

En vista de lo anterior, respetuosamente solicitamos el retiro de las objeciones a la presente solicitud y la concesión del privilegio solicitado, ya que en opinión del solicitante cumple con todos los requisitos establecidos en la decisión 486.

De la señora Jefe,



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Bogotá, 31 de agosto de 2010

MXB/NFA

Anexo

REIVINDICACIONES

1. Una formulación del cuidado de la piel hipoalergénica no irritante, caracterizada porque:

a) no contiene algún compuesto potencialmente irritante o alérgeno seleccionado del grupo que consiste de:

- fragancias
- conservadores
- colorantes
- extractos vegetales
- PEGs,
- alcohol cetilestearílico
- alcohol lanolínico
- alcoholes bajos
- proteínas;

b) comprende una fase acuosa dispersa en una fase de aceite en donde:

i. la fase de aceite comprende:

- entre 1% y 8% en peso de octanoato cetearílico,
 - entre 1% y 5% en peso de éter dicaprilílico,
 - entre 6% y 20% en peso de triglicérido caprílico/cáprico,
 - entre 1% y 4% en peso de poligliceril-3-diisostearato, y
 - entre 2% y 6% en peso de poliglicerilo-2-dipolihiidroxiestearato;
- y

ii. la fase acuosa comprende:

- agua purificada,
- entre 0.2% y 2% en peso de sulfato de magnesio,
- entre 0% y 2% en peso de ácido láctico, y
- entre 0.5% y 7% en peso de lactato de sodio.

2. La formulación del cuidado de la piel de acuerdo con la reivindicación 1, caracterizada porque la fase acuosa además comprende glicerina.

3. La formulación del cuidado de la piel de acuerdo con la reivindicación 1, caracterizada porque la fase de aceite además comprende etilhexilglicerina.

4. La formulación del cuidado de la piel de acuerdo con la reivindicación 1, caracterizada porque la fase de aceite de la formulación además comprende petrolato y cera alba.
5. La formulación del cuidado de la piel de acuerdo con la reivindicación 4, caracterizada porque la fase acuosa además comprende propilenglicol.
6. La formulación del cuidado de la piel de acuerdo con la reivindicación 1, caracterizada porque la fase acuosa además comprende urea.
7. Una formulación semi-sólida para el cuidado de la piel, caracterizada porque comprende los siguientes ingredientes, expresados como un rango de porcentaje en peso (%p/p):

(1) fase de aceite:

a) petrolato:	2 - 5%
b) octanoato cetearílico:	2 - 5%
c) éter dicaprilílico:	1 - 3%
d) triglicérido caprílico/ cáprico:	5 - 10%
e) cera alba:	1.0 - 2.5%
f) poligliceril-3-diisostearato:	4 - 5%
g) poliglicerilo-2-dipolihidroxiestearato:	1 - 2%
h) etilhexilglicerina:	0 - 0.8%

(2) fase acuosa:

a) glicerina:	0 - 5%
b) sulfato de magnesio:	0.5 - 1.5%
c) ácido láctico:	0.05 - 1.5%
d) lactato de sodio:	1 - 5%
e) agua purificada:	adicionar hasta 100%

8. Una formulación semi-sólida para el cuidado de la piel, caracterizada porque la formulación comprende los siguientes ingredientes, expresados como un rango de porcentaje en peso (%p/p):

(1) fase de aceite:

a) petrolato:	2 - 5%
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- b) octanoato cetearílico: 2 - 5%
- c) éter dicaprilílico: 1 - 3%
- d) triglicérido caprílico/ cáprico: 5 - 10%
- e) cera alba: 1.0 - 2.5%
- f) poligliceril-3-diisostearato: 4 - 5%
- g) poliglicerilo-2-dipolihiidroxiestearato: 1 - 2%

(2) fase acuosa:

- a) glicerina: 0 - 5%
- b) sulfato de magnesio: 0.5 - 1.5%
- e) ácido láctico: 0.05 - 1.5%
- d) lactato de sodio: 1 - 5%
- e) propilenglicol: 5 - 10%
- f) agua purificada: adicionar hasta 100%

9. Una formulación semi-líquida para el cuidado de la piel, caracterizada porque comprende los siguientes ingredientes, expresados como un rango de porcentaje en peso (%p/p):

(1) fase de aceite:

- a) octanoato cetearílico: 2 - 5%
- b) éter dicaprilílico: 1 - 3%
- c) triglicérido caprílico/ cáprico: 8 - 15%
- d) poligliceril-3-diisostearato: 1.5 - 3%
- e) poliglicerilo-2-dipolihiidroxiestearato: 3 - 5%
- f) etilhexilglicerina: 0-0.8%

(2) fase acuosa:

- a) glicerina: 0 - 5%
- b) sulfato de magnesio: 0.5 - 1.5%
- c) ácido láctico: 0.05 - 1.5%
- d) lactato de sodio: 1 - 5%
- e) urea: 0.5 - 10%
- f) agua purificada: adicionar hasta 100%

10. La formulación para el cuidado de la piel de acuerdo con cualquiera de las reivindicaciones anteriores, caracterizada porque la formulación además

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comprende uno o más compuestos farmacéuticamente activos, vitaminas o análogos de vitaminas y/o bloqueadores solares.

11. La formulación para el cuidado de la piel de acuerdo con la reivindicación 10, caracterizada porque el compuesto farmacéuticamente activo es un corticoide, un antimicótico, ácido salicílico, ácido alfa- o beta- hidroxi y/o ácido linolénico; la vitamina es Vitamina E, o Vitamina K; y el análogo de vitamina es Cacipotriol o Tacalcitol.
12. Un método para fabricar una formulación para el cuidado de la piel hipoalergénica y no irritante, caracterizado porque comprende los pasos de:
 - a) preparar una fase de aceite fundiendo los ingredientes de la fase de aceite tal como se define en la reivindicación 1;
 - b) preparar una fase acuosa calentando el agua purificada y disolviendo dentro de la misma los ingredientes de la fase acuosa mientras que se agita y se ajusta al valor de pH de la solución resultante con ácido láctico a 4.4 - 4.8;
 - c) preparar una emulsión de agua en aceite transfiriendo la fase de aceite fundida del paso (a) a la fase acuosa calentada del paso (b) y, mientras se agita y homogeneiza, enfriar la emulsión hasta temperatura ambiente mientras se aplica un vacío de -0.6 a -0.9 bar (-60,000 a -90,000 Pa).
13. El método de acuerdo con la reivindicación 12, caracterizado porque el paso (a) y el paso (b) se realizan a una temperatura de 75-85°C, el paso (c) comprende los pasos de
 - (i) transferir la fase de aceite del paso (a) a la fase acuosa del paso (b) mientras que se agita a 40 min^{-1} a 75-85°C,
 - (ii) enfriar la emulsión hasta aproximadamente 58-62°C mientras que se agita y homogeneiza a 3000 min^{-1} ,
 - (iii) enfriar la emulsión aún más hasta 38-42°C mientras que se agita y homogeneiza a 4000 min^{-1} ,
 - (iv) enfriar la emulsión aún más hasta 23-27°C mientras que se agita, y
 - (v) verter la emulsión dentro de contenedores apropiados.

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Contact Dermatitis to Cosmetics

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Cosmetics and skin care products have been used since the beginning of time to enhance the physical, mental, and spiritual well-being of mankind. While cosmetics were originally developed to add color, impart a fragrance, create a mood, or make a fashion statement, modern products also aim to repair damaged skin, reverse visual signs of aging, provide ultraviolet protection, enhance barrier function, and afford many other therapeutic advantages. Cosmetics are generally safe and well tolerated. Because all reputable cosmetic companies test their products on a large number of volunteer subjects before releasing the products on the market, most cosmetics do not cause adverse reactions in most people.

In spite of these precautions, side effects of cosmetic products do occur. It is to be expected that the improvements in safety, tolerance, and skin compatibility will not prevent side effects to cosmetic products from increasing in the future because of the continuing goals to intensify their biological activity and therapeutic efficacy. Therefore, now more than ever, dermatologists should be familiar with all possible side effects and reactions to cosmetics. The following chapter will provide this fundamental and ever more vital information for practicing dermatologists.

Allergic Reactions to Cosmetics

True allergic reactions to cosmetics constitute a small but significant portion of all adverse reactions to cosmetics, the majority of them being primary irritation. These reactions are of great importance to the dermatologist because they are usually more serious, more difficult to treat, and usually require absolute discontinuation of use of the causative agent.

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How Common are Allergic Reactions to Cosmetics?

A prospective study (1977–1980) of cosmetic adverse reactions by 11 American dermatologists identified 487 cases of cosmetic-induced dermatitis, 8% of which were due to allergic contact dermatitis (ACD).¹

In a 64-month study (1977–1983), 12 dermatologists belonging to the North American Contact Dermatitis Group patch tested 13,216 patients; 713 (5.4%) were identified as having reactions caused by cosmetics.²

Of 1,781 patients with contact dermatitis seen during a period of 6 years (1981–1986) in The Netherlands, 75 (4.2%) had allergy to cosmetic products.³

In another study from The Netherlands, 1,609 individuals (838 men, 771 women) were queried about adverse reactions to cosmetics and toiletries. Although 196 (12.2%) of them claimed to have suffered from side effects, none of the 20 patients tested showed any cosmetic allergy.⁴

In another related study by the same group,⁵ 982 female clients of beauticians were interviewed on cosmetic-related side effects they had experienced in the preceding 5 years: 254 (25.9%) claimed to have experienced such reactions. One-hundred and fifty women were tested with the European standard and with cosmetic series. Allergic reaction was considered “proven” in 3 patients (2%) and “possible” in 7 (4.7%). The authors conclude that “allergy is responsible for a minority (less than 10%) of all reactions to cosmetics and toiletries. The majority of reactions are due to irritation.”

The true incidence of reactions to cosmetics and their ingredients is clearly much higher than is reflected in the figures in any of the studies, because many of the patients who experience reactions seldom consult a physician but merely discard or discontinue using the suspected item, particularly when it is a newly purchased product.

Which body sites are most often affected and by what products?

More than half of the reported cases of cosmetic dermatitis occur on the face (including the eyelids).

Of 487 patients with cosmetic-related cutaneous re-

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actions detected in a prospective study by 11 American dermatologists,¹ the reactions occurred most often on the face (37%), followed by reactions around the eye (13%), the lower arm (11%), and the armpit (8%). In that study, skin care products caused the greatest number of adverse reactions (26%), followed by hair preparations other than hair colors (16%) and facial makeup products (12%).

Similar results were obtained in a 64-month study by 12 American dermatologists. Skin care products, hair preparations (including colors), and facial makeup were responsible for the majority of the reactions in 713 patients with cosmetic dermatitis.²

The face (40%) and the eyelids (18.7%) were also the most frequently affected sites in a study of 1,781 patients with contact dermatitis who were seen during a period of 6 years in The Netherlands.³ Skin care products (moisturizing and cleansing cream/lotion/milk) accounted for more than half of the cases (52.3%), followed by nail cosmetics (8%), shaving preparations (8%), and deodorants (6.8%).

These results were further supported by another study from The Netherlands.⁵ Of 254 female clients of beauticians who claimed to have experienced adverse reactions to cosmetics and toiletries in the preceding 5 years, skin care products were responsible for 36.6% of the reactions, followed by personal cleanliness products (29.9%), eye cosmetics (24.0%), deodorants and antiperspirants (12.6%), and facial make up products (8.3%).

In a study from the UK,⁶ 7% of 865 patchtested patients had facial dermatitis and 3% had eyelid dermatitis.

Skin care products also ranked first (56.3%) in another study from the Netherlands of 119 patients suffering from cosmetic-related contact dermatitis.⁷ Skin care products were followed by nail cosmetics (13.4%), perfumes (8.4%), and hair care products (5.9%).

The picture is somewhat different in patients with cosmetic intolerance. Soaps and shampoos were the most important types of cosmetics responsible for this syndrome.⁸

A cosmetic control system was introduced in 1989 at the Medical Products Agency in Sweden.⁹ The agency evaluated 191 reports on adverse effects of 253 cosmetics and toiletries between 1989 and 1994. The most prevalent product categories were moisturizers (99 cases), hair care products (30 cases), and nail care products (23 cases). The most common diagnosis was eczema (90%), mostly on the face. Of the eczemas, 70% were classified by patch test as allergic contact to the specific product tested as is. This is an unexpectedly high proportion compared with previous studies in selected groups of dermatological patients, which showed positive tests in 4-11.6% of patchtested patients.^{1,2,8,10-12} This may be explained by the tendency of Swedish

physicians to report only reactions that have been verified by patch testing.

Data were recently reported on 475 patients with contact allergy to cosmetic ingredients who were monitored during a 4-month period (January-April, 1996) in 5 European dermatology centers.¹³ The findings supported those found in previous studies on the order of frequency of product category: skin care products ranked first, followed by hair care products, cleansers, makeup, and sun-care products.

What are the Main Culprits in Cosmetic Allergy?

Fragrances

Fragrances are the leading cause of ACD due to cosmetics, accounting for more than 30% of identified cases.^{1-3,7,8,14}

The use of fragrances is ubiquitous and not limited to cosmetics that are primarily earmarked for providing a scent, such as perfumes, colognes, aftershave products, and deodorants. Virtually all cosmetics, toiletries, and skin care products contain ingredients that are added for fragrance alone; even an "unscented" cosmetic may contain a "masking" perfume. Detergents, fabric softeners, laundry products, oral hygiene products (toothpastes, mouthwash, dental floss), sanitary pads, household cleaning products, solvents, polishes, and waxes invariably contain pleasant fragrances.

Fragrances may be natural or synthetic. Natural fragrances are, with few exceptions, of botanical origin and contain several hundred different chemicals, usually a few major and many minor ones, which are responsible for the complexity of the odor. Today, synthetic chemicals are used much more commonly for reasons of cost, purity, compatibility, and quality control.

There are no legally defined concentrations of fragrance materials in cosmetics. In general, the approximate concentrations of perfumes in various products are: perfumes (12-20%), toilet water (5-8%), colognes (2-5%), soaps and bath formulations (0.5-4%), facial makeup and lipstick (1%), many other cosmetics (0.1-0.5%), and "masking" fragrance in ostensibly "unscented" cosmetics (<0.1%).

Considering the extensive use of fragrances, the frequency of contact allergy to these groups of materials is fortunately relatively small. In absolute numbers, however, fragrance allergy is common, with approximately 1% of the unselected population being sensitized to it.¹⁵

Because a perfume may contain as many as 300 or more individual ingredients, the detection of an allergy to one specific component is a difficult and complex matter.

In 1977, Larsen introduced a fragrance mixture as a screening patch-test substance for fragrance allergy.¹⁶

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Originally it contained 8 fragrance materials, each in a concentration of 2%. In 1984, the concentration was reduced to 1% of each constituent. Although this mix can cause both false positive¹⁷⁻¹⁹ and false negative reactions,²⁰⁻²² it has been used for years with satisfactory results.^{19,23-29} Furthermore, several analyses^{25,26,30} showed that between 1 to 3 constituents of the fragrance mix were detected in most perfumes and scented cosmetic products, thus indicating that it is a good reflection of actual exposure. In a worldwide multicenter study that examined positive fragrance mix reactions and concordance to individual fragrances both present and not found in the mix, reactions to the fragrance mix correlated with 86% of positive reactions to 32 fragrance ingredients.³¹

Several studies³²⁻³⁴ showed that some chemicals (e.g., eugenol) are capable of inhibiting contact dermatitis, and contact urticaria (both immunologic and non-immunologic) reactions. This phenomenon, called quenching, was blamed for false negative reactions to the fragrance mix in patch tests. This effect has, however, been questioned.³⁵

On the other hand, testing with the constituents of the fragrance mix is often negative in patients with positive patch tests to the mix itself.³⁶ This may be because each constituent acts as an irritant, which lowers the elicitation threshold for other allergens when testing to the mix or because 'compound allergy' occurs to new allergens formed in the mix.

Fragrance mix is part of the standard patch-test series and, together with balsam of Peru, serves as a screening agent for fragrance contact allergy. Although far from perfect it has been proven to be very useful. Between 6 and 11% of patients routinely tested because of suspected allergic contact dermatitis react to fragrance mix, in most centers, it ranks among the "top 5" frequent allergens, usually number 2 after nickel sulfate.³⁷⁻⁴¹ In a study of the North American Contact Dermatitis Group summarizing patch test results from 1994 to 1996, allergy to the fragrance mix was found in 14.0% of approximately 3,000 tested patients, making it a close second to nickel, the most common allergen with a prevalence of 14.3%; 10.4% of the tested patients reacted to balsam of Peru.⁴² In a more recent study of the same group that reported patch-testing results from 1996 to 1998, 11.8% of 3,400 tested patients reacted to balsam of Peru and 11.7% reacted to fragrance mix.⁴³

A recent study from the UK reviewed 25,545 patients who were patch tested with the European standard series during a 17-year period (1980-1996).⁴⁴ The incidence of positive results to fragrance was 8.5% in females and 6.7% in males. The higher prevalence of fragrance allergy that was found in females reflects more frequent exposure to perfume in cosmetic items and household products and correlates with the findings of other studies.^{21,26,36,45}

The problem of fragrance allergy is, however, not so much one of diagnosis, but rather of persuading patients of its relevance and the need for avoidance. Fragrances are not easily avoided and without being convinced of their role in causing eczema, few patients will make the effort. Furthermore, although European legislation requires full ingredient labelling, perfume being identified as 'parfum' in the International Nomenclature of Cosmetic Ingredients (INCI), we still see many cosmetics and medicaments without this important piece of information on the package, thus making avoidance no easier for the consumer.

Although there have been great steps forward as a result of full ingredient labelling on the packaging of products, the composition of the perfumed element of cosmetics is considered a trade secret and is still unknown.

To make matters more complicated and add to the difficulties of the fragrance-allergic patient and the dermatologist, usage of fragrance-free products does not guarantee that the product is actually free of any fragrance. Because the term "fragrance" is defined as natural or synthetic substance used *solely* to impart an odor to a cosmetic product, many fragrances that have more than one function and act also as preservatives, emollients, fixatives or disinfectants can be included in a fragrance-free product, because they do not fulfill the criteria of fragrance, e.g., they do not function as an odor-providing substance only.^{46,47} Furthermore, fragrance-free products may contain 'natural' plant extracts, flower extracts or essential oils (e.g., rose oil, chamomile oil, and sandalwood oil), all of which are actually fragrances. In fact, the earliest fragrances, before the development of organic chemistry were derived from herbs, wood, roots, and flowers. Natural products are therefore no less problematic to fragrance-sensitive patients, although it is often difficult to convince patients otherwise.

It is clear that dermatologists must educate their patients that products designated fragrance-free may not really be so; it goes without saying that terms such as "nonscented," "hypoallergenic," "dermatologist tested," "sensitive skin," or "dermatologist recommended" are worth even less.

Preservatives

Preservatives are second to cosmetics as the leading cause of ACD.¹

Cosmetic products come in frequent contact with the human skin, especially those packed as a cream in a jar. They are usually stored at room temperature and contain water, oils, peptides, and all kinds of carbohydrates—in short, everything that microorganisms are fond of. As a consequence, they need especially good preservation, much better than that required for food, for instance. The usage of preservatives is increasing; as

organic solvents and mineral oils are more and more often replaced with water, there is an increased need for inhibiting and preventing overgrowth of microorganisms. Most preservatives are low-molecular-weight compounds and are biologically active, thus making them potential sensitizers.

Most skin care products contain several types of preservatives whose type, concentration, and ratio vary between products, producers, and countries.

By far the most frequently used preservatives in cosmetics and toiletries are the parabens, followed by imidazolidinyl urea, quaternium-15 (Q-15) formaldehyde solution, isothiazolinones, etc.⁴⁸⁻⁵⁰

Considering the wide usage of parabens in cosmetic products (99% of leave-on products and 77% of rinse-off products were found to contain parabens⁵⁰), the incidence of allergic reaction to these products is very low. On the other hand, when they are used in topical therapeutic agents, these identical parabens sensitize approximately 1% of the population. This has caused most pharmaceutical manufacturers to remove them from topical therapeutics, but not, as mentioned earlier, from cosmetic products. Indeed, even preparations that are applied to the delicate skin of the eyelids, such as mascara, including the so-called hypoallergenic variety, also contain parabens and cause neither difficulties nor adverse reactions. The explanation for this apparent paradox is that while cosmetics are applied to normal skin, therapeutic agents are applied to inflamed, eczematous, excoriated, or otherwise damaged skin, which is much more readily sensitized than even the thinnest healthy skin. This, and several other puzzling aspects of the use of paraben preservatives, were discussed as being "paraben paradoxes."⁵¹⁻⁵³

While formaldehyde is rarely used today, other preservatives that release formaldehyde are widely used. Among these compounds for which the term formaldehyde-releasing preservatives has been used are diazolidinyl urea, imidazolidinyl urea, Q-15, DMDM hydantoin, and Bronopol. All of these substances are antibacterial and antifungal in their own right, but they also have a formaldehyde-releasing action. Although the free formaldehyde concentration released by these substances is very low, it might induce sensitization when applied repeatedly to damaged skin and may cause a moderate or severe reaction in patients who are already allergic to formaldehyde.

Imidazolidinyl urea is the next most commonly used preservative for cosmetics after the parabens, yet it was found to be responsible for fewer reactions than other formaldehyde releasers that are less frequently used.^{2,24,42,54} Q-15 is another widely used preservative. In the United States, it has accounted for a significant number of allergic reactions: in one study it was found to be the 6th most common allergen, with 9.2% positive

reactions.⁴² The prevalence rate of positive reactions in Europe is much lower, between 1 and 3%.⁵⁴⁻⁵⁸

Imidazolidinyl urea releases approximately one-eighth as much formaldehyde as Q-15. While most patients with a positive test reaction to Q-15 are also allergic to formaldehyde, less than 50% of those allergic to imidazolidinyl urea showed such a concordance.^{56,59}

Methylchloroisothiazolinone/methylisothiazolinone (trade names Kathon CG, Euxyl K100), a preservative that first appeared on file at the Food and Drug Administration in 1980, has become a very popular and widely used preservative for a variety of cosmetics and toiletries.^{60,61} Along with the increasing usage of this preservative also came reports on adverse and allergic reactions to it. After the first case reports from Europe in 1984/5,^{62,63} several studies on routine testing with Kathon CG were performed and documented.⁶⁰ Researchers finally came to the conclusion that Kathon CG is a common allergen with a prevalence of positive reactions of 3%-8% among patients with contact dermatitis.⁶⁴⁻⁷² Studies from the United States indicated a lower rate.⁷³ Guinea pig maximization testing⁷⁴ revealed Kathon CG to be a strong sensitizer. The induction/elicitation of ACD, however, showed a strong dependency upon the concentration, and there was a "no response concentration" zone in which the biocide could be used without concern for clinically significant ACD. This and studies on humans^{64,75-77} indicate that concentrations of Kathon CG of 15 ppm in rinse-off products and 7.5 ppm in leave-on products are apparently unlikely to produce sensitization and will only very rarely elicit ACD in patients with positive patch tests to the biocide.

Euxyl K400 was introduced in Europe in the middle 1980s and in the United States in 1990. It was developed as an alternative to the sensitizing Kathon CG. Euxyl K400 consists of two active ingredients, methyl dibromoglutaronitrile and phenoxyethanol, in a 1:4 ratio. Although no sensitizing capacity to the individual ingredients of Euxyl K400 could be demonstrated in a guinea pig maximization test,⁷⁸ it took only one year until the first report of contact allergy to Euxyl K400 was published,⁷⁹ and many other case reports followed.⁸⁰⁻⁸⁸ With the increased use of Euxyl K400, the prevalence of contact allergy to this preservative rose and it is now the most frequent cosmetic allergen in the Netherlands, exceeding all other preservatives, including Kathon CG.⁸⁹ In Europe, the prevalence of allergic reaction to Euxyl K400 or its ingredients among patients who were patch tested range between 1% and 4%.⁹⁰⁻⁹⁷ The prevalence reported by the North American Contact Dermatitis Group from 1992 to 1994 was 1.5%.²⁴

Current evidence indicates that Euxyl K400 is a sensitizer, and the benefits of replacing Kathon CG with this preservative are doubtful at best.

Vehicles

Vehicles, emulsifiers, surfactants, antioxidants, and other ingredients are also capable of inducing ACD.

Lanolin, a natural product obtained from the fleece of sheep and its various esters, is used in many cosmetics, skin care products, and topical medicaments. It has been used for centuries, even by the ancient Greeks and Romans, for skin care purposes. The incidence of lanolin sensitivity is a matter of controversy. It ranges from 1.5% in the US to 5-7% in Europe.^{98,99} The use of lanolin is associated with several puzzling aspects for which the name the "lanolin paradoxes" has been suggested in an analogy to the paraben paradoxes.⁹⁹ Lanolin in topical therapeutic agents sensitizes a high proportion of patients,¹⁰⁰⁻¹⁰⁴ whereas the same lanolin is generally 'safe' in cosmetics so widely used by millions of individuals. Patients with an ACD to lanolin in a medication applied to a stasis ulcer can nevertheless use lanolin-containing cosmetics, even on the delicate skin of the face, eyelids, and lips, and not experience a reaction.⁹⁹ Lanolin-sensitive individuals often show false-negative patch-test reactions to unaltered lanolin.¹⁰⁵⁻¹⁰⁸ Lanolin showed the lowest reproducibility, next to formaldehyde, in a large multicenter study of synchronous left- versus right-sided patch tests.¹⁰⁹

Propylene glycol, a solvent, humectant, and preservative with softening and lubricating features, is widely used as a vehicle for topical therapeutics, cosmetics, and various hand and body lotions. Although it is well suited for this purpose, it was reported to be a common cause of both primary irritant skin reactions and allergic sensitization.^{2,110,111} The true incidence of ACD from propylene glycol has not yet been defined insofar as the optimal patch-test concentration remains to be determined.^{112,113}

Irritant Reactions to Cosmetics

The majority (>90%) of adverse reactions to cosmetics are due to irritation.^{1,4,5,8} Most consumers who experience such reactions do not seek a doctor's care, but merely discontinue using the item. Consequently, dermatologists are not very often concerned with this type of reaction, in contrast to the cosmetic industry and its researchers who have vested interests in sales.

There are two forms of irritation: subjective and objective. Subjective, or sensory, irritation may be defined as chemically induced burning, stinging, itching, or other skin discomfort without visible, objective signs of inflammation. This is probably the most common cause of dissatisfaction with cosmetics and skin care products. Objective irritation is defined as nonimmunologically mediated inflammation of the skin with visible changes, such as mild erythema and scaling or, in more severe cases, dermatitis.

Development of irritant contact dermatitis (ICD) de-

pends on several factors, such as: the character, intensity, and concentration of the chemical substance, exposure time or interval between repetition of the reaction, current susceptibility of the skin, environmental conditions (especially climatic) and others.¹¹⁴

Because ICD was considered a simple reaction of the skin free of complex immunologic processes, it attracted little attention among scientists. Extensive research performed in the last decade has shown that this reaction is not at all simple, but that ICD is a rather a complex disease with a multifactorial pathogenesis to which environmental and individual factors contribute. As a result, generally accepted concepts that had been thought to stand on solid ground have changed considerably. The subject has recently gained much attention and aroused increasing interest because, aside from the theoretical medical implications, it is a serious commercial matter closely related to cosmetic formulation and production that forms the backbone of a worldwide, multibillion-dollar industry.

As mentioned earlier, knowledge of the various conditions that influence the susceptibility of the skin to irritation, and the capability of conducting an exact evaluation of the irritation potential of cosmetic products and their ingredients are major concerns of cosmetic manufacturers. It is, therefore, not surprising that so many laboratory tests have been proposed for the assessment of skin irritation *in vivo*,¹¹⁴⁻¹²¹ and *in vitro*.¹²²⁻¹²⁷ Although practicing dermatologists seldom encounter patients with ICD to cosmetics, they are actively involved in numerous other ways that bear upon the safety and quality assessments of cosmetics. Some dermatologists consult for companies while others conduct clinical testing or supervise the review of clinical studies of contract laboratories. I have no doubt that the demand for dermatologists to be involved in these areas will increase in the future, but this is a complex issue, not related to most practicing dermatologists and, therefore, beyond the scope of this article.

"Acne cosmetica," Comedogenicity of Cosmetics

The role of exogenous agents in inducing comedones and acne has been known for decades. Many reports described occupational acne due to petroleum and its derivatives,¹²⁸⁻¹³⁰ coal-tar products,¹³¹ and halogenated aromatic hydrocarbons.^{129,132-135}

In 1972, Kligman and Mills coined the term "acne cosmetica" for a clinical entity characterized by acneiform eruption occurring mainly on the lower cheek and chin area of women aged 20-50 years, and caused by cosmetic products.¹³⁶ The authors assayed 25 brands of foundation cream picked at random from the shelves of a cosmetic store and found 14 of them (among which were some of the more expensive brands) to be come-

dogenic in a rabbit ear-canal model. The authors also mentioned previous reports describing acneiform rash elicited by substances that were used for beautification. The term “pomade acne” had been coined two years earlier¹³⁷ to describe a comedonal eruption on the forehead of black men who applied various grooming substances as part of their daily toilet. In the northern parts of India, certain vegetable oils that were applied to the faces and scalps of children commonly produced an acneiform eruption,¹³⁸ a reaction that was also reported in association with the use of camphorated oil in infants and young children.¹³⁹ The use of brilliantines¹⁴⁰ and paraffin oil¹⁴¹ to beautify the hair was also associated with the outbreak of facial comedones.

Since those publications, dermatologists have widely accepted the concept that acne can be induced or aggravated by cosmetics, and have also accepted the term “acne cosmetica” for this phenomenon.

Another type of follicular reaction to cosmetics is a folliculitis, in which chemical irritation of the follicular epithelium by the cosmetic product is accompanied by inflammatory pustules and papules, usually without comedones.

The most widely used predictive animal model available for testing for comedogenicity is the rabbit-ear assay. This model was first used to demonstrate the comedogenic potential of chlorinated hydrocarbons,¹⁴² and further developments and improvements made it the standard test for assessing a product’s potential for inducing comedones.

It is important to bear in mind that neither the consumer nor the physician can assess whether a specific product will be acneogenic by a simple inspection, or by examining the list of ingredients. Furthermore, the product’s physical characteristics, such as oiliness or viscosity, are not in themselves predictors of an acneogenic response. While it may take up to 6 months for many commercial preparations to produce problems in human skin, the rabbit ear is so sensitive that follicular hyperkeratosis may be provoked in as little as one to two weeks, even with only moderately comedogenic materials.¹³⁶ Cosmetic manufacturers deserve to be congratulated for their ready acceptance of this concept and for performing comedogenicity assays on most of their products.¹⁴³

The cosmetic companies have been inconsistent, even within one product line. For example, Revlon’s Formula II foundation makeup is noncomedogenic, but the Formula II blusher and, especially, the Formula II highlighter are both considerably comedogenic.¹⁴⁴ This again emphasizes the need to rely only on tests of the specific final formula and not on lists of ingredients, the reputation of the cosmetic firm, or a special line of the firm of which only some products have been tested.

Finally, it is worth repeating that the rabbit model is more sensitive than the human one. This means that

substances that are weakly comedogenic in the rabbit are probably safe for human use, with the possible exception of acne-prone individuals. Therefore, unusually meritorious or desirable topical drugs or cosmetics that improve appearance or are valuable for other reasons should not be removed from the marketplace or be forbidden for use just because they did not rank “excellent” in the rabbit-ear assay. Potential consumers should be informed about the results of the testing and their possible consequences, but the final decision should depend on other considerations, in particular the individual’s susceptibility for acne, the time period that the specific product should be used, and the existence of other aggravating factors such as unavoidable exposure to sunlight, etc.

Pigmented Cosmetic Dermatitis

Pigmented cosmetic dermatitis is a type of pigmented contact dermatitis caused by cosmetic components that mainly affecting women’s faces.

Pigmented contact dermatitis was first reported by Osmundsen in Denmark in 1969.¹⁴⁵ He described an epidemic in Copenhagen caused by optic whiteners in washing powder.¹⁴⁶ The pigmentation developed on the areas covered by fabric, with or without a previous dermatitis. Interestingly, in one patient the pigmentation spread from the originally covered areas to those under the long sleeves and high neck of a sweater that she had washed with the same washing powder and had worn to conceal the discoloration of her skin. A patch test with the responsible compound 1% in petrolatum showed strongly positive reactions in the patients and negative results in control subjects with some patch-test sites actually becoming pigmented. Later, several other epidemics of pigmented dermatitis were reported from other parts of the world,^{147,148} and the concept of pigmented contact dermatitis became well established.

Pigmented contact dermatitis is believed to be induced by very small amounts of contact allergens that are in almost daily contact with the patients’ skin. This continuous exposure to low doses of allergens does not result in erythema, papules, or swelling and itching, as in ordinary contact dermatitis, but is often characterized only by hyperpigmentation. Histologically, pigmented contact dermatitis does not show spongiosis and other signs of acute dermatitis, but rather basal liquefaction, degeneration as a dominant feature and, consequently, incontinentia pigmenti. In short, pigmented contact dermatitis is actually a variant of contact dermatitis in which inflammatory components are slight and the pigmentation dominates the clinical picture.

The term pigmented cosmetic dermatitis was introduced in 1973 to describe what had previously been

known as *melanosis faciei feminae*¹⁴⁹⁻¹⁵¹ or, erroneously, Riehl's melanosis (although Riehl described another, unrelated disease, which he believed to be associated with abnormal diet during wartime¹⁵²). During the late 1960s, a research project was set up in Japan to discover the nature, mechanism, and causative agents of this disease. This study showed that the hyperpigmentation was a unique form of an allergic process and, after testing nearly 500 cosmetic ingredients, a number of contact sensitizers could be identified among the cosmetic ingredients. These were mainly fragrance materials and pigments, including jasmine absolute, ylang-ylang oil, cananga oil, benzyl salicylate, hydroxycitronellal, sandalwood oil, artificial sandalwood, geraniol, geranium oil, D&C Red 31, and Yellow No. 11. The researchers then introduced an "Allergen Controlled System," which means that patients exclusively used cosmetics that were completely allergen-free for them. The results were very impressive, with a complete cure in 30% of patients and a remarkable improvement in an additional 40% of the patients, who had a disease that until then had been of unknown etiology and was considered to be very difficult to treat.^{149-151,153,154}

Another Japanese group (Nakayama and colleagues) found that the mechanism of hyperpigmentation after allergic contact dermatitis and the melanogenic factors are different from those induced by ultraviolet radiation (UVR).¹⁵⁵⁻¹⁵⁷

A recent study from Israel showed that 16 out of 29 patients with pigmented contact dermatitis reacted to one of the allergens of the European standard series, whereas only 1 patient reacted to the fragrance series.¹⁵⁸

The impressive achievements made by the Japanese researchers notwithstanding, some areas in the pathogenesis of the disease remain obscure. The concept that pigmented cosmetic dermatitis is produced by the invasion of a very small amount of cosmetic components, leading to inconspicuous manifestations of dermatitis is, to say the least, very unsatisfactory. We still have no explanation for the most basic question of why some allergens cause pigmented dermatitis, while other very similar ones cause ordinary contact dermatitis. What we can say with certainty is that it is not only a matter of the amount and frequency of exposure.

Photocontact Dermatitis

Photocontact dermatitis is a condition in which UVR in combination with an exogenous substance evokes a dermatitis on sun-exposed skin. Exposure to radiation or to the offending agent alone may be harmless, but a combination of the two may produce damage through photosensitization. Photosensitivity can be divided into phototoxic and photoallergic reactions.

Phototoxic contact dermatitis is a form of light-acti-

vated irritation. Compared with photoallergy, this reaction is "simple" and is based on nonimmunologic mechanisms, i.e., on direct toxicity of the photoactivated agent to the skin. Radiation is absorbed by the chemical in the skin, which is then converted to an excited state and produces damage at cell and tissue levels through a variety of molecular and biochemical pathways.¹⁵⁹ Well-known topical phototoxic substances include psoralens (which appear in a large variety of plants), coal tar and derivatives, and dyes such as eosin and acridine orange, etc. The phototoxic reaction usually does not play a major role in cosmetic photocontact dermatitis compared with photoallergy.

Photoallergic contact dermatitis is a form of cell-mediated hypersensitivity in which a photoactivated chemical or a photoproduct acts as a hapten or a complete antigen. The reaction is based on the same immunological mechanisms as those of simple contact allergic reactions. Because UVR transforms certain chemicals into allergens, it is required both for induction and elicitation of the immune response. As in allergic contact dermatitis, photoallergic reactions are elicited in only a small number of individuals with a specifically altered immunological background. The concentration of a chemical that will elicit the reaction is much lower than that needed to produce a phototoxic reaction; it is not dose-dependent, and there is no clinical reaction on first exposure.¹⁶⁰⁻¹⁶³

The most widespread outbreak of photoallergic reactions to topically applied agents resulted from the use of soaps and cleansers containing halogenated salicylanilides and related compounds. In the 1960s, photocontact dermatitis reached the proportions of a mini-epidemic, when thousands of individuals were affected after exposure to these agents.¹⁶⁴⁻¹⁶⁸ After the removal of the responsible agents in soaps and toiletries, the number of photosensitivity cases decreased dramatically. It should be noted, however, that salicylanilides and related anti-infectants have not disappeared completely from the home environment; they are still used in soaps, shampoos, and deodorants and have ranked fairly high in several photopatch test series.¹⁶⁹⁻¹⁷⁶

Among the antimicrobial agents, fenticlor has been the leading photoallergen in many studies, although positive reactions have also been recorded for bithionol, hexachlorophene, and trichlorocarbanilide. It is noteworthy that all of these compounds (based on chlorinated phenol molecules) are chemically related, and cross-sensitivity between them has been recorded as well.^{170,177-179}

In the late 1970s, a group of investigators identified the musk ambrette present in toiletries with the dual function of fragrance and fixative as a photoallergen.^{180,181} In fact, musk ambrette, a synthetic chemical that was widely used in the 1970s in aftershave lotions and colognes, as well as in soaps, detergents, creams,

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lotions, and dentifrice, was the most commonly reported photoallergen of that time. Notably, most cases were recorded in male patients.^{165,172,182} Furthermore, many patients sensitive to musk ambrette developed persistent debilitating photosensitivity.^{180,183}

While the frequency of contact photoallergy to antibacterial agents, fragrance ingredients, and topical medications has decreased over the years, reactions to sunscreen products have rapidly increased in the last few years. The reason for this trend, which is probably not going to change in the near future, is the increasing awareness on the part of the public and the physicians of the carcinogenic potential of sunlight and even more its effect on premature aging of the skin. This has led not only to an increased use of sunscreen products, but to the incorporation of UV filters in a large variety of cosmetic products, such as anti-wrinkle creams, moisturizers, foundations, eye creams, makeup, lipsticks, etc.

The earliest publications, first appearing in 1949, on photoallergy to UV absorbers attributed the problem to para-aminobenzoic acid (PABA) and its esters.¹⁸⁴⁻¹⁸⁸

Increasing public awareness of PABA's sensitization potential and the possibility of cross-sensitization with other compounds has encouraged the use of "PABA-free" sunscreens in the US, Europe, Japan, and Australia.

Benzophenones have emerged as alternatives to PABA, and they are now found in many PABA-free sunscreens. The increased use of this agent (which was initially considered a relatively safe compound) brought about a parallel increase in reports of contact and photocontact allergic reactions.¹⁸⁹⁻¹⁹⁴

This has led to a new trend, namely, the introduction of "oxybenzone-free" sunscreens, which resulted in a third and fourth wave of photoallergy, this time attributed to dibenzoylmethanes^{171,195-197} and, recently, to cinnamates.¹⁹⁸⁻²⁰¹

The increased use of micronized physical UV blockers (e.g., coated micronized TiO₂ and ZnO) as a replacement of chemical absorbers is undoubtedly a welcome step toward reducing the incidence of adverse reactions to sunscreens and producing safe, well-tolerated products.

The Cosmetic Intolerance Syndrome

The term "status cosmeticus" or cosmetic intolerance syndrome, was coined by Fisher²⁰² to describe a condition in which patients are no longer able to tolerate the use of any cosmetic. Patients who have this syndrome typically present with an unremarkable clinical picture. They may have a mild erythema with slight edema of the eyelids, or occasionally show follicular eruption or may present with only subjective symptoms. The objective signs and symptoms are, however, not as vivid as

the patients' bitter complaints of burning, stinging sensations. These patients experience irritation (subjective or objective, or both) from cosmetics and are intolerant of many, if not all, topical agents.

Cosmetic intolerance syndrome is not a single entity but rather a symptom complex due to multiple exogenous and endogenous factors. Although 20 years have elapsed since its first description, our knowledge of this syndrome, its etiology, and mechanisms remains very limited.

Although cosmetic intolerance syndrome can be caused by allergic or photoallergic contact dermatitis, contact urticaria, endogenous diseases such as seborrheic dermatitis, rosacea, and perioral dermatitis, atopic dermatitis, or psoriasis, the most common cause is non-immunologically mediated primary irritation. This may be subjective (sensory without objective inflammation), or objective. It is worth mentioning that subjective irritation (which remains the commonest cause of cosmetic intolerance) is not merely the first stage or a mild form of objective irritation, but probably has a different mechanism with different mediators. Subjective and objective reactions are not always parallel. There are chemicals (e.g., alcohol) that cause irritation usually without objective inflammation; other chemicals (e.g., sodium lauryl sulfate) are known as strong irritants, but do not cause stinging.²⁰³ Patients with "cosmetic intolerance" usually show negative patch tests to various implicated cosmetics and soaps. Furthermore, they are negative to "use" tests done on the forearm, thus indicating that the problem is localized to the facial skin, which becomes intolerant to various cosmetics. Some dermatologists have called this syndrome "dermatological non-disease" and believe that it stems from psychological problems, a disturbed body image (dysmorphophobia), and depression. They emphasize the ominous prognosis of these patients both with regard to the risk of suicide and the development of psychosis.²⁰⁴⁻²⁰⁶ We think that, although psychological disturbances might on rare occasions cause subjective intolerance to cosmetics, the role of the psychological aspect has been exaggerated by dermatologists who are specifically interested in psychodermatology. Dermatologists should rather be aware that "true" cosmetic intolerance without any objective symptoms does exist, and that the feeling of irritation comes from the skin and not from the brain (mind, psyche), although we lack insight into the mechanism and mediators responsible for it. Patients with cosmetic intolerance syndrome seriously challenge our diagnostic skills as well as our ability to be empathetic. Suspecting that every patient "imagines" symptoms because of psychological disturbances would certainly not facilitate our job.

The management of patients with cosmetic intolerance syndrome includes avoidance of all skin care products and cosmetics for 3 to 12 months.^{203,207-209} Obvi-

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ously, this advice, which most of the patients have probably received in earlier consultations, is very difficult to accept and adhere to. Cosmetic alternatives that are allowed during this time are the following: water washing without soap or detergent, as much as needed. Lipstick (nonperfumed) may be used ad libitum, if lips are uninvolved with cheilitis. These products should be encouraged because they are well tolerated and may boost the patient's morale. The same goes for face powders and eye cosmetics, which are also well tolerated and, except in rare cases, may be permitted. Finally, the issue of moisturizers. According to our experience, avoidance of moisturizers is the most difficult for patients to accept. Unfortunately, moisturizers keep the syndrome alive because they are cumulative irritants, and these are certainly not the products one can compromise on. Instead, one may use the "good old" combination of glycerin and rose water.

The time required for normalization varies from weeks to one year, rarely longer. Then one can add other skin care products, one at a time, no more frequently than every 2 weeks.

The above are only general guidelines that might give the reader an idea of how to approach this specific group of patients. As mentioned, sensitive skin is not a single entity, but a heterogeneous syndrome, and each patient will have to be evaluated and treated individually, with a specifically tailored management plan.

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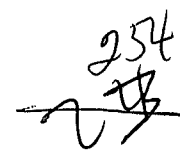
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Fragrance Allergens: Classification and Ranking by QSAR

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Abstract—Quantitative structure–activity relationship (QSAR) models which predict both skin penetration and cell mediated immunity for small molecular weight non-electrolytes developed earlier were validated on 74 known allergens and non-allergens chosen among fragrance chemicals in common use to test discriminating and grading power. While the test set used for classification was based on experience in humans exclusively, the rank model was tested for sensitization potency including guinea pig data also. In the classification test, 12 of 74 compounds fell in the indeterminate range and were non-classifiable by the present QSAR model. On the remaining 62 compounds the model performs with 90% sensitivity and 100% specificity at 92% concordance. The rank model correctly grades 65 of 74 compounds (88% concordance), with 60% specificity based on exact prediction of non-allergens (NON), and 95% sensitivity on allergens (ACD) allowing for a variance of $\pm$ one level among weak, moderate and severe ratings. In combination, the two models perform with 93% overall concordance on the test set of 74 compounds.

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Abbreviations: ACD = allergic contact dermatitis; allergens; FCA = Freund's complete adjuvant; GPMT = guinea pig maximization test; HBA = hydrogen bond acceptor; HBD = hydrogen bond donor; ICDRG = International Contact Dermatitis Research Group; IFRA = International Fragrance Research Association; MR = molar refraction; NACDGR = North American Contact Dermatitis Group; NON = non allergens; QSAR = quantitative structure–activity relationship; RIFM = Research Institute of Fragrance Manufacturers; Y-est = Y-estimate (model score).

INTRODUCTION

Increasingly, published data provide evidence that an important part of cutaneous cosmetic intolerance is due to their fragrance component, the incidence of sensitization ranging from 7% to 18% of a normal, asymptomatic test population (Dooms-Goossens, 1993; Dooms-Goossens *et al.*, 1992; Fisher, 1995; Guin and Berry, 1980; Larsen *et al.*, 1992; Maibach, 1991; Nielsen and Menne, 1992). It is understandable therefore that the fragrance and cosmetics industries, health professionals as well as regulatory agencies, assign high priority to the development of methods predictive of allergy that are robust and minimize use of experimental animals. Computers and statistical software now make it possible to move conventional animal evaluation programs away from unavoidable experimental and biological variables onto a more objective plane, where physicochemical properties and chemical reactivity can be evaluated individually as factors determining events such as skin penetration and allergic sensitization. Quantitative structure–

activity relationships (QSAR) is one such alternative to animal experimentation which objectively describes the interaction between chemicals and biological systems (Hansch and Leo, 1995; Hansch *et al.*, 1995), and is now increasingly used in the prediction of a variety of toxicological endpoints, including allergic contact dermatitis (ACD) (Cronin and Dearden, 1995).

Biologically-based, comprehensive QSAR models combining both structural alerts with barrier diffusion criteria have been developed through systematic analysis of known contact allergens, which identify both the features that make a chemical an allergen, as well as the physicochemical properties which determine penetration of a compound through the stratum corneum (Hostýnek, 1995; Magee *et al.*, 1994a). Development of these models seek to encompass the several characteristics known to be necessary attributes for immunogenic activity. Such determining factors are: (a) molecular size and hydrogen bonding critical for diffusivity through the stratum corneum; (b) metabolism of prohapten in the skin; (c) lipophilic substructures which have affinity for cell membrane lipids; and (d) electrophilic and nucleophilic haptens which bind to native

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proteins, as well as free radical generators which modify the structure of proteins, and by forming covalent bonds yield non-self proteins. Adequate factoring of all components however, poses significant problems of a statistical nature. To cover the diverse functional groups present among electrophiles, nucleophiles and potential radical generators and, most importantly, the spatial relations within molecules which often determine reactivity, a comprehensive database would necessarily consist of hundreds of compounds, as documented in the recent predictive systems DEREK (Ridings *et al.*, 1996), TOPKAT (Enslein *et al.*, 1996) and MULTICASE (Graham *et al.*, 1996). In these so-called expert systems, where at their present stage prediction rests on a set of rulebases, the larger the data set the more comprehensive is the analysis for toxophores statistically associated with protein reactivity. In our model development, which combines structural alerts for protein reactivity with criteria for diffusivity and metabolism, increasing sample size causes the importance of reactivity descriptors to outweigh the physicochemical parameters which account for the barrier permeation process, to the point where their statistical relevance disappears altogether. Thus, we could establish empirically (Magee *et al.*, 1994a) that the number of 60–80 compounds represents an optimal trade-off, where size, polarity and hydrogen bond formation are still adequately important in describing translation of non-electrolytes through a biological membrane such as the skin. To our knowledge, the QSAR model developed earlier using stepwise regression, discriminant and principal component analysis (Magee *et al.*, 1994a) and which we propose to test here, incorporates all the above prerequisites for adequate ACD prediction to a near-optimal degree. It lies in the nature of statistics mentioned that some exceptional biophores will occasionally remain outside that model.

Considering the prominence that fragrances have attained in the aetiology of contact hypersensitivity among the general population, demonstration of robust predictive performance of the QSAR model as applied to fragrance chemicals of well-documented sensitization potential could demonstrate its utility in the prediction of ACD potential of new, as-yet untested structures. With that intent, we proceeded to test the existing discriminant model in the classification of proven human allergens and non-allergens among a number of compounds frequently used in perfumery, and also evaluated the performance of a newly developed rank model in grading for allergenic potency.

MATERIALS AND METHODS

Criteria for compound selection

It is the primary objective of this study to establish the utility of QSAR to predict sensitization in man by

compounds used in perfumery, and thus it was of paramount importance for the validation of the previously constructed models to select compounds for which sensitizing properties had been demonstrated in humans. A reliable source for a list of sensitizers is IFRA, the International Fragrance Research Association. With headquarters in Geneva, Switzerland, IFRA is composed of the national associations of over 100 fragrance manufacturers in 15 countries. Its Technical Advisory Committee reviews all available data on fragrance ingredients and, when necessary, issues recommendations for the safe use of these materials, including restrictions on use levels and advisories not to use substances at all when warranted by safety considerations. Thus, to date, the use of nearly 100 fragrance raw materials has been either restricted or prohibited, in greatest part due to their potential for sensitization (Ford, 1991). Such risk assessment is based on information gathered by RIFM (Research Institute for Fragrance Materials), an association whose members represent most of the fragrance industry in the United States, Europe and Japan, and reflects the clinical experience gathered by dermatologists from most countries of the industrialized world.

For the fragrance test set, 33 sensitizers were culled from the IFRA list of compounds of established sensitizing potency; an additional 26 ACD actives were selected from the various lists of standard patch test series of allergens (ICDRG, 1988; Matsuo *et al.*, 1993; NACDG, 1984) and the RIFM Fragrance Raw Materials Monographs reflecting the result of human maximization tests which were also designed to evaluate the potency of allergens (Kligman, 1966). These were published over 25 years in *Food and Chemical Toxicology* (formerly *Food and Cosmetics Toxicology*), with the latest series in 1992 (Ford *et al.*, 1992). Furthermore, clinical test reports of reputable origin were included when they were based on clinical history, physical examination and patch testing (Klecak *et al.*, 1977; Larsen *et al.*, 1992), and data from multicenter ACD investigations (Eiermann *et al.*, 1982; Frosch *et al.*, 1995; Larsen, 1985; Larsen *et al.*, 1996). 15 non-sensitizers (NON) for the test set were selected based on a Medline search for the years 1966–1995, and also from the RIFM Fragrance Raw Materials Monographs.

For the graded test set, entries from the IFRA negative list in the 'prohibited' category were entered *a priori* as strong sensitizers; those in the 'restricted' category as moderate. Furthermore, in order to obtain additional data on potency for ACD compounds other than those on IFRA's negative list and the human maximization tests, it was necessary to include animal data obtained from experimental protocols precluded in human testing. Such complementary data were taken from the GPMT literature (Cronin and Basketter, 1994).

Prerequisite for selection of all compounds used in the validation studies was their listing in the reference

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book on perfumery chemicals by S. Arctander (Arctander, 1960).

QSAR model development

QSAR model development relies on the process of learning from experience. It is based on the assumption that a mathematical relationship exists between physicochemical and chemical properties of chemical agents and their action in the living organism. In that process a so-called training set is chosen which involves collection of pertinent clinical data, and the database thus obtained is then analysed for statistically significant parameters by discriminant or regression analysis from a wealth of chemical and physicochemical descriptors. This process yields information on structural elements (independent variables) statistically associated with biological activity (dependent variables), for instance on the interdependence of chemical causes and clinical effects. The output from this process, in the form of an algorithm or a mathematical equation, represents the knowledge gained from experience. QSAR studies applied to physiological phenomena such as the penetration of biological membranes or hypersensitivity reactions, also present the benefit of yielding detailed information on the processes occurring at the cellular and molecular level; those descriptors which survive the scrutiny for statistical significance are also those likely to determine course and end result in the real-life biological process. For validation, the algorithm derived is then applied to the analysis of a new set of compounds, the test set, and correlated with clinical data obtained *in vivo*. The more rigorous the selection of input data in model construction, the higher will be the correlation coefficient in the test set.

QSAR statistics

The statistics used in the models to measure goodness-of-fit are the student's *t*-value for the coefficients and the measures *s*, *r*² and *F*.

The student's *t*-value is the ratio of the coefficient to the error in the coefficient, larger values relating to smaller ranges of error.

The standard error of the equation, *s*, is essentially a standard deviation of the points from the *Y* estimate *v.* *Y* line. For larger datasets (*n* > 50), outliers are defined as points deviating from the line by more than 2.5 standard errors and are generally not included in the regression.

The correlation coefficient, *r*, is derived from the directly calculated *r*², which measures the variance in the data explained by the coefficients of the equation. We have used *r*² exclusively as a better measure of the goodness-of-fit and scatter about the regression line. The unexplained variance, 1-*r*², is a measure of the regression error, which must not exceed that of the original experimental error.

The Fisher distribution, *F*, is a measure of the

overall strength of the equation. Values greater than 10 are considered highly significant.

The *Y*-estimate (*Y*-est) is the model's output, the value derived by the equation for a specific query.

The discriminant model

A statistical discriminant QSAR model based on 72 ACD and NON compounds was developed and tested successfully in diverse studies (Hostýnek *et al.*, 1995; Magee *et al.*, 1994a,b). It is based on a combination of continuous transport/binding descriptors and dichotomous (0/1) descriptors reflecting protein reactivity by simple count of toxophores (haptens and prohaptens). A full description of model development is contained in the primary reference (Magee *et al.*, 1994a). Experience has led to stepwise modification of the model for improved performance, and the one applied here is the latest revised version. The descriptors used in this model are characterized as follows.

Continuous transport/binding descriptors are molar refraction (MR), the polarizable molecular volume modelling London forces in non-specific binding (Charton, 1983), and PL (lipophilic contribution of LogP_{octanol:water}; PL + PH = LogP) which models lipophilic interactions of compounds with proteins and membranes. Both are easily calculable from contributing fragments (Hansch and Clayton, 1973; Hansch and Dunn, 1972; Hansch and Leo, 1979; Magee, 1991). Of the ordinal descriptors, HBA is a simple count of the electron pairs on N and O that models the concentration potential of hydrogen bond acceptor groups, and HBD is a simple count of the N-H and O-H groups that models the concentration potential of hydrogen bond donor groups. Dichotomous descriptors are used to code for the presence or absence of protein reactive substructures (1/0). The descriptor ICOOR codes for simple aliphatic esters and models esterase degradation; ICONJ codes for conjugated olefins activated by groups that cause Michael addition of SH and NH₂ protein end-groups; IX codes for reactive aliphatic or aromatic halides; IArOH codes for easily metabolized phenols (to reactive quinones); IArNH₂ codes for easily metabolized anilines (to reactive quinones); IOH codes for easily oxidized primary alcohols (to reactive aldehydes); IUNIQ codes for strong nucleophiles and for unusual reactive electrophiles that occasionally require coding. In Table 1, the 1/0 values of the reactivity descriptors are omitted for reasons of space as they are easily recreated by visual inspection of the molecular structures.

In earlier studies involving diverse structures, the discriminating power of the equation fell in the range of 79–88% correct classification, predicting non-allergens somewhat more efficiently than allergens (Magee *et al.*, 1994a). Model output is read from the *Y*-estimate (*Y*-est). Allergens and

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Table 1. Compounds, ACD ratings, continuous descriptors and model performance in the fragrance test set

Compound [ratings]	CAS NO.	MR	PL	HBA/HBD	Score	Pass/fail
1,2-Propylene glycol [1a/2b]	57-55-6	19.56	1.62	4/2	0/1 ^d	0/0 ^e
1-(4-Methoxyphenyl)-1-pentene-3-one** [1/4]	104-27-8	57.88	4.53	4/0	1/3	1/1
1-Octene-3-yl acetate* [1/3]	2442-10-6	50.26	4.67	4/0	0/1	0/0
2-Amyl-cinnamaldehyde [1/3]	122-40-7	65.30	5.13	2/0	1/3	1/1
2-Hexyl-cinnamaldehyde [1/4]	101-86-0	69.92	5.90	2/0	Bg/3	-/1
2-Methyl-cinnamaldehyde [1/3]	101-39-3	46.82	2.97	2/0	1/4	1/1
2-Phenylethyl alcohol [0/1]	60-12-8	37.45	3.00	2/1	0/1	1/1
2-n-Pentylidene cyclohexanone** [1/4]	25677-40-1	52.77	4.97	2/0	1/3	1/1
3,5,5-Trimethylhexyl acetate [0/1]	58430-94-7	54.16	5.71	4/0	0/1	1/1
3-Methyl-2(3)-nonene nitrile* [1/3]	53153-66-5	49.66	4.41	1/0	0/2	0/1
4-Allyl anisole [1/4]	140-67-0	45.59	3.86	2/0	1/3	1/1
4-Hydroxybenzyl alcohol [1/4]	623-05-2	34.65	2.33	4/2	1/3	1/1
4-Methoxyacetophenone [0/1]	100-06-1	43.30	3.45	4/0	0/1	1/1
4-Methoxybenzaldehyde [1/3]	123-11-5	38.68	2.79	4/0	1/3	1/1
4-Methoxybenzyl alcohol [1/3]	105-13-5	39.27	3.22	4/1	1/3	1/1
4-Methylhydrocinnamaldehyde* [1/3]	99-72-9	46.10	3.87	2/0	1/3	1/1
6-Isopropyl-2-decalol** [1/4]	34131-99-2	59.82	5.79	2/1	0/1	0/0
6-Methylheptadienone* [1/3]	1604-28-0	41.69	3.13	2/0	1/3	1/1
7-Methoxycoumarin** [1/4]	513-59-9	46.63	2.86	6/0	1/3	1/1
Allylheptyne carboxylate* [1/3]	73157-43-4	50.76	4.63	4/0	1/3	1/1
Amylcyclopentenone* [1/3]	25564-22-1	48.15	4.18	2/0	1/3	1/1
Anethole [1/4]	4180-23-8	47.48	3.86	2/0	1/3	1/1
Anisylidene acetone** [1/4]	943-88-4	53.26	3.98	4/0	1/3	1/1
Benzophenone-2 [1/3]	119-61-9	56.57	3.80	2/0	1/4	1/1
Benzyl alcohol [1/4]	100-51-6	32.83	2.56	2/1	1/4	1/1
Benzyl dimethylcarbinol [0/1]	100-51-6	47.69	3.92	2/1	0/1	1/1
Benzyl salicylate [1/2]	118-58-1	63.06	4.23	5/0	B/2	-/1
Benzylidene acetone** [1/4]	122-57-6	46.82	3.32	2/0	1/3	1/1
Carvone [1/3]	2244-16-8	38.91	3.52	2/0	1/3	1/1
Cinnamaldehyde** [1/4]	104-55-2	42.20	2.72	2/0	1/3	1/1
Cinnamic alcohol* [1/3]	104-54-1	42.79	2.97	2/1	1/4	1/1
Citral** [1/4]	5392-40-5	50.93	3.73	2/0	1/3	1/1
Citronellal [1/3]	106-23-0	50.21	4.51	2/0	B/3	-/1
Coumarin [1/2]	91-64-5	40.19	2.20	4/0	1/3	1/1
Cyclamen alcohol** [1/4]	4756-19-8	60.55	5.42	2/1	1/4	1/1
Diethyl maleate** [1/4]	75554-12-3	42.30	3.15	8/0	1/3	1/1
Dihydrocoumarin** [1/4]	119-84-6	39.47	2.15	4/0	1/3	1/1
Dimethyl citraconate** [1/4]	617-54-9	37.68	2.72	8/0	1/3	1/1
Eugenol [1/3]	97-53-0	49.23	3.35	4/1	1/3	1/1
Farnesol [1/2]	4602-84-0	75.34	6.29	2/1	1/4	1/0
Fixolide [0/1]	1506-02-1	81.00	7.50	2/0	0/2	1/1
Folione* [1/3]	111-12-6	40.80	4.22	4/0	1/3	1/1
Geraniol [1/3]	106-24-1	51.52	4.27	2/1	1/4	1/1
Heliotropine [1/3]	120-57-0	38.44	2.33	6/0	1/3	1/1
Hexahydrocoumarin** [1/4]	700-82-3	41.62	3.31	4/0	1/3	1/1
Hexyl salicylate [0/1]	6259-76-3	61.83	5.14	5/0	0/1	1/1
Hydroabietyl alcohol** [1/4]	70775-80-3	90.10	8.87	2/1	B/4	-/1
Hydroxycitronellal* [1/3]	107-75-5	51.31	4.95	4/1	B/3	-/1
Isoamyl salicylate [0/1]	87-20-7	57.21	4.47	5/0	0/1	1/1
Isoeugenol* [1/3]	97-54-1	49.23	3.46	4/1	1/3	1/1
Lilial [0/1]	80-54-6	64.58	5.52	2/0	B/3	-/0
Limonene(dipentene) [0/1]	138-86-3	47.64	4.35	0/0	0/2	1/1
Menthhol [1/2]	89-78-1	48.02	5.35	2/1	0/1	0/1
Methyl cinnamate [1/3]	103-26-4	46.87	3.32	4/1	1/3	1/1
Methyl crotonate** [1/4]	623-43-8	27.16	2.19	4/0	1/3	1/1
Methyl eugenol [1/2]	93-15-2	55.91	4.52	4/0	1/3	1/1
Methyl N-methylanthranilate [0/1]	85-91-6	45.92	3.45	4/0	0/1	1/1
Methyl salicylate [0/1]	119-36-8	38.73	2.56	5/0	B/1	-/1
Musk ketone [0/1]	81-14-1	81.86	6.21	6/0	0/2	1/1
Musk xylene [0/1]	81-15-2	73.10	4.78	6/0	B/2	-/1
p-tert-Butyl phenol** [1/4]	98-54-4	46.69	3.92	2/1	B/3	-/1
Pentyl cyclopentanone propanone [0/1]	40942-73-2	62.52	5.80	4/0	0/1	1/1
Perillaldehyde* [1/3]	2111-75-3	48.87	3.27	2/0	1/4	1/1
Phenyl salicylate [1/3]	118-55-8	58.44	3.57	5/0	1/3	1/1
Phenylacetaldehyde** [1/4]	122-78-1	36.86	2.67	2/0	1/3	1/1
Phenylethyl salicylate [1/2]	87-22-9	67.68	4.65	5/0	B/2	-/1
Propyl paraben [1/2]	94-13-3	47.97	3.52	6/1	1/3	1/1
3-Propylidenephthalide* [1/3]	17369-59-4	49.43	3.28	4/0	1/3	1/1
Pseudomethyl ionone** [1/4]	26651-96-7	70.13	6.17	2/0	1/3	1/1
Thymol [1/3]	89-83-8	46.69	4.05	2/1	B/3	-/1
Trans-2-heptenal** [1/4]	18829-55-5	36.35	3.05	2/0	1/3	1/1
Trans-2-hexenal diethyl acetal** [1/4]	67746-30-9	52.62	5.31	4/0	B/3	-/1
Trans-2-hexenal dimethyl acetal** [1/4]	18318-83-7	43.88	4.47	4/0	1/3	1/1
Versalide [0/1]	88-29-9	81.00	7.45	2/0	0/2	1/1

(a) Input class ACD = 1; NON = 0. (b) input rank 1-4. (c) model class 1 = ACD; 0 = NON. (d) model rank 1-4. (e) model performance: 1 = pass; 0 = fail. (g) indeterminate class. (*) restricted by IFRA. (**) prohibited by IFRA.

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non-allergens are scored as Y-est values above and below 0.5, and we consider values falling in the range 0.4–0.6 to be of indeterminate category and beyond the classification ability of the model. The equation for the latest version of the model is given in Table 2.

The rank model

The construction of a rank model based on a different set of 89 compounds has been described elsewhere (Hostýnek *et al.*, 1996). The method of ranking is based on non, weak, moderate and strong responses (1–4); it follows the pattern established by Magnusson and Kligman (1969), but with significant numerical differences. The Magnusson–Kligman scale (1–5) is determined by the number of guinea pigs sensitized in the maximization test with 1 = weak (0–8%), 2 = mild (9–28%), 3 = moderate (29–64%), 4 = strong (65–80%) and extreme (81–100%). Our scale corresponds to 1 = non-allergenic (0%), 2 = weak to mild (1–28%), 3 = moderate (29–64%) and 4 = strong to extreme (65–100%). Thus, the compounds selected to represent the NON group are designated as '1' and are similar to the selection identified as NON in the discriminant model described above. All of the others (ranks 2–4) are allergens of weak-to-mild, moderate and strong-to-extreme ACD inducers. With these differences in mind, the graded responses were correlated by multiple regression against the full set of 22 descriptors studied for our discriminant model (Magee *et al.*, 1994a). The current version of the model is given in Table 3. Despite the difference in procedure and data set, the significant descriptors are found to be identical to those in the discriminant model (Table 2) and only the descriptor coefficients distinguish the two models. Formal differences in the grading model are that IArOH and IArNH₂ were combined to IQUIN, and ICONJ and IUNIQ to IPOS because the coefficients proved to be similar. Note that the sign of HBA is reversed and the dependence on ester degradation, ICOOR, is statistically weak.

Scoring rank model performance

Scoring the rank model is not as straightforward as the 'yes-no' scoring with the discriminant model, due to the significant overlap in the model's score for the respective class levels. The following ranges for classes 1–4 are: 1 = 0.63–1.97; 2 = 1.24–3.10; 3 = 1.81–4.14; 4 = 2.66–4.88. As the equation score Y-est can fall into more than one range, the criterion used is closest proximity to the mid-point value of each range. The mid-point values for each range are: 1 = 1.30; 2 = 2.17; 3 = 2.97; 4 = 3.77. Measured against these benchmarks, there are two levels of concordance possible for performance assessment. Ideally, the Y-est of the equation would accurately reflect the clinical result and fall exactly within one range. On a more realistic level, the experimental variability of $\pm$ one level described by Gad (1988) is applied in scoring here, as no model can perform better than the variance in the data employed.

Classes 1 and 4 are perfectly separated, but the overlap between successive classes is significant. Classes 2 and 3 are well represented by the average Y-est (2.1 and 3.1), but class 1 is overpredicted (av. Y-est = 1.3) while class 4 is underpredicted (av. Y-est = 3.5). The estimated span covers only 2.2–3.0 (73%) of the input scan. The problem, of course, is that dichotomous reactivity descriptors cannot successfully model a range of 1–4. Repairing this shortcoming is the subject of ongoing research towards further improvement of the models.

Aside from these problems, the ranked model performs well within the $\pm$ one level variance already inherent in experimental test data as described by Gad (1988). In an earlier validation study (Hostýnek *et al.*, 1996) of 61 allergens and non-allergens not used in the learning set, we find a concordance of 90% overall and 97% for separation of inactives from strong allergens. Application of the rank model for the rating of ACD response thus appears to be a useful corollary for confirmation of data obtained with the discriminant model.

Table 2. The statistical discriminant model

Descriptor	Coefficient	T-Value
Molar Refraction MR	0.0116	2.49
Lipophilicity Factor PL	−0.161	−3.38
Hydrogen Bond Acceptors HBA	0.0498	2.88
Hydrogen Bond Donor Groups HBD	−0.129	−2.91
Aliphatic Esters ICOOR	−0.284	3.55
Michael Reactants ICONJ	0.570	6.47
Reactive Halides IX	0.160	4.73
Aromatic Phenols IArOH	0.596	6.18
Aromatic Amines IArNH ₂	0.503	4.82
Primary Alcohols IOH	0.207	2.51
Reactive Nucleophiles and Electrophiles IUNIQ	0.512	4.12
Intercept	0.118	

Learning set: ACD (Class 1): n = 36 NON (Class 0): n = 36

t-value: Student's t-value; total sample size n = 70 (two outliers); explained variance r^2 = 0.750; standard error s = 0.275; Fisher statistics F = 15.81.

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Table 3. The statistical rank model

Descriptor	Coefficient	T-Value
Molar Refraction MR	0.0294	2.47
Lipophilicity Factor PL	-0.281	-2.55
Hydrogen Bond Acceptors HBA	-0.0960	-2.28
Hydrogen Bond Donors HBD	-0.207	-2.48
Aliphatic Esters ICOOR	-0.409	-1.69
Primary Alcohols IOH	0.547	2.84
Reactive Halides IX	0.519	3.54
Michael Reactants, Reactive Nu & El philes IPOS	1.375	10.70
Aromatic Amines and Alcohols IQUIN	1.390	9.17
Intercept	1.70	

Learning set: NON allergens (Class 1): n = 29 WEAK allergens (Class 2): n = 18
 MODERATE allergens (Class 3): n = 15 STRONG allergens (Class 4): n = 26
 t-value: Student's t-value; total sample size n = 88; explained variance $r^2 = 0.726$ standard error
 s = 0.680; Fisher statistics F = 23.00.

RESULTS

Discriminant model

Of the 74 fragrance chemicals in Table 1, the discriminant model places 12 (16%) in the indeterminate region, ($Y\text{-est} = 0.4\text{--}0.6$) and thereby they are not predictable by the equation. Of the 62 remaining chemicals, the model correctly predicts 57 (92% concordance). All five incorrectly predicted compounds are false negatives, rated as allergens in the literature. Thus, the model performs better on non-allergens (12/12, 100% specificity) than on allergens (45/50, 90% sensitivity), which is consistent with our previous studies (Magee *et al.*, 1994a,b).

Rank model

To evaluate rank model performance, it must be noted that all non-allergens have to be predicted exactly as such with a score falling within the $Y\text{-est}$ brackets of 0.63–1.97 to be correct, and are ranked as "1". By such convention, model specificity is 60% (9/15). For allergens (rank "2–4"), a correct score is the exact level $\pm$ one level for a pass score, in accord with the variance to be expected in experimental data (Gad, 1988). Thereby, model sensitivity is 95% (56/59). Of the 74 fragrance chemicals in the test set (Table 1), overall rank model performance is 88% (65/74). Of the six incorrectly predicted ranks (1–4), four are also incorrectly predicted by the discriminant model. As these four are false negatives, the rank model also performs better in predicting non allergens than allergens. Of the remaining two misses, one is correctly predicted by the discriminant model (ACD) while the other is borderline and not classifiable. Of greatest interest to this study is the fact that 11/12 (92%) of the borderline cases from the discriminant model are correctly assigned by the rank model. Thus the use of the two models is both confirmatory and supplementary.

DISCUSSION

The validation performance achieved by the two QSAR models, tested mainly on clinical evidence of

sensitization in man, demonstrates the importance of skin penetration and skin metabolism as relevant factors in an algorithm expected to predict ACD potential. Other approaches such as DEREK (Ridings *et al.*, 1996) or TOPKAT (Enslein *et al.*, 1996) which are based on a vast body of GPMT data, are eminently qualified for the determination of protein reactivity or allergenic potential of chemical structures of great diversity, but not for estimating the actual risk of sensitization in man.

It is not surprising that the discriminant model performs with high specificity (100%), since classification of the compounds for ACD activity in the test is entirely based on empirical evidence obtained from human exposure under realistic use patterns. Those reactions avoid limit conditions as they are provoked in animal experimentation, such as intracutaneous guinea pig tests or the use of FCA, and account for the barrier function of the skin. Prediction of a compound as an allergen by the model means that substructures were coded as protein reactive, while prediction as a non-allergen indicates that either no substructures were considered to be protein reactive or, as in some cases, the mechanistic factors determining barrier penetration outweigh the substructure descriptors.

Comparative evaluation of performance shows that the two QSAR models are confirmatory and supplement each other to a large extent, as the 'fails' in one overlap with the 'passes' in the other: four of the nine rank 'fails' are correctly predicted by the discriminant model; 10 of the 12 borderline cases in the discriminant model are correctly ranked, and only three of the 62 classified queries fail in both models. Concordance achieved by the two models applied in tandem thus is 93% overall (69/74). This is at least equal to the variance expected for such chemicals from human and animal testing. The present validation exercise demonstrates the advantage of using the two QSAR models in conjunction on a given set of compounds, as they are internally consistent to a large degree with discriminant failures

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being identical with three of the rank failures. A number of the 'fails' invite discussion.

1,2-Propylene glycol is reported as a weak/mild allergen (Corazza *et al.*, 1993; Eiermann *et al.*, 1982), presumably by metabolism to the protein reactive lactaldehyde. However, we coded the primary alcohol group as IOH = 0 for lack of direct evidence of oxidative metabolism in human skin. The glycol is too polar to be a good substrate for mixed-function oxydases (Hansch and Leo, 1995) and the very low oral and skin toxicity on several animals (LD₅₀ = 10–80 g/kg) (Sax, 1984) does not suggest any metabolic conversion to a toxic electrophile such as lactaldehyde. Perhaps this is a case where the known mild-moderate skin irritation (Sax, 1984) has been misinterpreted as an ACD response.

1-Octene-3-yl acetate and 3-methyl-(2,3)-nonene nitrile are restricted in perfumery use (classified here as moderate allergens) and 6-isopropyl-2-decalol is prohibited there (classified as a strong/extreme allergen) (Ford, 1991). None contain substructures that we would normally code as protein reactive in these models. However, there is one difference. In the case of 1-octene-3-yl acetate, our current rules of coding do not allow for sequential coding of activation steps such as ester hydrolysis and subsequent oxidation to the obviously ACD active vinyl ketone. Thus, the model fails in these cases even though in some instances we can anticipate probable mechanisms.

The case of 6-isopropyl-2-decalol, prohibited by RIFM (Ford, 1991), is different in that metabolism to other than a ketone of low protein reactivity is not expected. While speculative, it seems that air oxidation of one or more of the tertiary C–H bonds to a reactive hydroperoxide contaminant is a more likely event. Its presence would be readily detected in the commercial grade of the compound.

Menthol is reported to be a weak/mild allergen (Hayakawa *et al.*, 1996; Sharp, 1978; Wilkinson and Beck, 1994) and, like the decalol discussed above, contains none of the protein reactive structures normally coded for these models. Again, metabolic oxidation to the ketone is likely, but as ketones are not normally considered protein reactive haptens, the coding still would be IOH = 0. However, menthol has substructures in common with 6-isopropyl-2-decalol, and the possibility of air oxidation contaminants is of similar credibility. Such scenarios currently lie outside the model and can only be addressed on a case-by-case basis.

Limonene, a hydrocarbon with no protein reactive structures, is correctly predicted as a non-allergen by the discriminant model. However, the rank model overpredicts limonene by one class, based on the Y-est, revealing the present weakness of the model to accurately bracket the lowest and highest ranks. As mentioned under Materials and Methods, in its present state the statistical model overpredicts at the

low end of the scale, and underpredicts at its upper end.

Overall, the successes in the two models clearly outweigh the failures. We have not succeeded in developing models with $n = 72$ and 88 compounds that will cover all conceivable hapten/prohapten structures and at the same time adequately factor in physicochemical parameters. However, each failed prediction represents a far more important piece of information than the successes. It is through insights gained from predictive failures that the models can be further refined and strengthened.

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Review

Safety assessment on polyethylene glycols (PEGs) and their derivatives as used in cosmetic products

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Abstract

This assessment focusses on polyethylene glycols (PEGs) and on anionic or nonionic PEG derivatives, which are currently used in cosmetics in Europe. These compounds are used in a great variety of cosmetic applications because of their solubility and viscosity properties, and because of their low toxicity. The PEGs, their ethers, and their fatty acid esters produce little or no ocular or dermal irritation and have extremely low acute and chronic toxicities. They do not readily penetrate intact skin, and in view of the wide use of preparations containing PEG and PEG derivatives, only few case reports on sensitisation reactions have been published, mainly involving patients with exposure to PEGs in medicines or following exposure to injured or chronically inflamed skin. On healthy skin, the sensitising potential of these compounds appears to be negligible. For some representative substances of this class, information was available on reproductive and developmental toxicity, on genotoxicity and carcinogenic properties. Taking into consideration all available information from related compounds, as well as the mode and mechanism of action, no safety concern with regard to these endpoints could be identified. Based on the available data it is therefore concluded that PEGs of a wide molecular weight range (200 to over 10,000), their ethers (laureths, ceteths, cetareths, steareths, and oleths), and fatty acid esters (laurates, dilaurates, stearates, distearates) are safe for use in cosmetics. Limited data were available for PEG sorbitan/sorbitol fatty acid esters, PEG sorbitan beeswax and PEG soy sterols. Taking into account all the information available for closely related compounds, it can be assumed that these compounds as presently used in cosmetic preparations will not present a risk for human health. PEG castor oils and PEG hydrogenated castor oils have caused anaphylactic reactions when used in intravenous medicinal products. Their topical use in cosmetics is, however, considered safe as they are not expected to be systemically available. As all PEGs and PEG derivatives, they must not be applied to damaged skin. Manufacturers of PEGs and PEG derivatives must continue their efforts to remove impurities and by-products such as ethylene oxide and 1,4-dioxane. Overall, it is concluded, that the PEGs covered in this review are safe for use in cosmetics under the present conditions of intended use.

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Keywords: Polyethylene glycol; PEG; Cosmetics; Safety assessment; Toxicology

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1. Introduction

Polyethylene glycols (PEGs) and their anionic or nonionic derivatives are widely used in cosmetics as surfactants, cleansing agents, emulsifiers, skin conditioners, and humectants. They comprise a class of compounds varying in molecular weights between 200 and over 10,000. Due to their presence in many cosmetics, an evaluation of their safety is critical, the more so, as potential exposure of consumers may be chronic and extensive.

The following assessment focusses on PEGs and on anionic or nonionic PEG derivatives that are currently used in cosmetics in Europe. Relevant compounds are listed in Table 1, together with their CAS numbers, synonyms and their function in cosmetics.

Further to their use in cosmetics, many of the compounds have other applications. Available information from these uses is included in this assessment where relevant. In the pharmaceutical industry, for instance, they are used as vehicles for drugs and as ointment bases, capsules, tablet and pill binders, suppositories,

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Table 1
Overview on PEG and PEG derivatives

CLASS General Formula	Substances	Common other names	CAS register numbers	Function in cosmetics	Examples for use levels in cosmetics	Chemical name	
PEGs HO(CH ₂ CH ₂ O) _n H	PEG-4	Macrogol 200; PEG-200	112-60-7 25322-68-3	humectants / solvents	Up to: - 3% in styling products - 5% in hair colorants, bath and shower products - 10% in toothpaste, shampoo - 25% in foundation, make-up - 30% skin care creams/lotions - 90% in bath oils	3, 6, 9- trioxaundecane- 1, 11- diol	
	PEG-6	PEG-300	2615-15-8			3, 6, 9, 12, 15- pentaoxaheptadecane- 1, 17- diol	
	PEG-8	PEG-400	5117-19-1 25322-68-3			3, 6, 9, 12, 15, 18, 21- heptaoxatricosane- 1, 23- diol	
	PEG -9, -10		25322-68-3			Poly(oxy- 1, 2- ethanediyl), α- hydro- ω-	
	PEG-12		6790-09-6 25322-68-3			3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33- undecaioxapentatriacontane- 1, 35- diol	
	PEG-14		25322-68-3			humectants binders / humectants / solvents humectants / solvents humectants humectants / solvents binders / humectants / solvents humectants humectants / solvents binders / solvents binders / emulsion stabilisers / viscosity controlling agents	Poly(oxy- 1, 2- ethanediyl), α- hydro- ω-
	PEG-16, -18						
	PEG-20	Macrogol 1000					
	PEG-32	Macrogol 1540					
	PEG-40						
	PEG-60						
	PEG-75	Macrogol 4000; PEG 3350;					
	PEG-90						
	PEG -100						
	PEG-135						
	PEG-150	Macrogol 6000					
	PEG-180						
	PEG-200						
	PEG-240						
	PEG-350						
PEG-2M, -5M, -7M, -9M, - 14M, -20M, - 23M, -25M, - 45M, -90M, -115M							
PEG fatty acid esters							
<u>- laurates</u>	PEG-2 laurate		141-20-8	emulsifying agents	Up to 5-10% in skin care products, cleansers, bath foams, conditioners, shampoos	2- (2- hydroxyethoxy)ethyl laurate	
	PEG-4 laurate		9004-81-3			Poly(oxy- 1, 2- ethanediyl), α- (1- oxododecyl)- 2- hydroxy-	
	PEG-6 laurate		9004-81-3 2370-64-1			26- hydroxy- 3, 6, 9, 12, 15, 18, 21, 24- octaoxahehexacos- 1- yl laurate	
	PEG-9 laurate		106-08-1			Poly(oxy- 1, 2- ethanediyl), α- (1- oxododecyl)- ω- hydroxy-	
	PEG -10, -12, -14 laurates		9004-81-3	emulsifying agents / surfactants			
	PEG-8, -20 laurates			surfactants			
<u>- dilaurates</u>	PEG-32, -75, - 150 laurates				emulsifying agents	Up to 5-10% in skin care products, cleansers, bath foams	Poly(oxy- 1, 2- ethanediyl), α- (1- oxododecyl)- ω- [(1- oxododecyl)oxy]-
	PEG-2 dilaurate		9005-02-1				
	PEG-4, -6, -8, -12, -20, -32 dilaurates						

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Table 1 (Continued)

CLASS General Formula	Substances	Common other names	CAS register numbers	Function in cosmetics	Examples for use levels in cosmetics	Chemical name
	PEG-75, -150 dilaureates				conditioners, shampoos	
- stearates (C ₁₇ H ₃₅ COO.(O.CH ₂ CH ₂) _n	PEG-2 stearate		106-11-6	emulsifying agents / opacifiers		2- (2- hydroxyethoxy)ethyl stearate
	PEG-3 stearate		9004-99-3	humectant		Poly(oxy- 1, 2- ethanediyl), α- (1- oxooctadecyl)- ω- hydroxy-
	PEG-4 stearate		106-07-0			2- [2- (2- hydroxyethoxy)ethoxy]ethox y]ethyl stearate
	PEG-4 isostearate		56002-14-3	emulsifying agents		
	PEG-5, -6, -7 stearates		9004-99-3			
	PEG-6, -8 isostearates		56002-14-3			Poly(oxy- 1, 2- ethanediyl), α- (1- oxooctadecyl)- ω – hydroxy-
	PEG-8 stearate	polyoxyl 8 stearate	9004-99-3 70802-40-3	emulsifying agents / humectants / surfactants		
	PEG-9 stearate		5349-52-0 9004-99-3	emulsifying agents		26- hydroxy- 3, 6, 9, 12, 15, 18, 21, 24- octaoxahexacos- 1- yl stearate
	PEG-10 isostearate		56002-14-3	emulsifying agents / surfactants	Up to 5-10 % in facial cleansers, moisturizers, body lotions, skin care, conditioners, hair treatment products, and styling gels	
	PEG-10 stearate		9004-99-3	emulsifying agents / surfactants		Poly(oxy- 1, 2- ethanediyl), α- (1- oxooctadecyl)- ω- hydroxy-
	PEG-12 isostearate		56002-14-3			
	PEG-12, -14, - 18 stearates		9004-99-3	emulsifying agents		
	PEG-15 hydroxysteara te					
	PEG-20 stearate			emulsifying agents / humectants / surfactants		
	PEG-23, -25 stearates			emulsifying agents		
	PEG -30, -32, -35, -36 stearates					
	PEG-40 stearate	Macrogol ester 2000		emulsifying agents / surfactants		
	PEG-45 stearate					
	PEG-50 stearate	polyoxyl 50 stearate				
	PEG-75, -90, - 100, -120, - 150 stearates			surfactants		
- distearates C ₁₇ H ₃₅ COO.(O.CH ₂ CH ₂) _n . COOC ₁₇ H ₃₅ .	PEG-2 distearate		109-30-8	emulsifying agents	Up to 10% in facial cleansers, moisturizers, body lotions, skin care, conditioners, and shampoos	Oxydiethane- 1, 2- diyl distearate
	PEG-3, -4, -6, -8, -9, -12, -20, -32, -75, -120 distearates					
	PEG -150, -175 distearates		9005-08-7	emulsifying agents / surfactants / viscosity controlling agents	Up to 10% in shaving gel	Poly(oxy- 1, 2- ethanediyl), α- (1- oxooctadecyl)- ω- [(1- oxooctadecyl)oxy]-

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Table 1 (Continued)

CLASS General Formula	Substances	Common other names	CAS register numbers	Function in cosmetics	Examples for use levels in cosmetics	Chemical name
PEG ethers						
of lauryl alcohol (n- dodecanol) = laureths C ₁₂ H ₂₅ (OCH ₂ CH ₂) _n OH	Laureth-1		4536-30-5	emulsifying agents / surfactants	Up to 11% in hair colorants	2- (dodecyloxy)ethanol
	Laureth-2		3055-93-4 9002-92-0		Up to: -1% in conditioners and treatments; - 2% in styling products; - 3% in cleansing products; - 10% in bath oils, hair shampoos, deodorants, skin cleansing products; - 25% in hair dyes/colours	2- [2- (dodecyloxy)ethoxy]ethanol
	Laureth-3		3055-94-5			2- [2- [2- (dodecyloxy)ethoxy]ethoxy]e thanol
	Laureth-4		5274-68-0			3, 6, 9, 12- tetraoxatetracosan- 1- ol
	Laureth-5		3055-95-6			3, 6, 9, 12, 15- pentaohaheptacosan- 1- ol
	Laureth-6		3055-96-7			3, 6, 9, 12, 15, 18- hexaoxatriacontan- 1- ol
	Laureth-7		3055-97-8			3, 6, 9, 12, 15, 18, 21- heptaoxatriacontanol
	Laureth-8		3055-98-9 9002-92-0	emulsifying agents		Poly(oxy- 1, 2- ethanediyl), α- dodecyl- ω- hydroxy-
	Laureth-9	Polidocanol Lauryl Macrogol	3055-99-0 9002-92-0			3, 6, 9, 12, 15, 18, 21, 24, 27- nonaoxanonatriacontan- 1- ol; α-Dodecyl-ω- hydroxypoly(oxy-1,2- ethanediyl)
	Laureth-10		6540-99-4 9002-92-0	emulsifying agents / surfactants		Poly(oxy- 1, 2- ethanediyl), α- dodecyl- ω- hydroxy-
	Laureth-11		9002-92-0 3056-00-6	emulsifying agents		
	Laureth-12, 13, -14, -15, - 16, -20, -23, - 25, -30		9002-92-0	emulsifying agents / surfactants	Up to 20% in hair colorants, hair bleach	
	Laureth -40			surfactant		
- of cetyl alcohol (C16 alcohols) = ceteths	Ceteth-1		2136-71-2 9004-95-9	emulsifying agent	Up to - 2% in styling products;	2-(hexadecyloxy)ethanol
	Ceteth-2, -3, - 4, -5, -6, -10, - 12, -14, -15, - 16, -20, -24, - 25, -30, -45		9004-95-9	emulsifying agents and/or surfactants	- 10% in hair conditioner, hair color restorer; - 20% in facial wash	Poly(oxy- 1, 2- ethanediyl), α- hexadecyl- ω- hydroxy-
- of stearyl alcohol (C18 alcohols) = steareths	Steareth-2		9005-00-9	emulsifying agent / surfactant	> 1% in skin care products, moisturizers, hair dyes, conditioners, styling gels	Poly(oxy- 1, 2- ethanediyl), α- octadecyl- ω - hydroxy
	Steareth-3,-4,- 5,-6,-7,-8			emulsifying agents		
	Steareth-10			emulsifying agent / surfactant		
	Steareth -11, - 13, -14, -15, - 16			emulsifying agents		
	Steareth-20, - 21, -25			emulsifying agent s/ surfactants		
	Steareth-27, - 30, -40, -50, - 100			surfactants		
- of cetearyl alcohol (C16/18- alcohols) = ceteareths	Ceteareth-2, - 3, -4, -5, -6, - 7, -8, -9, -10, - 11, -12, -13, - 14		68439-49-6	emulsifying agents	Up to - 1% in cleansing products; - 4% in styling products	

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Table 1 (Continued)

CLASS General Formula	Substances	Common other names	CAS register numbers	Function in cosmetics	Examples for use levels in cosmetics	Chemical name
cetareths R(OCH ₂ CH ₂) _n OH (R: mixture of alkyl groups derived from cetyl and stearyl alcohols)	Cetareth-15, -16, -17, -18			emulsifying agents/surfact ants	Up to 10% in skin care and cleansing products, conditioners, and hair treatment products	
	Cetareth-20				Up to - 1% in conditioners and treatments; - 3% in styling products	
	Cetareth-22, -23, -25, -27, - 28, -29, -30, - 33, -34			emulsifying agents/ surfactants	Up to - 1% in perms - 10% in antiperspirants - 18% in styling products	
	Cetareth-40			surfactant	Up to 1.5 % in colorants	
	Cetareth-50			emulsifying agents/ surfactants	Up to 10% in skin care and cleansing products, conditioners, and hair treatment products	
	Cetareth-55			surfactants		
	Cetareth-60			emulsifying agents		
	Cetareth-80, -100			surfactants		
	- of <u>oleyl alcohol</u> (octadec-9- enol) = <u>oleths</u> CH ₂ (CH ₂) ₇ CH =CH(CH ₂) ₇ (O .CH ₂ CH ₂) _n OH	Oleth-2, -3, -4, -5,-6, -7, -8, -9		9004-98-2	emulsifying agents / surfactants	Up to 10% in hair colorant and in styling products
Oleth-10		polyoxyl 10 oleyl ether	9004-98-2 24871-34-9	Up to 12% in various formulations		
Oleth-12, -15, -16, -30, -40			9004-98-2			
Oleth-20, -23, -25, -44, -50			9004-98-2	surfactants	Up to - 1% in styling products; - 5% in hair mousse, refreshing wet wipes	
PEG glyceryl cocoates RCOOCH ₂ C HCH ₂ (OCH ₂ CH ₂) _n OH R: coconut oil derived fatty acids	PEG-7 glyceryl cocoate		68201-46-7 66105-29-1	emulsifying agents / surfactants	Up to - 5% in cleansing products, liquid soap - 15% in styling products, shampoos	Glycerides, coco mono- and di- , ethoxylated
	PEG-30 glyceryl cocoate		68201-46-7			
	PEG-40 glyceryl cocoate			emulsifying agents		
	PEG-78, -80 glyceryl cocoate			emulsifying agents / surfactants		
Others						
PEG castor oils	PEG-2, -3, -4, -5, -9, -10 castor oil		61791-12-6	emulsifying agents / surfactants / solvent	Up to : - 1% in styling products, conditioners and treatments,	Castor oil, ethoxylated
	PEG-11 castor oil			emollients / emulsifying agents		

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Table 1 (Continued)

CLASS General Formula	Substances	Common other names	CAS register numbers	Function in cosmetics	Examples for use levels in cosmetics	Chemical name		
	PEG-15, -20, -25, -26, -29, -30, -33, -35, -36, -40, -44, -50, -54, -55, -60, -75, -100, -200 castor oils			emulsifying agents / surfactants	- 3% in perms, neutralizers, aftershave products, perfume, shampoos			
	PEG, -2, -5, -7, -16, -20, -25, -30, -35, -40, -44, -50, -54, -55, -60, -100, -200 hydrogenated castor oil		61788-85-0	emulsifying agents / surfactants / solvent	up to - 1% in conditioners, hair treatments, cleansing products; - 2% in perfume, mouthwash, toothpaste; - 10% in tan gel, shampoos, skin care, make-up, deodorants	Castor oil, hydrogenated, ethoxylated		
PEG soy sterols	PEG-5, -10, -16, -25, -30, -40 soy sterol			emulsifying agents	0.05 – 2 % in skin care products, moisturizers, facial cleansers, mascara, and make-up			
PEG sorbitan fatty acids	PEG-2 sorbitan isostearate			surfactants / emulsifying agents	Up to 1% in conditioner / treatments/hair tonics, make-up foundation, styling gel, body lotions	Sorbitan, monooctadecanoate, poly(oxy- 1, 2- ethanediyl) derivative		
	PEG-3, -5, -6, -20 sorbitan oleate		9005-65-6	emulsifying agents / surfactants		Sorbitan, mono- 9-octadecenoate, poly(oxy- 1, 2- ethanediyl) derivs., (Z)-		
	PEG-3, -4, -6, -20, -40, -60 sorbitan stearate		9005-67-8			Sorbitan, monooctadecanoate, poly(oxy- 1, 2- ethanediyl) derivatives		
	PEG-4, -10, -20, -40, -44, -75, -80 sorbitan laurate		9005-64-5			Sorbitan, dodecanoate, poly(oxy- 1, 2- ethanediyl) derivatives		
	PEG-5, -20 sorbitan isostearate		66794-58-9			Sorbitan, monooctadecanoate, poly(oxy- 1, 2- ethanediyl) derivatives		
	PEG-20 sorbitan cocoate					Sorbitan, cocoate, poly(oxy- 1, 2- ethanediyl) derivative		
	PEG-20 sorbitan tristearate			emulsifying agents		Sorbitan, trisoctadecanoate, poly(oxy- 1, 2- ethanediyl) derivative		
	PEG-20 sorbitan palmitate					Sorbitan, palmitate, poly(oxy- 1, 2- ethanediyl) derivative		
	PEG-20 sorbitan trioleate					Sorbitan, trioleate, poly(oxy- 1, 2- ethanediyl) derivative		
	PEG-30, -40, -60 sorbitan tetraoleate					Sorbitan, tetraoleate, poly(oxy- 1, 2- ethanediyl) derivative		
		PEG-40 sorbitan diisostearate				emulsifying agents / surfactants		Sorbitan, dioctadecanoate, poly(oxy- 1, 2- ethanediyl) derivative
		PEG-60 sorbitan tetrastearate						Sorbitan, tetraoctadecanoate, poly(oxy- 1, 2- ethanediyl) derivative
PEG (sorbitan) beeswax	PEG-6 sorbitan beeswax	G 1703	8051-15-8	emulsifying agents / surfactants	Up to -8% in mascara, lipsticks			

Table 1 (Continued)

CLASS General Formula	Substances	Common other names	CAS register numbers	Function in cosmetics	Examples for use levels in cosmetics	Chemical name
	PEG-8 sorbitan beeswax, PEG-8 beeswax	G 1726	8051-73-8		-11% in blusher	
	PEG-20 sorbitan beeswax					
Propylene glycol copolymers	PEG-8 propylene glycol cocoate		126645-98-5	emulsifying agents / surfactants	Up to 2 % in cleansing products	Fatty acids, coco, ethoxylated, propoxylated
	PEG-10 propylene glycol		9003-11-6	humectants		Oxirane, methyl-, polymer with oxirane
	PEG-25, -76, - 120 propylene glycol stearate			emulsifying agents		Fatty acids, stearyl, ethoxylated, propoxylated
	PEG-55 propylene glycol oleate		86481-08-5	viscosity controlling agents		Poly(oxy- 1, 2- ethanediyl), α, α'- (1- methyl- 1, 2- ethanediyl)bis[ω- [(1- oxo- 9- octadecenyl)oxy]- , (Z, Z)-

liquid prescriptions, and in veterinary drugs, including parenteral, topical, ophthalmical, oral, and rectal preparations. Further applications include use as ingredients in soaps and detergents, in the textile and leather industry, in plastics and resins, in the paper industry, in printing, in the ceramics and glass industry, in the rubber, petroleum, mining and metal industries, for wood preservation and as chemical intermediates. Polyoxyethylene sorbitan esters (polysorbates) and polyethylene glycol with an average molecular weight of 6000 are permitted as food additives in various foods according to the European Parliament and Council Directive No. 95/2/EC of 20 February 1995. The WHO has set an estimated acceptable daily intake of polyethylene glycols at up to 10 mg/kg bw (FAO/WHO, 1980).

2. PEGs and PEG derivatives used in cosmetics

Polyethylene glycols (PEGs) are polymers of ethylene oxide with the generalised formula HO–(CH₂–CH₂–O)_n–H, and “n” indicating the average number of oxyethylene groups. They have been assigned the CAS register number 25322-68-3 and the scientific name “poly(oxy-1,2-ethanediyl)-α-hydro-ω-hydroxy”. Common synonyms are listed in Table 1.

PEGs and PEG derivatives do not represent definite chemical entities, but are mixtures of compounds with varying polymer chain lengths. The average number or

the molecular weight of the polymer chain is often indicated in the generic name of the specific substance, as, for instance, in PEG-8 which is equivalent to PEG-400. The first nomenclature, i.e. using the average length of the polymer chain, will be used in the following assessment, as it is the common naming convention in the cosmetics industry.

In cosmetics, PEGs are used either as such, or in form of their derivatives. Having two terminal primary hydroxyl groups, the PEGs can form mono-, di- and polyesters, ethers, amines and acetals. PEGs are also able to react by forming addition compounds or complexes on their ether bridges. PEG derivatives, therefore, include PEG fatty acid esters (e.g. PEG laurates, dilaurates, stearates, and distearates), PEG ethers (e.g. laureths, ceteths, ceteareths, oleths, and PEG ethers of glyceryl cocoates), PEG amine ethers (PEG cocamines), PEG castor oils, PEG propylene glycols, and other derivates (e.g. PEG soy sterols, PEG beeswax).

PEGs with mean molecular weights of up to 400 are clear viscous liquids at room temperature. PEGs of higher molecular weights are white waxy solids. All PEGs are readily miscible with water, the solid PEGs are slightly less soluble in water with their solubility decreasing as molecular weight increases.

The outstanding property of this class of compound is their solubility in water and their capability to solubilise other substances in preparations. They are non-

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volatile, stable compounds, which do not hydrolyse or, in the absence of oxygen, deteriorate on storage.

With the exception of PEG amine ethers, the substances are anionic or nonionic compounds. PEG amine ethers are cationic in character but become increasingly nonionic with increasing degree of ethoxylation. PEG amine ethers are not covered in the following assessment.

2.1. Methods of manufacture, composition

PEGs are manufactured by the polymerization of ethylene oxide (EO) with water, monoethylene glycol or diethylene glycol, under alkaline conditions (Asmussen, 2000).

PEG ethers of lauryl, cetearyl, cetyl, stearyl or oleyl alcohol (“laureths, cetareths, ceteths, steareths, oleths”) are manufactured by the ethoxylation of lauryl, cetearyl, cetyl, stearyl or oleyl alcohol with the number of moles of ethylene oxide corresponding to the average polyethylene glycol chain length desired. Laureths with an average polymer chain length between 1 and 40 are currently listed for use in cosmetics in the INCI list, for ceteths, steareths, cetareths, oleths the chain lengths range between 1 and 45, 2 and 100, 2 and 100, and 2 and 50, respectively (INCI, 2005).

PEG esters are produced by the ethoxylation of fatty acids. PEG laurates, dilaurates, stearates and distearates are ethoxylated carboxylic acids derived from lauric acid and stearic acid, respectively, and the number of moles of ethylene oxide corresponding to the average polyethylene glycol chain length desired. No information was available for PEG glyceryl derivatives.

PEG castor oils and PEG hydrogenated castor oils are PEG derivatives of castor oil and hydrogenated castor oil of various chain lengths, depending on the quantity of ethylene oxide used in synthesis. PEG castor and hydrogenated castor oils are mixtures of components, predominantly glyceryl triricinoleyl PEGs, and tri-12-hydroxyl-stearyl-PEGs, respectively. Fatty acid esters of polyethylene glycols are also present, as well as hydrophilic PEGs and ethoxylated glycerol.

PEGs soy sterols are the reaction products of soy sterol hydroxyls with ethylene oxide. Mainly used soy sterols include campesterol, stigmasterol, and β -sitosterol.

The PEG sorbitan fatty acid esters (also known as “polysorbates”)/sorbitol fatty acid esters are ethoxy-

lated sorbitan and sorbitol esters of fatty acids. These ingredients are formed by the esterification of sorbitol or sorbitan with a fatty acid, followed by the chemical addition of ethylene oxide.

Polyethylene glycol (PEG)-6, -8, and -20 sorbitan beeswax are ethoxylated derivatives of beeswax. Beeswax is a complex mixture of several fatty esters, fatty alcohols, and hydrocarbons.

PEG glyceryl cocoate polymers are the polyethylene glycol ethers of glyceryl cocoate.

PEG polypropylene polymers are polyethylene glycol ethers of propylene glycol itself, propylene glycol stearate, propylene glycol oleate, or propylene glycol cocoate. Polyethylene glycol (PEG) propylene glycol cocoates and PEG propylene glycol oleates are produced by the esterification of polyoxyalkyl alcohols with lauric acid and oleic acid, respectively.

2.2. By-products and impurities

Impurities found in various PEGs and PEG derivatives may include residual ethylene oxide, 1,4-dioxane, polycyclic aromatic compounds, and heavy metals. Pesticide residues may be present in PEG derivatives made from plants, such as PEG soy sterols. PEGs and their derivatives can contain 1,4-dioxane as a by-product of ethoxylation, as well as traces of the reactants (fatty acids, ethylene oxide, any catalysts, etc.). Oxidation of PEGs may occur if exposed for long periods to temperatures exceeding 50 °C. Peroxides, formed as a result of autoxidation, were found in PEG-32 and PEG-75, with the concentration being dependent on age and storage conditions (Hamburger et al., 1975). Finished products may therefore contain anti-oxidants to prevent the initiation of radical mechanisms.

Further to the recommendations of the German Cosmetic, Toiletry, Perfumery and Detergent Association (IKW), the following concentrations of impurities should not be exceeded in PEGs and PEG derivatives for use in cosmetics (IKW, 2005):

- maximum 10 mg/kg (10 ppm) 1,4-dioxane;
- maximum 0.3% (by weight) total ethylene and diethylene glycol;
- maximum 1 mg/kg (1 ppm) ethylene oxide;
- maximum 10 mg/kg (10 ppm) heavy metals (combined).

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Specifications exist for pharmaceutical qualities of polyethylene glycols (“macrogols”), e.g. in the European Pharmacopeia (PhEur), the U.S. Pharmacopeia (USP), and the Japanese Pharmacopeia (JP).

Specific production processes guarantee that the formation of monoethylene glycol ethers is avoided or minimized, in order to prevent the easy formation of metabolites that are considered to be reprotoxic. In fact, concentrations of monoethylene glycol ethers do not exceed trace levels in the PEGs and PEG derivatives under review here.

As outlined before, PEGs and PEG derivatives do not represent definite chemical entities, but are mixtures of compounds with varying polymer chain lengths. For instance, PEG-4 contains substantial levels of diethylene glycol (3%), triethylene glycol (17%), tetraethylene glycol (29%), pentaethylene glycol (25%), hexaethylene glycol (16%), heptaethylene glycol (8%), and octaethylene glycol (2%) (Bailey and Koleske, 1966).

3. Use levels

PEGs and PEG derivatives are used as humectants, solvents, binders, emulsion stabilizers, and viscosity-increasing agents in a wide variety of personal care products. Most common uses for PEG and PEG derivatives include those in toothpaste, skin lotions, deodorant sticks, shaving creams, hand creams, face makeup, cream rouge, blush, mascara, lipsticks, bath products, and hair care products. Maximum use levels with product type examples are given in Table 1. The information is based on information from the European Frame Formulations (Colipa, 2000), information from European manufacturers and formulators, and information published in the open literature (e.g. Bangha et al., 1996; Beyer et al., 1983; Conrad et al., 1995; Uter et al., 2000).

4. Toxicology/safety

4.1. Toxicokinetics and metabolism

4.1.1. Absorption

PEGs can be absorbed by the gastrointestinal tract with the fraction absorbed being dependent on the

molecular weight of the compound. PEG-8 is well absorbed via the gastrointestinal tract and approximately 50% of the administered dose is excreted via the urine in humans within 24 h (Chadwick et al., 1977; Shaffer et al., 1950). Likewise, an extensive absorption of PEG-4 and PEG-6 via the oral route can be assumed, while less than 10% of PEG-75 and less than 2% of the greater molecular weight PEGs are absorbed after oral intake (DiPiro et al., 1986; Leung et al., 2000). There was no evidence that PEG-150 was absorbed at all (Shaffer and Critchfield, 1947).

Lower molecular weight PEGs are only minimally absorbed through the intact skin, and PEGs with molecular weights of 4000 or greater (PEG-75 or greater) are not absorbed at all (Smyth et al., 1942; Principe, 1968). PEGs, independent of their molecular weight, can however penetrate through injured skin with compromised barrier function (Herold et al., 1982).

Recent studies on the clinical effects and permeability of various emulsifiers in human skin have demonstrated that low molecular weight PEG stearates, such as PEG-2 stearate and PEG-9 stearate (at a concentration of 5%, w/v), are able to influence the skin barrier function (Bárány et al., 2000). In contrast, higher molecular weight PEGs (PEG-40 stearate) did not show these features (Bárány et al., 2000).

Nishiyama et al. (1983) studied the percutaneous absorption of ^{14}C -labelled laureths in hairless mice, treated with 0.25% solutions in ethanol. The amount of percutaneous absorption after 4 h was 17.7% for lauryl alcohol, 22.9% for laureth-1, 15.5% for laureth-2.6, 10.4% for laureth-6.4 and 2.1% for laureth-10. Short chain laureths are capable to diffuse from human skin and mucuous membranes into nerval tissue as evidenced by their analgesic and antipruritic effects (Ring and Fröhlich, 1985).

In a study with ^{14}C -labelled branched chain alkylpolyethoxylate ($\text{H}(\text{CO}_2)_{12}(\text{OCH}_2\text{CH}_2)_6\text{OH}$) on rats, about 25% of the dermally applied dose were absorbed, mainly during the first 12 h. In this study, the test substance was applied as 2% (w/v) aqueous solution over four days under occlusive conditions (Calvin et al., 1983). Drotman (1980) reported a percutaneous absorption of about 48% for the corresponding straight-chain analogue. As different techniques were used in the two studies, a direct comparison is difficult. In contrast to the results obtained in the animal

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studies, only 2% of straight-chain alkylpolyethoxylates ($\text{H}(\text{CO}_2)_{12}(\text{OCH}_2\text{CH}_2)_6\text{OH}$) were absorbed through the skin of two volunteers (100 mg applied over 90 cm^2 on the forearm; Drotman, 1980). The area of application was protected by a nonocclusive metal shield for 8 h. A 2% of the administered radioactivity appeared in the urine, and no activity was found in faeces or expired air. Radioactivity in the blood was barely detectable (equivalent to $0.02\text{--}0.14\text{ }\mu\text{g/g}$ blood at 8 h, $0.02\text{ }\mu\text{g/g}$ at 12 h, and $0.01\text{ }\mu\text{g/g}$ at 24 h).

Twenty-two atopic dermatitis patients were treated with a laureth (“polidocanol”)-containing bath oil either by bathing in the diluted product or by applying the oil onto the skin for 8 h after having showered (Buhles and Richter, 1989). Percutaneous penetration was quantified by measuring polidocanol blood concentrations and urinary excretion rates. The blood concentrations resulting from bath or after-shower application was $0.015\text{--}0.021\text{ }\mu\text{g/ml}$ and hence more than 1000-fold smaller than those possibly reached with intravenous use of polidocanol as a sclerosing agent. The calculated absorption was 0.0017% for the bath application and 0.0035% for the after-shower application.

PEG soy sterols are poorly absorbed by the gastrointestinal tract (<5%) and did not result in significant systemic exposure (CIR, 2004). While the polyoxyethylene sorbitan moiety is poorly absorbed by the gastrointestinal tract, the fatty acid portions of the PEG sorbitan fatty acid esters is almost quantitatively taken up by the body (CIR, 2000b).

4.1.2. Excretion/metabolism

After oral and intravenous exposure, PEGs are excreted mainly unchanged in the urine and faeces. Part of the absorbed PEGs is metabolised to lower oligomers, glycolic acid, hydroxyglycolic acids and the diglycolic acids homologs, carbon dioxide (CO_2 , detected in exhaled air), and – in very minor quantities – oxalic acid (DiPiro et al., 1986; Herold et al., 1982; Marshall, 1982; Corley et al., 2002). The lack of toxicity typical for ethylene glycol in repeat dose studies with high exposure levels of PEGs does not indicate that ethylene glycol is a metabolite that is produced from PEGs or their derivatives in relevant quantities in vivo.

The pathways leading to CO_2 are probably saturable, as the percent eliminated as CO_2 decreases at

higher dose rates. The percentage eliminated as CO_2 decreases also with increasing molecular weight within the homologous series (Matthews et al., 1991).

Biochemical studies have demonstrated that mammalian alcohol dehydrogenase (ADH) is able to initiate the oxidation of PEG-6 (Herold et al., 1989). Diacid metabolites as well as hydroxy acid metabolites were found in the serum and urine of burn patients after treatment with a PEG-based antimicrobial cream containing PEG-6 (63%), PEG-20 (5%) and PEG-75 (32%) (Bruns et al., 1982).

PEG fatty acid ester and sorbitan/sorbitol fatty acid esters undergo rapid hydrolysis with the fatty acid moiety being metabolized by β -oxidation, and the PEG sorbitan moiety being excreted mainly in the urine.

Absorbed laureths were generally rapidly metabolized to CO_2 , and excreted with the expired air (lauryl alcohol: 60%, laureth-1: 21%, laureth-2.6: 6.9%, laureth-10: 6.0%). With increasing number of ethylene oxide units, the percentage in expired air was reduced, and the amount excreted in feces and urine increased by approximately 50–60% (lauryl alcohol: 2.6%; laureth-1: 31%, laureth-2.6: 62%, laureth-10: 51%) (Nishiyama et al., 1983).

4.2. Effects of PEGs on skin/mucosa penetration of other molecules

Nonionic surfactants have the potential to act as penetration enhancers by decreasing surface tension and conditioning the stratum corneum and hence may enable or enhance diffusion of other molecules or drugs through the skin. PEGs and their derivatives may therefore exert effects on the disposition or activity of other molecules. The quality and magnitude of such effects are, however, mainly dependent on the structure and molecular weight of the PEG derivative, and also on the other constituents in the formulation, and can therefore be influenced by the manufacturer. For certain PEGs an enhancing effect on the skin penetration of other molecules has indeed been demonstrated, particularly in injured skin or mucosa with a compromised barrier function, while an effect to the contrary, i.e. a reduction of the skin permeability has been found with other PEG derivatives (GD, 2001).

Since long, certain PEGs are used as barriers to dermal penetration. A mixture of high- and low-molecular-

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weight PEGs (“PEG-540”), for instance, was shown to effectively reduce skin penetration of organophosphate compounds (Olson et al., 1991), and PEG-8 significantly reduced phenol absorption (Schutz, 1958; Monteiro-Riviere et al., 2001), as well as skin permeation of the insect repellent DEET (Qiu et al., 1998). PEG-8 is also reported to reduce the penetration rate of drugs, and to raise the skin barrier function by forming complexes and/or by increasing viscosity (Degim et al., 1998; Hatanaka et al., 1993; Sarpotdar et al., 1986; Valia et al., 1984). The properties of the stratum corneum were not influenced by PEG-8 concentrations as high as 40% (v/v) (Valia et al., 1984).

Skin penetration enhancing effects have been shown to occur particularly with PEG-ethers and some PEG-fatty acid esters, such as PEG-2 stearate and PEG-9 stearate, while higher molecular weight PEG fatty acid esters, like PEG-40 stearate do not have this property (Biondi et al., 2002). Laureth-9 has been shown to enhance the nasal absorption of drugs in a concentration dependent manner (Donovan et al., 1990). Oleths increased the permeability of isolated human stratum corneum in *in vitro* studies (Kadir et al., 1993). The enhancing effect of PEG-7 glyceryl cocoate in gels was similar to those from other dermatological vehicles (CIR, 1999a). The substance was shown to affect the structure of the human stratum corneum structure, probably due to an insertion of the surfactant molecules in the lipid bilayers (De Vos and Kinget, 1993). No effect on the stratum corneum was found with cetareth-20 (De Vos and Kinget, 1993), while Fabregas et al. (1986) had found that the percutaneous absorption of the analgesic pikeprofen was increased in rabbits following topical application of aqueous and anhydrous creams containing 2%, 3% or 5% of cetareth-20.

In vitro, PEG-20 sorbitan oleate caused significant increases in rabbit and canine oral mucosa permeability of only three out of eight tested compounds (i.e. of heptanediol, sucrose and inuline), and only at the highest concentration tested (1.0%) (Siegel and Gordon, 1985, 1986).

From the available data it can therefore be concluded, that PEGs and PEG derivatives in some cases may support penetration or permeation of substances across biological barriers, but this is not true as a general principle. Moreover, the effects are often tiny and, for instance, for pharmaceuticals not sufficient.

4.3. Acute toxicity

4.3.1. Oral route

After acute oral exposure, PEGs are practically non-toxic with animal LD₅₀ values generally greater than 2000 mg/kg bw. Oral administration of large quantities of PEGs can have a laxative effect. In clinical practice, PEG-75 is widely used for colon cleansing; no major side-effects have been reported so far with the exception of one single case of acute (reversible) renal insufficiency in a patient with massive intestinal bacterial overgrowth after receiving 18 l of a PEG-75 solution (Descamps et al., 2000). Ingestion of Lava light liquid containing 13% of PEG-4 induced acute renal toxicity in a 65-year-old man (Erickson et al., 1996).

While PEG fatty acid esters, sorbitan esters and PEG castor oils are of similarly low toxicity, PEG ethers demonstrate slight toxicity with animal LD₅₀ values between 1000 and 2000 mg/kg bw (for details see Table 2).

4.3.2. Dermal route

After acute dermal exposure, PEGs are practically non-toxic with animal LD₅₀ values generally greater than 10,000 mg/kg bw. The only reported cases of systemic toxicity with a possible relationship to polyethylene glycols occurred in three burn patients after treatment with a topical antimicrobial ointment (Bruns et al., 1982). No evidence of a systemic toxicity was seen in animal studies on intact skin with PEGs or PEG derivatives (for details see Table 2).

4.3.3. Inhalation route

In a bioassay to predict the acute pulmonary toxicity of aerosols for human use, male Syrian-golden-hamsters were exposed by intratracheal instillation to suspensions of PEG-6 in saline at 3.75 mg/100 g body weight. Cellular changes and biochemical indicators were measured in bronchoalveolar lavage fluid (BALF) recovered 1 day later. The numbers of BALF polymorphonuclear leukocytes or pulmonary macrophages were not significantly different from those in saline controls. Albumin levels were not changed, and BALF lactate-dehydrogenase, peroxidase, or β -N-acetylglucosaminidase activities were all within normal ranges (Brain et al., 1996).

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Table 2
Acute toxicity data for PEG and PEG compounds

Compound	Species	Result (LD ₅₀ , effect)	Reference
Oral route			
PEG-4	Human	Ingestion of Lava light liquid containing low molecular weight PEGs induced acute renal toxicity in a 65-year-old man	Erickson et al. (1996)
PEG-6	Rat; rabbit	31,700 mg/kg bw; 17,300 mg/kg bw	Smyth et al. (1945, 1950)
PEG-8	Rat	32,800 mg/kg bw	Smyth et al. (1945)
PEG-8	Dog; rat	1000 mg/kg bw/d: no adverse effects noted	Hoffmann-La Roche (1982)
PEG-32	Rat	51,200 mg/kg bw (50% aqueous solution)	Smyth et al. (1950)
PEG-75	Rat; rabbit	59,000 mg/kg bw (50% aqueous solution); 76,000 mg/kg bw	Smyth et al. (1950)
PEG-75	Human	18 l per os caused acute renal insufficiency (reversible) in a patient with massive intestinal bacterial overgrowth	Descamps et al. (2000)
PEG-150	Human	10,000 mg: no clinical signs	Shaffer and Critchfield (1947)
PEG-150	Rat	>50,000 mg/kg bw (50% aqueous solution)	Smyth et al. (1950)
PEG-12 laurate	Mouse	>25,000 mg/kg bw	Hopper et al. (1949)
PEG-2 stearate (50% preparation)	Rat	>10,000 mg/kg bw (in corn oil)	Elder (1983)
PEG-6 stearate (1.5% in cream)	Rat	>34,600 mg/kg bw (in corn oil)	Elder (1983)
PEG-8 stearate (50% preparation)	Rat	>10,000 mg/kg bw (in corn oil); >31,600 mg/kg bw (in water)	Elder (1983)
PEG-12 stearate (50% preparation)	Rat	>10,000 mg/kg bw (in corn oil)	Elder (1983)
PEG-20 stearate (50% preparation)	Rat	>10,000 mg/kg bw (in corn oil); 19,900 mg/kg bw (in water)	Elder (1983)
PEG-32 stearate (50% preparation)	Rat	>10,000 mg/kg bw (in corn oil)	Elder (1983)
PEG-40 stearate (50% preparation)	Rat	>10,000 mg/kg bw (in corn oil)	Elder (1983)
PEG-50 stearate (50% preparation)	Rat	>25,000 mg/kg bw (in water)	Elder (1983)
PEG-100 stearate (50% preparation)	Rat	>25,000 mg/kg bw (in water)	Elder (1983)
PEG-150 stearate (50% preparation)	Rat	>10,000 mg/kg bw (in corn oil)	Elder (1983)
Laureth 6.5–7.0 (range 0–14)	Rat; dog; monkey	≥1400 mg/kg bw	Benke et al. (1977)
Laureth-9	Rat	1190 mg/kg bw (administered over 5 days)	Berberian et al. (1965)
“Polidocanol”	Mouse	1170 mg/kg bw	Zipf et al. (1957)
Steareth-2	Rat	>5000 to >25,100 mg/kg bw	CIR (1988)
Steareth-10	Rat	2910 to >16,000 mg/kg bw	CIR (1988)
Steareth-20	Rat	1920 to >10,000 mg/kg bw	CIR (1988)
Oleth-10	Rat	>5000 mg/kg bw	CIR (1999c)
PEG-7 glyceryl cocoate	Rat	>19,900 mg/kg bw	Henkel Corp. (1996)
PEG-5-25 soy sterol	Rat	>10,000 mg/kg bw	CIR (2004)
PEG-6 sorbitan beeswax	Rat	No acute toxicity	CIR (2001a)
PEG-20 sorbitan stearate	Human	20 g, as a single dose, had no effects	CIR (2000b)
PEG-40 sorbitan lanolate	Rat	>39,800 mg/kg bw	CTFA (1998)
PEG-40 sorbitan peroleate	Rat	>28,200 mg/kg bw	CTFA (1998)

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Table 2 (Continued)

Compound	Species	Result (LD ₅₀ ; effect)	Reference
PEG-50 sorbitol hexaoleate, PEG-30 sorbitol tetraoleate laurate	Rat; mouse	>31,600 mg/kg bw	CTFA (1998)
PEG-25 propylene glycol stearate	Rat	Non-toxic	CIR (2001b)
Dermal route			
PEG-6	Rabbit	>20 ml/kg bw	Smyth et al. (1945)
PEG-blend (PEG-6, 63%; PEG-20, 5%; PEG-75, 32% in antimicrobial cream)	Rabbit; 20 g every 12 h for 7 days	Increase in anion gap, hypercalcemia, renal failure; lethal for 10 out of 12 rabbits with full-thickness skin defects	Herold et al. (1982)
PEG-blend (PEG-6, 63%; PEG-20, 5%; PEG-75, 32% in antimicrobial cream)	Three burn patients	increase in serum osmolality, acidosis and hypercalcemia, renal failure and death (burn area between 20 and 56% of body surface; no data on dose and duration of treatment)	Bruns et al. (1982)
PEG-75 (40%)	Rabbit	>20 ml/kg bw	Mellon Institute (1956)
PEG-20M (40%)	Rabbit	>20 ml/kg bw (vehicle not specified)	Mellon Institute (1956)
PEG-8 Stearate (15%)	Rabbit	>10 ml/kg bw (vehicle not specified)	Elder (1983)
Laureth 6.5–7.0 (range 0–14)	Rabbit, guinea pig	Low dermal toxicity	Benke et al. (1977)
Inhalation/Intratracheal Instillation			
PEG-6, intratracheal injection (aerosol in saline)	Hamster	No toxicity at 37.5 mg/kg bw (only tested concentration)	Brain et al. (1996)
PEG-75, endotracheal injection	Rat	1 g/kg bw (50% in saline): lung weight [†] , alveolar histiocytosis (reversible); 2 ml/kg bw (7.5% in saline; 150 mg/kg bw): no adverse effect	Bushy Run Research Center (1988)
Laureth 6.5–7.0 (range 0–14)	Rat	1500–3000 mg/m ³ (4 h; measured concentrations)	Benke et al. (1977)
PEG-PPG copolymer	Rat	100 mg/m ³ (up to 14 days), no significant lung toxicity	Warheit et al. (1995)
PEG-20 sorbitan oleate, intratracheal instillation of 7% solution (vehicle not specified)	Rat	Treatment with 0.1–0.2 ml did not result in deaths. Of the rats treated with 0.4 ml 30% died (the negative control, saline, killed 20%); no effects on lungs were seen at 0.1 and 0.2 ml, but at 0.4 ml a “little obvious dysfunction” was described	Martinez and Brown (1991)
Intravenous			
PEG-150	Rabbit	10,000 mg/kg bw (as 5% solution): the two animals survived to termination (day 14), one animal had renal tubular swelling	Smyth et al. (1947)
PEG-40 Stearate (5% preparation)	Dog	5 ml: prolonged hypotensive response (no further details reported)	Elder (1983)
PEG-8 Distearate	Mouse	365 mg/kg bw	Hopper et al. (1949)
PEG-20 Distearate	Mouse	220 mg/kg bw	Hopper et al. (1949)
PEG-12 Laurate	Mouse	500 mg/kg bw	Hopper et al. (1949)
Steareth-2	Rat	41 mg/kg bw (in propylene glycol)	CIR (1988)
Steareth-20	Rat	164 mg/kg bw (in isotonic NaCl)	CIR (1988)

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Aerosols generated from ethylene oxide/propylene oxide copolymers (about 100 mg/m³ on 6 h/d for up to 2 weeks; MMADs < 2.6 µm) produced only minimal and reversible effects in rats, but significant lung toxicity was found in the same studies with ethylene oxide butylether/propylene oxide copolymers (Ulrich et al., 1992; Warheit et al., 1995).

Exposure via the respiratory route to PEG and PEG-derivatives contained in emulsions used in pump sprays is considered negligible, as only 0.1–0.3% of the generated aerosol is in the respirable size as shown by laser diffraction spectrometry measurements (Henkel KGaA, 2004). Based on particle size considerations, PEG ethers are not expected to be respirable from cosmetic formulations.

4.3.4. Other routes

Results from animal studies indicate a very low toxicity of PEGs, even after intravenous administration, with some evidence of acute nephrotoxicity in rats and dogs after high doses. Intramuscular injection produced no toxicity in several species, including dogs.

After intravenous administration to laboratory animals, some PEG laureths caused a decrease in heart rate and blood pressure (Soehring et al., 1951, 1952). Because a principal noncosmetic use of PEG castor oils is as solvents for intravenous medicinal products, clinical data are available indicating that intravenous exposure can result in cardiovascular changes.

4.4. Eye and mucosa irritation

Irritation of the eye and mucous membranes is very much dependent on the chemical structure and the corresponding dipole moment of the chemical considered, i.e. the balance between the hydrophilic PEG domain and the hydrophobic moiety. However, there are no strong irritants in the group of chemicals under review here. In fact, PEGs, PEG fatty and sorbitan esters and PEG castor oils cause only mild and transient ocular irritation. Probably because of the irritant effects of the alcohol moieties, PEG–alcohol ethers may induce moderate eye and mucosal irritation. Undiluted PEG-6 sorbitan beeswax was non-irritating to the eyes of rabbits. An antiperspirant product containing 2.0% PEG-25 propylene glycol stearate was mildly irritating to the eyes of rabbits (for details see Table 3).

4.5. Skin irritation

PEGs, PEG fatty esters, and PEG sorbitan fatty esters were not or very slightly irritating to the skin of rabbits and humans. A single, occlusive application of PEG-2, PEG-9, PEG-40, and PEG-100 stearate, and of steareth-2, -10, and -21 for 48 h on intact human skin (5% in a 50:50 water/mineral oil mixture) induced only sporadically slight erythema on intact skin with no difference between the treatments. However, independent of the erythema, increased transepidermal water loss (TEWL) was induced by some of the emulsifiers, indicating an invisible impairment of the stratum corneum barrier function (Bárány et al., 2000). No dermal irritation was observed with PEG castor oils or undiluted PEG-6 sorbitan beeswax. Depending on concentration and duration of application, PEG ethers may irritate the skin (for details see Table 4).

4.5.1. Photo-irritation

A chemical that might have a phototoxic potential must absorb sufficient light energy to become excited and reactive as toxicant. This is not the case for the type of substances considered here, as long as there is no corresponding chromophore linked to the PEG-moiety.

Hence, the potential of PEGs to cause photo-irritation is negligible, but photo-irritation may possibly occur in PEG derivatives with unsaturated structures, e.g. unsaturated fatty acid derivatives, such as oleic acid esters, or be caused by impurities. As no case reports could be located in the open literature, the potential to induce photo-toxicity is probably very low. An animal study with hairless mice gave no indication for a relevant phototoxic effect of PEG-7 glyceryl cocoate (see Table 5).

4.6. Skin sensitisation

In view of the wide use of preparations containing PEG and PEG derivatives, only few case reports on sensitisation reactions have been published, mainly involving patients with exposure of injured, e.g. chronically inflamed, skin to PEGs in medicines. Interpretation of the sensitising potential of PEGs in these cases is complicated because of the involvement of multiple chemicals and medicines, and the fact that in many cases the positive reactions were not reproduced at

Table 3
Eye irritation data for PEG and PEG compounds

Compound	Concentration/condition	Species	Result	Reference
PEG-6	0.5 ml, undiluted	Rabbit	Not irritating	Carpenter and Smyth (1946) Grant (1974)
PEG-8	50%, 33% aqueous solutions	Human	50% only slight burning sensation, no injury; 30% completely non-irritating	
PEG-8	0.5 ml, undiluted	Rabbit	Not irritating	Carpenter and Smyth (1946) Guillot et al. (1982) Lailier et al. (1976) Carpenter and Smyth (1946) Bushy Run Research Center (1987)
PEG-8	French national standard method (1973)	Rabbit	Not irritating	
PEG-8	0.1 ml, 35% solution multiple instillations	Rabbit	Little or not irritating	
PEG-6-32	0.5 ml, undiluted	Rabbit	Not irritating	
PEG-32	0.1 ml, melted in water bath	Rabbit	Mild conjunctival irritation in all six animals, iritis in three of six animals; all effects reversible within 48 h	
PEG-6-75	0.5 ml, undiluted	Rabbit	Not irritating	Carpenter and Smyth (1946) Elder (1983) Henkel Corp. (1996) Benke et al. (1977)
PEG-stearates	100%	Rabbit	Minimal irritation	
PEG-7 glyceryl cocoate	10% solution, Draize test	Rabbit	Not irritating	
Laureths	not specified	Rabbit, monkey	Severely irritating to the rabbit eye, but had a much less severe and transient effect on the monkey eye	
"Polidocanol"	0.5% in water	Rabbit	Anaesthetic effect on cornea; not irritating	Soehring et al. (1952)
Steareth-2, steareth-10	Up to 60% in water, Draize test	Rabbit	Mildly irritating	CIR (1988)
Oleth-10	Undiluted, Draize test	Rabbit	Moderately irritating	CIR (1999c)
Oleth-20	5%, Draize test	Rabbit	Very mild, transient conjunctival redness and chemosis	Marzulli and Ruggles (1973)
Oleth-20	50% and 70%, Draize tests	Rabbit	Moderately irritating	CIR (1999c)
PEG castor oils	100%	Rabbit	Not irritating	CIR (1997)
PEG-5, -10, -16, -25 soy sterol	Draize test	Rabbit	Not irritating	Warf Inst. (1974) and Henkel Corp. (1995)
PEG-5 soy sterol	2% in eyeliner	Rabbit	Not irritating	North American Science Associates (1987)
PEG-20 sorbitan laurate	Clinical ocular irritation test	Human	Not irritating	CIR (2000b)
PEG-30 sorbitol tetraoleate	Undiluted, Draize test	Rabbit	Slight redness at 1 h, but not at 24 h; classified as "not irritating"	CTFA (1998)
PEG-40 sorbitan lanolate	Undiluted, Draize test	Rabbit	Conjunctival irritation at 1 h, but not at 96 h; classified as "non-irritating"	CTFA (1998)
PEG-40 sorbitan peroleate	100% and 10% in water; Draize tests	Rabbit	Not irritating	CTFA (1998)
PEG-50 sorbitol hexaoleate	Undiluted, Draize test	Rabbit	Not irritating	CTFA (1998)
PEG-80 sorbitan palmitate	Undiluted, Draize test	Rabbit	Minimally irritating	CTFA (1998)
PEG-25 propylene glycol stearate	2% in antiperspirant	Rabbit	Minimally irritating	CIR (2001b)

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Table 4
Skin irritation data for PEG and PEG compounds

Compound	Concentration/condition	Species	Result	Reference
PEG-4	Draize test	Rabbit	Mildly irritating	BIBRA (1990)
PEG-8	0.2 ml, undiluted, 4 h-patch test on 30 human volunteers, skin of the upper outer arm	Human	Not irritating	Basketter et al. (1997)
PEG-6-32	3 g, clipped abdomen, 4 days (10 animals)	Guinea pig	Not irritating	Smyth et al. (1942)
PEG-6-32	20 g (5 d/wk, 13 wk), abdominal skin	Rabbit	Less irritating than petrolatum	Smyth et al. (1942)
PEG-32	Draize test (0.5 ml, melted in water bath, occlusive, 4 h)	Rabbit	Not irritating	Bushy Run Research Center (1987)
PEG-75	6 ml of 50% solution, clipped abdomen, 4 days (10 animals)	Guinea pig	Not irritating	Smyth et al. (1942)
PEG-75	40 ml of 50% solution (5 d/wk, 13 wk), abdominal skin	Rabbit	Not irritating	Smyth et al. (1942)
PEG stearates	100%	Rabbit	Mildly irritating	Elder (1983)
PEG stearates	100%	Human	Not irritating	Elder (1983)
Laureth-3	0.2 ml, undiluted, 4 h-patch test on 30 human volunteers, skin of the upper outer arm	Human	Not irritating	Basketter et al. (1997)
“Polidocanol”	Patch Test, 25 or 100% 1.5%, 20% and undiluted	Human Rabbit	Minimally irritating 15% and 20% had no irritating effect on either intact or scarified skin in rabbits, while the undiluted substance caused mild irritation on intact skin and moderate irritation on scarified skin	Benke et al. (1977) Berberian et al. (1965)
Ceteth-2, ceteth-10	Draize test	Rabbit	2.5% was irritating to abraded skin, but 3.0% was not irritating to intact skin. Dose-dependent irritation was noted for ceteth-2 and ceteth-10 at concentrations ranging from 5% to 100%	CIR (1999b)
Steareth-2, -10, -20 Ceteareth-5, -14	Patch test 0.2 ml, undiluted, 4 h-patch test on 30 human volunteers, skin of the upper outer arm	Human Human	Not irritating Not irritating	CIR (1988) Basketter et al. (1997)
Ceteareth-15 Ceteareth-15	10% in hair dress formulation 1.5% in lotion, 21 days; 11 panelists	Rabbit Human	Minimally irritating (PII: 1.5/8) Transient erythema in 1/11 at day 19; judged as “essentially non-irritating”	CIR (1999d) CIR (1999d)
Ceteareth-15	1.5% in cleaning lotion, 4 days	Human	No reaction in seven, minimal reaction in nine, slight reaction in one (overall PII: 0.39/47.5).	CIR (1999d)

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Table 4 (Continued)

Compound	Concentration/condition	Species	Result	Reference
Oleth-10	3%, 21 days; cologne stick applied to the back of 8 panelists	Human	5/8 panelists: no reaction; two had scores of 3.5 and 8.5, and one had a score of 27.5 (of a maximum score of 84; maximum daily score of 4 × 21)	CIR (1999c)
Oleth-10	undiluted, occlusive	Rabbit	Minimal to mild irritation	CIR (1999c)
Oleth-20	10% in water, occlusive	Rabbit	Irritating in abraded and intact skin	CIR (1999c)
Oleth-20	50% in water, open application	Rabbit	Minimally irritating	CIR (1999c)
PEG-7 glyceryl cocoate	50% in Vaseline, 24 h, semi-occlusive	Rabbit, guinea pig, hairless mouse	Slight reaction in rabbits (grade 3 of 5), no reaction in guinea pigs or mice	CIR (1999a)
PEG-7 glyceryl cocoate	Draize test	Rabbit	Mild irritation (PII 1.66); if rinsed after 1 h, no erythema at 24 h after exposure	Henkel Corp. (1996)
PEG-5, -10, -16, -25 soy sterol	Draize test	Rabbit	PEG-10 soy sterol: PII = 0.5; other PEG soy sterols: PII = 0	Warf Inst., (1974) and Henkel Corp. (1995)
PEG-5 soy sterol	2% in eyeliner	Rabbit	PII = 0.96 ("barely perceptible effect")	North American Science Associates (1987)
PEG-30 sorbitol tetraoleate laurate	Draize test; undiluted	Rabbit	Not irritating	CTFA (1998)
PEG-40 sorbitan lanolate	Draize test; undiluted	Rabbit	Very slight to well-defined erythema within 24 h of treatment; very slight erythema was still present at 72 h after treatment (PII = 0.83/8) ("slightly irritating")	CTFA (1998)
PEG-50 sorbitol hexaoleate	Draize test; undiluted	Rabbit	Not irritating	CTFA (1998)
PEG-80 sorbitan palmitate	Draize test; undiluted	Rabbit	Not irritating	CTFA (1998)
PEG-25 propylene glycol stearate	2% in antiperspirant; single-insult occlusive patch test	Rabbit	Practically non-irritant	CTFA (1980)

PII: primary irritation index.

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Table 5
Phototoxicity data for PEG and PEG compounds

Compound	Concentration	Species	Result	Reference
PEG-2 stearate, PEG-8 stearate PEG-7 glyceryl cocoate	25% 50% in olive oil	No data Hairless mice	No evidence of phototoxicity Not phototoxic. Mild irritation (PII 1.66); if rinsed after 1 hour, no erythema was observed at 24 h after exposure.	Elder (1983) Henkel Corp. (1996)
Steareth-2, -20	Two cosmetic formulations with 2.75 and 3.30% steareth-2, and 2.23 and 2.70% steareth-20,	Human, 25 panelists	No evidence of phototoxicity	CIR (1988)

PII: primary irritation score.

follow-up examinations. Overall, the problem of skin sensitisation is clearly more related to pharmaceutical uses of dermatological ointments and preparations than to cosmetic use.

In human repeat insult patch tests (HRIPT) with PEGs ranging in molecular weight between 200 and 8000 a very low incidence of responses (0–0.5%) was observed, suggesting that PEGs are not relevant human skin sensitisers (Hill Top Research and Inc., 1982/1983; Leung and Ballantyne, 1998). In animal tests, the pure materials were also practically without sensitising properties (Leung and Ballantyne, 1998) indicating that impurities or oxidation products may have been the culprit for the observed effects in earlier studies on humans and guinea pigs with certain PEGs (Braun, 1969; Fisher, 1978; Maibach, 1975; Smyth et al., 1942).

Cases of contact dermatitis in burn patients were attributed to a PEG-8 based topical antimicrobial ointment. In clinical testing, PEG-6 and PEG-8 caused mild cases of immediate hypersensitivity. In other tests, PEG-8 has however not demonstrated a sensitising potential, and PEG-6-32 and PEG-75 were also not sensitisers. No evidence of sensitisation occurred in studies with intact skin (CIR, 1993).

Clinical studies on the PEG stearates indicated that these ingredients are neither irritants nor sensitisers at concentrations of $\leq 25\%$ (CIR, 1999e).

Bergh et al. (1998a, 1998b) studied the formation of some potentially allergenic oxidation products by the exposure of laureth-5 to air. The allergenic activity of the oxidation products was studied after topical application to the shaved epidermis of Dunkin–Hartley

guinea pigs. Air exposure of laureth-5 yielded various aldehyde oxidation products, including formaldehyde and the major oxidation product dodecyltetraoxyethylene oxyacetaldehyde. The aldehydes were shown to be contact allergens, and a dose-response relationship was observed in the sensitisation experiments. A case of allergic contact dermatitis to laureth-4 was reported by Svensson (1988), and Kimura and Kawada (2000) report on a single case of follicular contact dermatitis due to laureth-7.

Laureth-9 (“polidocanol”) was shown to be capable of inducing contact allergy in a substantial number of elderly patients with lower leg dermatitis, but the allergy risk was not increased in patients treated for atopic dermatitis with polidocanol containing skin care products (Freitag and Hoppner, 1997; Uter et al., 2000). Gallo et al. (2001) report a single case of contact allergy to polidocanol in a nurse. Repeated patch tests carried out on volunteers revealed no evidence of sensitisation. No hypersensitivity reactions were observed in guinea pigs after daily intracutaneous injections of polidocanol over a period of 10 days followed by a further injection 2 weeks later (Berberian et al., 1965). Brown and Benke (1977) found a low incidence of skin hyper-reactivity to laureths in the repeated insult patch test, and tests using over 500 human volunteers produced no evidence suggestive of sensitisation to formulations containing 33% alkyl polyethoxylates. In view of the wide use of preparations containing polidocanol and the fact that in many cases the positive reactions were not reproduced at follow-up examinations, the clinical relevance of positive reactions to polidocanol remains unclear in many cases.

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Steareth-2 and steareth-20 (60% in water) were not sensitising to human skin (CIR, 1988). Cetareth-15 (1.35% in an unspecified formulation) was not sensitising in a human repeat insult patch test (HRIPT) with 98 panelists. Faint erythema was observed in one panelist during the induction phase, but no reaction was reported to challenge (CIR, 1999d).

Only two case reports of sensitisation to oleths were located in the literature, one relating to the compound used in an ointment (Nishimura, 1993), the other referring to oleth-5 in a hair wax (Abdullah et al., 1997).

PEG-7 glyceryl cocoate (10% solution) was not sensitising in a guinea pig test (Henkel Corp., 1996).

Irritation was seen during induction, but no sensitisation was found on challenge in guinea-pig studies using up to 50% PEG-35 castor oil; however, this ingredient was found to be a potent adjuvant in guinea pigs and mice (CIR, 1997).

PEG-5–25 soy sterol was not a skin sensitiser in a guinea pig study (CIR, 2004).

Sorbitan fatty acid esters generally were not skin sensitisers. Only one case report described contact sensitivity to PEG-40 sorbitan lanolate in a styling gel (Pazzaglia et al., 1995), while patch tests with PEG-40 sorbitan lanolate, PEG-50 sorbitol hexaoleate, PEG-40 sorbitan peroleate, and PEG-30 sorbitol tetraoleate gave no evidence of an allergy reaction (CTFA, 1998).

Neither beeswax nor synthetic beeswax produced significant skin irritation, or skin sensitisation (CIR, 2000a; CIR, 2001a), and therefore the allergenic potential of the ethoxylated derivative is considered to be low.

PEG-25 propylene glycol stearate and PEG-55 propylene glycol oleate were not found to be sensitisers in animal studies and in human clinical tests (CIR, 2001b).

4.6.1. Photo-allergy

UV-absorbing chemicals may induce sensitisation after exposure to UV light. As PEGs do not absorb UV light, their potential for causing photo-allergy is negligible.

Photo-allergy may, however, possibly occur with PEG derivatives with unsaturated structures, e.g. unsaturated fatty acid derivatives, such as oleic acid esters or it may be caused by impurities. As no case reports could be found in the literature, the potential of PEG derivatives to induce photo-allergy is probably

very low. There was also no indication for a photo-sensitising effect from the available clinical and animal studies.

No photo-allergy reaction occurred in 31 human subjects treated with a cosmetic formulation containing 4% steareth-20 (CIR, 1988).

There was no evidence for a potential to induce photo-allergy in tests with PEG-2 stearate and PEG-8 stearate. Facial creams containing 0.3% PEG-7 glyceryl cocoate did not produce signs of photo-allergy during clinical trials (Henkel Corp., 1996). Cosmetic formulations containing 2.8% stearic acid were not photosensitising in guinea pigs (CIR, 1999a).

In a clinical study, PEG-5 soy sterol (at 2% in a formulation) did not induce photo-sensitisation (CIR, 2004).

4.7. Repeated dose toxicity

4.7.1. Oral route

The toxicity of PEGs, PEG fatty acid esters, PEG sorbitan esters and PEG castor oils after repeated oral exposure is exceptionally low. Only at extreme doses which exceed the maximum dose levels recommended in current testing guidelines (i.e. doses greater than 1000 mg/kg bw/d) there is an indication of kidney damage. PEG-stearate and PEG sorbitan laurate, but not PEG sorbitan stearate were reported to induce lesions of the urinary bladder, kidneys, spleen, and gastrointestinal tract in hamsters at very high exposure levels ($\geq 5\%$ in the diet), whereas other studies in monkeys, mice, rats, and dogs did not show adverse effects. Feeding high concentrations of PEG-ethers (ca. 5%) to rats and dogs, led to reduced food intake and, as a consequence, to reduced body weight gain (details see Table 6).

4.7.2. Dermal route

The only cases of systemic toxicity possibly related to PEGs were reported in burn patients after treatment with a topical antimicrobial cream, and in rabbits with full-thickness skin defects treated with the same antimicrobial cream (see above, Section 4.3). Cumulative skin irritation was observed with some PEGs, PEG fatty acids, and PEG ethers with accompanying changes in blood parameters indicating an inflammatory reaction. No pathological changes were found in organs (for details see Table 6).

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Table 6
Repeat dose animal toxicity data for PEG and PEG compounds

Compound	Type of study	Species	Doses/results	Reference
Oral route				
Tetraethylene glycol	Gavage, 33 days	Wistar rat (m, f)	2000 mg/kg bw/d: NOAEL (highest tested dose level)	Schladt et al. (1998)
PEG-4	Diet, 90 days	Rat (<i>n</i> = 5/sex/group)	24% (about 18,000 mg/kg bw/d): increases in kidney and liver weights; 16% (about 12,000 mg/kg bw/d), increase in liver weight; 8% (about 6000 mg/kg bw/d): NOAEL	Smyth et al. (1955)
PEG-4	Drinking water, 90 days	Rat	4% (about 8000 mg/kg bw/d): two out of nine rats died after eighty days with liver and kidney pathology but the seven survivors were normal	Smyth et al. (1945)
PEG-4	13 weeks	Rat	Up to 5600 mg/kg bw/d: no adverse effects on blood chemistry, biochemical parameters and histology of various (unspecified) organs	Smyth et al. (1945)
PEG-4	13 weeks	Monkey (2 ♀; <i>Macaca fascicularis</i>)	2820 mg/kg bw/d: microscopic kidney damage	Prentice and Majeed (1978)
PEG-6	Diet, drinking water, 90 days	Rat (<i>n</i> = 5/sex/group; 2%, 4%, 8%, 16%, 24% in diet)	16% (in diet; about 8000 mg/kg bw/d): increases in kidney and liver weights; 8% (in diet; about 4000 mg/kg bw/d): weight gain ↓; 4% (in drinking water): no clinical signs of toxicity (NOAEL)	Smyth et al. (1945, 1950, 1955)
PEG-8	13 weeks, gavage	F344 rat (10/sex/group); 1.1, 2.8, 5.6 g/kg bw/d	2.8 and 5.6 g/kg bw/d: loose faeces and body weight ↓, water consumption ↑, slight reversible renal toxicity; 1.1 g/kg bw/d: NOEL	Hermansky et al. (1995)
PEG-8	Diet, 90 days	Rat (<i>n</i> = 5/sex/group); 2%, 4%, 8%, 16%, 24% in diet	24% (about 12,000 mg/kg bw/d): increases in kidney and liver weights; 16% (about 8000 mg/kg bw): decreased weight gain	Smyth et al. (1955)
PEG-8	Drinking water, 90 days	Rat	4% (about 5000 mg/kg bw/d): reduced kidney weights without microscopic changes	Smyth et al. (1950)

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Table 6 (Continued)

Compound	Type of study	Species	Doses/results	Reference
PEG-8	Diet, 2 years	Rat (<i>n</i> = 5/sex/group): 1–8% in diet	4%, 8%: reduced male body weight. Liver and kidney weights were unaffected, but no tissue examinations were performed. No effects were seen at a level of 2% (about 1000 mg/kg bw/d)	Smyth et al. (1955)
PEG-8	Diet, 1 year	Dog (<i>n</i> = 4)	2% of PEG-400 (about 500 mg/kg bw/d): no adverse effects	Smyth et al. (1955)
PEG-32	Diet; drinking water, 90 days	Rat (<i>n</i> = 5/sex/group) 2%, 4%, 8%, 16%, 24% in diet	4% in diet (about 3000 mg/kg bw/d): No effect. Kidney damage was observed when about 4000 mg/kg bw/d were administered via the drinking water	Smyth et al. (1955, 1942)
PEG-32	Diet, 2 years	Rat (<i>n</i> = 5/sex/group) 2%, 4%, 8%, 16%, 24% in diet	4% (about 3000 mg/kg bw/d): no effect	Smyth et al. (1955)
PEG-32	Diet, 1 years	Dog (<i>n</i> = 2)	2% (about 500 mg/kg bw/d): no effect	Smyth et al. (1955)
PEG-75	Diet, 2 years	Rat (<i>n</i> = 5/sex/group) 2%, 4%, 8%, 16%, 24% in diet	16%: increased kidney weights; 4% (about 3000 mg/kg bw/d): no effect	Smyth et al. (1955)
PEG-75	Drinking water, 90 days	Rat, 230–19,000 mg/kg bw/d	The growth rate of rats drinking 7000 or 19,000 mg/kg bw/d was reduced and the high dose caused renal lesions. Degenerative changes in the testes were observed at 230 mg/kg/d. However, the same authors explained later that the results observed in the earlier study might be due to contaminations of the test substance	Smyth et al. (1942, 1950)
PEG-75	Gavage, 5 weeks	Rabbit	Up to 20,000 mg/kg bw: no signs of kidney damage	Smyth et al. (1942)
PEG-75	Diet, 1 year	Dog (<i>n</i> = 4)	2% (about 500 mg/kg bw) no adverse effects	Smyth et al. (1955)

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PEG-150	Diet, 90 days	Rat ($n = 5/\text{sex}/\text{group}$) 2%, 4%, 8%, 16%, 24% in diet	24% (about 18,000 mg/kg bw/d) increased kidney weight and decreased body weight; 16% (about 12,000 mg/kg bw/d) no effect	Smyth et al. (1955)
PEG-220	Diet, 90 days	Rat	2.5% (about 1600 mg/kg bw/d): no effect	Smyth et al. (1950)
Polyox N-10 (MG about 1,000,000)	Diet; 0; 0.1; 0.5; 1.5; 3% (corresponding to about 0, 78, 388, 1159 and 2400 mg/kg bw for males and 87, 429, 1308 and 2667 mg/kg bw in females)	F344 rats	Slight increases in food consumption, body weight, and body weight gain were found (females). A dose-related increase in liver weight was observed, but this was not associated with any histopathology and morphometric analysis showed no alteration of the number or size of the hepatocytes. Thus, the liver weight increase was considered a secondary response to increased food consumption. Absolute and relative weights of the kidneys were statistically significantly increased in the 1.5% and 3% female groups and remained increased after a 6 week recovery period. In both sexes there were no necropsy or microscopic findings that were considered treatment-related	Leung et al. (2000)
Polyox N-10 (MG about 1,000,000)	Diet, 2 years	F344 rat	2% (1026 mg/kg bw for ♂ and 1269 mg/kg bw for ♀): no organ/tissue toxicity nor tumour induction	Leung et al. (2000)
PEG-20M	Diet, drinking water, 90 days	Rat	Up to 4%: no deaths; no clinical signs of toxicity	CIR (1993)
PEG-4,000,000	Diet, 2 years	Rat	2760 mg/kg bw/d: no effect	Smyth et al. (1979)
PEG-4,000,000	Diet, 2 years	Dog	560 mg/kg bw/d: no effect	Smyth et al. (1979)

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Table 6 (Continued)

Compound	Type of study	Species	Doses/results	Reference
PEG-8 stearate	Diet, 59 days	Rat, ♂, 13/group	25% in diet: no effect on blood clotting; no clinical signs; body weight gain ↓ 5% in diet, sequentially increased to 10%, 15%, and 25% during the first 10 days; diarrhea; body weight gain ↓ (67% of controls); no effect on organ weights; gastrointestinal irritation; no significant changes in the liver; giant cells more frequently in the spleen, with monocyte/macrophage hyperplasia; incomplete maturation of the testes	Harris et al. (1951)
PEG-8 stearate	Diet, 70 days	Rat, 16♂, 14♂	4%: no treatment-related effects over three generations	Harris et al. (1951)
PEG-8 stearate	Diet, 2 years	Rat	5%: no treatment-related effects	Elder (1983)
PEG-8 stearate	Diet, 19 weeks	Rabbit	4%: no treatment-related effects	Elder (1983)
PEG-8 stearate	Diet, 4 months	Rabbit	2%: no treatment-related effects over three generations	Elder (1983)
PEG-100 stearate	Diet, 2 years	Rat	5%, 15%: severe lesions in duodenum, ileum, liver, kidneys, and testes. Severe erosion of the ileal mucosa and necrosis of the liver, spermatogenic activity ↓, tubular degeneration in kidneys	Elder (1983)
PEG-monostearate	Diet, 2–10 weeks	Hamster	5–15%: high mortality, chronic diarrhea, atrophic testes, enlarged kidneys, thickened urinary bladder walls, hepatic, cecal, and splenic hemosiderosis, enlarged ceca, and obstructive nephropathy	Elder (1983)

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PEG-8, -40, -50, -100 stearate	Diet	Rat, monkey, mouse, dog	Up to 4% (in diet): no signs of toxicity (NOAEL)	Elder (1983)
PEG stearates (unspecified)	Diet, 74–260 days	Hamster	Large calculi in the urinary bladders	Elder (1983)
Laureth 6.5–7.0 (range 0–14)	0, 1000, 5000, 10,000 ppm in diet; 90 days	Rat	10,000 ppm: decreased liver-to-body weight ratio, growth depression	Brown and Benke (1977)
Laureth-9	195, 390, 780 mg/kg bw/d	Rat	780 mg/kg bw/d: lethargy, dyspnoea, salivation, 2/10 animals died; no pathological changes at necropsy, no effects on hematology; 195, 390 mg/kg bw/d: slight salivation	Berberian et al. (1965)
Oleth-20	90 days; 0.01, 0.04, 0.16, 0.64, 2.5, 5% in diet	Rat	≥2.5% (m): food intake and body weight gain ↓; ≥ 5% (f): food intake and body weight gain ↓; no changes in hematology	CIR (1999c)
Oleth-20	90 days; 0.04, 0.64, 5% in diet	Dog	≥5%: food intake and body weight gain ↓; 0.64%: hepatic lesions in 1/1 dog; no changes in hematology	CIR (1999c)
PEG-20 laurate	Diet, 59 days	Rat, 13♂	25% in diet: diarrhea; no effect on blood clotting; body weight gain ↓; one rat died; three rats with bladder stones	Harris et al. (1951)
PEG-20 laurate	Diet, 70 days	Rat, 16♀, 14♂	5% in diet, sequentially increased to 10%, 15%, and 25% during the first 10 days: diarrhea; body weight gain ↓ (62% of controls); no effect on organ weights; gastrointestinal irritation; giant cells more frequently in the spleen, with monocyte/macrophage hyperplasia; incomplete maturation of the testes	Harris et al. (1951)

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Table 6 (Continued)

Compound	Type of study	Species	Doses/results	Reference
PEG-20 laurate	Diet, 2 years	Rat, 12♀ and 12♂/group	25%: growth reduction ↓ (males), three rats with slight gastric mucosa hyperplasia; hepatic cysts in five rats; cecal enlargement in 17 animals; 10%: hepatic cysts in four rats; cecal enlargement in four animals; 5%: one hepatic cyst; cecal enlargement in three animals; 2%: one hepatic cyst; cecal enlargement in two animals	Fitzhugh et al. (1960)
PEG-8 dilaurate	Diet, 505 days	Rat (n = 9)	6%: feed consumption ↑ (n.s.); four rats died (four out of nine rats died also in the control group); at necropsy one rat had cystic spots on the liver, one had hemorrhagic lungs, and one had a fibrosarcoma; microscopically focal parenchymal hepatitis was found in three treated rats	Krehl et al. (1955)
PEG-20 sorbitan laurate	Chronic dietary study	Hamster	5–15% caused microscopic lesions of the urinary bladder, kidneys, spleen and gastrointestinal tract.	CIR (2000b)
PEG-20 sorbitan laurate PEG-20 sorbitan laurate	17 months, diet 2 years, diet	Monkey Rat	1 g/day had no adverse effects Up to and including 2%: no signs of toxicity	CIR (2000b) CIR (2000b)
PEG-20 sorbitan stearate, PEG-20 sorbitan oleate, PEG-20 sorbitan tristearate	Long-term feeding studies	Rat, mouse, dog, hamster	At concentrations <20% non-toxic; at 20% some growth retardation and diarrhea	CIR (2000b)
Dermal PEG-4, -6, -8, -150	2000–10,000 mg/kg bw/d, 13 weeks (covered), 18 weeks (uncovered); 5 d/w	Rabbit	No adverse effects	Smyth et al. (1947) and Tusing et al. (1954)
PEG-4	300 and 1000 mg/kg bw/d (6 d/w for 60 days on clipped skin)	Rabbit	In some animals increase in blood urea; some died, but this appears to have been influenced by the diet used (rolled barley diet); no data on impurities of test material	Luduenia et al. (1947)

PEG-8	3% formulation; corresponding to about 886 mg/kg bw/d; 13 weeks (once daily for 5d/w)	Rat	Moderate irritation, but no systemic toxicity	CTFA (1981)
PEG-8	5% formulation; corresponding to about 2400 mg/kg bw/d, 13 weeks (once daily for 5 d/w)	Rat	Dermal irritation. Elevated neutrophil/lymphocyte ratio for male rats, and elevated activities of serum glutamic pyruvic transaminase (SGPT), serum alkaline phosphatase (SAP) and serum glutamic oxaloacetic transaminase (SGOT) for male rats, and SGOT and SGPT for female rats. There were no significant gross or microscopic changes in the liver, brain, heart, testes, or spleen	CTFA (1985)
PEG-8, -32, -75	1000 and 2000 mg/kg bw/d (6 d/w for 60 days on clipped skin)	Rabbit	In some animals increase in blood urea; some died, but this appears to have been influenced by the diet used (rolled barley diet); no data on impurities of test material	Luduena et al. (1947)
PEG-75, -20M	800 mg/kg bw/d; 30 days (1 h/d)	Rabbit	Mild transient erythema was observed at the application sites; no systemic effects	Mellon Institute (1956)
PEG-20, -32, -90	About 10,000 mg/kg bw/d, 13 weeks, 5d/w	Rabbit	No adverse effects	Smyth et al. (1947, 1950)
PEG-20M	30 days	Rabbit		CIR (1993)
PEG-6 stearate (1.5% in formulation)	20 days	Rabbit	800 mg/kg bw/d: transient mild erythema; no clinical signs of toxicity 500–2000 mg/kg bw/d: erythema, dryness, wrinkling, desquamation, and hyperkeratosis at the application sites. No other signs of toxicity were noted	Elder (1983)
Laureth 6.5–7.0 (range 0–14)	20, 50 mg/kg bw/d; 4 and 13 weeks	Rabbit	No systemic toxicity; skin irritation	Brown and Benke (1977)

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Table 6 (Continued)

Compound	Type of study	Species	Doses/results	Reference
Steareth-20	Cosmetic formulation with 4%; 0, 4.4, 6.6, 7.5 and 15 mg/cm ² daily for 3 months	Rabbit; 5 m/5f per group	No systemic toxicity, only slight to moderate dermal irritation	CIR (1988)
Inhalation PEG-4	Up to 1000 mg/m ³ for 4 weeks (6 h/d, 5 d/w)	F344 rats B6C3F1 mice	No adverse effects (NOAEC: 1000 mg/m ³)	Crook et al. (1980)
PEG-8	Nose only; 1288 mg/m ³ for 13 weeks (6 h/d, 5 d/w) 109, 567 and 1000 mg/m ³ for 2 weeks (6 h/d, 5 d/w)	F344 rats	No treatment related effects	Bayer (1989, 1995)
PEG-75		F344 rats	Increase in absolute lung weights and an increase in the number of alveolar macrophages in the mid- and high dose animals. Decreases in male body weight gain were reversible after a 2 week recovery period	Klonne et al. (1989)
Other routes PEG-4, -6, -8, -20, -32, -75, -150	Intravenous, 350 mg/kg bw/d for 5 weeks	Rabbit	Cloudy swelling of renal tubular epithelium and hepatic parenchyma amongst all treatment groups	Smyth et al. (1947)
PEG-4	Subcutaneous, 1000 mg/kg bw/d (6 d/w for 60 days)	Rabbit	In some animals increase in blood urea; two out of six treated rabbits died on days 6 and 21 after start of the application, respectively; 3/3 rabbits died that were fed with rolled barley diet	Ludueno et al. (1947)
PEG-6	Intravenous, up to 500 mg/kg bw/d for 5 weeks	Rabbit	No adverse effects	Smyth et al. (1947)
PEG-6	Intravenous; 1250 mg/kg bw/d for 4 weeks	Rat	No adverse effects	Hoffmann-La Roche (1980)
PEG-6	Intravenous; 350 mg/kg bw/d for 29 days	Monkey	No adverse effects	Hoffmann-La Roche (1980)

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PEG-8	Subcutaneous, 1000 mg/kg bw/d (6 d/w for 60 days)	Rabbit	No adverse effects	Luduena et al. (1947)
PEG-75	Intravenous, 90 mg/kg bw/d, 12 months	Dog	No adverse effects	Carpenter et al. (1971)
PEG-75	Subcutaneous, 3000 mg/kg bw/d (6 d/w for 60 days)	Rabbit	Increase in blood urea; two out of three treated rabbits died on days 23 and 31 after start of the application, respectively	Luduena et al. (1947)
"Polidocanol"	Subcutaneous, 4 weeks; 10–20 mg/kg bw/d	Rabbit	Slight atrophy of liver, kidneys and adrenal glands, slight hemosiderosis; not considered as of biological relevance by the authors	Soehring et al. (1951)

NO(A)EL = No observed (adverse) effect level; NO(A)EC = No observed (adverse) effect concentration.

4.7.3. Inhalation route

Only limited data were available on repeated inhalation toxicity. Although possible interactions with cellular surfaces and sensitive membranes, in particular for those PEG derivatives with more pronounced hydrophobic properties may be expected in the respiratory tract, the available data do not indicate a specific hazard (for details see Table 6).

4.8. Genotoxicity

4.8.1. In vitro

Tetraethylene glycol, PEG-4, PEG-8, PEG-150 and Polyox N-10 were tested negative in several Ames-Tests (BIBRA, 1993; Hoechst, 1978; Mortelmans et al., 1986; Slesinski et al., 1989; Wagner and Sly, 1995) and in mammalian gene mutation tests (BIBRA, 1993; Slesinski et al., 1989; Bushy Run Research Center, 1980), both with and without metabolic activation. Some PEGs have been tested positive in the Ames test by Ivanchenko et al. (1992); as there is insufficient documentation of the study conditions and as osmolality of the culture medium may have been influenced, the reliability of these results is uncertain. PEG-8 was negative in the Chinese Hamster Ovary (CHO) cell mutation test, the sister-chromatid exchange (SCE) test and the unscheduled DNA synthesis assay. PEG-150 was not mutagenic in the mouse lymphoma forward mutation assay (Mitchell et al., 1997). In an earlier mouse lymphoma assay, a small increase in the mutation frequency (2.3-fold) was observed at a cytotoxic concentration (about 20 mM), exceeding current recommended practices. This test was only performed in the absence of a metabolic activation system (Wangenheim and Bolcsfoldi, 1988).

Cytogenetic assays with PEG-8 and Polyox N-10 in CHO cells were negative, both with and without metabolic activation (Bushy Run Research Center, 1980; Curry, 1996).

Biondi et al. (2002) reported on the induction of chromosome aberrations in Chinese Hamster Epithelial Cells in the absence of osmolality changes by tetraethylene glycol, an impurity contained in amounts of up to 29% in PEG-4 and 9% in PEG-6. No information on purity or ethylene oxide content of the tested tetraethylene glycol was provided by Biondi et al. Significant increases in sister chromatid exchanges and chromosome damage were also found in Chinese Hamster

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Ovary (CHO) cells treated with tetraethylene glycol (of unknown purity) both in the absence and presence of metabolic activation, but the low level increases were variable and did not have a dose-related trend (Slesinski et al., 1989).

As PEGs have the ability to alter osmolality in culture media, some of the reported positive results could be indirect effects due to an unphysiological change of osmolality under *in vitro* test conditions.

There is no indication of a genotoxic effect of PEG fatty acids or PEG ethers. Laureth-9 (“polidocanol”) was tested negative in the standard Ames-test with and without metabolic activation (Zeiger et al., 1987), and in a battery of short-term tests (Buzzi and Wuerkler, 1990). PEG-5 soy sterol was no mutagenic in the Ames test with and without metabolic activation (CIR, 2004). PEG-40 sorbitan peroleate was not mutagenic in the Ames test (CTFA, 1998).

4.8.2. *In vivo*

No increase in the frequency of chromosomal aberrations was observed in rat bone marrow cells after a single oral administration of up to 5000 mg/kg bw of PEG-4 (Union Carbide, 1988). An ambiguous result was found in a micronucleus test in Swiss–Webster mice after single intraperitoneal injection of PEG-4. Only at 30 h after administration (not at 24 and 72 h) a slight increase of micronuclei was observed in high-dose males (5000 mg/kg bw). However, when the number of scored erythrocytes was doubled, an increase in micronuclei was also observed in the low-dose group. According to the authors the effects could be due to testing artefacts (Union Carbide, 1987). A micronucleus test with Polyox N-10 in mice was negative (Putman and Gudi, 1995).

Ethoxylated dodecyl alcohol (“laureth”) did not induce chromosomal aberrations in the mouse bone marrow micronucleus assay (Shelby et al., 1993). No *in vivo* data could be located for oleths and cetareths, and for PEG fatty acid esters and glyceryl cocoate.

4.9. Carcinogenicity

Early 2-year feeding studies on rats with tetraethylene glycol and PEG-4, limited by small animal numbers and a reduced scope of organ and tissue examinations, gave no evidence of carcinogenicity at dietary doses as high as 4% (Union Carbide, 1965; Weil and

Smyth, 1956). In rats, the tumour frequency was not increased after administration via the drinking water of 60 mg/kg bw/d of PEG-32, or 20 mg/kg bw/d of PEG-75 for 2 years (Smyth et al., 1947). A series of other studies in rats and mice with oral, dermal or subcutaneous administration of PEG-8 or with intravaginal intillation of PEG-20 are considered invalid due to short exposure periods and insufficient study design (Berenblum and Haran, 1955; Boyland et al., 1961, 1968; Carter, 1969; Field and Roe, 1965; Roe, 1970; Union Carbide, 1978). In a recent 2-year study with a 100 kDa PEG, no effects on survival, tumor incidence or time to tumor were produced in F344 rats fed a diet containing up to 2% of the substance, corresponding to about 1000 mg/kg bw/d (Leung et al., 2000).

No carcinogenicity studies could be located for PEG fatty acids. Negative carcinogenicity studies performed within the frame of the U.S. National Toxicology Program on rats and mice with ethoxylated dodecyl alcohol (laureth) were later considered inadequate (NTP, 2004).

No evidence of carcinogenicity was found in female rats or mice of either sex fed up to 50,000 ppm PEG-20 sorbitan oleate, but an increased incidence in pheochromocytomas of the adrenal medulla existed in male rats of the high-dose group (NTP, 1992a), presumably secondary to the effects on calcium absorption. As there is no evidence of a mutagenic activity, and because a threshold mechanism can therefore be assumed, PEG sorbitan fatty acid esters do not pose a carcinogenic risk for humans at the concentrations as currently used in cosmetics and body care formulations.

4.10. Reproductive and developmental toxicity

4.10.1. Reproductive toxicity

No notable adverse effects on the reproduction of rats occurred in oral studies over three generations with PEG-6-32 and PEG-75 (Smyth et al., 1947, 1955). Reproductive parameters were not influenced in studies with PEG-8 when pregnant Sprague–Dawley rats and New Zealand White rabbits (10/group) were dosed between gestation days 6 and 17 (rats) or 6 and 18 (rabbits) by oral gavage (Gupta et al., 1996).

Damage to the testes, as well as sperm abnormalities were reported in rats after 2–6 months of oral administration of 2500 mg PEG-4/kg bw/d (Byshovets

et al., 1987). Because of inadequate reporting the relevance and reliability of these results cannot be judged. Furthermore, the available data for a very similar product, tetraethylene glycol, indicate a low potential for reproductive toxicity, as repeated dosing with up to 2000 mg/kg bw/d for 4 weeks (Schladt et al., 1998) produced no notable changes in the histopathology of the testes and epididymides of rats.

No studies were available on the reproductive toxicity of PEG soy sterols. In a series of modern studies, phytosterols and phytosterol esters were however shown to be without effect on the reproductive function and fertility (CIR, 2004).

4.10.2. Developmental toxicity

PEG-4 did not cause developmental toxicity in rats when administered at 10,000 mg/kg bw/d on gestation days 6–15 (Starke and Pellerin, 1981). In a poorly documented study (only the abstract is available), PEG-4 was, however, reported to induce malformations of the skull (exencephaly, fissure in the median facial line), of the paws (dysgenesis of long bones and digits) and of the thoracic skeleton (joined ribs and vertebrae) in mice at excessively high oral doses (approximately 23,000 mg/kg bw/d). No signs of maternal toxicity were recorded except for the death of one animal. In rats, PEG-4 was without effect (Vannier et al., 1989). Brain malformations were noted in rat embryo cultures when treated with mouse liver S-9 mix at concentrations of 0.25% or 0.5% PEG-4 and foetotoxicity was observed at $\geq 0.5\%$ in the presence of S-9 from hamster, rat, rabbit or humans. No effects were seen in the absence of metabolic activation (Spezia et al., 1992).

In the rabbit, administration of PEG-6 or PEG-8 caused maternal toxicity at dose volumes of 2 ml/kg bw and above (Lewis et al., 1997), but no adverse effects on development were seen with PEG-8 in rats and rabbits, though high doses were administered orally (Hoechst, 1979), on the skin (Hoechst, 1979) or intravenously (Hoffmann-La Roche, 1979) during days 7–16 (rats) or 7–19 (rabbits) of gestation. No effect on development was seen when pregnant Sprague–Dawley rats and New Zealand White rabbits (10/group) were dosed between gestational days 6 and 17 (rats) or 6 and 18 (rabbits) by oral gavage with PEG-8 (Gupta et al., 1996). A poorly documented study (Kartashov and Belous, 1984) reported on an increase in the number of early foetal deaths and slightly reduced foetal weights when

a maternal toxic dose of PEG-8 (6500 mg/kg bw/d) was administered via an unspecified route for 3 days to rats during pregnancy.

No notable adverse effects on the development of rats occurred in oral studies over three generations with PEG-6–32 and PEG-75 (Smyth et al., 1947, 1955). A slight, non-significant and reversible decrease in fetal size was the only finding in rabbits after single oral treatment of dams with 250 mg/kg bw of a carrier containing 27.5% PEG-75. There was no indication of a teratogenic effect (Gottschewski, 1967).

Multiple generation studies with PEG-8 and PEG-40 stearates showed no adverse effects on reproduction and development (CIR, 1999e).

In a review of safety data on laureth-4, no influence on reproduction and development is reported from dermal studies on rats with a 6% solution of laureth-4 in 52% aqueous ethanol (Beyer et al., 1983). As no details on controls were available from the publication, the reliability of this information can however not be judged.

No evidence of developmental toxicity was seen in mice and rat feeding studies with PEG-35 castor oil.

PEG-20 sorbitan laurate had no adverse effects on the development of offspring from rats treated on gestational days 6–15 with 500 or 5000 mg/kg bw/d (NTP, 1992b). Similarly, PEG-20 sorbitan stearate had no adverse effect on the development of rats up to and including the highest tested dose (10% in the diet, corresponding to about 7700 mg/kg bw/d from gestational day 7 to 14) (Ema et al., 1988), and PEG-20 oleate did not cause developmental toxicity in CD-1 mice treated by gavage on gestational days 8–12 with 2500 mg/kg bw/d (Kavlock et al., 1987).

5. Discussion

The PEGs and most of their derivatives under review here have low mammalian toxicity following single or repeated exposure with generally decreasing toxicity as the molecular weight is increased. The biological activity varies with the size of the hydrophobic and hydrophilic domain and the balance between them.

Low molecular weight PEGs and some of their derivatives may be absorbed by the gastrointestinal tract and may penetrate the skin, whereas all PEGs are capable of penetrating injured skin and mucosa

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with compromised barrier function. While PEG-8 was shown to reduce skin penetration of other molecules, a penetration enhancing effect has been demonstrated for some other PEG derivatives, probably because of the skin conditioning effect. The magnitude of such effects is, however, dependent on the structure and molecular weight of the PEG derivative, and also on the other constituents in the formulation, and can therefore be influenced by the manufacturer.

All compounds have a very low acute oral and dermal toxicity, with PEG ethers demonstrating a somewhat higher toxicity than the other substances. Acute inhalation toxicity is very unlikely to occur in humans. Repeat dose toxicity of PEGs and their derivatives is very low, with kidney and liver being identified as target organs in animal studies at extremely high exposure levels, which exceed the recommended levels in current testing guidelines.

An irritant effect was demonstrated for most of the PEG classes, with the magnitude of the effect being dependent of the compound class and the molecular weight. While the irritating effects of PEGs on skin, eye and mucosa were generally very mild and transient in nature, more pronounced effects were seen with PEG ethers. The effects observed were also dependent on skin condition and length of application, and some cumulative irritant effect was typically seen.

Case reports of sensitisation were available for practically all of the PEG classes under review here. In view of the wide use of the compounds, the few reported cases and the lack of significant effects in clinical studies however indicate that these compounds are not relevant sensitisers. There is also evidence that oxidation products (e.g. ethoxyaldehydes) may have been responsible for some of the observed effects. It is further noted that many of the case reports were from patients receiving medications in parallel, or from patients with injured or chronically inflamed skin (e.g. leg ulcer patients), so that it is difficult to differentiate the influence of the PEGs from that of other substances and medications applied simultaneously to the damaged skin.

While there is no indication for a point mutagenic effect from standard *in vitro* tests, some PEGs did show positive results in cytogenetic tests. As these compounds are known to influence osmolality in cell culture media, an indirect effect due to perturbations of the culture conditions is more probable than a direct geno-

toxicity of these compounds. It is noted, however, that tetraethylene glycol, which may be present as impurity in PEGs had caused chromosome aberrations in the absence of osmolality changes, so that a direct effect for this compound cannot be excluded. On the other hand, there is sufficient evidence that tetraethylene glycol is not genotoxic *in vivo*, so that the presence of tetraethylene glycol impurities in cosmetics does not seem to present an unacceptable risk to humans. Furthermore, there are no structural alerts for genotoxicity and the overall weight of evidence indicates that the class of PEG compounds under consideration here has no relevant genotoxicity.

Carcinogenicity studies with PEGs have been conducted, but suffer from limitations such as small animal numbers and a limited scope of tissue examinations. None of the studies gave any indication of a tumorigenic effect of PEGs.

While induction of brain and skeletal malformations was reported for PEG-4 in mice at excessively high oral doses, there was no evidence of developmental toxicity in rats. As the study is only available in the form of a short abstract, the interpretation of the results is difficult, and the findings appear to be secondary to the excessive dosing (23,000 mg/kg bw/d) or to impurities rather than caused by a direct effect of PEG-4 on development. Furthermore, there was no evidence for an adverse effect on reproduction and development of other PEGs and their derivatives from a variety of further studies. Although many of the studies were limited and not performed up to current standards, the overall weight-of-evidence indicates that the PEGs and PEG derivatives under review here do not pose an unacceptable risk for humans under the current use conditions in cosmetics.

Some monoalkyl ether glycols are known reproductive toxicants. From the available data on the manufacturing process there is however no evidence, that relevant monoalkyl ethers are contained as impurities in the reviewed PEG and PEG derivatives, or that they may be formed metabolically under *in vivo* conditions from the reviewed compounds (see also Lanigan, 1999).

Concerns about a potential antiestrogenic, antiprogestational, gonadotrophic, antigonadotrophic, or antiandrogenic effects of PEG soy sterols through the systemic presence of free phytosterols and β -sitosterol were not corroborated by experimental results. Campes-

terol, sitosterol, and stigmasterol are the most frequently occurring plant sterols (Kallianos et al., 1963), and about 0.25–0.5 g of plant sterols are consumed each day in a typical diet (Heinemann et al., 1993). The potential exposure to phytosterols through the use of cosmetics is considered negligible as compared to the usual dietary exposure. Furthermore, in a series of modern studies, phytosterols and phytosterol esters were shown to be not estrogenic and without adverse effects on the reproductive function. An adverse effect of PEG soy sterols on reproductive function is therefore not expected.

6. Conclusion

This assessment focusses on polyethylene glycols (PEGs) and on anionic or nonionic PEG derivatives, which are currently used in cosmetics in Europe. These compounds are used in a great variety of cosmetic applications because of their solubility and viscosity properties, and because of their low toxicity. The PEGs, their ethers, and their fatty acid esters produce little or no ocular or dermal irritation and have extremely low acute and chronic toxicities. They do not readily penetrate intact skin, and in view of the wide use of preparations containing PEG and PEG derivatives, only few case reports on sensitisation reactions have been published, mainly involving patients with exposure to PEGs in medicines or following exposure to injured or chronically inflamed skin. On healthy skin, the sensitising potential of these compounds appears to be negligible. For some representative substances of this class, information was available on reproductive and developmental toxicity, on genotoxicity and carcinogenic properties. Taking into consideration all available information from related compounds, as well as the mode and mechanism of action, no safety concern with regard to these endpoints could be identified. Based on the available data it is therefore concluded that PEGs of a wide molecular weight range (200 to over 10,000), their ethers (laureths, ceteths, ceteareths, steareths, and oleths), and fatty acid esters (laurates, dilaurates, stearates, distearates) are safe for use in cosmetics. Limited data were available for PEG sorbitan/sorbitol fatty acid esters, PEG sorbitan beeswax and PEG soy sterols. Taking into account all the information available for closely related compounds, it can

be assumed that these compounds as presently used in cosmetic preparations will not present a risk for human health. PEG castor oils and PEG hydrogenated castor oils have caused anaphylactic reactions when used in intravenous medicinal products. Their topical use in cosmetics is, however, considered safe as they are not expected to be systemically available. As all PEGs and PEG derivatives, they must not be applied to damaged skin. Manufacturers of PEGs and PEG derivatives must continue their efforts to remove impurities and by-products such as ethylene oxide and 1,4-dioxane. Overall, it is concluded, that the PEGs covered in this review are safe for use in cosmetics under the present conditions of intended use.

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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCION DE NUEVAS CREACIONES**

Radicación No. 0350565

Clasificación Internacional (IPC): A61K7/48

Concepto Técnico No. 4136

Patente de Invención ☒ Patente de Modelo de Utilidad ☐
 Vía Nacional ☐
 Vía PCT (fase nacional) ☐ Cap. I ☐ Cap. II ☒
 No. Sol. Internacional PCT/EP01/14825
 Fecha de Presentación Internal. 14/12/2001

Como resultado del examen definitivo, realizado con fundamento en el artículo 48 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

- 1.1. Descripción: Folios: 59 a 94 como se radico inicialmente
 Folios: 191 a 211 modificada, 2009/07/29.
- 1.2. Reivindicaciones: Folios: 95 a 100 como se radicó inicialmente.
 Folios: 212 a 215 2009/07/29.
 Folios: 240 a 243 2010/09/03.
- 1.3. Respuestas del Solicitante: Folios: 144 a 147 1ª respuesta
 Folios: 185 a 215 2ª respuesta
 Folios: 231 a 302 3ª respuesta
- 1.4. Prioridad: 15/12/2000; EP; 00127555.1
 15/12/2000; US; 60/255.379

2. Objeto de la invención

Título de la solicitud: **FORMULACIONES PARA EL CUIDADO DE LA PIEL HIPOALERGENICAS Y NO IRRITANTES.**

Problema Técnico Planteado: Necesidad de una formulación, para el cuidado de la piel, hipoalergénica y no irritante.

Solución: Una emulsión, agua en aceite, hipoalergénica de acuerdo a la reivindicación 1.

IPC: A61K7/48.

3. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria: 15/12/2000.

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación*
D1	EP0847750	Sunscreening compositions containing mono-oligoglyceryl compounds as surface-active agents and hydrosoluble UV filtros	17/06/1998
D4	WO1998/017246	Use of complexes for the preparation of composition for the treatment of sensitive skin preparation process and hypoallergenic compositions	30/04/1998
D5	US4832858	Water dispersible petroleum jelly compositions	Mayo 23, 1989
D6	US5017605	Cosmetic cream preparation containing water/oil and oil/water emulsions	Mayo21, 1991

D1 (folios: 216-218) da a conocer composiciones cosméticas que comprenden, entre otros, los siguientes ingredientes: éter dicaprilílico, triglicérido caprílico/caprico, poligliceril 3-diisostearato, poliglicerilo-2-dipolihiidroxiestearato, Sulfato de Magnesio, ácido láctico, lactato de sodio.

D4 (folios:219-220); tarta de composiciones cosméticas hipoalergénicas, que entre otros componentes contiene Octanoato cetearílico.

D5 (folios: 221-222); enseña un método para la fabricación de emulsiones en agua.

D6 (folios: 223-224); describe un método para preparar emulsiones que utiliza vacío.

4. Respuesta a los argumentos del solicitante:

ARGUMENTOS DEL SOLICITANTE:

“En primer lugar, adjuntamos un nuevo capítulo reivindicatorio de 1-13 reivindicaciones que subsana las objeciones realizadas por el señor examinador, sin ampliar en ningún momento la materia divulgada inicialmente y encontrando entero sustento e la descripción. En particular, haciendo referencia a las objeciones a la claridad de la solicitud, se ha eliminado la característica relacionada con el número de ingredientes presentes en la composición de la reivindicación 1, con el fin de garantizar la concesión d la solitud. De igual manera, la antigua reivindicación 5 ha sido eliminada, dado que el ingrediente ahí mencionado estaba ya incluido en la reivindicación 3, siguiendo las recomendaciones del señor examinador (folio 233)”.

Se verificó que en la reivindicación 1, del nuevo capítulo reivindicatorio (folios 240 a 243), se elimino el número de ingredientes presentes y se elimino la reivindicación 5. Se acepta el nuevo capítulo ya que no amplía materia y esta en esencia es la misma materia a proteger del capítulo anterior.

"De acuerdo a la discusión sostenida durante nuestra entrevista, el solicitante ha decidido sostener la característica bajo el numeral (a), donde se especifican los componentes que no están presentes dentro de la formulación reclamada. Es porque consideramos que en este caso particular, dado el problema técnico resuelto y el concepto inventivo en que se centra la solicitud, esta forma de descripción es la única que permite definir adecuadamente la invención de manera que el aporte al estado del arte que de completamente claro. De esta manera, es imprescindible tener en cuenta el siguiente aparte de la descripción para definir adecuadamente el problema técnico resuelto por la presente invención"

La técnica anterior no ha podido proporcionar una formulación del cuidado de la piel que evite ingredientes irritantes y alergénicos, pero que retengan las propiedades favorables, en particular en el campo médico del cuidado de la piel. Esto puede atribuirse al hecho que el evitar estrictamente tales ingredientes afecta otras propiedades deseadas tales como humedad efectiva de la piel seca, estabilidad de la formulación y atributos sensoriales favorables desde el punto de vista del paciente/ consumidor" (página 6, párrafo 2) (folio 234, pg2 de la repuesta).

Contrario a lo afirmado por el solicitante, respecto a que especificar los componentes que no están presentes dentro de la formulación reclamada, (literal a) es la única forma de descripción que permite definir adecuadamente la invención de manera que el aporte al estado del arte quede completamente claro; esta oficina desea aclarar que en términos de patente solamente existen las reivindicaciones de procedimientos y/o productos (composiciones), y que para los últimos, la parte caracterizante se debe redactar detallando los componentes que conforman una composición así como las proporciones en que ellos se encuentran; ya que el privilegio de patente solo es concedido a composiciones reales que han sido desarrolladas por ejemplo a nivel de laboratorio, tal como el solicitante lo presenta en el capítulo descriptivo con los ejemplos (1, 2 y 3 de los folios 75-78, pgs 18-20). Así mismo, de acuerdo a lo anterior, una invención que posea el privilegio de patente debe cumplir con el requisito de ser reproducida, con éxito, por un técnico medio, con la información aportada, en dicha invención.

Además se aclara que la composición comprende un sistema de tampón el cual le garantiza un pH entre 4,2-4,6 en donde esta es estable; lo que permite concluir que la estabilidad física y microbiológica, no esta dada por los componentes que se excluyen, específicamente, en la composición reclamada. También, se observa que el solicitante, no mostró que las composiciones, que contengan: Fragancias, conservantes, colorantes, extractos vegetales, PEGs, alcohol cetilestearílico, alcohol lanolínico, alcoholes bajos y proteínas; que sean inestables física y microbiológicamente.

"De acuerdo con la información aquí contenida puede establecerse entonces que el problema técnico no es únicamente obtener una composición hipoalergénica y no irritante para el cuidado de la piel, como lo menciona el señor examinador, sino además obtener una composición con estas características que no contenga ningún ingrediente irritante y/o alergénico, conservando al mismo tiempo una estabilidad física y microbiológica adecuada.

Se aclara que el problema objetivo de la presente solicitud, es obtener una composición hipoalergénica y no irritante para el cuidado de la piel, la cual debe ser estable física y microbiológicamente (debe cumplir estos requerimientos, por ejemplo, los de la USP, como lo afirma el solicitante, folio 79, pg 21). Además, se

observa que el solicitante, no mostró que las composiciones, emulsiones, que contienen componentes como: Fragancias, conservantes, colorantes, extractos vegetales, PEGs, alcohol cetilestearílico, alcohol lanolínico, alcoholes bajos y proteínas; presentaran alguna inestabilidad física o microbiológica, porque no era el objetivo de la presente solicitud, resolver un problema de estabilidad.

En particular, como puede observarse en la descripción de la solicitud y en la reivindicación 1, los ingredientes que pueden llegar a causar este tipo de reacciones adversas en la piel son fragancias, conservantes, colorantes, extractos vegetales, PEGs (polietilen glicoles), alcohol cetilestearílico, alcoholes bajos y proteínas. Por esta razón, resulta imprescindible incluir en las reivindicaciones la ausencia de estos ingredientes para definir adecuadamente la invención y demostrar la novedad e inventiva de la misma. De acuerdo con esto, respetuosamente solicitamos al señor examinador la aceptación de este tipo de lenguaje dentro de las reivindicaciones, ya que no es posible definir la invención únicamente por los ingredientes contenidos en la composición, sin comprometer la adecuada especificación del aporte realizado al estado de la técnica por la presente invención.

Se reitera que la presente reivindicación de producto (composiciones), se puede definir adecuadamente por sus características esenciales, o sea por los componentes que la conforman y las proporciones en que ellos se encuentran. Así mismo se aclara que la composición reclamada puede ser es nueva, pero no inventiva (ver 5.1).

Ahora en referencia a las objeciones al nivel inventivo, en vista de los documentos EP084770 (D1), WO1998/017246 (D4), US4832858 (D5) y US5017605 (D6), presentamos los siguientes comentarios.

El señor examinador objeta el nivel inventivo de las reivindicaciones 1-12(nuevas reivindicaciones 1-11) teniendo en cuenta a D1, como arte previo más cercano, y a D2 como complemento que permite a un técnico entrenado en la materia a derivar la presente invención de manera obvia. En este sentido, es preciso señalar que D1 describe composiciones que contienen un filtro ultravioleta, mono y/o oligoésteres de glicerina, fragancias y preservativos.

Se aclara que, si bien en el D1 existen ejemplos que contienen fragancias y preservativos, también el mismo documento, en el párrafo 156 menciona que la preparación cosmética y dermatológica de esa invención puede contener ingredientes auxiliares como perfumes y preservativos, lo cual sugiere que pueden no estar presentes en una composición específica diseñada eliminando estos ingredientes, con el fin de lograr hipoalergenicidad y que no produzca irritación, como la aquí reclamada.

Por otra parte, D4 se refiere a una formulación hipoalergénica que comprende un extracto vegetal de Ginkgo biloba y un β -Glucano o uno de sus derivados.

Se aclara que este documento, muestra que el extracto de Ginkgo biloba y β -Glucano o uno de sus derivados, se utilizan en composiciones para el tratamiento de pieles sensibles y que la función de este extracto en ella, es precisamente como un excelente antialérgico y antiinflamatorio, pg 7, líneas 13-15.

De esta forma, estos dos documentos se alejan sustancialmente del concepto inventivo de la presente solicitud, ya que ambos sugieren que las propiedades adecuadas de las composiciones para el cuidado de la piel solo se alcanzan mediante la inclusión de varios ingredientes que no se encuentran presentes dentro de la composición reclamada. Incluso cuando D4 se refiere a una composición hipoalergénica, este efecto se alcanza solamente mediante la inclusión de un extracto vegetal dentro de la misma, por lo que las enseñanzas de este documento, en complemento con D1, no llevarían en ningún momento al técnico a prescindir de las fragancias, conservantes y extractos vegetales para lograr una composición hipoalergénica estable física y microbiológicamente así mismo agradable para el usuario.

Se reitera que aunque en el documento D1, se enseñen ejemplos que contienen fragancias y preservativos, en el párrafo 156 de este mismo documento se menciona que la preparación cosmética y dermatológica de esa invención puede contener ingredientes auxiliares como perfumes y preservativos, lo cual sugiere que pueden estar presentes de manera opcional en una composición. Por lo tanto esto sugiere claramente excluir dichos ingredientes para lograr la composición reclamada, con el efecto deseado esperado, que sea hipoalergénica y que no produzca irritación en la piel.

Se aclara con respecto a D4, que contrario a lo afirmado por el solicitante un extracto vegetal como Ginkgo biloba, en esta formulación se utilizó, por sus propiedades como antialérgico y antiinflamatorio, como se mencionó antes.

De acuerdo con lo anterior, los inventores encontraron de manera sorprendente que al omitir ingredientes específicos, como conservantes, fragancias, PEG y alcohol cetilestearílico, se obtiene una composición que es estable y al mismo tiempo un humectante eficiente. Esta efectividad fue especialmente sorprendente ya que el alcohol cetilestearílico y el PEG son usados normalmente como emulsificantes y compuestos grasos que mejoran la capacidad de esparcir la composición sobre la piel. Además, la estabilidad de la emulsión de agua en aceite (W/O), como se reivindica, fue lograda sin la necesidad de incluir los parabenos, que son conservantes comúnmente usados para este fin. Vale la pena resaltar que la estabilidad fue lograda entonces exclusivamente por el sistema amortiguador o buffer compuesto de ácido láctico y lactato de sodio. De acuerdo con esto, ninguno de los documentos citados contiene enseñanza alguna acerca de la efectividad del sistema amortiguador ni de la posibilidad de omitir tales ingredientes, por lo que la composición reivindicada no resulta obvia en ningún momento.

Por lo tanto, no es sorprendente y era de esperarse, que si la composición de la invención no incluye ninguno de los componentes que potencialmente den origen a una alergia ó irritación, esta, mostrara en los resultados de los ensayos: una baja irritación y sensibilidad (ej 5 y ej 6, folios 79-90, pgs 21-32) y además buenas propiedades sensoriales, debido a las propiedades funcionales de los componentes conocidos en el campo de la cosmética (como emolientes, hidratantes, y humectantes), que hacen parte de la formulación.

El señor examinador, en relación a la no inclusión de ciertos ingredientes dentro de la composición, afirma que era de esperarse que si la composición de la invención no incluye ninguno de los componentes que potencialmente

dan origen a una alergia o irritación, esta mostraría un bajo nivel de irritación y sensibilidad. A este respecto, consideramos que el señor examinador tiene razón, sin embargo en caso que una de las composiciones del arte previo prescindiera de estos ingredientes, aunque no tendría potencial alguno de generar alguna alergia o irritación, perdería completamente su estabilidad y su capacidad de perdurar en el tiempo. Para soportar esto, adjuntamos a este memorial tres artículos que ilustran la importancia de incluir ingredientes conservantes, fragancias, y PEG dentro de formulaciones cosméticas así como su potencial demostrado de generar alguna reacción alérgica en la piel.

Se aclara que la estabilidad física y microbiológica de la composición reclamada, no esta dada por los componentes que se excluyen, específicamente, en la composición reclamada, sino por el tampón Acido láctico / Lactato de sodio, el cual mantiene el pH 4,2-4,6, que es el rango donde se encontró la mayor estabilidad, en el desarrollo de la formulación reivindicada; además, ingredientes como el sulfato de magnesio, que es un equilibrador de densidades y el propilenglicol, un conservante, favorecen la estabilidad, de la composición.

Este material soporta entonces la necesidad de proporcionar composiciones, como la reivindicada, que omitan la inclusión de estos ingredientes. Las referencias bibliográficas son: Artículo 1..., Artículo 2..., Artículo 3, (folios 236-237)

Se responde que los artículos citados, precisamente mencionan que existen ingredientes que son potencialmente alérgenos y que el experto en la materia por sus sugerencias, pudo diseñar una composición sin incluir dichos ingredientes, para lograr el efecto esperado hipoalergenicidad y que no produzca irritación en la piel.

El artículo 2 profundiza en las reacciones alérgicas causadas por las fragancias y establece que, incrementalmente, los datos disponibles muestran evidencia que un aparte importante de la intolerancia cutánea a los cosméticos se debe a sus componentes de fragancia ver artículo 2, página 377, párrafo 1). Por esta razón, se puede reafirmar que al formular una composición que omita estos compuestos es un aporte al estado del arte. Ya que soluciona efectivamente cualquier inconveniente alérgico que pueda llegar a presentarse.

Se aclara que no utilizar ingredientes, que ya se conoce son potencialmente alérgicos, para el desarrollo de una composición hipoalérgica y no irritante, no tiene altura inventiva.

En conclusión, consideramos que en vista de lo expuesto anteriormente se ha demostrado que la presente invención cumple con los requisitos de claridad, concisión y nivel inventivo. En particular, se ha demostrado que al describir la composición reclamada por medio de los componentes que no contiene es adecuada en este caso, dado el problema técnico resuelto y el concepto inventivo de la solicitud, que hacen necesario el uso de este lenguaje para lograr una definición adecuada y completa. Además, se han aportado argumentos y pruebas suficientes que permiten observar que la presente invención no es una derivación obvia del arte previo, y que resuelve problemas de alergenidad y toxicidad recurrentes en el campo de la cosmética. Aún cuando todos los ingredientes que contiene la composición se describen en el arte previo, tuvo que realizarse una selección inventiva que permita proporcionar una composición sin ningún compuesto potencial alérgico o irritante, ya que como se demostró, son compuestos

generalmente necesarios en este tipo de formulaciones y que son imprescindibles en los documentos citados por el señor examinador. Por esta razón, las reivindicaciones 1-11 cumplen con el requisito de nivel inventivo.

Se aclara que no se desconoce que la presente composición tiene propiedades hipoalergénicas y no irritantes, pero como se ha aclarado antes este efecto era de esperarse, lo cual no le da Nivel inventivo.

Ahora en cuanto a las reivindicaciones 13-14 (nuevas reivindicaciones 12-13) que describen un proceso, el señor examinador objeta el nivel inventivo con los documentos D5 y D6. Sin embargo, dado que las reivindicaciones de composición son inventivas, como se demostró anteriormente. El proceso para elaborarlas resulta en consecuencia inventivo, en concordancia con todos los requerimientos de patentabilidad establecidos.

Se aclara que como la composición no es inventiva, el proceso para elaborarlas tampoco lo es.

5. Análisis de patentabilidad (artículo 14 D486)

5.1 Nivel inventivo (artículo 18 D486)

La reivindicación 1 consiste en:
Una formulación del cuidado de la piel, hipoalergénica no irritante, caracterizada porque comprende:
Una fase acuosa dispersa en una fase de aceite en donde:

- La fase aceite comprende: Octanoato cetearílico, éter dicaprilílico, triglicérido caprílico/caprico, poligliceril 3-diisostearato, poliglicerilo-2-dipolihidroxiestearato;
- y
- La fase acuosa comprende: agua purificada, Sulfato de Magnesio, ácido láctico, lactato de sodio.

El Estado de la Técnica más cercano es D1 (EP0847750, todo el documento) que da a conocer composiciones cosméticas que comprenden, entre otros, los siguientes ingredientes:

Solicitud (Reiv 1)	D1	D4
Emulsión de fase acuosa en aceite	Composiciones cosméticas, que comprenden los siguientes ingredientes, estables y bien toleradas por la piel (párrafo 120-121)	Composiciones cosméticas, hipoalergénicas y antiinflamatorias, que comprenden los siguientes ingredientes (pgs 10-11, líneas 35-39 y 1)
-Fase oleosa:		
Octanoato cetearílico	Sugerido (párrafo 162)	Si (pg 26 , línea 36)
éter dicaprilílico	Si (párrafo 165)	
triglicérido caprílico/caprico	Si (párrafo 165)	
poligliceril 3-diisostearato	Si (párrafo 99)	
poliglicerilo-2-dipolihidroxiestearato	Si (párrafo 99)	

-fase acuosa:		
Sulfato de Magnesio	Si (párrafo 151)	
ácido láctico	Si (párrafo 158)	
lactato de sodio	Si (párrafo 150)	

La composición objeto de esta solicitud se diferencia de las composiciones de D1, en que contiene, además, el componente Octanoato Cetearílico.

El hecho de incluir Octanoato Cetearílico, en las composiciones, para el cuidado de la piel, que se daban a conocer en D1, causa que la composición reclamada, sea hipoalergénica y no irritante.

El Problema Técnico Objetivo era “cómo obtener una composición hipoalergénica y no irritante, alternativa, para el cuidado de la piel”.

D4 (WO1998/017246) describe una manera de solucionar el problema técnico, mediante composiciones cosméticas hipoalergénicas, que entre otros componentes contiene Octanoato Cetearílico (pg 26, línea 36).

Por otro lado era de esperarse, que si la composición de la invención no incluye ninguno de los componentes que potencialmente den origen a una alergia ó irritación, esta, mostrara, en los resultados de los ensayos: una baja irritación y sensibilidad (ej 5 y ej 6) y buenas propiedades sensoriales, debido a las propiedades funcionales de los componentes conocidos (como emolientes, hidratantes, y humectantes), que hacen parte de la formulación.

Por tanto, la solicitud, tal como se reivindica, es obvia, porque el Experto en la Materia enfrentado al problema de “cómo obtener una composición hipoalergénica y no irritante, alternativa, para el cuidado de la piel”, incluiría el componente, Octanoato cetearílico; que se revela en D4, dentro de las composiciones que se enseñan en D1, logrando de esta forma la composición objeto de esta solicitud.

Por lo tanto las reivindicaciones 1-11, no muestran nivel inventivo.

La reivindicación 12, se refiere a un método de preparación de la formulación reclamada en la reivindicación 1; que comprende:

- a) Fundir los ingredientes de la fase oleosa
- b) Preparar la fase acuosa calentando el agua purificada y disolviendo los ingredientes de la fase acuosa mientras se agita y ajusta el pH con acido láctico a 4.4 - 4.8.
- c) Preparar una emulsión de agua en aceite transfiriendo la fase de aceite fundida del paso a) a la fase oleosa calentada del paso b) y mientras se agita y homogeniza, enfriar la emulsión hasta temperatura ambiente mientras se aplica un vacío de -0.6 a -.9 bar (-60.000 a -90.000 Pa).

D5 (US4832858), enseña un método para la fabricación de emulsiones agua en aceite que consiste en:

- a) Fundir los ingredientes de la fase oleosa, a 70 grados centígrados.
- b) Calentar el agua a 70 grados centígrados y disolver los ingredientes solubles en agua y mezclar bien.
- c) Adicionar la fase acuosa a la fase oleosa, y mezclar hasta una emulsión homogénea y enfriar.

El método reclamado se diferencia de D5, en que utiliza ácido láctico para ajustar el pH final de la emulsión y que utiliza vacío.

El hecho de utilizar ácido láctico y ultrasonido, en el método de fabricación de D5, causa que se obtenga una emulsión como la reclamada.

Por lo tanto se concluye que: el Problema Técnico Objetivo era “establecer un método de obtención de una composición hipoalérgica y no irritante, para el cuidado de la piel, que utilice ácido láctico y vacío”.

D6 (US5017605) describe una manera de solucionar el problema técnico, mediante un método para preparar emulsiones que utiliza vacío (folio 224, columna 2, líneas 40-68); además el ajuste de pH, para llegar a 4,4-4,8, es un paso general y conocido, por un experto en la materia, el cual puede realizar con algún ácido, farmacéuticamente aceptable.

Por tanto, la solicitud, tal como se reivindica, es obvia, porque el Experto en la Materia enfrentado al problema de “establecer un método de obtención de una composición hipoalérgica y no irritante, para el cuidado de la piel, que utilice ácido láctico y vacío”, utilizaría el vacío revelado en D6 y el ácido láctico para ajustar el pH final de la emulsión, logrando de esta forma el método de preparación objeto de esta reivindicación.

La reivindicación 14, que muestra rangos de temperaturas, velocidad y presión, no agrega altura inventiva, ya que descubrir los rangos óptimos es labor de rutina del experto en la materia.

Por lo anterior las reivindicaciones 12 y 13, no muestran Nivel inventivo.

6. Conclusión:

En consecuencia y por todo lo expuesto anteriormente, se recomienda **Negar** las reivindicaciones: 1 a 13 (folios: 240-243)

Bogotá, D.C.,

CONCEPTO TECNICO No. 4136	EXAMINADOR TECNICO Código No.202078
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