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Toxicology 214 (2005) 1–38
TOXICOLOGY
www.elsevier.com/locate/toxicol

Review

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

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Received 29 April 2005; received in revised form 2 June 2005; accepted 3 June 2005
Available online 11 July 2005

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 genotoxicty 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.

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

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doi:10.1016/j.tox.2005.06.001

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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,

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 $HO(CH_2CH_2O)_nH$	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- undecaoxapentatriacontane- 1, 35- diol
	PEG-14		25322-68-3			Poly(oxy- 1, 2- ethanediyl), α- hydro- ω-
	PEG-16, -18					
	PEG-20	Macrogol 1000				
	PEG-32	Macrogol 1540				
	PEG-40					
	PEG-60			humectants		
	PEG-75	Macrogol 4000; PEG 3350;		binders / humectants / solvents		
	PEG-90			humectants / solvents		
	PEG -100			humectants		
	PEG-135			humectants / solvents		
	PEG-150	Macrogol 6000		binders / humectants / solvents		
	PEG-180			humectants		
	PEG-200			humectants / solvents		
	PEG-240			humectants		
	PEG-350			binders / solvents		
	PEG-2M, -5M, -7M, -9M, -14M, -20M, -23M, -25M, -45M, -90M, -115M			binders / emulsion stabilisers / viscosity controlling agents		
PEG fatty acid esters						
- laurates	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), a- (1- oxododecyl)- ?- hydroxy-
	PEG-6 laurate		9004-81-3 2370-64-1			26- hydroxy- 3, 6, 9, 12, 15, 18, 21, 24- octaoxahexacos- 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			
	PEG-8, -20 laurates			emulsifying agents / surfactants		
	PEG-32, -75, -150 laurates			surfactants		
- dilaurates	PEG-2 dilaurate		9005-02-1	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-4, -6, -8, -12, -20, -32 dilaurates					

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 dilaurates				conditioners, shampoos	
- stearates ($C_{17}H_{35}COO.(O.CH_2CH_2)_n$	PEG-2 stearate		106-11-6	emulsifying agents / opacifiers	Up to 5-10 % in facial cleansers, moisturizers, body lotions, skin care, conditioners, hair treatment products, and styling gels	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	emulsifying agents		2- [2- [2- (2- hydroxyethoxy)ethoxy]ethoxy]ethyl stearate
	PEG-4 isostearate		56002-14-3			Poly(oxy- 1, 2- ethanediyl), a- (1- oxoisooctadecyl)- ω – hydroxy-
	PEG-5, -6, -7 stearates		9004-99-3			
	PEG-6, -8 isostearates		56002-14-3			
	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		Poly(oxy- 1, 2- ethanediyl), α- (1- oxooctadecyl)- ω- hydroxy-
	PEG-10 stearate		9004-99-3	emulsifying agents / surfactants		
	PEG-12 isostearate		56002-14-3	emulsifying agents		
	PEG-12, -14, -18 stearates		9004-99-3			
	PEG-15 hydroxystearate					Poly(oxy- 1, 2- ethanediyl), α- (1- oxooctadecyl)- ω- hydroxy-
	PEG-20 stearate		9004-99-3	emulsifying agents / humectants / surfactants		
	PEG-23, -25 stearates			emulsifying agents		
	PEG -30, -32, -35, -36 stearates			emulsifying agents / surfactants		
	PEG-40 stearate	Macrogol ester 2000				
	PEG-45 stearate					
	PEG-50 stearate	polyoxyl 50 stearate				
	PEG-75, -90, -100, -120, -150 stearates			surfactants		
- distearates $C_{17}H_{35}COO.(O.CH_2CH_2)_n.COOC_{17}H_{35}$.	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		9005-08-7			Poly(oxy- 1, 2- ethanediyl), a- (1- oxooctadecyl)- ω- [(1- oxooctadecyl)oxy]-
	PEG -150, -175 distearates			emulsifying agents / surfactants / viscosity controlling agents	Up to 10% in shaving gel	

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** $C_{12}H_{25}(OCH_2CH_2)_nOH$	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]ethanol
	Laureth-4		5274-68-0			3, 6, 9, 12-tetraoxatetracosan- 1- ol
	Laureth-5		3055-95-6			3, 6, 9, 12, 15-pentaoxaheptacosan- 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-heptaoxatritriacontanol
	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; - 10% in hair conditioner, hair color restorer; - 20% in facial wash	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		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	

Table 1 (*Continued*)

CLASS General Formula	Substances	Common other names	CAS register numbers	Function in cosmetics	Examples for use levels in cosmetics	Chemical name
ceteareths $R(OCH_2CH_2)_nOH$ (R: mixture of alkyl groups derived from cetyl and stearyl alcohols)	Ceteareth-15, -16, -17, -18			emulsifying agents/surfactants	Up to 10% in skin care and cleansing products, conditioners, and hair treatment products	
	Ceteareth-20				Up to - 1% in conditioners and treatments; - 3% in styling products	
	Ceteareth-22, -23, -25, -27, -28, -29, -30, -33, -34			emulsifying agents/ surfactants	Up to - 1% in perms - 10% in antiperspirants - 18% in styling products	
	Ceteareth-40			surfactant	Up to 1.5 % in colorants	
	Ceteareth-50			emulsifying agents/ surfactants	Up to 10% in skin care and cleansing products, conditioners, and hair treatment products	
	Ceteareth-55			surfactants		
	Ceteareth-60			emulsifying agents		
	Ceteareth-80, -100			surfactants		
- of oleyl alcohol (octadec-9-enol) = **oleths** $CH_2(CH_2)_7CH=CH(CH_2)_7(O.CH_2CH_2)_nOH$	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	Poly(oxy- 1, 2- ethanediyl), α- 9- octadecenyl-ω- hydroxy-
	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 $RCOOCH_2CHCH_2(OCH_2CH_2)_nOH$ 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		

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				-11% in blusher	
	PEG-20 sorbitan beeswax	G 1726	8051-73-8			
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–(CH_2–CH_2–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-

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, ceteareths, 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, ceteareths, 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 ethoxylated 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).

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. Toxikokinetics 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 antipruretic effects (Ring and Fröhlich, 1985).

In a study with ^{14}C-labelled branched chain alkylpolyethoxylate ($H(CO_2)_{12}(OCH_2CH_2)_6OH$) 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 comparision is difficult. In contrast to the results obtained in the animal

studies, only 2% of straight-chain alkylpolyethoxylates ($H(CO_2)_{12}(OCH_2CH_2)_6OH$) 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 0.02–0.14 μg/g blood at 8 h, 0.02 μg/g at 12 h, and 0.01 μg/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 0.015–0.021 μg/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-

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 ceteareth-20 (De Vos and Kinget, 1993), while Fabregas et al. (1986) had found that the percutaneous absorption of the analgesic piketoprofen was increased in rabbits following topical application of aqueous and anhydrous creams containing 2%, 3% or 5% of ceteareth-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 LD_{50} 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 LD_{50} 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 LD_{50} 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).

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	32,000 mg/kg bw (vehicle not reported)	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)

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	Rar	41 mg/kg bw (in propylene glycol)	CIR (1988)
Steareth-20	Rar	164 mg/kg bw (in isotonic NaCl)	CIR (1988)

Aerosols generated from ethylene oxide/propylene oxide copolymers (about 100 mg/m^3 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. Intramusuclar 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)
PEG-8	50%, 33% aqueous solutions	Human	50% only slight burning sensation, no injury; 30% sompletely non-irritating	Grant (1974)
PEG-8	0.5 ml, undiluted	Rabbit	Not irritating	Carpenter and Smyth (1946)
PEG-8	French national standard method (1973)	Rabbit	Not irritating	Guillot et al. (1982)
PEG-8	0.1 ml, 35% solution multiple instillations	Rabbit	Little or not irritating	Laillier et al. (1976)
PEG-6-32	0.5 ml, undiluted	Rabbit	Not irritating	Carpenter and Smyth (1946)
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	Bushy Run Research Center (1987)
PEG-6-75	0.5 ml, undiluted	Rabbit	Not irritating	Carpenter and Smyth (1946)
PEG-stearates	100%	Rabbit	Minimal irritation	Elder (1983)
PEG-7 glyceryl cocoate	10% solution, Draize test	Rabbit	Not irritating	Henkel Corp. (1996)
Laureths	not specified	Rabbit, monkey	Severely irritating to the rabbit eye, but had a much less severe and transient effect on the monkey eye	Benke et al. (1977)
“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)

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 aninals)	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 aninals)	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%	Human	Minimally irritating	Benke et al. (1977)
	15%, 20% and undiluted	Rabbit	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	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	Patch test	Human	Not irritating	CIR (1988)
Ceteareth-5, -14	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)
Ceteareth-15	10% in hair dress formulation	Rabbit	Minimally irritating (PII: 1.5/8)	CIR (1999d)
Ceteareth-15	1.5% in lotion, 21 days; 11 panelists	Human	Transient erythema in 1/11 at day 19; judged as “essentially non-irritating”	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)

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 treatement (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.

Table 5
Phototoxicity data for PEG and PEG compounds

Compound	Concentration	Species	Result	Reference
PEG-2 stearate, PEG-8 stearate	25%	No data	No evidence of phototoxicity	Elder (1983)
PEG-7 glyceryl cocoate	50% in olive oil	Hairless mice	Not phototoxic. Mild irritation (PII 1.66); if rinsed after 1 hour, no erythema was observed at 24 h after exposure.	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 hyperreactivity 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.

Steareth-2 and steareth-20 (60% in water) were not sensitising to human skin (CIR, 1988). Ceteareth-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 FEG-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 photosensitising 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-sensisitsation (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 accompagnying changes in blood parameters indicating an inflammatory reaction. No pathological changes were found in organs (for details see Table 6).

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 (n = 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 ♀; *Macaca fascicularis*)	2820 mg/kg bw/d: microscopic kidney damage	Prentice and Majeed (1978)
PEG-6	Diet, drinking water, 90 days	Rat (n = 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 (n = 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)

Table 6 (*Continued*)

Compound	Type of study	Species	Doses/results	Reference
PEG-8	Diet, 2 years	Rat (n = 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 (n = 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 (n = 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 (n = 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 (n = 2)	2% (about 500 mg/kg bw/d): no effect	Smyth et al. (1955)
PEG-75	Diet, 2 years	Rat (n = 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 (n = 4)	2% (about 500 mg/kg bw) no adverse effects	Smyth et al. (1955)

PEG-150	Diet, 90 days	Rat (n = 5/sex/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)

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 ↓	Harris et al. (1951)
PEG-8 stearate	Diet, 70 days	Rat, 16♀, 14♂	5% in diet, sequentially increasd 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, 2 years	Rat	4%: no treatment-related effects over three generations	Elder (1983)
PEG-8 stearate	Diet, 19 weeks	Rabbit	5%: no treatment-related effects	Elder (1983)
PEG-8 stearate	Diet, 4 months	Rabbit	4%: no treatment-related effects	Elder (1983)
PEG-100 stearate	Diet, 2 years	Rat	2%: no treatment-related effects over three generations	Elder (1983)
PEG-monostearate	Diet, 2–10 weeks	Hamster	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, 28-39 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)

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 increasd 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)

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	17 months, diet	Monkey	1 g/day had no adverse effects	CIR (2000b)
PEG-20 sorbitan laurate	2 years, diet	Rat	Up to and including 2%: no signs of toxicity	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	Luduena 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	800 mg/kg bw/d: transient mild erythema; no clinical signs of toxicity	CIR (1993)
PEG-6 stearate (1.5% in formulation)	20 days	Rabbit	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)

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)	F344 rats	No treatment related effects	Bayer (1989, 1995)
PEG-75	109, 567 and 1000 mg/m^3 for 2 weeks (6 h/d, 5 d/w)	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	Luduena 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)

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

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 Wuergler, 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 ceteareths, 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 subcutanous 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 phaeochromocytomas 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

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 magniturde 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 genotoxicity 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 corrobated 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 genotoxicty 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.

References

Abdullah, A., Walker, S., Tan, C.Y., Foulds, I.S., 1997. Sensitization to oleth-3-phosphate and oleth-5 in a hair wax. Contact Dermatitis 37, 188.

Asmussen, C., 2000. Chemische Charakterisierung von Alkylethoxylaten. Technische Universität, Berlin (in German).

Bailey Jr., F.E., Koleske, J.V., 1966. Configuration and hydrodynamic properties of the polyoxyethylene chain in solution. In: Schick, M.J. (Ed.), Nonionic Surfactants. Marcel Dekker, New York (Chapter 23).

Bangha, E., Maibach, H.I., Elsner, P., 1996. Toxicology of topical local anesthetics. Skin Pharmacol. 9, 376–380.

Bárány, E., Lindberg, M., Lodén, M., 2000. Unexpected skin barrier influence from non-ionic emulsifiers. Int. J. Pharmacol. 195, 189–195.

Basketter, D.A., Chamberlain, M., Griffiths, H.A., Rowson, M., Whittle, E., York, M., 1997. The classification of skin irritants by human patch test. Food Chem. Toxicol. 35, 845–852.

Bayer AG, 1989. In: MAK, 1995. Gesundheitschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten. VCH Verlagsgesellschaft, Weinheim, Germany (in German).

Bayer AG, 1995. In: MAK, 1995. Gesundheitschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten. VCH Verlagsgesellschaft, Weinheim, Germany (in German).

Benke, G.M., Brown, N.M., Walsh, M.J., Drotman, R.B., 1977. Safety testing of alkyl polyethoxylate nonionic surfactants. I. Acute effects. Food Cosmet. Toxicol. 15, 309–318.

Berberian, D.A., Gorman, W.G., Drobeck, H.P., Coulston, F., Slighter, R.G., 1965. The toxicology and biological properties of laureth 9 (a polyoxyethylene lauryl ether), a new spermicidal agent. Toxicol. Appl. Pharmacol. 7, 206–214.

Berenblum, I., Haran, N., 1955. The influence of croton oil and of polyethylene glycol-400 on carcinogenesis in the forestomach of the mouse. Cancer Res. 15, 510–516.

Bergh, M., Shao, L.P., Hagelthorn, G., Gafvert, E., Karlberg, A.T., 1998a. Contact allergens from surfactants. Atmospheric oxidation of polyoxyethylene alcohols, formation of ethoxylated aldehydes, and their allergenic activity. J. Pharm. Sci. 87, 276–282.

Bergh, M., Magnusson, K., Nilsson, J.L., Karlberg, A.T., 1998b. Formation of formaldehyde and peroxides by air oxidation of high purity polyoxyethylene surfactants. Contact Dermatitis 39, 14–20.

Beyer Jr., K.H., Bergfeld, W.F., Berndt, W.O., Boutwell, R.K., Carlton, W.W., Hoffmann, D.K., Schroeter, A.L., 1983. Final report on the safety assessment of laureths-4 and -23. J. Am. Coll. Toxicol. 2, 1–15.

British Industrial Biological Research Association (BIBRA), 1990. Toxicity profile: polyethylene glycol 400. BIBRA International, Carshalton, Surrey, UK.

British Industrial Biological Research Association (BIBRA), 1993. Toxicity profile tetraethylene glycol. BIBRA International, Carshalton, Surrey, UK.

Biondi, O., Motta, S., Mosesso, P., 2002. Low molecular weight polyethylene glycol induces chromosome aberrations in Chinese hamster cells cultured in vitro. Mutagenesis 17, 261–264.

Boyland, E., Charles, R.T., Gowing, N.F.C., 1961. The induction of tumors in mice by intravaginal application of chemical compounds. Br. J. Cancer 15, 252.

Boyland, E., Carter, R.L., Gorrod, J.W., Roe, F.J.C., 1968. Carcinogenic properties of certain rubber additives. Eur. J. Cancer 4, 233–239.

Brain, J.D., Blanchard, J.D., Heyder, J., Wolfthal, S.F., Beck, B.D., 1996. Relative toxicity of di(2-ethylhexyl) sebacate and related compounds in an in vivo hamster bioassay. Inhal. Toxicol. 8, 579–593.

Braun, W., 1969. Contact allergies to polyethylene glycols. Z. Haut Geschlechtskr. 44, 385–389 (in German).

Brown, N.M., Benke, G.M., 1977. Safety testing of alkyl polyethoxylate nonionic surfactants. II. Subchronic studies. Food Cosmet. Toxicol. 15, 319–324.

Bruns, D.E., Herold, D.A., Rodeheaver, G.T., Edlich, R.F., 1982. Polyethylene glycol intoxication in burn patients. Burns 9, 49–52.

Buhles, N., Richter, R., 1989. Balneologische Therapie der Neurodermitis mit polidocanol-haltigem Badezusatz. Akt. Dermatol. 15, 249–253 (in German).

Bushy Run Research Center, 1980. Polyethylene glycol-400 Carbowax. In vitro mutagenesis studies, 3-test battery, 15 pp., unpublished data. In: CIR (1993).

Bushy Run Research Center, 1987. Carbowax PEG-1450 NMW. Acute toxicity and primary irritancy studies, 3 pp., unpublished data. In: CIR (1993).

Bushy Run Research Center, 1988. Carbowax PEG-600, PEG-3350 and MPEG-2000. Assessment of pulmonary effects in the rat following single endoracheal injection, unpublished data. In: CIR (1993).

Buzzi, R., Wuergler, F.E., 1990. Knowledge-based battery design of short-term tests based on dose information. Mutat. Res. 234, 269–288.

Byshovets, T.F., Barilyak, I.R., Korkach, V.I., Spitkovskaya, L.D., 1987. The gonadotoxic activity of glycols. Gig Sanit 0 (9), 84–85 (in Russian).

Calvin, G., Chasseaud, L.F., Down, W.H., Ballard, S.A., Hawkins, D.R., 1983. Absorption and elimination of a branched-chain alkylpolyethoxylate surfactant in rats. Toxicol. Lett. 18, 351–357.

Carpenter, C.P., Smyth Jr., H.F., 1946. Chemical burns of the rabbit cornea. Am. J. Ophthalmol. 29, 1363–1372.

Carpenter, C.P., Woodside, M.D., Kinkead, E.R., King, J.M., Sullivan, L.J., 1971. Response of dogs to repeated intravenous injection of polyethylene glycol 4000 with notes on excretion and sensitization. Toxicol. Appl. Pharmacol. 18, 35–40.

Carter, R.L., 1969. Early development of injection site sarcomas in rats: a study of tumors induced by a rubber additive. Br. J. Cancer 23, 408–416.

Chadwick, V.S., Phillips, S.F., Hofmann, A.F., 1977. Measurements of intestinal permeability using low molecular weight polyethylene glycols (PEG-400). 2. Application to normal and abnormal permeability states in man and animals. Gastroenterology 73, 247–251.

Cosmetic ingredient review (CIR), 1988. Final report on the safety assessment of steareth-2, -4, -6, -7, -10, -11, -13, -15, and -20. J. Am. College Toxicol. 7, 881–910.

Cosmetic ingredient review (CIR), 1993. Final report on the safety assessment of polyethylene glycols (PEGs)-6, -8, -32, -75, -150, -14M, -20M. J. Am. College Toxicol. 12, 429–457.

Cosmetic ingredient review (CIR), 1997. Final report on the safety assessment of PEG-30, -33, -35, -36, and -40 castor oil and PEG-30 and -40 hydrogenated castor oil. Int. J. Toxicol. 16, 269–306.

Cosmetic ingredient review (CIR), 1999a. Final report on the safety assessment of PEG-7, -30, -40, -78, and -80 glyceryl cocoate. Int. J. Toxicol. 18 (Suppl. 1), 33–42.

Cosmetic ingredient review (CIR), 1999b. Final report on the safety assessment of ceteth-1, -2, -3, -4, -5, -6, -10, -12, -15, -16, -20, -24, -25, -30, and -45. Int. J. Toxicol. 18 (Suppl. 2), 1–8.

Cosmetic ingredient review (CIR), 1999c. Final report on the safety assessment of oleth-2, -3, -4, -5, -6, -7, -8, -9, -10, -11, -12, -15, -16, -20, -23, -25, -30, -40, -44, and -50. Int. J. Toxicol. 18 (Suppl. 2), 17–24.

Cosmetic ingredient review (CIR), 1999d. Final report on the safety assessment of ceteareth-2, -3, -4, -5, -6, -7,-8, -9, -10, -11, -12, -13, -14, -15, -16, -17, -18, -20, -22, -23, -24, -25, -27, -28, -29, -30, -33, -34, -40, -50, -55, -60, -80 and -100. Int. J. Toxicol. 18 (Suppl. 3), 41–49.

Cosmetic ingredient review (CIR), 1999e. Final report on the safety assessment of PEG-2, -3, -4, -6, -8, -9, -12, -20, -32, -50, -75, -120, -150, and -175 distearate. Int. J. Toxicol. 18 (Suppl. 1), 51–59.

Cosmetic ingredient review (CIR), 2000a. Final report on the safety assessment of PEG-5, -10, -16, -25, -30, and -40 soy sterol. Int. J. Toxicol. 19 (Suppl. 1), 29–46 and amendment.

Cosmetic ingredient review (CIR), 2000b. Final report on the safety assessment of PEG-20 sorbitan cocoate; PEG-40 sorbitan diisostearate; PEG-2, -5, and -20 sorbitan isostearate; PEG-40 and -75 sorbitan lanolate; PEG-10, -40, -44, -75, and -80 sorbitan laurate; PEG-3, and -6 sorbitan oleate; PEG-80 sorbitan palmitate; PEG-40 sorbitan perisostearate; PEG-40 sorbitan peroleate; PEG-3, -6, -40, and -60 sorbitan stearate; PEG-20, -30, -40, and -60 sorbitan tetraoleate; PEG-60 sorbitan tetrastearate; PEG-20 and -160 sorbitan triisostearate; PEG-18 sorbitan tri-

oleate; PEG-40 and -50 sorbitol hexaoleate; PEG-30 sorbitol tetraoleate laurate; and PEG-60 sorbitol tetrastearate. Addendum to the final report on the safety assessment of polysorbates. Int. J. Toxicol. 19 (Suppl. 2), 43–89.

Cosmetic ingredient review (CIR), 2001a. Final report on the safety assessment of PEG-6, -8, and -20 sorbitan beeswax. Int. J. Toxicol. 20 (Suppl. 4), 27–38.

Cosmetic ingredient review (CIR), 2001b. Final report on the safety assessment of PEG-25 propylene glycol stearate, PEG-75 propylene glycol stearate, PEG-120 propylene glycol stearate, PEG-10 propylene glycol, PEG-8 propylene glycol cocoate, and PEG-55 propylene glycol oleate. Int. J. Toxicol. 20 (Suppl. 4), 13–26.

Cosmetic ingredient review (CIR), 2004. Final report of the amended safety assessment of PEG-5, -10, -16, -25, -30, and -40 soy sterol. Int. J. Toxicol. 23 (Suppl. 2), 23–47.

Colipa, 2000. The European Cosmetic Toiletry and Perfumery Association. Cosmetic Frame Formulations, 2000.

Conrad, P., Malouf, G.M., Stacey, M.C., 1995. The Australian Polidocanol (Aethoxysclerol) study. Results at 2 years. Dermatol. Surg. 21, 334–336.

Corley, R.A., Weitz, K.K., Soelberg, J.J., 2002. Toxicokinetics of ethylene glycol in male F344 and Wistar rats following 1 and 16 weeks of dietary administration (Study No. WIL-186027). Battelle Project No. 29812. Pacific Northwest National Laboratory, Richland, WA. Final Report, December 5, 2002. In: Organisation for Economic Co-operation and Development (OECD), 2004. Screening Information Data Set (SIDS) for Ethylene Glycols (Draft), discussed at SIAM 18, April 2004.

Crook, et al., 1980. In: MAK, 1995. Gesundheitschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten. VCH Verlagsgesellschaft, Weinheim, Germany (in German).

Cosmetic, Toiletry, and Fragrance Association (CTFA), 1980. Primary skin irritation test on an antiperspirant containing 2.0% PEG-25 propylene glycol stearate, unpublished data. In: CIR (2001b).

Cosmetic, Toiletry, and Fragrance Association (CTFA), 1981. The safety evaluatin of 14A/16427-14 containing 3.0% PEG-8 (RI 0639)/group 6, 13 week subchronic dermal toxicity study using male and female albino rats. Study Project: AT0173, 15 pp. In: CIR (1993).

Cosmetic, Toiletry, and Fragrance Association (CTFA), 1985. The safety evaluatin of 14A/25363-17 containing 5.0% PEG-8 (RI 0639)/group 6, 13 week subchronic dermal toxicity study using male and female albino rats. Study Project Code 219, 14 pp. In: CIR (1993).

Cosmetic, Toiletry, and Fragrance Association (CTFA), 1998. Data on PEG sorbitans/sorbitols, unpublishd data. In: CIR (2000b).

Curry, P.T., 1996. Unpublished data. In: Leung et al. (2000).

Degim, I.T., Pugh, W.H., Hadgraft, J., 1998. Effect of ion complexants on the iontophoresis of salbutamol. Int. J. Pharm. 167, 220–231.

Descamps, C., Cabrera, G., Depierreux, M., Devière, J., 2000. Acute Renal Insufficiency after colon cleansing. Endoscopy—Unusual Cases and Technical Notes, 02. http://www.thieme.de/endoscopy/02_00/uctn_03.html (November 01, 2004).

De Vos, A.M., Kinget, R., 1993. Study of the penetration-enhancing effect of two nonionic surfactants (cetiol HE and eumulgin B3) on human stratum corneum using differential scanning calorimetry. Eur. J. Pharm. Sci. 1, 89–93.

DiPiro, J.T., Michael, K.A., Clark, B.A., Dickson, P., Tedesco, F.J., 1986. Absorption of polyethylene glycol after administration of a PEG-electrolyte lavage solution. Clin. Pharm. 5, 153–155.

Donovan, M.D., Flynn, G.L., Amidon, G.L., 1990. The molecular weight dependence of nasal absorption. The effect of absorption enhancers. Pharm. Res. 7, 808–815.

Drotman, R.B., 1980. The absorption, distribution and excretion of alkylpolyethoxylates by rats and humans. Toxicol. Appl. Pharmacol. 52, 38–44.

Elder, R.L., 1983. Final report on the safety assessment of PEG-2, -6, -8, -12, -20, -32, -40, -50, -100, and -150 stearates. J. Am. College Toxicol. 2, 17–34.

Ema, M., Itami, T., Kawasaki, H., Kanoh, S., 1988. Teratology study of Tween 60 in rats. Drug Chem. Toxicol. 11, 249–260.

Erickson, T.B., Aks, S.E., Zabaneh, R., Reid, R., 1996. Acute renal toxicity after ingestion of Lava light liquid. Ann. Emerg. Med. 27, 781–784.

Fabregas, J.L., Cucala, J., Segua, J., Tarrus, E., 1986. Percutaneous absorption of piketoprofen in rabbits: effect of nonionic surface active agents. Farmaco Ed. Prat. 41, 177–183.

FAO/WHO, 1980. Evaluation of certain food additives. Twenty-third report of the joint FAO/WHO expert committee on food additives. World Health Organ Tech. Rep. Ser. No. 648.

Field, W.E.H., Roe, F.J.C., 1965. Tumor promotion in the forestomach epithelium of mice by oral administration of citrus oils. J. Natl. Cancer Inst. 35, 771–787.

Fisher, A.A., 1978. Immediate and delayed allergic contact reactions to polyethylene glycol. Contact Dermatitis 4, 135–138.

Fitzhugh, O.G., Schouboe, P.J., Nelson, A.A., 1960. Oral toxicities of lauric acid and certain lauric acid derivatives. Toxicol. Appl. Pharmacol. 2, 59–67.

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

Gallo, R., Basso, M., Voltolini, S., Guarrera, M., 2001. Allergic contact dermatitis from laureth-9 and polyquaternium-7 in a skincare product. Contact Dermatitis 45, 356–357.

Gesellschaft für Dermopharmazie (GD), 2001. Stellungnahme: Potential einer Penetrationsförderung durch Polyethylenglykol (PEG)-Verbindungen in Kosmetika. Mitteilungen der Gesellschaft für Dermopharmazie, 4 (in German).

Gottschewski, G.M., 1967. Kann die Trägersubstanz von Wirkstoffen in Dragees eine teratogene Wirkug haben? [Can carriers of active ingredients in coated tablets have teratogenic effects]. Arzneim. Forsch. 17, 1100–1103 (in German).

Grant, W.M. (Ed.), 1974. Toxicology of the Eye, 2nd ed. Charles C. Thomas, Springfield, IL, p. 845.

Guillot, J.P., Martini, M.C., Giauffret, J.Y., Gonnet, J.F., Guyot, J.Y., 1982. Safety evaluation of some humectants and moisturizers used in cosmetic formulations. Int. J. Cosmet. Sci. 4, 67–79. In: CIR (1993).

Gupta, U., Beaulieu, J., Chapin Hopper, J., Hagler, A.R., Hills-Perry, P., 1996. Teratogenic evaluation of alternative vehicles: PEG-400, cremophor, carboxy-methylcellulose; comparisons with methylcellulose. Teratology 53, 111.

Hamburger, R., Azaz, E., Donbrow, M., 1975. Autoxidation of polyoxyethyleneic non-ionic surfactants and of polyethylene glycols. Pharm. Acta Helv. 50, 10–17.

Harris, R.S., Sherman, H., Jetter, W.W., 1951. Nutritional and pathological effects of sorbitan monolaurate, polyoxyethylene sorbitan monolaurate, polyoxyethylene monolaurate, and polyoxyethylene monostearate when fed to rats. Arch. Biochem. Biophys. 34, 249–258.

Hatanaka, T., Shimoyama, M., Sugibayashi, K., Morimoto, Y., 1993. Effect of vehicle on the skin permeability of drugs: polyethylene glycol 400–water and ethanol–water binary solvents. J. Contr. Release 23, 247–260.

Heinemann, T., Axtmann, G., von Bergmann, K., 1993. Comparison of intestinal absorption of cholesterol and different plant sterols.in man. Eur. J. Clin. Invest. 23, 827–831.

Henkel Corp., 1995. Data on the PEGs soya sterol, unpublished data submitted toCTFA, April 22, 1996. In: CIR (2000a).

Henkel Corp., 1996. Toxicological tests on cetiol HE (PEG-7 glyceryl cocoate), unpublished data submitted toCTFA, April 22, 1996. In: CIR (1999a).

Henkel KGaA, 2004. VTF Human Safety Assessment Department, February 13, 2004, Personal communication.

Hermansky, S.J., Neptun, D.A., Loughran, K.A., Leung, H.W., 1995. Effects of polyethylene glycol 400 (PEG-400) following 13 weeks of gavage treatment in Fischer-344 rats. Fd. Chem. Toxicol. 33, 139–149.

Herold, D.A., Rodeheaver, G.T., Bellamy, W.T., Fitton, L.A., Bruns, D.E., Edlich, R.F., 1982. Toxicity of topical polyethylene glycol. Toxicol. Appl. Pharmacol. 65, 329–335.

Herold, D.A., Keil, K., Bruns, D.E., 1989. Oxidation of polyethylene glycols by alcohol dehydrogenase. Biochem. Phamacol. 38, 73–76.

Hill Top Research Inc., 1982/1983. Repeated insult patch test. 12J/25402-09 containing 1.0% PEG-8 (RI 0639), 13 pages and 12J/25402-16 containing 1.0% PEG-8 (RI 0639), unpublished data submitted toCTFA, 20 pp. In: CIR (1993).

Hoechst AG, 1978. In: MAK, 1995. Gesundheitschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten. VCH Verlagsgesellschaft, Weinheim, Germany (in German).

Hoechst AG, 1979. In: MAK, 1995. Gesundheitschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten, VCH Verlagsgesellschaft, Weinheim, Germany (in German).

Hoffmann-La Roche AG, 1979. In: MAK, 1995. Gesundheitschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten. VCH Verlagsgesellschaft, Weinheim, Germany (in German).

Hoffmann-La Roche AG, 1980. In: MAK, 1995. Gesundheitschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten. VCH Verlagsgesellschaft, Weinheim, Germany (in German).

Hoffmann-La Roche AG, 1982. In: MAK, 1995. Gesundheitschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten. VCH Verlagsgesellschaft, Weinheim, Germany (in German).

Hopper, S.S., Hulpieu, H.R., Cole, V.V., 1949. Some toxicological properties of surface-active agents. J. Am. Pharm. Assoc. 38, 428–432.

Industrieverband Körperpflege und Waschmittel e.V. (IKW), 2005. Frankfurt am Main, Personal communication.

International Nomenclature of Cosmetic Ingredients (INCI), 2005. http://pharmacos.eudra.org/F3/inci/index.htm (August 5, 2004).

Ivanchenko, O.B., Ilinskaya, O.N., Fattakhova, A.N., Skipina, I.M., Cherepneva, I.E., 1992. Assessment of the genotoxicity of non-ionogenic surfactants. Biol Nauki (Mosc) 0, 75–80 (in Russian).

Kadir, R., Tiemessen, H.I.G.M., Ponec, M., Junginger, H.E., Bocklé, H.E., 1993. Oleyl surfactant as skin penetration enhancers. Effect on human stratum corneum permeability and in vitro toxicity to cultured human skin cells. Drug Pharm. Sci. 59, 215–227.

Kallianos, A.G., Shelburne, F.A., Means, R.E., Stevensk, R.K., Lax, R.E., Mold, J.E., 1963. Identification of the D-glucosides of stigmasterol, sitosterol, and campesterol in tobacco and cigarette smoke. Biochem. J. 87, 596–600.

Kartashov, Belous, 1984. In: BIBRA (1990).

Kavlock, R.J., Short Jr., R.D., Chernoff, N., 1987. Further evaluation of an in vivo teratology screen. Teratog. Carcinog. Mutag. 7, 7–16.

Kimura, M., Kawada, A., 2000. Follicular contact dermatitis due to polyoxyethylene laurylether. J. Am. Acad. Dermatol. 42, 878–880.

Klonne, D.R., Dodd, D.E., Losco, P.E., Troup, C.M., 1989. Two-week inhalation study on polyethylene glycol (PEG) 3350 in F-344 rats. Drug Chem. Toxicol. 12, 39–48.

Krehl, W.A., Cogwell, G.R., Whedon, A.D., 1955. Non-deleterious effects of polyoxyethylene esters in the nutrition of rats and cats. J. Nutr. 55, 35–61.

Laillier, J., Plazonnet, B., Le Douarec, J.C., 1976. Evaluation of ocular irritation in the rabbit: development of an objective method of studying eye iritation. Proc. Eur. Soc. Toxicol. 17, 336–350 (Predict. Chronic. Toxic. Short Term Stud., Proc. Meet., 1975). In: CIR (1993).

Lanigan, R.S., 1999. Special report: reproductive and developmental toxicity of ethylene glycol and its ethers. Int. J. Toxicol. 18 (Suppl. 2), 53–67.

Leung, H.W., Ballantyne, B., 1998. Skin sensitization potential of polyethylene glycols evaluated in the guinea pig maximization test and the human repeat insult patch test. J. Toxicol. Cut. Ocular Toxicol. 17, 81–88.

Leung, H.W., Ballantyne, B., Hermansky, S.J., Frantz, S.W., 2000. Peroral subchronic, chronic toxicity and pharmacokinetic studies of a 100-kDa polymer of ethylene oxide (Polyox N-10) in the Fischer 344 rat. Int. J. Toxicol. 19, 305–312.

Lewis, R.W., Moxon, M.E., Botham, P.A., 1997. Evaluation of oral dosing vehicles for use in developmental toxicity studies in the rat and rabbit. Toxicologist 36 (1 Pt. 2), 259–260.

Luduena, F.P., Fellows, J.K., Laqueur, G.L., Driver, R.C., 1947. Toxicity of polyethylene glycols by repeated epidermal applications. J. Ind. Hyg. Toxicol. 29, 390–392.

Maibach, H.I., 1975. Polyethyleneglycol: allergic contact dermatitis potential. Contact Dermatitis 1, 247.

Marshall, T.C., 1982. Dose-dependent disposition of ethylene glycol in the rat after intravenous administration. J. Toxicol. Environ. Health 10, 397–409.

Martinez, T.T., Brown, K., 1991. Oral and pulmonary toxicology of the surfactant used in roundup herbicide. Proc. West Pharmacol. Soc. 34, 43–46.

Marzulli, F.N., Ruggles, D.I., 1973. Rabbit eye irritation test: collaborative study. J. Ass. Off. Anal. Chem. 56, 905–914.

Matthews, J.M., Parker, M.K., Matthews, H.B., 1991. Metabolism and disposition of diethylene glycol in the rat and dog. Drug Metab. Dispos. 19, 1066–1070.

Mellon Institute, 1956. Gross results of 90-day feeding of Carbowax compound 20-M to rats and of 30-dose rabbit inunction and single skin penetration of 20-M and Carbowax compound 4000, unpublished data. In: CIR (1993).

Mitchell, A.D., Auletta, A.E., Clive, D., Kirby, P.E., Moore, M.M., Myhr, B.C., 1997. The L5178Y/tk+/− mouse lymphoma specific gene and chromosomal mutation assay, a phase III report of the U.S. Environmental Protection Agency Gene-Tox Program. Mutat. Res. 394, 177–303.

Monteiro-Riviere, N.A., Inman, A., Jackson, H., Cunn, B., Dimond, S., 2001. Efficacy of topical phenol decontamination strategies on severity of acute phenol chemical burns and dermal absorption: in vitro and in vivo studies in pig skin. Toxicol. Ind. Health 17, 95–104.

Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B., Zeiger, E., 1986. Salmonella mutagenicity tests. II. Results from the testing of 270 chemicals. Environ. Mutagen. 8 (Suppl. 7), 1–119.

Nishimura, O.A., 1993. Case of allergic contact dermatitis in polyoxyethylene oleylether of the Myser® ointment. Skin Res. 225 (Suppl. 16), 265–269 (in Japanese).

Nishiyama, T., Iwata, Y., Nakajima, K., Mitsui, T., 1983. In vivo percutaneous absorption of polyoxyethylene lauryl ether surfactants in hairless mice. J. Soc. Cosmet. Chem. 34, 263–271.

North American Science Associates Inc., 1987. Ocular irritation test and primary skin irritation test in the rabbit of liquid eyeliner formula no. 2506-130, unpublished data submitted toCTFA, January 5, 1996. In: CIR (2000a).

National Toxicology Program (NTP), 1992a. TR-415. Toxicology and carcinogenesis studies of polysorbate 80 (CAS No. 9005-65-6) in F344/N rats and B6C3F1 mice (feed studies), 1992.

National Toxicology Program (NTP), 1992b. Final report on the developmental toxicity of polyoxyethylene sorbitan monolaurate (CAS-No. 9005-64-5) in Sprague–Dawley CD® rats on gestational days 6 through 15. NTIS No. PB93-123800.

National Toxicology Program (NTP), 2004. TR-264. Ethoxylated dodecyl alcohol. http://ntp-server.niehs.nih.gov/htdocs/LT-Studies/tr264.html (August 5, 2004).

Olson, C.T., Feder, P.I., Hobson, D.W., Kiser, R.C., Joiner, R.L., 1991. Evaluation of compounds as barriers to dermal penetration of organophosphates using acetylcholinesterase inhibition. Toxicol. Lett. 55, 325–334.

Pazzaglia, M., Vincenti, C., Spiller, M., Tosti, A., 1995. Contact sensitivity to Atlas G-1441. Contact Dermatitis 33, 208.

Prentice, D.E., Majeed, S.K., 1978. Toxicol. Lett. 2, 119–122. In: FAO/WHO, 1973. Joint FAO/WHO Expert Committee on Food Additives. Polyethylene glycols. WHO Food Additives Series No. 14.

Principe, A.H., 1968. Polyethylene glycols. Studies of absorption, excretion, retention, and identification. J. Forencsic Sci. 13, 90–113.

Putman, D.L., Gudi, R., 1995. Unpublished data. In: Leung et al. (2000).

Qiu, H., McCall, J.W., Won Jun, H., 1998. Formulation of topical insect repellent *N*,*N*-diethyl-*m*-toluamide (DEET): vehicle effects on DEET in vitro skin permeation. Int. J. Pharm. 163, 167–176.

Ring, J., Fröhlich, H.H. (Eds.), 1985. Wirkstoffe in der Dermatologischen Therapie, 2nd ed. Springer Verlag, Berlin, p. 182 (in German).

Roe, F.J.C., 1970. In: BIBRA (1990).

Sarpotdar, P.P., Gaskill, J.L., Giannini, R.P., 1986. Effect of polyethylene glycol 400 on the penetration of drugs through human cadaver skin in vitro. J. Pharm. Sci. 75, 26–28.

Schladt, L., Ivens, I., Karbe, E., Ruehl-Fehlert, C., Bomhard, E., 1998. Subacute oral toxicity of tetraethylene glycol and ethylene glycol administered to Wistar rats. Exp. Toxicol. Pathol. 50, 257–265.

Schutz, E., 1958. Effect of polyethyleneglycol 400 on the percutaneous absorption of active ingredients. Archiv für Experimentelle Pathologie und Pharmakologie 232, 237–238 (in German).

Shaffer, C.B., Critchfield, F.H., 1947. The absorption and excretion of the solid polyethylene glycols (carbowax compounds). J. Am. Pharm. Assoc. Sci. Ed. 36, 152–157.

Shaffer, C.B., Critchfield, F.H., Nair III, J.H., 1950. The absorption and excretion of a liquid polyethylene glycol. J. Am. Pharm. Assoc. Sci. Ed. 39, 340–344.

Shelby, M.D., Erexson, G.L., Hook, G.J., Tice, R.R., 1993. Evaluation of a three-exposure mouse bone marrow micronucleus protocol: Results with 49 chemicals. Environ. Mol. Mutagen. 21, 160–179.

Siegel, I.A., Gordon, H.P., 1985. Effects of surfactants on the permeability of canine oral mucosa in vitro. Toxicol. Lett. 26, 153–157.

Siegel, I.A., Gordon, H.P., 1986. Surfactant-induced alterations of permeability of rabbit oral mucosa in vitro. Exp. Mol. Pathol. 44, 132–137.

Slesinski, R.S., et al., 1989. Genotoxicity of tetraethylene glycol evaluated with multiple in vitro and in vivo assays. Toxicologist 9, 232.

Smyth Jr., H.F., Carpenter, C.P., Shaffer, C.B., Seaton, J., Fischer, L., 1942. Some pharmacological properties of polyethylene glycols of high molecular weight ("carbowax" compounds). J. Ind. Hyg. Toxicol. 24, 281–284.

Smyth Jr., H.F., Carpenter, C.P., Shaffer, C.B., 1945. The subacute toxicity and irritation of polyethylene glycols of approximate molecular weights of 200, 300 and 400. J. Am. Pharm. Assoc. 34, 172–174.

Smyth Jr., H.F., Carpenter, C.P., Shaffer, C.B., 1947. The toxicity of high molecular weight polyethylene glycols: chronic oral and parenteral administration. J. Am. Pharm. Assoc. Sci. Ed. 36, 157–160.

Smyth Jr., H.F., Carpenter, C.P., Weil, C.S., 1950. The toxicology of the polyethylene glycols. J. Am. Pharm. Assoc. 39, 349–354.

Smyth Jr., H.F., Carpenter, C.P., Weil, C.S., 1955. The chronic oral toxicology of the polyethylene glycols. J. Am. Pharm. Assoc. Sci. Ed. 44, 27–30.

Smyth Jr., H.F., Weil, C.S., King, J.M., Knaak, J.B., Sullivan, L.J., Carpenter, C.P., 1979. Oral toxicity and excretion of four commercial polyoxyalkylene glycol compounds. Toxicol. Appl. Pharmacol. 16, 675–680.

Soehring, K., Scriba, K., Frahm, M., Zoellner, G., 1951. Beiträge zur Pharmakologie der Alkyl-Polyäthylenoxydderivate. I. Untersuchungen über die akute und subchronische Toxizität bei verschiedenen Tierarten. Arch. Int. Pharmacodyn. 87 (3), 301–320 (in German).

Soehring, K., Frahm, M., Mletzko, K., 1952. Beiträge zur Pharmakologie der Alkyl-Polyäthylenoxydderivate. IV. Lokalanalgetische Wirkungen und Bemerkungen zur vergleichenden Auswertung leitungshemmender Substanzen. Arch. Int. Pharmacodyn. 91, 112 (in German).

Spezia, F., Julien, P., Fournex, R., Vannier, B., 1992. In vitro dysmorphogenic effects of PEG-200 on rat whole-embryo cultures in relation to the species origin of the metabolic activating system used. Teratology 46, 28A.

Starke, W.C., Pellerin, R.J., 1981. Oral toxicity and teratogenicity of PEG-200 and N-butyl mercaptan in rats. ARCSL-TR-81029. Aberdeen Proving Ground, Chemical Systems Laboratory, Maryland. In: Organisation for Economic Co-operation and Development (OECD), 2004. Screening Information Data Set (SIDS) for Ethylene Glycol (Draft).

Svensson, A., 1988. Allergic contact dermatitis to laureth-4. Contact Dermatitis 18, 113–114.

Tusing, T.W., Elsea, J.R., Saureur, A.B., 1954. The chronic dermal toxicity of a series of polyethylene glycols. J. Am. Phamr. Assoc. 43, 489–490.

Ulrich, C.E., Geil, R.G., Tyler, T.R., Kennedy Jr., G.L., 1992. Two-week aerosol inhalation study in rats of ethylene oxide/propylene oxide copolymers. Drug Chem. Toxicol. 15, 13–31.

Union Carbide, 1965. In: 23rd Report of the Joint FAO/WHO Expert Committee on Food Additives, 1980. Techn. Rep. Ser., No. 648. World Health Organization, Geneva, pp. 76–83.

Union Carbide, 1978. In: MAK, 1995. Gesundheitschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten. VCH Verlagsgesellschaft, Weinheim, Germany (in German).

Union Carbide, 1987. In: MAK, 1995. Gesundheitschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten. VCH Verlagsgesellschaft, Weinheim, Germany (in German).

Union Carbide, 1988. In: MAK, 1995. Gesundheitschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten. VCH Verlagsgesellschaft, Weinheim, Germany (in German).

Uter, W., Geier, J., Fuchs, Th., 2000. Kontaktsensibilisierung gegen Polidocanol. Allergologie 23, 475–480 (in German).

Valia, K.H., Chien, Y.W., Shinal, E.C., 1984. Long-term skin permeation kinetics of estradiol (1): effects of drug solubilizer—polyethylene glycol 400. Drug Dev. Ind. Pharm. 10, 951–981.

Vannier, B., Bremaud, R., Benicourt, M., Julien, P., 1989. Teratogenic effect of polyethylene glycol 200 in the mouse but not in the rat. Teratology 40, 302.

Wagner, V.O., Sly, E., 1995. Unpublished data. In: Leung et al. (2000).

Wangenheim, J., Bolcsfoldi, G., 1988. Mouse lymphoma L5178Y thymidine kinase locus assay of 50 compounds. Mutagenesis 3, 193–205.

Warf Institute Inc., 1974. Oral LD50, skin irritation and eye irritation of the PEGs Soy Sterol. (Henkel Corp.). Unpublished data submitted to CTFA, April 22, 1996. In: CIR (2000a).

Warheit, D.R., Fogle, H., Thomas, W.C., Murphy, S.R., Tyler, T.R., Reinhold, R.W., Kennedy Jr., G.L., 1995. Pulmonary toxicity assessments of inhaled ethylene oxide propylene oxide copolymer lubricants in rats. Inhal. Toxicol. 7, 377–392.

Weil, C.S., Smyth Jr., H.F., 1956. In: British Industrial Biological Research Association (BIBRA), 1991. Toxicity profile: polyethylene glycol 300. BIBRA International, Carshalton, Surrey, UK.

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K., Speck, W., 1987. Salmonella mutagenicity tests. III. Results from the testing of 255 chemicals. Environ. Mutagen. Suppl. 9, 1–110.

Zipf, H.F., Wetzels, E., Ludwig, H., Friedrich, M., 1957. Allgemein und lokal toxische Wirkungen von Dodexylpolyethylenoxydethern. Arzneim. Forschung 7, 162 (in German).