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PHARMACEUTICAL RESEARCH AND DEVELOPMENT

Proposta n.º P135B13

Estudo de estabilidade e realização de trâmites legais necessários à colocação de produtos cosméticos no mercado no âmbito do projeto "EURORREGIAO TERMAL E DA AGUA" (0504_EUROREGION_TERMAL_AGUA_1_E)

Promotor:

Município de Chaves

Outubro 2015

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PROGRAMA COOPERACIÓN TRANSFRONTERIZA ESPAÑA - PORTUGAL COOPERAÇÃO TRANSFRONTEIRIÇA 2007 - 2013

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PHARMACEUTICAL RESEARCH AND DEVELOPMENT

Relatório Final FR01A/P135B13

Avaliação da eficácia do sistema conservante de um produto cosmético (Challenge Test) – Creme de mãos

Promotor:

Município de Chaves

Julho 2015

A informação contida neste relatório é confidencial e não será divulgada, na totalidade ou em parte, sem o devido consentimento prévio do promotor.

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Relatório Elaborado/~~Alterado~~ por:

INOVAPOTEK

Liliana Ferraz, responsável pela elaboração/~~alteração~~ do relatório

Data: 01/07/2015

Relatório Aprovado por:

INOVAPOTEK

Marta Ferreira, Diretor do Estudo

Data: 02/07/2015

PROMOTOR (quando aplicável)

Nome do responsável

_____ Data:_____

Relatório Verificado por:

INOVAPOTEK

Yogeeta Rocha, responsável pela Qualidade

Data: 02/07/2015

HISTÓRICO DE ALTERAÇÕES

Revisão	Alteração	Data
00	Primeira versão	02/07/2015

1 – Identificação do estudo

Proposta n.	P135B13
Relatório n.	FR01A/P135B13
Título	Avaliação da eficácia do sistema conservante de um produto cosmético (Challenge Test) – Creme de mãos
Data Início do Estudo	10/07/2014
Data Início da análise	-
Data Conclusão da análise	-
Data Conclusão do Estudo	-
Data do Relatório	02/07/2015

Identificação das substâncias e produtos em estudo e de referência (quando aplicável)

Designação comercial do produto em estudo	Tipo de formulação	Princípio activo (quando aplicável)	Observações
Creme mãos	Emulsão	-	Número de lote: L530061

Designação da(s) substância(s) em estudo	Denominação IUPAC	Número CAS	Parâmetros Biológicos
-	-	-	-

Designação da(s) substância(s) de referência	Denominação IUPAC	Número CAS	Parâmetros Biológicos
-	-	-	-

2 – Identificação dos responsáveis pelo Estudo

Promotor	Município de Chaves
	Câmara Municipal de Chaves Praça de Camões, 5400-150 Chaves
Proponente	INOVAPOTEK, Pharmaceutical Research and Development Lda
	UPTEC, Parque de Ciência e Tecnologia da Universidade do Porto Rua Alfredo Allen, n.º 455/461 4200-135 Porto – PORTUGAL
Director do Estudo	Marta Ferreira
Técnico(s) de Laboratório(s)	Liliana Ferraz
	Responsável pelo envio das amostras para o laboratório subcontratado e elaboração dos relatórios
Local(is) de Ensaio	Labfit. Health Products Research and Development Av. Infante D. Henrique. Fac. Ciências da Saúde. Piso 0 6200-506 Covilhã

3 – Relatório do Estudo

3.1 Introdução

O objetivo deste estudo foi avaliar a eficácia do Sistema de conservantes de um produto cosmético através de um teste de eficácia de conservantes de acordo com a Farmacopeia Europeia 8.0.

3.2 Materiais e métodos

Materiais

Neutralizante: Água peptonada tamponada (Prolabo, França) aditivada de polissorbato 80 (Prolabo, França) a 3%, lecitina de soja (Prolabo, França) a 0.3%, saponinas (Prolabo, França) a 3% e Triton X100 (Prolabo, França) a 0.1%

Diluente: Água peptonada tamponada (Prolabo, França)

Meios de cultura utilizados:
Saboraud dextrose agar (SDA), Prolabo, França
Potato dextrose agar (PDA), Prolabo, França
Tryptic soy agar (TSA), Prolabo, França

Microrganismos incluídos no ensaio e condições de incubação:
Staphylococcus aureus ATCC 6538 - 35º C, 2 dias
Pseudomonas aeruginosa ATCC 9027 - 35º C, 2 dias
Candida albicans ATCC 10231 - 25º C, 2 dias
Aspergillus brasiliensis ATCC 16404 - 25º C, 5 dias

Condições de embalagem e acondicionamento:
Até início do teste, a amostra é armazenada na embalagem original à temperatura ambiente (22 °C) e ao abrigo da luz. Quando em teste, a amostra é acondicionada em tubos com tampas de rosca à temperatura ambiente (22 °C) e ao abrigo da luz.

Métodos

Qualidade microbiológica da amostra

A elegibilidade da amostra para inclusão no ensaio é avaliada com base na conformidade da sua qualidade microbiológica, segundo os critérios definidos na monografia 5.1.4 da Farmacopeia Europeia 8.0 e de acordo com o tipo de amostra testada.

Validação das condições do ensaio para a amostra em estudo:

A amostra foi diluída no neutralizante selecionado e inoculada individualmente com concentração conhecida dos microrganismos em estudo. A capacidade de recuperação de cada um dos microrganismos na amostra foi avaliada após incorporação de uma alíquota no meio de cultura apropriado e comparada com a recuperação dos mesmos no neutralizante na ausência da amostra. Foi realizada a verificação da qualidade microbiológica do produto de modo a garantir que esta não invalidava os resultados do ensaio.

Teste de eficácia de conservantes:

- Norma: Farmacopeia Europeia 8.0

- Princípio do método: A avaliação da capacidade conservante de uma formulação cosmética é baseada na inoculação da formulação com uma suspensão calibrada de microrganismos definidos. O número de microrganismos viáveis é determinado em intervalos definidos, ao longo de 28 dias de ensaio. Os microorganismos e intervalos seleccionados estão de acordo com a norma referenciada.

- Critérios de aceitação:

O sistema de conservantes da formulação é adequado se, nas condições do teste, se verifica um decréscimo ou estabilização, como apropriado, no número de microorganismos da solução inoculada após o período de ensaio descrito na norma referenciada.

Em cada momento e para cada microrganismo é calculada a redução logarítmica do seu crescimento e comparada com os requisitos mínimos presentes na tabela 1.

Tabela 1: Critérios de aceitação do teste de eficácia de conservantes de acordo com a Farmacopeia Europeia 8.0

Valores de redução logarítmica ($R_x = lg_{N0} - lg_{Nx}$) [a]

Microrganismos	**Bactérias**				**Fungos**			
Tempo de análise	T2 dias	T7 dias	T14 dias	T28 dias	T2 dias	T7 dias	T14 dias	T28 dias
Critério A	2	3	NR[d]	s/A[b]	NR	NR	2	s/A
Critério B	NR	NR	3	s/A	NR	NR	1	s/A

[a] Neste teste é aceitável uma variação de 0.5 log no valor de redução logarítmica para efeitos de classificação do produto.

[b] S/A - sem aumento no nº UFC relativamente à contagem no tempo anterior

[c] R_x=0 quando lg_{N0}= lg_{Nx} (sem aumento a partir da contagem inicial)

[d] NR – não realizado

UFC – unidades formadoras de colónias

Produtos que cumpram o critério A apresentam o melhor perfil de redução logarítmica ao longo do tempo.

Produtos que cumpram o critério B apresentam um perfil de redução da carga microbiana aceitável se ao produto estiverem associados outros factores de controlo que indiquem que o risco microbiológico é tolerável para o produto cosmético em estudo.

- Inoculação da formulação para o ensaio: O produto foi inoculado separadamente com cada um dos microrganismos em teste, na proporção de 200 µL de suspensão celular calibrada para 20 g de produto. A inoculação foi realizada através da técnica de contagem "Pour Plate".

3.3. Resultados

Qualidade microbiológica da amostra:

A qualidade microbiológica da amostra foi verificada e confirmou-se que esta cumpre as especificações para produtos de aplicação tópica (contagem de aeróbios totais ≤ 10^2 UFC/ml ou g de produto e contagem de fungos-leveduras totais ≤10^1 UFC/ml ou g de produto).

Validação das condições do ensaio:

As concentrações de inóculo para cada microrganismo estão apresentadas na tabela 2 e a eficácia do neutralizante utilizado é evidenciada na Tabela 3.

Tabela 2: Concentração da suspensão calibrada para cada microrganismo e respectiva concentração na amostra após inoculação no início do ensaio (UFC/mL)

Microrganismos	Suspensão calibrada	Concentração inóculo na amostra	Recomendação para a concentração do inoculo na amostra
S. aureus ATCC 6538	8,25E+07	8,25E+05	10^5- 10^6
P. aeruginosa ATCC 9027	1,24E+08	1,24E+06	10^5- 10^6
C. albicans ATCC 10231	1,90E+07	1,90E+05	10^4- 10^5
A. brasiliensis ATCC 16404	7,15E+06	7,15E+04	10^4- 10^5

Tabela 3: Teste da eficácia do neutralizante - Recuperação dos microrganismos na amostra diluída em neutralizante (Amostra) e no neutralizante puro (Controlo).

Microrganismos	Amostra (UFC/mL)	Controlo (UFC/mL)	50% Controlo (UFC/mL)
S. aureus ATCC 6538	74	98	49
P. aeruginosa ATCC 9027	113	146	73
C. albicans ATCC 10231	175	206	103
A. brasiliensis ATCC 16404	97	94	47

Verificou-se que o neutralizante é eficaz na neutralização do conservante desta formulação, visto que a recuperação dos microrganismos a partir da amostra neutralizada é maior ou igual a 50% do valor de UFC recuperado a partir do controlo (neutralizante puro). A comprovação da inocuidade do neutralizante utilizado, para cada um dos microrganismos testados, foi realizada em controlo interno do laboratório.

Teste de eficácia de conservantes:

Os resultados do ensaio são apresentados na Tabela 4 e Gráfico 1.

Tabela 4: Contagens de unidades formadoras de colónias (UFC) e respectiva variação logarítmica (Δlog) tendo por referência a concentração do inóculo inicial na amostra

Microrganismos	**2 dias (UFC)**	**2 dias (Δlog)**	**7 dias (UFC)**	**7 dias (Δlog)**	**14 dias (UFC)**	**14 dias (Δlog)**	**28 dias (UFC)**	**28 dias (Δlog)**	**Critério**
S. aureus ATCC 6538	1,47E+03	2,75	0	5,92; s/A	0	5,92; s/A	0	5,92; s/A	A
P. aeruginosa ATCC 9027	0	6,09	0	6,09; s/A	0	6,09; s/A	0	6,09; s/A	A
C. albicans ATCC 10231	---	---	---	---	0	5,28; s/A	0	5,28; s/A	A
A. brasiliensis ATCC 16404	---	---	---	---	1,50E+03	1,68	0	4,85; s/A	B

s/A – sem aumento no nº de UFC em comparação com leitura anterior

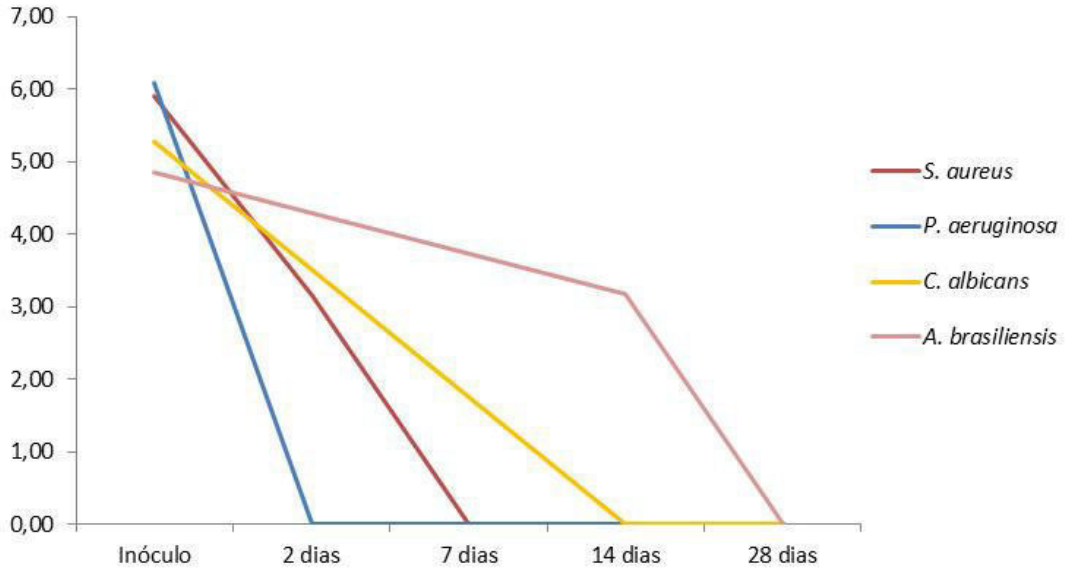

Gráfico 1: Valores de logaritmo de unidades formadoras de colónias (UFC) para os quatro microrganismos incluídos no teste no inóculo inicial (concentração na amostra) e na amostra em estudo ao longo do tempo.

Para *Staphylococcus aureus* o produto está conforme o critério A já que se verifica uma redução logarítmica de 2,75 após 2 dias de teste, uma redução logarítmica de 5,92 após 7 dias de teste e nenhum aumento após 14 e 28 dias.
Para *Pseudomonas aeruginosa*, o produto cumpre os requisitos do critério A já que se verifica uma redução logarítmica de 6,09 após 2 dias de teste e nenhum aumento após 7, 14 e 28 dias.
Para *Candida albicans* s, o produto cumpre o critério A já que se verifica uma redução logarítmica de 5,28 após 14 dias de teste e nenhum aumento após 28 dias.
Para *Aspergillus brasiliensis*, o produto cumpre o critério B já que se verifica uma redução logarítmica de 1,68 após 14 dias de teste e nenhum aumento após 28 dias.

3.4 Conclusão

O estudo realizado na amostra do produto cosmético "Creme de Mãos" permite concluir que o referido produto cumpre os requisitos do critério B de proteção do produto contra a proliferação microbiana de acordo com a Farmacopeia Europeia 8.0.

4 – Arquivo

Os documentos e registos associados ao estudo serão arquivados na inovapotek durante 10 anos.

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PHARMACEUTICAL RESEARCH AND DEVELOPMENT

Relatório Final FR02A/P135B13

Avaliação da eficácia do sistema conservante de um produto cosmético – Creme de rosto

Promotor:
Município de Chaves

Julho 2015

A informação contida neste relatório é confidencial e não será divulgada, na totalidade ou em parte, sem o devido consentimento prévio do promotor.

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Relatório Elaborado/~~Alterado~~ por:

INOVAPOTEK

Liliana Ferraz, responsável pela elaboração/~~alteração~~ do relatório

Data: 02/07/2015

Relatório Aprovado por:

INOVAPOTEK

Marta Ferreira, Diretor do Estudo

Data: 02/07/2015

PROMOTOR (quando aplicável)

Nome do responsável

_____ Data:_____

Relatório Verificado por:

INOVAPOTEK

Yogeeta Rocha, responsável pela Qualidade

Data: 02/07/2015

HISTÓRICO DE ALTERAÇÕES

Revisão	Alteração	Data
00	Primeira versão	02/07/2015

1 – Identificação do estudo

Proposta n.	P135B13
Relatório n.	FR02A/P135B13
Título	Avaliação da eficácia do sistema conservante de um produto cosmético – Creme de rosto
Data Início do Estudo	10/07/2014
Data Início da análise	-
Data Conclusão da análise	-
Data Conclusão do Estudo	-
Data do Relatório	02/07/2015

Identificação das substâncias e produtos em estudo e de referência (quando aplicável)

Designação comercial do produto em estudo	Tipo de formulação	Princípio activo (quando aplicável)	Observações
Creme Rosto	Emulsão	-	Número de lote: L530060

Designação da(s) substância(s) em estudo	Denominação IUPAC	Número CAS	Parâmetros Biológicos
-	-	-	-

Designação da(s) substância(s) de referência	Denominação IUPAC	Número CAS	Parâmetros Biológicos
-	-	-	-

2 – Identificação dos responsáveis pelo Estudo

Promotor	Município de Chaves
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Director do Estudo	Marta Ferreira
Técnico(s) de Laboratório(s)	Liliana Ferraz
	Responsável pelo envio das amostras para o laboratório subcontratado e elaboração dos relatórios
Local(is) de Ensaio	Labfit. Health Products Research and Development Av. Infante D. Henrique. Fac. Ciências da Saúde. Piso 0 6200-506 Covilhã

3 – Relatório do Estudo

3.1 Introdução

O objetivo deste estudo foi avaliar a eficácia do Sistema de conservantes de um produto cosmético através de um teste de eficácia de conservantes de acordo com a Farmacopeia Europeia 8.0.

3.2 Materiais e métodos

Materiais

Neutralizante: Água peptonada tamponada (Prolabo, França) aditivada de polissorbato 80 (Prolabo, França) a 3%, lecitina de soja (Prolabo, França) a 0.3%, saponinas (Prolabo, França) a 3% e Triton X100 (Prolabo, França) a 0.1%

Diluente: Água peptonada tamponada (Prolabo, França)

Meios de cultura utilizados:
Saboraud dextrose agar (SDA), Prolabo, França
Potato dextrose agar (PDA), Prolabo, França
Tryptic soy agar (TSA), Prolabo, França

Microrganismos incluídos no ensaio e condições de incubação:
Staphylococcus aureus ATCC 6538 - 35º C, 2 dias
Pseudomonas aeruginosa ATCC 9027 - 35º C, 2 dias
Candida albicans ATCC 10231 - 25º C, 2 dias
Aspergillus brasiliensis ATCC 16404 - 25º C, 5 dias

Condições de embalagem e acondicionamento:
Até início do teste, a amostra é armazenada na embalagem original à temperatura ambiente (22 °C) e ao abrigo da luz. Quando em teste, a amostra é acondicionada em tubos com tampas de rosca à temperatura ambiente (22 °C) e ao abrigo da luz.

Métodos

Qualidade microbiológica da amostra

A elegibilidade da amostra para inclusão no ensaio é avaliada com base na conformidade da sua qualidade microbiológica, segundo os critérios definidos na monografia 5.1.4 da Farmacopeia Europeia 8.0 e de acordo com o tipo de amostra testada.

Validação das condições do ensaio para a amostra em estudo:

A amostra foi diluída no neutralizante selecionado e inoculada individualmente com concentração conhecida dos microrganismos em estudo. A capacidade de recuperação de cada um dos microrganismos na amostra foi avaliada após incorporação de uma alíquota no meio de cultura apropriado e comparada com a recuperação dos mesmos no neutralizante na ausência da amostra. Foi realizada a verificação da qualidade microbiológica do produto de modo a garantir que esta não invalidava os resultados do ensaio.

Teste de eficácia de conservantes:

- Norma: Farmacopeia Europeia 8.0

- Princípio do método: A avaliação da capacidade conservante de uma formulação cosmética é baseada na inoculação da formulação com uma suspensão calibrada de microrganismos definidos. O número de microrganismos viáveis é determinado em intervalos definidos, ao longo de 28 dias de ensaio. Os microorganismos e intervalos seleccionados estão de acordo com a norma referenciada.

- Critérios de aceitação:

O sistema de conservantes da formulação é adequado se, nas condições do teste, se verifica um decréscimo ou estabilização, como apropriado, no número de microorganismos da solução inoculada após o período de ensaio descrito na norma referenciada.

Em cada momento e para cada microrganismo é calculada a redução logarítmica do seu crescimento e comparada com os requisitos mínimos presentes na tabela 1.

Tabela 1: Critérios de aceitação do teste de eficácia de conservantes de acordo com a Farmacopeia Europeia 8.0

Valores de redução logarítmica ($R_x = lg_{N0} - lg_{Nx}$) [a]

Microrganismos	**Bactérias**				**Fungos**			
Tempo de análise	T2 dias	T7 dias	T14 dias	T28 dias	T2 dias	T7 dias	T14 dias	T28 dias
Critério A	2	3	NR[d]	s/A[b]	NR	NR	2	s/A
Critério B	NR	NR	3	s/A	NR	NR	1	s/A

[a] Neste teste é aceitável uma variação de 0.5 log no valor de redução logarítmica para efeitos de classificação do produto.

[b] S/A - sem aumento no nº UFC relativamente à contagem no tempo anterior

[c] R_x=0 quando lg_{N0}= lg_{Nx} (sem aumento a partir da contagem inicial)

[d] NR – não realizado

UFC – unidades formadoras de colónias

Produtos que cumpram o critério A apresentam o melhor perfil de redução logarítmica ao longo do tempo.

Produtos que cumpram o critério B apresentam um perfil de redução da carga microbiana aceitável se ao produto estiverem associados outros factores de controlo que indiquem que o risco microbiológico é tolerável para o produto cosmético em estudo.

- Inoculação da formulação para o ensaio: O produto foi inoculado separadamente com cada um dos microrganismos em teste, na proporção de 200 µL de suspensão celular calibrada para 20 g de produto. A inoculação foi realizada através da técnica de contagem "Pour Plate".

3.3. Resultados

Qualidade microbiológica da amostra:

A qualidade microbiológica da amostra foi verificada e confirmou-se que esta cumpre as especificações para produtos de aplicação tópica (contagem de aeróbios totais ≤ 10^2 UFC/ml ou g de produto e contagem de fungos-leveduras totais ≤10^1 UFC/ml ou g de produto).

Validação das condições do ensaio:

As concentrações de inóculo para cada microrganismo estão apresentadas na tabela 2 e a eficácia do neutralizante utilizado é evidenciada na Tabela 3.

Tabela 2: Concentração da suspensão calibrada para cada microrganismo e respectiva concentração na amostra após inoculação no início do ensaio (UFC/mL)

Microrganismos	Suspensão calibrada	Concentração inóculo na amostra	Recomendação para a concentração do inoculo na amostra
S. aureus ATCC 6538	8,25E+07	8,25E+05	10^5- 10^6
P. aeruginosa ATCC 9027	1,24E+08	1,24E+06	10^5- 10^6
C. albicans ATCC 10231	1,90E+07	1,90E+05	10^4- 10^5
A. brasiliensis ATCC 16404	7,15E+06	7,15E+04	10^4- 10^5

Tabela 3: Teste da eficácia do neutralizante - Recuperação dos microrganismos na amostra diluída em neutralizante (Amostra) e no neutralizante puro (Controlo).

Microrganismos	Amostra (UFC/mL)	Controlo (UFC/mL)	50% Controlo (UFC/mL)
S. aureus ATCC 6538	67	98	49
P. aeruginosa ATCC 9027	138	146	73
C. albicans ATCC 10231	188	206	103
A. brasiliensis ATCC 16404	93	94	47

Verificou-se que o neutralizante é eficaz na neutralização do conservante desta formulação, visto que a recuperação dos microrganismos a partir da amostra neutralizada é maior ou igual a 50% do valor de UFC recuperado a partir do controlo (neutralizante puro). A comprovação da inocuidade do neutralizante utilizado, para cada um dos microrganismos testados, foi realizada em controlo interno do laboratório.

Teste de eficácia de conservantes:

Os resultados do ensaio são apresentados na Tabela 4 e Gráfico 1.

Tabela 4: Contagens de unidades formadoras de colónias (UFC) e respectiva variação logarítmica (Δlog) tendo por referência a concentração do inóculo inicial na amostra

Microrganismos	**2 dias (UFC)**	**2 dias (Δlog)**	**7 dias (UFC)**	**7 dias (Δlog)**	**14 dias (UFC)**	**14 dias (Δlog)**	**28 dias (UFC)**	**28 dias (Δlog)**	**Critério**
S. aureus ATCC 6538	4,72E+05	0,24	4,46E+04	1,27; s/A	0	5,92; s/A[a]	0	5,92; s/A	B
P. aeruginosa ATCC 9027	0	6,09	0	6,09; s/A	0	6,09; s/A	0	6,09; s/A	A
C. albicans ATCC 10231	---	---	---	---	0	5,28; s/A	0	5,28; s/A	A
A. brasiliensis ATCC 16404	---	---	---	---	0	4,85	0	4,85; s/A	A

s/A – sem aumento no nº de UFC em comparação com leitura anterior

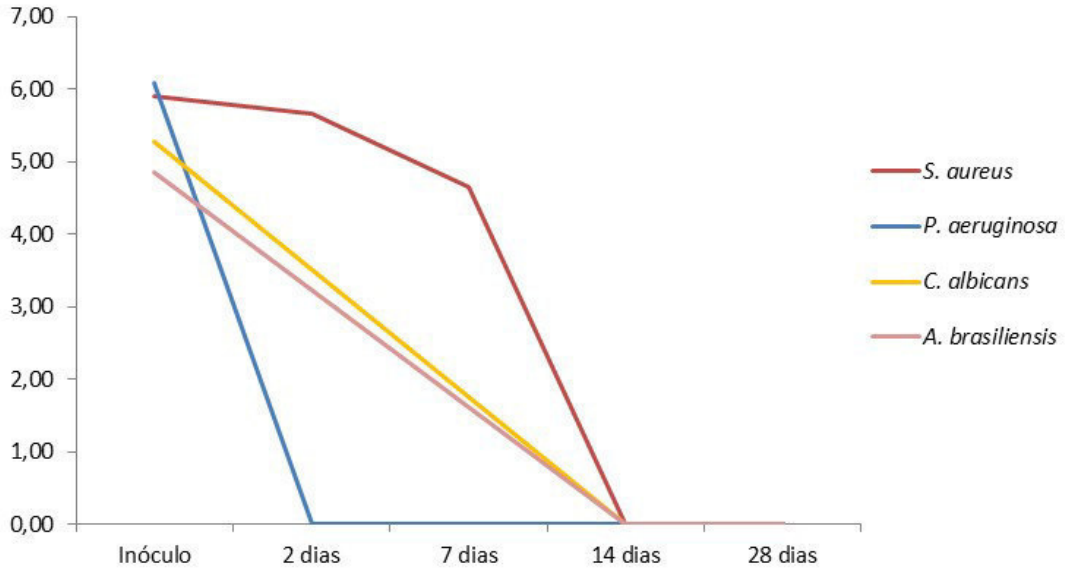

Gráfico 1: Valores de logaritmo de unidades formadoras de colónias (UFC) para os quatro microrganismos incluídos no teste no inóculo inicial (concentração na amostra) e na amostra em estudo ao longo do tempo.

Para *Staphylococcus aureus*, o produto cumpre o critério B já que se verifica uma redução logarítmica de 5,92 após 14 dias de teste e nenhum aumento após 28 dias.
Para *Pseudomonas aeruginosa*, o produto cumpre os requisitos do critério A já que se verifica uma redução logarítmica de 6,09 após 2 dias de teste e nenhum aumento após 7, 14 e 28 dias.
Para *Candida albicans*, o produto cumpre o critério A já que se verifica uma redução logarítmica de 5,28 após 14 dias de teste e nenhum aumento após 28 dias.
Para *Aspergillus brasiliensis*, o produto cumpre o critério A já que se verifica uma redução logarítmica de 4,85 após 14 dias de teste e nenhum aumento após 28 dias.

3.4 Conclusão

O estudo realizado na amostra do produto cosmético "Creme de Rosto" permite concluir que o referido produto cumpre os requisitos do critério B de proteção do produto contra a proliferação microbiana de acordo com a Farmacopeia Europeia 8.0.

4 – Arquivo

Os documentos e registos associados ao estudo serão arquivados na inovapotek durante 10 anos.

inovapotek
PHARMACEUTICAL RESEARCH AND DEVELOPMENT

Relatório Final FR03A/P135B13

Estudo de estabilidade acelerada e compatibilidade produto-embalagem de dois produtos cosméticos no âmbito do projeto "EURORREGIAO TERMAL E DA AGUA" (0504_EUROREGION_TERMAL_AGUA_1_E):

Creme de mãos – Resultados 3 meses

Promotor:

Município de Chaves

Setembro 2015

A informação contida neste relatório é confidencial e não será divulgada, na totalidade ou em parte, sem o devido consentimento prévio do promotor.

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CIDADE DE CHAVES

PROGRAMA COOPERACIÓN TRANSFRONTERIZA ESPAÑA – PORTUGAL COOPERAÇÃO TRANSFRONTEIRIÇA 2007 - 2013

União Europeia
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CHAVES TERMAS&SPA

Relatório Elaborado/Alterado por:

INOVAPOTEK

Liliana Ferraz, responsável pela elaboração/~~alteração~~ do relatório

Data:09/09/2015

Relatório Aprovado por:

INOVAPOTEK

Marta Ferreira, Director do Estudo

Data: 14/09/2015

PROMOTOR (quando aplicável)

Nome do responsável

_____ Data:_____

Relatório Verificado por:

INOVAPOTEK

Yogeeta Rocha, responsável pela Qualidade

Data: 14/09/2015

HISTÓRICO DE ALTERAÇÕES

Revisão	Alteração	Data
A	Primeira versão	14/09/2015

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1 – Identificação do estudo

Proposta n.	P135B13
Relatório n.	FR03A/P135B13
Título	Estudo de estabilidade acelerada de dois produtos cosméticos no âmbito do projeto "EURORREGIAO TERMAL E DA AGUA" (0504_EUROREGION_TERMAL_AGUA_1_E): Creme de mãos – Resultados 3 meses
Data Início do Estudo	05/05/2014
Data Início da análise (se aplicável)	-
Data Conclusão da análise (se aplicável)	-
Data Conclusão do Estudo	-
Data do Relatório	14/09/2015

Identificação das substâncias e produtos em estudo e de referência (quando aplicável)

Designação comercial do produto em estudo	Tipo de formulação	Princípio activo (quando aplicável)	Observações
Creme mãos	Emulsão	-	Lote: L530061

Designação da(s) substância(s) em estudo	Denominação IUPAC	Número CAS	Parâmetros Biológicos
-	-	-	-

Designação da(s) substância(s) de referência	Denominação IUPAC	Número CAS	Parâmetros Biológicos
-	-	-	-

2 – Identificação dos responsáveis pelo Estudo

Promotor	Munícipio de Chaves
	Câmara Municipal de Chaves Praça de Camões, 5400-150 Chaves
Proponente	INOVAPOTEK, Pharmaceutical Research and Development Lda
	UPTEC, Parque de Ciência e Tecnologia da Universidade do Porto Rua Alfredo Allen, n.º 455/461 4200-135 Porto – PORTUGAL
Director do Estudo	Marta Ferreira
Investigador (es)	Yogeeta Rocha
	Responsável pela(s) Fase(s) do Estudo n.º 4
Técnico(s) de Laboratório(s)	Liliana Ferraz
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Local(is) de Ensaio	INOVAPOTEK, Pharmaceutical Research and Development Lda
	UPTEC, Parque de Ciência e Tecnologia da Universidade do Porto Rua Alfredo Allen, n.º 455/461 4200-135 Porto – PORTUGAL

3 – Relatório do Estudo

3.1 Introdução

3.1.1 Teste de Estabilidade Acelerada e compatibilidade produto-embalagem

Amostras do produto nas embalagens finais e numa embalagem de controlo foram armazenadas em condições de temperatura ambiente, a temperatura elevada (40ºC±2ºC) e a baixa temperatura (T=4ºC±2ºC) durante 3 meses. As amostras foram submetidas às seguintes análises físico-químicas antes e após 1 e 3 meses em cada condição de armazenamento:

a) Avaliação das características organoléticas do produto (aspeto, cor e odor);
b) Determinação de pH;
c) Determinação de viscosidade;
d) Controlo do peso;
e) Ensaios microbiológicos (contagens de germes aeróbios viáveis totais a 30-35ºC e a 20-25ºC);
f) Avaliação do material de embalagem (cor, aspeto e integridade).

As amostras foram também armazenadas com exposição à luz solar durante 1 mês sendo submetidas às análises físico-químicas referidas no item anterior antes e após 1 mês.

Este relatório contempla os resultados das análises físico-químicas realizadas antes e após 3 meses de armazenamento nas diferentes condições definidas para o Creme de Mãos.

3.2 Métodos e Resultados

Embalagem Final

Tabela 1. Resultados das análises físico-químicas efetuadas antes e após 1 e 3 meses do estudo de estabilidade acelerada.

Parâmetros		Métodos	Especificações	T0		T1 mês								T3 meses					
				Temperatura ambiente		Temperatura ambiente		4ºC		40ºC		Exposição luz solar		Temperatura ambiente		4ºC		40ºC	
				Média	DP	Média	DP	Média	DP	Média	DP	Média	DP	Média	DP	Média	DP	Média	DP
Características organoléticas do produto	**Aspeto**	Visual	Emulsão homogénea brilhante	Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme	
	Cor		Branco	Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme	
	Odor		Característico à fragrância	Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme	
pH	**T=20±2º C**	Potenciómetro pHenomenal 662-1152 VWR, Protocolo interno PE 01	5,5 - 6,5	6,22	0,03	6,23	0,19	6,23	0,03	6,27	0,02	6,25	0,02	6,24	0,02	6,24	0,02	6,34	0,00
				Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme	
Viscosidade (cP)	**T=20±2º C**	Brookfield LVDV-E, Agulha S64/ 5 rpm, Protocolo interno PE 04	65000 - 85000	67700	-	78900	-	71300	-	75700	-	79100	-	94800	-	106100	-	92400	-
				Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme	
Características organoléticas da embalagem	**Aspeto**	Visual	Plástico	Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme	
	Cor		Branco opaco	Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme	
	Integridade		Íntegra	Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme	
Peso embalagem (g)	**Temperatura ambiente**	Balança de precisão EMB 2000 KERN	115,02 - 140,58	127,80	0,01	127,76	0,01	128,35	0,01	126,98	0,00	128,64	0,01	127,68	0,00	128,34	0,01	126,67	0,01
	4ºC		115,51 - 141,19	128,35	0,01														
	40ºC		114,40 - 139,82	127,11	0,00														
	Exposição luz solar		115,79 - 141,52	128,65	0,00														
				Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme	
Qualidade microbiológica (UFC/mL)	**Contagem de germes aeróbios viáveis totais**	ISO 21149 e ISO 16212	≤1000	≤ 10 (5)		≤ 10 (0)		≤ 10 (0)		≤ 10 (0)		-		≤ 10 (0)		≤ 10 (0)		≤ 10 (0)	
				Conforme		Conforme		Conforme		Conforme		-		Conforme		Conforme		Conforme	

Embalagem Controlo

Tabela 2. Resultados das análises físico-químicas efetuadas antes e após 1 e 3 meses do estudo de estabilidade acelerada.

				T0		**T1 mês**								**T3 meses**					
Parâmetros		**Métodos**	**Especificações**	**Temperatura ambiente**		**Temperatura ambiente**		**4ºC**		**40ºC**		**Exposição luz solar**		**Temperatura ambiente**		**4ºC**		**40ºC**	
				Média	**DP**	**Média**	**DP**	**Média**	**DP**	**Média**	**DP**	**Média**	**DP**	**Média**	**DP**	**Média**	**DP**	**Média**	**DP**
Características organoléticas do produto	**Aspeto**	Visual	Emulsão homogénea brilhante	Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme	
	Cor		Branco	Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme	
	Odor		Característico à fragrância	Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme	
pH	**T=20±2º C**	Potenciómetro pHenomenal 662-1152 VWR, Protocolo interno PE 01	5,5 - 6,5	6,22	0,03	6,25	0,02	6,14	0,01	6,18	0,04	6,02	0,02	6,30	0,07	6,25	0,02	6,36	6,35
				Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme	
Viscosidade (cP)	**T=20±2º C**	Brookfield LVDV-E, Agulha 64/ 5 rpm, Protocolo interno PE 04	65000 - 85000	67700		88100		86900		72800		52300		76800		95400		81700	
				Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme	

3.3 Discussão e conclusão

Após 3 meses em estabilidade, o Creme de Mãos apresentava as suas características organolépticas inalteradas.

Os valores de pH não sofreram alterações significativas, mantendo-se dentro das especificações estabelecidas tanto para as amostras armazenadas nas embalagens controlo como para as amostras armazenadas nas embalagens finais.

Relativamente à viscosidade, ao fim de 3 meses verificou-se uma tendência deste parâmetro para aumentar em todas as condições de armazenamento, ultrapassando as especificações estabelecidas nas amostras armazenas a 4ºC. No entanto, estas alterações não afetaram a cosmeticidade do produto. Estas flutuações poderão estar relacionadas com o período de maturação da própria emulsão.

As embalagens finais não demonstraram qualquer alteração a nível do seu aspeto, cor e integridade e os resultados do controlo de peso evidenciam que o tipo de embalagem selecionado é estanque.

As propriedades microbiológicas do produto Creme de Mãos permaneceram dentro dos limites estabelecidos pelo SCCS (Scientific Committee on Consumer Safety) para produtos cosméticos de categoria 2 (contagem de aeróbios totais $\leq 10^3$ UFC/mL de produto) antes e após 3 meses em estabilidade nas diferentes condições.

De acordo com os resultados obtidos, é possível concluir que o produto Creme de Mãos é estável ao fim de 3 meses de estudo de estabilidade acelerada e é compatível com a embalagem selecionada. Com base nestes resultados, uma data de durabilidade mínima de 24 meses poderá ser estipulada.

4 – Arquivo

Os documentos e registos associados ao estudo serão arquivados na inovapotek durante 10 anos.

inovapotek
PHARMACEUTICAL RESEARCH AND DEVELOPMENT

Relatório Final FR04A/P135B13

Estudo de estabilidade acelerada e compatibilidade produto-embalagem de dois produtos cosméticos no âmbito do projeto "EURORREGIAO TERMAL E DA AGUA" (0504_EUROREGION_TERMAL_AGUA_1_E):

Creme de Rosto – Resultados 3 meses

Promotor:

Município de Chaves

Setembro 2015

A informação contida neste relatório é confidencial e não será divulgada, na totalidade ou em parte, sem o devido consentimento prévio do promotor.

UPTEC, Parque de Ciências e Tecnologia da Universidade do Porto ·Rua Alfredo Allen, n.º 455/461 · 4200-135 Porto · Portugal · tel.: +351 220 301 531 · fax: +351 220 301 532 · geral@inovapotek.com · www.inovapotek.com

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CHAVES TERMAS&SPA

Relatório Elaborado/Alterado por:

INOVAPOTEK

Liliana Ferraz, responsável pela elaboração/~~alteração~~ do relatório

Data: 09/09/2015

Relatório Aprovado por:

INOVAPOTEK

Marta Ferreira, Director do Estudo

Data: 14/09/2015

PROMOTOR (quando aplicável)

Nome do responsável

_____ Data:_____

Relatório Verificado por:

INOVAPOTEK

Yogeeta Rocha, responsável pela Qualidade

Data: 14/09/2015

HISTÓRICO DE ALTERAÇÕES

Revisão	Alteração	Data
A	Primeira versão	14/09/2015

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1 – Identificação do estudo

Proposta n.	P135B13
Relatório n.	FR04A/P135B13
Título	Estudo de estabilidade acelerada de dois produtos cosméticos no âmbito do projeto "EURORREGIAO TERMAL E DA AGUA" (0504_EUROREGION_TERMAL_AGUA_1_E): Creme de Rosto – Resultados 3 meses
Data Início do Estudo	05/05/2014
Data Início da análise (se aplicável)	-
Data Conclusão da análise (se aplicável)	-
Data Conclusão do Estudo	-
Data do Relatório	14/09/2015

Identificação das substâncias e produtos em estudo e de referência (quando aplicável)

Designação comercial do produto em estudo	Tipo de formulação	Princípio activo (quando aplicável)	Observações
Creme rosto	Emulsão	-	Lote: L530060

Designação da(s) substância(s) em estudo	Denominação IUPAC	Número CAS	Parâmetros Biológicos
-	-	-	-

Designação da(s) substância(s) de referência	Denominação IUPAC	Número CAS	Parâmetros Biológicos
-	-	-	-

2 – Identificação dos responsáveis pelo Estudo

Promotor	Munícipio de Chaves
	Câmara Municipal de Chaves Praça de Camões, 5400-150 Chaves
Proponente	INOVAPOTEK, Pharmaceutical Research and Development Lda
	UPTEC, Parque de Ciência e Tecnologia da Universidade do Porto Rua Alfredo Allen, n.º 455/461 4200-135 Porto – PORTUGAL
Director do Estudo	Marta Ferreira
Investigador (es)	Yogeeta Rocha
	Responsável pela(s) Fase(s) do Estudo n.º 4
Técnico(s) de Laboratório(s)	Liliana Ferraz
	Responsável pela(s) Fase(s) do Estudo n.º 4
Local(is) de Ensaio	INOVAPOTEK, Pharmaceutical Research and Development Lda
	UPTEC, Parque de Ciência e Tecnologia da Universidade do Porto Rua Alfredo Allen, n.º 455/461 4200-135 Porto – PORTUGAL

3 – Relatório do Estudo

3.1 Introdução

3.1.1 Teste de Estabilidade Acelerada e compatibilidade produto-embalagem

Amostras do produto nas embalagens finais e numa embalagem de controlo foram armazenadas em condições de temperatura ambiente, a temperatura elevada (40ºC±2ºC) e a baixa temperatura (T=4ºC±2ºC) durante 3 meses. As amostras foram submetidas às seguintes análises físico-químicas antes e após 1 e 3 meses em cada condição de armazenamento:

a) Avaliação das características organoléticas do produto (aspeto, cor e odor);
b) Determinação de pH;
c) Determinação de viscosidade;
d) Controlo do peso;
e) Ensaios microbiológicos (contagens de germes aeróbios viáveis totais a 30-35ºC e a 20-25ºC);
f) Avaliação do material de embalagem (cor, aspeto e integridade).

As amostras foram também armazenadas com exposição à luz solar durante 1 mês sendo submetidas às análises físico-químicas referidas no item anterior antes e após 1 mês.

Este relatório contempla os resultados das análises físico-químicas realizadas antes e após 3 meses de armazenamento nas diferentes condições definidas para o Creme de Rosto.

3.2 Métodos e Resultados

Embalagem Final

Tabela 1. Resultados das análises físico-químicas efetuadas antes e após 1 e 3 meses do estudo de estabilidade acelerada.

Parâmetros		Métodos	Especificações	T0		T1 mês								T3 meses					
				Temperatura ambiente		Temperatura ambiente		4ºC		40ºC		Exposição luz solar		Temperatura ambiente		4ºC		40ºC	
				Média	DP	Média	DP	Média	DP	Média	DP	Média	DP	Média	DP	Média	DP	Média	DP
Características organoléticas do produto	**Aspeto**	Visual	Emulsão homogénea brilhante	Conforme		Conforme		Conforme		Conforme		Conforme		Não Conforme (emulsão mais liquida)		Conforme		Conforme	
	Cor		Branco	Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme	
	Odor		Característico à fragrância	Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme	
pH	**T=20±2º C**	Potenciómetro pHenomenal 662-1152 VWR, Protocolo interno PE 01	5,5 - 6,5	6,38	0,05	6,34	0,02	6,19	0,01	6,14	0,05	6,18	0,05	6,14	0,00	6,11	0,01	6,04	0,00
				Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme	
Viscosidade (cP)	**T=20±2º C**	Brookfield LVDV-E, Agulha S64/ 5 rpm, Protocolo interno PE 04	20000-40000	21200	-	23800	-	25700	-	33400	-	34800	-	16100	-	33400	-	28700	-
				Conforme		Conforme		Conforme		Conforme		Conforme		Não Conforme		Conforme		Conforme	
Características organoléticas da embalagem	**Aspeto**	Visual	Plástico com tampa semi-opaca e doseador "pump"	Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme	
	Cor		Branca, tampa semi-opaca branca e doseador branco	Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme	
	Integridade		Íntegra	Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme	
Peso embalagem (g)	**Temperatura ambiente**	Balança de precisão EMB 2000 KERN	70,84 - 106,26	88,55	0,00	88,49	0,01	89,31	0,01	88,59	0,00	89,23	0,01	88,39	0,04	89,27	0,00	88,31	0,00
	4ºC		71,46 - 107,18	89,32	0,02														
	40ºC		70,98 - 106,48	88,73	0,01														
	Exposição luz solar		71,39 - 107,01	89,24	0,01														
				Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme	
Qualidade microbiológica (UFC/mL)	**Contagem de germes aeróbios viáveis totais**	ISO 21149 e ISO 16212	≤1000	≤ 10		≤ 10		≤ 10		≤ 10		≤ 10		≤ 10		≤ 10		≤ 10	
				Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme	

Embalagem Controlo

Tabela 2. Resultados das análises físico-químicas efetuadas antes e após 1 e 3 meses do estudo de estabilidade acelerada.

				T0		T1 mês								T3 meses					
Parâmetros		**Métodos**	**Especificações**	**Temperatura ambiente**		**Temperatura ambiente**		**4ºC**		**40ºC**		**Exposição luz solar**		**Temperatura ambiente**		**4ºC**		**40ºC**	
				Média	**DP**	**Média**	**DP**	**Média**	**DP**	**Média**	**DP**	**Média**	**DP**	**Média**	**DP**	**Média**	**DP**	**Média**	**DP**
Características organoléticas do produto	**Aspeto**	Visual	Emulsão homogénea brilhante	Conforme		Conforme		Conforme		Conforme		Conforme		Não Conforme (emulsão mais liquida)		Conforme		Conforme	
	Cor		Branco	Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme	
	Odor		Característico à fragrância	Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme	
pH	**T=20±2º C**	Potenciómetro pHenomenal 662-1152 VWR, Protocolo interno PE 01	5,5 - 6,5	6,38	0,05	6,16	0,03	6,14	0,02	6,18	0,01	6,16	0,00	6,19	0,04	6,14	0,02	6,03	0,02
				Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme		Conforme	
Viscosidade (cP)	**T=20±2º C**	Brookfield LVDV-E, Agulha S64/ 5 rpm, Protocolo interno PE 04	20000-40000	21200		18100		20600		31600		23500		3035		26300		24500	
				Conforme		Conforme		Conforme		Conforme		Conforme		Não Conforme		Conforme		Conforme	

3.3 Discussão e conclusão

Após 3 meses em estabilidade o Creme de Rosto apresentava a sua cor e odor inalterados para todas as condições de armazenamento. No que diz respeito ao aspeto, apesar de visivelmente mais fluídas, as amostras armazenadas à temperatura ambiente apresentavam um aspeto homogéneo.

Verificou-se uma tendência dos valores de pH para baixar ao fim de 3 meses, no entanto mantiveram-se dentro das especificações estabelecidas.

Como referido, as amostras armazenadas à temperatura ambiente apresentaram-se mais fluídas, sendo que se verificou um decréscimo do valor da viscosidade, mais significativo para a amostra acondicionada na embalagem controlo.

As embalagens finais não demonstraram qualquer alteração a nível do seu aspeto, cor e integridade e os resultados do controlo de peso evidenciam que o tipo de embalagem selecionado é estanque.

As propriedades microbiológicas do produto Creme de Rosto permaneceram dentro dos limites estabelecidos pelo SCCS (Scientific Committee on Consumer Safety) para produtos cosméticos de categoria 2 (contagem de aeróbios totais $\leq 10^3$ UFC/mL de produto) antes e após 3 meses em estabilidade nas diferentes condições.

Com base nestes resultados, conclui-se o produto Creme de Rosto apresenta tendência para diminuir a sua viscosidade ao longo do tempo quando armazenado à temperatura ambiente. Recomenda-se a extensão do estudo de estabilidade de modo a verificar se a tendência da viscosidade para diminuir se mantém com o tempo.

4 – Arquivo

Os documentos e registos associados ao estudo serão arquivados na inovapotek durante 10 anos.

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PHARMACEUTICAL RESEARCH AND DEVELOPMENT

Relatório Final FR05A/P135B13

Estudo de estabilidade e realização de trâmites legais necessários à colocação de produtos cosméticos no mercado no âmbito do projeto "EURORREGIAO TERMAL E DA AGUA" (0504_EUROREGION_TERMAL_AGUA_1_E):

Estimativa teórica do PAO do Creme de Rosto

Promotor:

Município de Chaves

Julho, 2015

A informação contida neste relatório é confidencial e não será divulgada, na totalidade ou em parte, sem o devido consentimento prévio do promotor.

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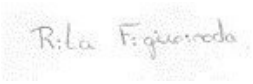
CHAVES TERMAS&SPA

Relatório Elaborado/~~Alterado~~ por:

INOVAPOTEK

Rita Figueiredo, responsável pela elaboração/~~alteração~~ do relatório



Data: 15/07/2015

Relatório Aprovado por:

INOVAPOTEK

Marta Ferreira, Directora do Estudo

Data: 16/07/2015

PROMOTOR (quando aplicável)

Nome do responsável

_____ Data:_____

Relatório Verificado por:

INOVAPOTEK

Yogeeta Rocha, responsável pela Qualidade

Data: 21/07/2015

HISTÓRICO DE ALTERAÇÕES

Revisão	Alteração	Data
A	Primeira versão	21/07/2015

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1 – Identificação do estudo

Proposta n.	P135B13
Relatório n.	FR05A/P135B13
Título	Estudo de estabilidade e realização de trâmites legais necessários à colocação de produtos cosméticos no mercado no âmbito do projeto "EURORREGIAO TERMAL E DA AGUA" (0504_EUROREGION_TERMAL_AGUA_1_E): Estimativa teórica do PAO do Creme de Rosto
Data Início do Estudo	05/05/2014
Data Início da análise (se aplicável)	-
Data Conclusão da análise (se aplicável)	-
Data Conclusão do Estudo	-
Data do Relatório	21/07/215

Identificação das substâncias e produtos em estudo e de referência (quando aplicável)

Designação comercial do produto em estudo	Tipo de formulação	Princípio activo (quando aplicável)	Observações
Creme de rosto	Emulsão	-	-

Designação da(s) substância(s) em estudo	Denominação IUPAC	Número CAS	Parâmetros Biológicos
-	-	-	-

Designação da(s) substância(s) de referência	Denominação IUPAC	Número CAS	Parâmetros Biológicos
-	-	-	-

2 – Identificação dos responsáveis pelo Estudo

Promotor	Município de Chaves
	Câmara Municipal de Chaves Praça de Camões, 5400-150 Chaves
Proponente	INOVAPOTEK, Pharmaceutical Research and Development Lda
	UPTEC, Parque de Ciência e Tecnologia da Universidade do Porto Rua Alfredo Allen, n.º 455/461 4200-135 Porto – PORTUGAL
Diretor do Estudo	Marta Ferreira
Investigador (es)	Rita Figueiredo
	Responsável pela (s) Fase (s) Estimativa teórica de PAO
Técnico (s) de Laboratório (s)	-
	-
Local (is) de Ensaio	INOVAPOTEK, Pharmaceutical Research and Development Lda
	UPTEC, Parque de Ciência e Tecnologia da Universidade do Porto Rua Alfredo Allen, n.º 455/461 4200-135 Porto – PORTUGAL

3 – Relatório do Estudo

3.1. Introdução

O objetivo desta tarefa é determinar o período de tempo durante o qual o produto cosmético "Creme de Rosto" desenvolvido podem ser utilizado sem provocar danos à saúde do consumidor (PAO).

3.2. Métodos

O PAO será estimado teoricamente segundo a metodologia da norma *Recommandations relatives a l'estimation de la Period Apres Ouverture (PAO)*, da *Agence Française de securité sanitaire de produits de santé*, partindo dos dados de:

- Composição do produto;
- Tipo de embalagem;
- Modo de utilização;
- Dados de estabilidade existentes, etc.

3.3. Resultados

Creme de Rosto

Os critérios e a cotação dos critérios utilizados para calcular o risco total e, posteriormente o PAO foram:

A - Microbiologia

Critério	Cotação do critério	Cotação global	Fator de ponderação	Cotação do item
Ensaio de eficácia de conservantes de acordo com os requisitos da Farmacopeia Europeia (Ph. Eur.)	2	2,00	2,00	4,00

Cotação do critério:	
Passa o critério A da Ph. Eur. ou ensaio não necessário	*1*
Passa o critério B da Ph. Eur. ou passa o ensaio de acordo Farmacopeia Francesa	2
Não passa os critérios da Ph. Eur. ou ensaio não realizado	*3*

B - Composição - Processo de fabrico

Critério	Cotação do critério	Cotação global	Fator de ponderação	Cotação do item
% Água	3	2,29	1,50	3,43
% Solvente	2			
Substância nutritivas	2			
Substâncias degradáveis	1			
Controlo de processo de fabrico	3			
Controlo de processo de enchimento	3			
Especificações (pH,…)	2			
Cotação dos critérios:				

Baixo	1
Moderado	2
Elevado	3

C - Embalagem

Critério	Cotação do critério	Cotação global	Fator de ponderação	Cotação do item
Contato entre o produto e o consumidor (Tendo em conta o tipo e o tamanho da embalagem)	1	1,00	1,50	1,50

Cotação dos critérios:	
Sem contacto	1
Contacto reduzido	2
Elevado contacto	3
Volume/Dose/Frequência (Tendo em conta o tipo e o tamanho da embalagem)	1
Cotação dos critérios:	
Apropriado	1
Inapropriado	3

D - Função e instruções de uso

Critério	Cotação do critério	Cotação global	Fator de ponderação	Cotação do item
Enxaguar	3	2,00	2,00	4,00

Cotação dos critérios:	
Imediatamente enxaguado	1
Não imediatamente enxaguado	2
Não enxaguado (leave-on)	3
Consumidores	1
Cotação dos critérios:	
Adultos	1
Crianças	2
Bebés e/ou idosos	3
Zona de aplicação	2
Nível de risco:	**Cotação dos critérios:**
Baixo	1
Moderado	2

Elevado	3

E - Riscos específicos

Critério	Cotação do critério	Cotação global	Fator de ponderação	Cotação do item
Risco de uso (por exemplo: misturas extemporâneas,...)	1	1,00	3,00	3,00
Condições de armazenamento	1			
Productos nómadas (por exemplo: protetores solares,…)	1			
Múltiplos-utilizadores (por exemplo: produtos profissionais,...)	1			
Se existe algum risco em particular: por exemplo, para ser usado nos mamilos antes da amamentação				

Nível de risco:	**Cotação dos critérios:**
Baixo	1
Moderado	2
Elevado	3

Risco Total
15,93

Nome do produto	**Creme de rosto**
PAO (meses)	**14**

Concluiu-se que o PAO máximo esperado para o produto "Creme de Rosto" é de 14 meses.

4 – Arquivo

Os documentos e registos associados ao estudo serão arquivados na inovapotek durante 10 anos.

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PHARMACEUTICAL RESEARCH AND DEVELOPMENT

Relatório Final FR06A/P135B13

Estudo de estabilidade e realização de trâmites legais necessários à colocação de produtos cosméticos no mercado no âmbito do projeto "EURORREGIAO TERMAL E DA AGUA" (0504_EUROREGION_TERMAL_AGUA_1_E):

Estimativa teórica do PAO do Creme de Mãos

Promotor:

Município de Chaves

Julho, 2015

A informação contida neste relatório é confidencial e não será divulgada, na totalidade ou em parte, sem o devido consentimento prévio do promotor.

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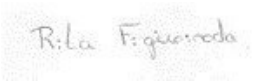
Rita Figueiredo, responsável pela elaboração/~~alteração~~ do relatório



Data: 15/07/2015

Relatório Aprovado por:

INOVAPOTEK

Marta Ferreira, Directora do Estudo

Data: 16/07/2015

PROMOTOR (quando aplicável)

Nome do responsável

_____ Data:_____

Relatório Verificado por:

INOVAPOTEK

Yogeeta Rocha, responsável pela Qualidade

Data: 21/07/2015

HISTÓRICO DE ALTERAÇÕES

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A	Primeira versão	21/07/2015

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1 – Identificação do estudo

Proposta n.	P135B13
Relatório n.	FR06A/P135B13
Título	Estudo de estabilidade e realização de trâmites legais necessários à colocação de produtos cosméticos no mercado no âmbito do projeto "EURORREGIAO TERMAL E DA AGUA" (0504_EUROREGION_TERMAL_AGUA_1_E): Estimativa teórica do PAO do Creme de Mãos
Data Início do Estudo	05/05/2014
Data Início da análise (se aplicável)	-
Data Conclusão da análise (se aplicável)	-
Data Conclusão do Estudo	-
Data do Relatório	21/07/2015

Identificação das substâncias e produtos em estudo e de referência (quando aplicável)

Designação comercial do produto em estudo	Tipo de formulação	Princípio activo (quando aplicável)	Observações
Creme de mãos	Emulsão	-	-

Designação da(s) substância(s) em estudo	Denominação IUPAC	Número CAS	Parâmetros Biológicos
-	-	-	-

Designação da(s) substância(s) de referência	Denominação IUPAC	Número CAS	Parâmetros Biológicos
-	-	-	-

2 – Identificação dos responsáveis pelo Estudo

Promotor	Município de Chaves
	Câmara Municipal de Chaves Praça de Camões, 5400-150 Chaves
Proponente	INOVAPOTEK, Pharmaceutical Research and Development Lda
	UPTEC, Parque de Ciência e Tecnologia da Universidade do Porto Rua Alfredo Allen, n.º 455/461 4200-135 Porto – PORTUGAL
Diretor do Estudo	Marta Ferreira
Investigador (es)	Rita Figueiredo
	Responsável pela (s) Fase (s) Estimativa teórica de PAO
Técnico (s) de Laboratório (s)	-
	-
Local (is) de Ensaio	INOVAPOTEK, Pharmaceutical Research and Development Lda
	UPTEC, Parque de Ciência e Tecnologia da Universidade do Porto Rua Alfredo Allen, n.º 455/461 4200-135 Porto – PORTUGAL

3 – Relatório do Estudo

3.1. Introdução

O objetivo desta tarefa é determinar o período de tempo durante o qual o produto cosmético "Creme de Mãos" pode ser utilizado sem provocar danos à saúde do consumidor (PAO).

3.2. Métodos

O PAO será estimado teoricamente segundo a metodologia da norma *Recommandations relatives a l'estimation de la Period Apres Ouverture (PAO)*, da *Agence Française de securité sanitaire de produits de santé*, partindo dos dados de:

- Composição do produto;
- Tipo de embalagem;
- Modo de utilização;
- Dados de estabilidade existentes, etc.

3.3. Resultados

Creme de Mãos

Os critérios e a cotação dos critérios utilizados para calcular o risco total e, posteriormente o PAO foram:

A - Microbiologia

Critério		Cotação do critério	Cotação global	Fator de ponderação	Cotação do item
Ensaio de eficácia de conservantes de acordo com os requisitos da Farmacopeia Europeia (Ph. Eur.)		2	2,00	2,00	4,00
Cotação do critério:					
Passa o critério A da Ph. Eur. ou ensaio não necessário	*1*				
Passa o critério B da Ph. Eur. ou passa o ensaio de acordo Farmacopeia Francesa	*2*				
Não passa os critérios da Ph. Eur. ou ensaio não realizado	*3*				

B - Composição - Processo de fabrico

Critério	Cotação do critério	Cotação global	Fator de ponderação	Cotação do item
% Água	3	2,57	1,50	3,86
% Solvente	3			
Substância nutritivas	3			
Substâncias degradáveis	1			
Controlo de processo de fabrico	3			
Controlo de processo de enchimento	3			
Especificações (pH,…)	2			
Cotação dos critérios:				

Baixo	1
Moderado	2
Elevado	3

C - Embalagem

Critério	Cotação do critério	Cotação global	Fator de ponderação	Cotação do item
Contato entre o produto e o consumidor (Tendo em conta o tipo e o tamanho da embalagem)	2	1,50	1,50	2,25

Cotação dos critérios:	
Sem contacto	1
Contacto reduzido	2
Elevado contacto	3
Volume/Dose/Frequência (Tendo em conta o tipo e o tamanho da embalagem)	1
Cotação dos critérios:	
Apropriado	1
Inapropriado	3

D - Função e instruções de uso

Critério	Cotação do critério	Cotação global	Fator de ponderação	Cotação do item
Enxaguar	3	2,00	2,00	4,00

Cotação dos critérios:	
Imediatamente enxaguado	1
Não imediatamente enxaguado	2
Não enxaguado (leave-on)	3
Consumidores	1
Cotação dos critérios:	
Adultos	1
Crianças	2
Bebés e/ou idosos	3
Zona de aplicação	2
Nível de risco:	**Cotação dos critérios:**
Baixo	1
Moderado	2

Elevado	3

E - Riscos específicos

Critério	Cotação do critério	Cotação global	Fator de ponderação	Cotação do item
Risco de uso (por exemplo: misturas extemporâneas,...)	1	1,00	3,00	3,00
Condições de armazenamento	1			
Productos nómadas (por exemplo: protetores solares,...)	1			
Múltiplos-utilizadores (por exemplo: produtos profissionais,...)	1			
Se existe algum risco em particular: por exemplo, para ser usado nos mamilos antes da amamentação				

Nível de risco:	**Cotação dos critérios:**
Baixo	1
Moderado	2
Elevado	3

Risco Total
17,11

Nome do produto	**Creme de mãos**
PAO (meses)	**13**

Concluiu-se que o PAO máximo esperado para o produto "Creme de Mãos" é de 13 meses.

4 – Arquivo

Os documentos e registos associados ao estudo serão arquivados na inovapotek durante 10 anos.

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PHARMACEUTICAL RESEARCH AND DEVELOPMENT

Relatório Final FR07A/P135B13

Estudo de estabilidade e realização de trâmites legais necessários à colocação de produtos cosméticos no mercado no âmbito do projeto "EURORREGIAO TERMAL E DA AGUA" (0504_EUROREGION_TERMAL_AGUA_1_E):

Estimativa teórica do PAO do Creme de Corpo

Promotor:

Município de Chaves

Julho, 2015

A informação contida neste relatório é confidencial e não será divulgada, na totalidade ou em parte, sem o devido consentimento prévio do promotor.

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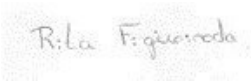
CHAVES TERMAS&SPA

Relatório Elaborado/~~Alterado~~ por:

INOVAPOTEK

Rita Figueiredo, responsável pela elaboração/~~alteração~~ do relatório



Data: 15/07/2015

Relatório Aprovado por:

INOVAPOTEK

Marta Ferreira, Directora do Estudo

Data: 16/07/2015

PROMOTOR (quando aplicável)

Nome do responsável

_____ Data:_____

Relatório Verificado por:

INOVAPOTEK

Yogeeta Rocha, responsável pela Qualidade

Data: 21/07/2015

HISTÓRICO DE ALTERAÇÕES

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A	Primeira versão	21/07/2015

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2 – Identificação dos responsáveis pelo Estudo 5
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1 – Identificação do estudo

Proposta n.	P135B13
Relatório n.	FR07A/P135B13
Título	Estudo de estabilidade e realização de trâmites legais necessários à colocação de produtos cosméticos no mercado no âmbito do projeto "EURORREGIAO TERMAL E DA AGUA" (0504_EUROREGION_TERMAL_AGUA_1_E): Estimativa teórica do PAO do Creme de Corpo
Data Início do Estudo	05/05/2014
Data Início da análise (se aplicável)	-
Data Conclusão da análise (se aplicável)	-
Data Conclusão do Estudo	-
Data do Relatório	21/07/2015

Identificação das substâncias e produtos em estudo e de referência (quando aplicável)

Designação comercial do produto em estudo	Tipo de formulação	Princípio activo (quando aplicável)	Observações
Creme de corpo	Emulsão	-	-

Designação da(s) substância(s) em estudo	Denominação IUPAC	Número CAS	Parâmetros Biológicos
-	-	-	-

Designação da(s) substância(s) de referência	Denominação IUPAC	Número CAS	Parâmetros Biológicos
-	-	-	-

2 – Identificação dos responsáveis pelo Estudo

Promotor	Município de Chaves
	Câmara Municipal de Chaves Praça de Camões, 5400-150 Chaves
Proponente	INOVAPOTEK, Pharmaceutical Research and Development Lda
	UPTEC, Parque de Ciência e Tecnologia da Universidade do Porto Rua Alfredo Allen, n.º 455/461 4200-135 Porto – PORTUGAL
Diretor do Estudo	Marta Ferreira
Investigador (es)	Rita Figueiredo
	Responsável pela (s) Fase (s) Estimativa teórica de PAO
Técnico (s) de Laboratório (s)	-
	-
Local (is) de Ensaio	INOVAPOTEK, Pharmaceutical Research and Development Lda
	UPTEC, Parque de Ciência e Tecnologia da Universidade do Porto Rua Alfredo Allen, n.º 455/461 4200-135 Porto – PORTUGAL

3 – Relatório do Estudo

3.1. Introdução

O objetivo desta tarefa é determinar o período de tempo durante o qual o produto cosmético "Creme de Corpo" pode ser utilizado sem provocar danos à saúde do consumidor (PAO).

3.2. Métodos

O PAO será estimado teoricamente segundo a metodologia da norma *Recommandations relatives a l'estimation de la Period Apres Ouverture (PAO)*, da *Agence Française de securité sanitaire de produits de santé*, partindo dos dados de:

- Composição do produto;
- Tipo de embalagem;
- Modo de utilização;
- Dados de estabilidade existentes, etc.

3.3. Resultados

Creme de Corpo

Os critérios e a cotação dos critérios utilizados para calcular o risco total e, posteriormente o PAO foram:

A - Microbiologia

Critério	Cotação do critério	Cotação global	Fator de ponderação	Cotação do item
Ensaio de eficácia de conservantes de acordo com os requisitos da Farmacopeia Europeia (Ph. Eur.)	2	2,00	2,00	4,00

Cotação do critério:	
Passa o critério A da Ph. Eur. ou ensaio não necessário	*1*
Passa o critério B da Ph. Eur. ou passa o ensaio de acordo Farmacopeia Francesa	*2*
Não passa os critérios da Ph. Eur. ou ensaio não realizado	*3*

B - Composição - Processo de fabrico

Critério	Cotação do critério	Cotação global	Fator de ponderação	Cotação do item
% Água	3	2,29	1,50	3,43
% Solvente	2			
Substância nutritivas	2			
Substâncias degradáveis	1			
Controlo de processo de fabrico	3			
Controlo de processo de enchimento	3			
Especificações (pH,…)	2			
Cotação dos critérios:				

Baixo	1
Moderado	2
Elevado	3

C - Embalagem

Critério	Cotação do critério	Cotação global	Fator de ponderação	Cotação do item
Contato entre o produto e o consumidor (Tendo em conta o tipo e o tamanho da embalagem)	2	1,50	1,50	2,25

Cotação dos critérios:	
Sem contacto	1
Contacto reduzido	2
Elevado contacto	3
Volume/Dose/Frequência (Tendo em conta o tipo e o tamanho da embalagem)	1
Cotação dos critérios:	
Apropriado	1
Inapropriado	3

D - Função e instruções de uso

Critério	Cotação do critério	Cotação global	Fator de ponderação	Cotação do item
Enxaguar	3	1,67	2,00	3,33

Cotação dos critérios:	
Imediatamente enxaguado	1
Não imediatamente enxaguado	2
Não enxaguado (leave-on)	3
Consumidores	1
Cotação dos critérios:	
Adultos	1
Crianças	2
Bebés e/ou idosos	3
Zona de aplicação	1
Nível de risco:	**Cotação dos critérios:**
Baixo	1
Moderado	2
Elevado	3

E - Riscos específicos

Critério	Cotação do critério	Cotação global	Fator de ponderação	Cotação do item
Risco de uso (por exemplo: misturas extemporâneas,...)	1	1,00	3,00	3,00
Condições de armazenamento	1			
Productos nómadas (por exemplo: protetores solares,…)	1			
Múltiplos-utilizadores (por exemplo: produtos profissionais,...)	1			
Se existe algum risco em particular: por exemplo, para ser usado nos mamilos antes da amamentação				

Nível de risco:	Cotação dos critérios:
Baixo	1
Moderado	2
Elevado	3

Risco Total
16,01

Nome do produto	**Creme de corpo**
PAO (meses)	**14**

Concluiu-se que o PAO máximo esperado para o produto "Creme de Corpo" é de 14 meses.

4 – Arquivo

Os documentos e registos associados ao estudo serão arquivados na inovapotek durante 10 anos.

inovapotek
PHARMACEUTICAL RESEARCH AND DEVELOPMENT

Cosmetic Product Safety Report

Report number FR08A/P135B13

Cosmetic Product Safety Report of the cosmetic product
DERMOCOSMÉTICA TERMAL AQUAE CREME HIDRATANTE ROSTO

30-10-2015

Promoter:
Município de Chaves

All information contained herein is confidential and will not be disclosed, whole or in part, without the proper written consent of the promoter.

CIDADE DE CHAVES
COOPERACIÓN TRANSFRONTERIZA ESPAÑA - PORTUGAL COOPERAÇÃO TRANSFRONTEIRIÇA
União Europeia Fundo Europeu de Desenvolvimento Regional Investimos no seu futuro
EURO-REGIÓN termal y del agua
CHAVES TERMAS&SPA

Identification of the study

Proposal Number	P135B13
Report number	FR08A/P135B13
Safety Assessment Report	Cosmetic Product Safety Report of the cosmetic product DERMOCOSMÉTICA TERMAL AQUAE CREME HIDRATANTE ROSTO
Beginning Date	13-10-2015
Report Date	30-10-2015

Identification of the study responsible personnel

Promoter	**Name**	Município de Chaves
	Address	Câmara Municipal de Chaves Praça de Camões, 5400-150 Chaves
Proponent	**Name**	INOVAPOTEK, Pharmaceutical Research and Development Lda
	Address	UPTEC, Parque de Ciência e Tecnologia da Universidade do Porto, Rua Alfredo Allen, n.º 455/461 4200-135 Porto – PORTUGAL
Safety Assessor	**Name**	Marta Alexandra de Oliveira Ferreira
	Qualifications of the safety assessor	Master in Pharmaceutical Sciences

History of the document

Version	Alterations	Date
A	First version	30-10-2015

Part A. Cosmetic Product Safety Information

1. Quantitative and qualitative composition of the cosmetic product

1.1 By trade name

Raw material (trade name)	Supplier	Function	Conc. (%)
White Oil Light	Mosselman	Emollient; skin protecting	5.00000
Myritol 318	COGNIS	Emollientskin conditioning	8.00000
Glycerin 4810	Oleon NV	Humectant	3.00000
Tegin Pellets	Evonik Industries AG	Emulsifying	8.00000
Goma xantana	Guinama	Emulsion StabilisingViscosity Controlling	0.30000
Água Termal das Termas de Chaves	Termas de Chaves	Solvent	72.70000
Sabowax CS 20	SABO SpA	Emulsifying	1.00000
1051936 NIVAL	Iberchem, S.A.	Fragrance	0.10000
Phenonip ME	Clariant	Preservative	1.20000
Acido Clorhídrico 37% grado técnico	Panreac AppliChem	Buffering	0.40000
SABONAL C1618 50/50	SABO SpA	Emulsifying	2.00000

1.2 By trade name and respective INCI name

Raw material (trade name)	INCI	IUPAC	CAS	EINECS/ELINCS	Function	Conc. of the substance in the raw material (%)	Conc. of the substance in the cosmetic product (%)
White Oil Light	Paraffinum Liquidum	Paraffin oils. Liquid hydrocarbons from petroleum	8012-95-1/8042-47-5	232-384-2/232-455-8	Emollient; skin protecting	100.00000	5.00000
Myritol 318	Caprylic/Capric Triglyceride	-	73398-61-5/65381-09-1	277-452-2/265-724-3	Emollient; skin conditioning	100.00000	8.00000
Glycerin 4810	Glycerin	Glycerol	56-81-5	200-289-5	Humectant	100.00000	3.00000
Tegin Pellets	Glyceryl stearate SE	Octadecanoic acid, reaction products with 1,2,3-propanetriol (1:1), neutralized	11099-07-3	234-325-6	Emulsifying	100.00000	8.00000
Goma xantana	Xanthan Gum	-	11138-66-2	234-394-2	Emulsion StabilisingViscosity Controlling	108.00000	0.32400
Água Termal das Termas de Chaves	Chaves Thermal Water (Chaves Aqua)	-	7732-18-5	231-791-2	Solvent	100.00000	72.70000
Sabowax CS 20	Ceteareth-20	-	68439-49-6	-	Emulsifying	100.00000	1.00000
1051936 NIVAL	Parfum	-	-	-	Perfuming	100.00000	0.10000
Phenonip ME	Ethylparaben	Ethyl 4-hydroxybenzoate	120-47-8	204-399-4	Preservative	12.50000	0.15000
	Methylparaben	Methyl 4-hydroxybenzoate	99-76-3	202-785-7	Preservative	12.50000	0.15000
	Phenoxyethanol	2-	122-99-6	204-589-7	Preservative	75.00000	0.90000

		phenoxyethanol					
Acido Clorhídrico 37% grado técnico	Hydrochloric acid	Hydrogen chloride	7647-01-0	231-595-7	Buffering	39.00000	0.15600
	Aqua	-	7732-18-5	231-791-2		63.50000	0.25400
SABONAL C1618 50/50	Cetearyl alcohol	-	67762-27-0 / 8005-44-5	267-008-6 / -	Emulsifying	100.00000	2.00000

1.3 By INCI name

INCI	Total Concentration In The Final Product (%)
Chaves Thermal Water (Chaves Aqua)	72.700000000000
Caprylic/Capric Triglyceride	8.000000000000
Glyceryl stearate SE	8.000000000000
Paraffinum Liquidum	5.000000000000
Glycerin	3.000000000000
Cetearyl alcohol	2.000000000000
Ceteareth-20	1.000000000000
Phenoxyethanol	0.900000000000
Xanthan Gum	0.324000000000
Aqua	0.254000000000
Hydrochloric acid	0.156000000000
Ethylparaben	0.150000000000
Methylparaben	0.150000000000
Parfum	0.100000000000
Hexyl Cinnamal	0.006640000000
Alpha-Isomethyl Ionone	0.004900000000
Benzyl Salicylate	0.004230000000
Butylphenyl Methylpropional	0.003910000000
Geraniol	0.003150000000
Linalool	0.003000000000
Hydroxycitronellal	0.001910000000
Coumarin	0.001640000000
Citronellol	0.001090000000
Eugenol	0.001000000000
Benzyl Alcohol	0.001000000000

2. Physical/chemical characteristics and stability of the cosmetic product

2.1 Physical/chemical characteristics of the raw materials

White Oil Light

CHEMICAL AND PHYSICAL COMPOSITION			
Composition	**Conc. (%)**	**CAS**	**EINECS**
Paraffinum Liquidum	100	8012-95-1/8042-47-5	232-384-2/232-455-8

Comments:

It is described as white mineral oil (petroleum) a highly refined petroleum mineral oil consisting of a complex combination of hydrocarbons obtained from the intensive treatment of a petroleum fraction with sulfuric acid and oleum, or by hydrogenation, or by a combination of hydrogenation and acid treatment. Additional washing and treating steps may be included in the processing operation. It consists of saturated hydrocarbons having carbon numbers predominantly in the range of C15 through C50. Mineral oil (US).

CHEMICAL AND PHYSICAL SPECIFICATIONS	
Molecular Weight	-
Physical State	Liquid
Organoleptic Properties	Colorless and odorless viscous liquid.
Solubility	Practically insoluble in ethanol (95%), glycerin, and water. Soluble in acetone, benzene, chloroform, carbon disulfide, ether, and petroleum ether. Miscible with volatile oils and fixed oils with the exception of castor oil.
Partition coefficient (Log Pow)	-
pH	-
Nanomaterials	NO

Comments:

IMPURITIES AND/OR ALLERGEN SUBSTANCES

This ingredient does not contain impurities and/or allergen substances.

Myritol 318

CHEMICAL AND PHYSICAL COMPOSITION			
Composition	**Conc. (%)**	**CAS**	**EINECS**
Caprylic/Capric Triglyceride	-	73398-61-5/65381-09-1	277-452-2/265-724-3

Comments:

It is medium-chain triglycerides (a mixed triester of glycerin and caprylic and capric acids).

Fatty Acid	Concentration
C6	0.1%
C8	55.8%
C10	44.1%

The Ph. Eur. 6.0 describes medium-chain triglycerides as the fixed oil extracted from the hard, dried fraction of the endosperm of *Cocos nucifera* L. or from the dried endosperm of *Elaeis guineenis* Jacq. They consist of a mixture of triglycerides of saturated fatty acids, mainly of caprylic acid and of capric acid. They contain not

less than 95% of saturated fatty acids.	
CHEMICAL AND PHYSICAL SPECIFICATIONS	
Molecular Weight	408.57 g/mol
Physical State	Liquid
Organoleptic Properties	Clear, colorless oil with characteristic odour
Solubility	Soluble in acetone, chloroform, dichloromethane, ethanol and ether. Insoluble in water.
Partition coefficient (Log Pow)	8.2 - 10.9
pH	-
Nanomaterials	NO
Comments: Density: 0.945-0.949g/cm3 Viscosity: 27-33mPas (20°C) Acid number: maximum 0.1 Saponification Value: 335-350 Hydroxyl Number: maximum 5 Iodine Number: maximum 0.5 Unsaponification content: maximum 0.5%.	
IMPURITIES AND/OR ALLERGEN SUBSTANCES	
This ingredient does not contain impurities and/or allergen substances.	

Glycerin 4810

CHEMICAL AND PHYSICAL COMPOSITION			
Composition	**Conc. (%)**	**CAS**	**EINECS**
Glycerin	99.5-100	56-81-5	200-289-5
Comments: -			

CHEMICAL AND PHYSICAL SPECIFICATIONS	
Molecular Weight	92.09 g/mol
Physical State	Liquid
Organoleptic Properties	Clear, colorless syrupy liquid
Solubility	Completely soluble in water and ethanol; Slightly soluble in acetone. Solubility in ether: 0.2g/100 mL
Partition coefficient (Log Pow)	-1.76
pH	-
Nanomaterials	NO
Comments: Water content: max.: 0.5% Other impurity eluating before glycerol % <0.1 Total impurity eluating after glycerol % <0.5	

IMPURITIES AND/OR ALLERGEN SUBSTANCES	
Impurity/Allergen substance	**Concentration (%)**
Halogenated compounds	0-0.0030
Chlorides	0-0.0010
Heavy metals	0-0.0005
diethylene glycol	0-0.1

Tegin Pellets

CHEMICAL AND PHYSICAL COMPOSITION			
Composition	**Conc. (%)**	**CAS**	**EINECS**
Glyceryl stearate SE	-	11099-07-3	234-325-6
Comments: Stearic acid, monoester with glycerol			

CHEMICAL AND PHYSICAL SPECIFICATIONS	
Molecular Weight	358.6 g/mol
Physical State	Solid
Organoleptic Properties	Ivory pellets with a slight characteristic odor.
Solubility	Dispersible in water.
Partition coefficient (Log Pow)	-
pH	5-7.5 (100 g/L)
Nanomaterials	NO

Comments:

Melting point: 57-60°C

Ignition point: >200°C

Total monoester content: 32-40%

Free Glycerol: 5.0-8.0%

Iodine value: <= 3.00 g I/100g

Acid Value: 32.00-36.00 mg KOH/g

Melting point: 56.0-61.0 °C

Saponification value: 145.0-160.0 mg KOH/g

IMPURITIES AND/OR ALLERGEN SUBSTANCES
This ingredient does not contain impurities and/or allergen substances.

Goma xantana

CHEMICAL AND PHYSICAL COMPOSITION			
Composition	**Conc. (%)**	**CAS**	**EINECS**
Xanthan Gum	91 - 108	11138-66-2	234-394-2
Comments: Xanthan gum is purified by extraction with ethanol or isopropyl alcohol and			

then dried therefore, traces of this component may be found on its composition.

CHEMICAL AND PHYSICAL SPECIFICATIONS	
Molecular Weight	2-50x106 Da
Physical State	Solid
Organoleptic Properties	Creamy-white odourless free-flow powder
Solubility	Soluble in water giving a highly viscous solution practically insoluble in organic solvents.
Partition coefficient (Log Pow)	-
pH	6.0-8.0
Nanomaterials	NO

Comments:

Viscosity: 1400-1600 mPas (1% in KCl 1%, 60 rpm, 25 °C)

Loss on drying: max 12%.

Granulometry:

- < 80 mesh (0.180 mm) = 100%

- < 200 mesh (0.075 mm) = 92 %

Ash: 6.5%-16%

Pyruvic acid: min 1.5%

IMPURITIES AND/OR ALLERGEN SUBSTANCES	
Impurity/Allergen substance	**Concentration (%)**
Heavy metals	0-0.0020
Arsenic	0-0.0002
Lead	0-0.0002
Mercury	0-0.0001
Nitrogen	0-1.5
Cadmium	0-0.0001
Isopropanol	0-0.0500

Água Termal das Termas de Chaves

CHEMICAL AND PHYSICAL COMPOSITION			
Composition	**Conc. (%)**	**CAS**	**EINECS**
Chaves Thermal Water (Chaves Aqua)	100	7732-18-5	231-791-2

Comments:

The majority components of the analysed thermal water are described below.

Water hole AC1

Anions:

Fluoride (F^-): 7.8 mg/L

Chloride (Cl^-): 40.0 mg/L

Hydrogen carbonate (HCO_3^-): 1624 mg/L

Carbonate (CO_3^{2-}): -

Hydrogen sulfide (HS^-): -

Sulfate (SO_4^{2-}): 25.9 mg/L

Silicate ($H_3SiO_4^-$): -

Phosphate ($H_2PO_4^{-}$): 0.42 mg/L

Nitrate (NO_3^-): 0.31 mg/L

Nitrite (NO_2^-): < 0.01mg/L

Cyanide (CN^-): < 1.0 microg/L

Bromide (Br^-): 0.26 mg/L

Bromate (BrO_3^-): < 0.20

Iodide (I^-): 6 microg/L

Cations:

Lithium (Li^+): 2.4 mg/L

Sodium (Na^+): 581 mg/L

Potassium (K^+): 59.7 mg/L

Magnesium (Mg^{2+}): 5.2 mg/L

Calcium (Ca^{2+}): 21.6 mg/L

Iron (Fe^{2+}): 0.19 mg/L

Iron (Fe^{3+}): 0.03 mg/L

Ammonium (NH_4^+): 1.2 mg/L

Strontium(Sr^{2+}): 0.37 mg/L

Water hole AC2

Anions:

Fluoride (F^-): 8.2 mg/L

Chloride (Cl^-): 38.5 mg/L

Hydrogen carbonate (HCO_3^-): 1760 mg/L

Carbonate (CO_3^{2-}): -

Hydrogen sulfide (HS^-): -

Sulfate (SO_4^{2-}): 18.8 mg/L

Silicate ($H_3SiO_4^-$): -

Phosphate ($H_2PO_4^{-}$): 0.13 mg/L

Nitrate (NO_3^-): 0.30 mg/L

Nitrite (NO_2^-): < 0.01mg/L

Cyanide (CN^-): < 1.0 microg/L

Bromide (Br^-): 0.23 mg/L

Bromate (BrO_3^-): < 0.20

Iodide (I^-): 6 microg/L

Cations:

Lithium (Li^+): 2.6 mg/L

Sodium (Na^+): 630 mg/L

Potassium (K^+): 61.1 mg/L

Magnesium (Mg^{2+}): 5.1 mg/L

Calcium (Ca^{2+}): 21.2 mg/L

Iron (Fe^{2+}): 0.19 mg/L

Iron (Fe^{3+}): 0.02 mg/L

Ammonium (NH_4^+): 1.2 mg/L

Strontium(Sr^{2+}): 0.4 mg/L	
CHEMICAL AND PHYSICAL SPECIFICATIONS	
Molecular Weight	18 g/mol
Physical State	Liquid
Organoleptic Properties	Clear, colorless liquid with sulfuric odor
Solubility	-
Partition coefficient (Log Pow)	-
pH	8.86 (21.2 °C)
Nanomaterials	NO

Comments:

Water hole AC1

Anions: 1698 mg/L

Cations: 672 mg/L

Silica: 79.5 mg/L

Conductivity (20 °C): 2150 µS/cm

Alkalinity: 266.2 (mL/L de HCl 0.1M)

Total hardness: 7.5 p.p. 10^5 $CaCO_3$

Total CO_2 : - (mmol/L de CO_2)

Total sulfidation: - (mL/L I_2 0.01N)

Dry residue (180°C): 1606 mg/L

Water hole AC2

Anions: 1826 mg/L

Cations: 722 mg/L

Silica: 84.6 mg/L

Conductivity (20 °C): 2300 µS/cm

Alkalinity: 288.6 (mL/L de HCl 0.1M)

Total hardness: 7.4 p.p. 10^5 $CaCO_3$

Total CO_2 : - (mmol/L de CO_2)

Total sulfidation: - (mL/L I_2 0.01N)

Dry residue (180°C): 1722 mg/L

IMPURITIES AND/OR ALLERGEN SUBSTANCES	
Impurity/Allergen substance	**Concentration (%)**
Aluminium	0.00000146
Arsenic	0.0000128
Lead	0-0.000000006
Mercury	0-0.000000054
Selenium	0-0.00000149
Silver	0-0.000000012
Boron	0.0000729
Barium	0.0000431
Beryllium	0.00000144
Cadmium	0-0.000000015
Cobalt	0.000000073
Chromium	0.00000076
Copper	0-0.000000039
Cesium	0.0000407
Manganese	0.00000429
Molybdenum	0.00000014
Nickel	0-0.00000076
Rubidium	0.0000492
Antimony	0.00000032
Tin	0-0.000000026
Tantalum	0-0.000000001
Tellurium	0-0.00000011
Thallium	0.00000078
Uranium	0.000000025
Vanadium	0.000000054
Tungsten	0.00000347
Zinc	0.00000213
Zirconium	0-0.00000019
Bismuth	0-0.000000005
yttrium	0-0.000000001
niobium	0-0.000000005

Sabowax CS 20

CHEMICAL AND PHYSICAL COMPOSITION			
Composition	**Conc. (%)**	**CAS**	**EINECS**
Ceteareth-20	99-100	68439-49-6	-
Comments: -			

CHEMICAL AND PHYSICAL SPECIFICATIONS	
Molecular Weight	-
Physical State	Solid
Organoleptic Properties	White, waxy, flakes
Solubility	Soluble in water and alcohol. Insoluble in paraffinic oils
Partition coefficient (Log Pow)	-
pH	at 5%: 5.5 - 7.5
Nanomaterials	NO
Comments: Moisture: 1% max	

IMPURITIES AND/OR ALLERGEN SUBSTANCES	
Impurity/Allergen substance	**Concentration (%)**
1,4-Dioxane	0
Ethylene oxide	0

1051936 NIVAL

CHEMICAL AND PHYSICAL COMPOSITION			
Composition	**Conc. (%)**	**CAS**	**EINECS**
Parfum	-	-	-

Comments:

It is not known the exact composition of the perfume. This perfume is a mixture of natural and synthetic odour compounds, without ethanol. The following table shows the hazardous components for human health and their content, present in this perfume.

Compound	CAS	EINECS	Concentration (%)
4-tert-Butylcyclohexyl Acetate	32210-23-4	250-954-9	10 - 25
Linalyl Acetate	115-95-7	204-116-4	1 -5
Tricyclodecenyl Propionate	17511-60-3	241-514-7	1 - 5
Phenethyl acetate	103-45-7	203-113-5	1 - 5
Terpineol	8000-41-7	232-268-1	1 - 5
Coumarin	91-64-5	202-086-7	1 - 5
a-terpinyl acetate	80-26-2	201-265-7	1 - 5
Nerol	106-25-2	203-378-7	1 - 5
2,6-dimethyl-7-octen-2-ol	18479-58-8	242-362-4	1 - 5
Undecylenal	112-45-8	203-973-1	1 - 5
Citronellyl acetate	150-84-5	205-775-0	0.1 - 1
Geranyl acetate	105-87-3	203-341-5	0.1 - 1

CHEMICAL AND PHYSICAL SPECIFICATIONS	
Molecular Weight	-

Physical State	Liquid
Organoleptic Properties	Transparent, yellow liquid with a floral-aldehyde characteristic odour
Solubility	-
Partition coefficient (Log Pow)	-
pH	-
Nanomaterials	NO
Comments: Flashpoint: > 100 °C Density: 0.9740 - 1.0140 g/cc (20 °C)	

IMPURITIES AND/OR ALLERGEN SUBSTANCES

Impurity/Allergen substance	Concentration (%)
Alpha-Isomethyl Ionone	4.9050
Benzyl Alcohol	1.0021
Benzyl Benzoate	0.0128
Benzyl Salicylate	4.23
Butylphenyl Methylpropional	3.9091
Citral	0.0014
Citronellol	1.0909
Coumarin	1.6364
Eugenol	1
Geraniol	3.1547
Hexyl Cinnamal	6.6364
Hydroxycitronellal	1.9091
Hydroxyisohexyl 3-Cyclohexene Carboxaldehyde	0.5455
Isoeugenol	0.9091
Linalool	3
Limonene	0.0036

Phenonip ME

CHEMICAL AND PHYSICAL COMPOSITION

Composition	Conc. (%)	CAS	EINECS
Ethylparaben	12.5	120-47-8	204-399-4
Methylparaben	12.5	99-76-3	202-785-7
Phenoxyethanol	75	122-99-6	204-589-7

Comments: -

CHEMICAL AND PHYSICAL SPECIFICATIONS

Molecular Weight	-
Physical State	Liquid
Organoleptic Properties	Colourless to light straw viscous liquid with a characteristic odour
Solubility	Solubility: water (approx. 0.7 %), ethanol/water 50/50 (> 95 %), Liquid Paraffin (< 0.1 %), Glycerol (approx. 8 %). Soluble in Ethanol. Miscible in Isopropanol, Acetone, Propylene Glycol and Sodium Laureth Sulfate (28 %)
Partition coefficient (Log Pow)	-
pH	-

Nanomaterials	NO

Comments:

Compound	Molecular Weight (g/mol)	Partition coefficent
Ethylparaben	166.17	2.47
Methylparaben	152.15	1.96
Phenoxyethanol	138.16	1.16

IMPURITIES AND/OR ALLERGEN SUBSTANCES

This ingredient does not contain impurities and/or allergen substances.

Acido Clorhídrico 37% grado técnico

CHEMICAL AND PHYSICAL COMPOSITION

Composition	Conc. (%)	CAS	EINECS
Hydrochloric acid	36.5-39	7647-01-0	231-595-7
Aqua	61-63.5	7732-18-5	231-791-2

Comments: -

CHEMICAL AND PHYSICAL SPECIFICATIONS

Molecular Weight	36.46 g/mol
Physical State	Liquid
Organoleptic Properties	Colorless liquid with characteristic odor.
Solubility	Miscible in water.
Partition coefficient (Log Pow)	-
pH	-
Nanomaterials	NO

Comments:

Relative density: 1.185 - 1.195

Compound	Molecular weight (g/mol)	Partition Coefficient
Water	18.01528	-0.5
Hydrochloric acid	36.46	-

IMPURITIES AND/OR ALLERGEN SUBSTANCES

Impurity/Allergen substance	Concentration (%)
iron	0.005
Sulfate	0.005
Arsenic	0.0003
Lead	0.005
Ammonium	0.005

SABONAL C1618 50/50

CHEMICAL AND PHYSICAL COMPOSITION			
Composition	**Conc. (%)**	**CAS**	**EINECS**
Cetearyl alcohol	100	67762-27-0 / 8005-44-5	267-008-6 / -

Comments:

C16 (Cetyl alcohol) content: 45% - 55%

C18 (Stearyl alcohol) content: 45% - 55%

CHEMICAL AND PHYSICAL SPECIFICATIONS	
Molecular Weight	512.93 g/mol
Physical State	Solid
Organoleptic Properties	White flakes (at 20°C)
Solubility	Insoluble in water
Partition coefficient (Log Pow)	-
pH	-
Nanomaterials	NO

Comments:
This ingredient is mainly constituted by two compounds, which molecular weights and partition coefficients are represented in the table below:

Compound	Molecular weight (g/mol)	Partition Coefficient
Stearyl alcohol	270.49	8.4
Cetyl alcohol	242.44	7.3

IMPURITIES AND/OR ALLERGEN SUBSTANCES

This ingredient does not contain impurities and/or allergen substances.

2.2 Stability and reactivity of the raw materials

White Oil Light

Stability and Reactivity
Mineral oil should be stored in an airtight container, protected from light, in a cool, dry place. The contact with strong oxidizing agents, O_2 and Cl_2 should be avoided. Mineral oil undergoes oxidation when exposed to heat and light. Oxidation begins with the formation of peroxides, exhibiting an "induction period". Under ordinary conditions, the induction period may take months or years. However, once a trace of peroxide is formed, further oxidation is autocatalytic and proceeds very rapidly. Oxidation results in the formation of aldehydes and organic acids, which impart taste and odor. Stabilizers may be added to retard oxidation, being butylated hydroxyanisole, butylated hydroxytoluene and alpha tocopherol the most commonly used antioxidants.

Myritol 318

Stability and Reactivity
This substance is stable under normal conditions of use. Should be stored in well-closed recipients, protected from moisture, in well-ventilated place at temperatures below 30ºC.

Glycerin 4810

Stability and Reactivity
Store at room temperature in a clean and aerated place. For bulk storage, it is recommended to keep the product in nitrogen flushed tanks. This ingredient is hygroscopic. It decomposes by temperature rise, releasing corrosive, toxic vapors (acrolein). It may form CO and CO2 in case of combustion. It can polymerize by increase of temperature. Reacts violently with (strong) oxidizing agents and with (some) acids (increased) with risk of fire or explosion. Avoid heat sources, oxidizing agents, strong acids and strong alkalis. The container must be kept in a well-ventilated space at room temperature and protected from direct sun light. Storage material: steel, aluminium, iron or glass.

Tegin Pellets

Stability and Reactivity
It is stable under normal conditions. No hazardous reactions or decomposition products when properly stored and handled.

Goma xantana

Stability and Reactivity
Stable under normal storage and handling conditions. Aqueous solutions are stable over a wide pH range (pH 3–12), although they demonstrate maximum stability at pH 4–10 and temperatures of 10–60°C. Xanthan gum solutions of less than 1% w/v concentration may be adversely affected by higher than ambient temperatures: for example, viscosity is reduced. Xanthan gum provides the same thickening, stabilizing, and suspending properties during long-term storage at elevated temperatures as it does at ambient conditions. In addition, it ensures excellent freeze–thaw stability. Solutions are also stable in the presence of enzymes, salts, acids, and bases. Xanthan gum is an anionic material and is not usually compatible with cationic surfactants, polymers, or preservatives, as precipitation occurs. Anionic and amphoteric surfactants at concentrations above 15% w/v cause precipitation of xanthan gum from a solution. Under highly alkaline conditions, polyvalent metal ions such as calcium cause gelation or precipitation; this may be inhibited by the addition of a glucoheptonate sequestrant. The presence of low levels of borates (Store in a covered, well-ventilated place in the original packaging unopened. This ingredient will not undergo hazardous polymerization. Avoid the formation of dust when handling and avoid head, sparks and all possible sources of ignition (spark or flame). Take precautionary measures against electrostatic discharges. To avoid fire or explosion, dissipate static electricity during transfer by grounding and bonding containers and equipment before transferring material. Prevent dust accumulation. Reactive or incompatible with the following materials: oxidizing materials. There is the risk of combustion when in contact with: carbon dioxide and carbon monoxide. Avoid draining containers in the presence or near flammable vapors.

Água Termal das Termas de Chaves

Stability and Reactivity
This water is stable for one month after its abstraction, when kept in a tightly closed HDPE bottle, at room temperature.

Sabowax CS 20

Stability and Reactivity
No decomposition if used according to specifications. The contact with strong acids, oxidizers and bases must be avoided. Suitable materials are: polyethylene (PE) resin, phenol-epoxy EHD0022, Oven-varnish R 78433 and High density polyethylene (HDPE). Store at temperatures below 30 °C, protected from moisture. The product melts above 35 °C. Should be kept away from heat, sparks, open flames and hot surfaces. It has to be stored in a cool place in closed original container. Depending on the temperature, the pH value may decrease during storage. However, the product quality is not negatively influenced above a pH value of 4.0.

1051936 NIVAL

Stability and Reactivity
Keep the product in a tightly closed container, in a dry and well-ventilated place. Keep the product away from ignition sources and protected from light. Incompatible with strong reducing agents, azo and diazo compounds, hydrazines, nitrides, caustics, strong oxidizing agents, epoxides and acids. During combustion, carbon monoxide and unidentified

organic compounds may be formed.

Phenonip ME

Stability and Reactivity
Phenonip ME remains fully stable over a wide pH range from 3- 8. The product must be protected from excessively high temperatures during storage. This mixture may react with oxidant agents and strong oxidant agents.

Acido Clorhídrico 37% grado técnico

Stability and Reactivity
This mixture is stable under normal conditions. Store in well-closed recipients at room temperature, in well-ventilated area. Do not store in metallic recipients. The contact with several materials must be avoided: aluminium, amines, carbons, fluor, alkaline metals, strong bases, halogenates, concentrated sulfuric acid, metalloid oxides. aldehydes.

SABONAL C1618 50/50

Stability and Reactivity
Store in a cool, dry and well ventilated area. Hazardous polymerization will not occur. Incompatible with strong oxidizing materials. Hazardous decomposition products are oxides of carbon (CO, CO2).

2.3 Physical/chemical characteristics of the cosmetic product

	Specifications	**Method**
Organoleptic Properties	White homogeneous emulsion with characteristic odour of the fragrance	Sensorial analysis
pH	5.5 - 6.0	Potentiometer
Viscosity	20000 – 30000 cP	Viscometer (T=25°; t=1min; v=12RPM; Spindle R5)
Specific gravity	-	-

Comments: -

2.4 Stability of the cosmetic product

At the time of this report, a long term stability study is under course. Samples will be stored at room temperature in the final packaging for 30 months and physical-chemical analysis will be performed after 3 months, 6 months and 30 months. Moreover, the experimental determination of PAO is also being performed to confirm the theoretically estimated value of 14 months. The theoretical estimation of the PAO of the product was performed according to the guidelines "Recommandations relatives a l'estimation de la Period Apres Ouverture (PAO)", from the "Agence Française de securité sanitaire de produits de santé".

3. Microbiological quality

3.1 Microbiological specifications of the raw materials

White Oil Light

The microbiological specifications for this ingredient are not known.

Myritol 318

The microbiological specifications for this ingredient are unknown.

Glycerin 4810

The microbiological specifications for this ingredient are unknown.

Tegin Pellets

The microbiological specifications for this ingredient are unknown.

Goma xantana

The microbiological specifications for this ingredient are:

Total Plate Count: 1000/g maximum

E. Coli: negative/25g

Coliforms: negative per MPN

Salmonella: negative/25g

Pseudomonas aeruginosa: negative/g

Staphylococcus aureus: negative/g

Enterococcus faecalis: negative/ g

Moulds: maximum 50 CFU/g

Yeasts: 50 /g CFU maximum

Xanthomonas campestris: negative/ g

Água Termal das Termas de Chaves

The microbiological specifications for this ingredient are:

Clostridium sulfite reducers: 0 CFU / 50 mL

Fecal coliforms: 0 CFU / 250 mL

Total coliforms: 0 CFU / 250 mL

Enterococci: 0 CFU / 250 mL

Escherichia coli: 0 CFU / 250 mL

Total viable count (22 ° C): < 100 CFU/ml

Total viable count (36 ° C): < 20 CFU/ml

Pseudomonas aeruginosa: 0 CFU / 250 mL

Staphylococcus Coagulase (+): 0 CFU / 100 mL

Sabowax CS 20

The microbiological specifications of this ingredient are not known.

1051936 NIVAL

The microbiological specifications for this ingredient are unknown.

Phenonip ME

The microbiological specifications for this ingredient are not known. However, once it is a preservative agent, microbiological contamination is not expected to occur.

Acido Clorhídrico 37% grado técnico

The microbiological specifications for this mixture are not known. Nevertheless, the pH of this raw material is very low, therefore microbial contamination is unlikely to occur.

SABONAL C1618 50/50

The microbiological specifications for this ingredient are not known.

3.2 Microbiological characteristics of the final cosmetic product

The microbiological specifications for this product are:

- Bacteria: < 50 CFU/g;
- Yeast and Mold: < 50 CFU/g;
- *Candida albicans*: absent;
- *Staphilococus aureus*: absent;
- *Pseudomonas aeroginosa*: absent

3.3 Results of preservation challenge test

A challenge test according to European Pharmacopoeia 8 was performed to evaluate the efficacy of the preservative system of the cosmetic product Creme de Rosto, which was not the final formula of DERMOCOSMÉTICA TERMAL AQUAE CREME HIDRATANTE ROSTO. Nevertheless, the preservative system was not altered and the differences in the other ingredients are minimal, therefore the results of this Challenge Test can be considered valid.

The following microorganisms were included in the assay and incubated in the coditions as described:

Staphylococcus aureus ATCC 6538 - 35º C, 2 days
Pseudomonas aeruginosa ATCC 9027 - 35º C, 2 days
Candida albicans ATCC 10231 - 25º C, 2 days
Aspergillus brasiliensis ATCC 16404 - 25º C, 5 days

The test product was inoculated separately with each one of the test microorganisms at a ratio of 200 µL calibrated cell suspension to 20 g of test product. The results of the challenge test are shown in the table below:

Microorganisms	**2 days (CFU)**	**2 days (Δlog)**	**7 days (CFU)**	**7 days (Δlog)**	**14 days (CFU)**	**14 days (Δlog)**	**28 days (CFU)**	**28 days (Δlog)**	**Criteria**
S. aureus ATCC 6538	4.72E+05	0.24	4.46E+04	1.27; N/I *	0	5.92; N/I*	0	5.92; N/I*	B
P. aeruginosa ATCC 9027	0	6.09	0	6.09; N/I *	0	6.09; N/I*	0	6.09; N/I*	A
C. albicans ATCC 10231	---	---	---	---	0	5.28; N/I*	0	5.28; N/I*	A
A. brasiliensis ATCC 16404	---	---	---	---	0	4.85	0	4.85; N/I*	A

- N/I – No increase

The study performed with the sample of product "Creme de Rosto" allows to conclude that the product meets criteria B of European Pharmacopoeia 8, and therefore the product is protected against microbial proliferation which could pose a potential risk for the consumer. Since the formula of DERMOCOSMÉTICA TERMAL AQUAE CREME HIDRATANTE ROSTO is equivalent, it can be assumed that it will have the same profile.

4. Impurities, traces, information about the packaging material

4.1 Impurities of the Raw Materials

Besides the possible impurities that this cosmetic product may contain, it is also included in this section all its allergen substances.

IMPURITIES AND/OR ALLERGEN SUBSTANCES	
Impurity/Allergen substance	**Total Concentration (%)**
iron	0.00002
Halogenated compounds	0.00009
Chlorides	0.00003
Sulfate	0.00002
1,4-Dioxane	unknown
Heavy metals	0.00002
Ethylene oxide	unknown
Alpha-Isomethyl Ionone	0.00490
Benzyl Alcohol	0.00100
Benzyl Benzoate	0.00001
Benzyl Salicylate	0.00423
Butylphenyl Methylpropional	0.00391
Citral	0.000001
Citronellol	0.00109
Coumarin	0.00164
Eugenol	0.00100
Geraniol	0.00315
Hexyl Cinnamal	0.00664
Hydroxycitronellal	0.00191
Hydroxyisohexyl 3-Cyclohexene Carboxaldehyde	0.00055
Isoeugenol	0.00091
Linalool	0.00300
Aluminium	0.000001
Arsenic	0.00001
Lead	0.00002
Mercury	0.0000003
Limonene	0.000004
Selenium	0.000001
Nitrogen	0.00450
Silver	0.00000001
Boron	0.00005
Barium	0.00003

Beryllium	0.000001
Cadmium	0.0000003
Cobalt	0.0000001
Chromium	0.000001
Copper	0.00000003
Cesium	0.00003
Manganese	0.000003
Molybdenum	0.0000001
Nickel	0.000001
Rubidium	0.00004
Antimony	0.0000002
Tin	0.00000002
Tantalum	0.000000001
Tellurium	0.0000001
Thallium	0.000001
Uranium	0.00000002
Vanadium	0.00000004
Tungsten	0.000003
Zinc	0.000002
Zirconium	0.0000001
Ammonium	0.00002
Isopropanol	0.00015
Diethylene glycol	0.00300
Bismuth	0.000000004
Yttrium	0.000000001
Niobium	0.000000004

4.2 Traces of prohibited compounds in the cosmetic product

Some impurities present in this product are in the list of substances prohibited in cosmetic products (Annex II of the Regulation EC 1223/2009). However, according the article 17 of the same regulation, the non-intended presence of a small quantity of a prohibited substance, stemming from impurities of natural or synthetic ingredients, the manufacturing process, storage, migration from packaging, which is technically unavoidable in good manufacturing practice, shall be permitted provided that such presence is in conformity with Article 3, when used under normal or reasonably foreseeable conditions of use. The presence of these traces is technically unavoidable, even following good manufacturing practices, because they are impurities of raw materials used and they are: Arsenic (present in Goma xantana, Água Termal das Termas de Chaves and Acido Clorhídrico 37% grado técnico); Lead (present in Goma xantana, Água Termal das Termas de Chaves and Acido Clorhídrico 37% grado técnico); Mercury (present in Goma xantana and Água Termal das Termas de Chaves); Cadmium (present in Goma xantana and Água Termal das Termas de Chaves); Diethylene glycol (present in Glycerin 4810); Selenium, Beryllium, Chromium, Nickel, Antimony, Thallium and Zirconium (present in Água Termal das Termas de Chaves).

The substances 1,4-dioxane and Ethylene Oxide may be present in the raw material Sabowax CS 20, although it is not mentioned by the supplier.

It is also important to point out that one of these substances has carcinogenic, mutagenic or reproductive potential, being listed in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labeling of hazardous substances):

- 1,4-Dioxane - Carcinogenic Category 2
- Ethylene Oxide - Mutagenicity toxicity and Carcinogenic Category 1B
- Lead - Reproductive toxicity Category 1A
- Mercury – Reproductive toxicity Category 1B
- Beryllium - Carcinogenic Category 1B
- Cadmium - Mutagenicity and reproductive toxicity Category 2
- Nickel - Carcinogenic Category 2.

4.3 Characteristics of the packaging material

The packaging of this cosmetic product is an Airless Flask provided by Eurovetrocap, S.r.l under the reference Airless Nina 50cc 24/410 Assieme – Bocca 24/4110. This flask is composed of several parts as follows:

Part	Material
Flask	
Body	PP
Piston	HDPE
Base	PP
Pump	
Regulator	PP
Stem	HDPE
Spring	TPE
Body	PBT
Ring	PP
Membrane	TPV
Seal	EPE / LDPE

Flask:

- The body is made of Polypropylene, supplied by REPSOL – D.E. Química EURM, under the trade name Polipropileno ISPLEN® PR 280 P1M.
- The piston is made of High Density Polyethylene, supplied by Versalis S.p.A., under the trade name ERACLENE® MP 90 U.

Pump:

- The regulator is made of Polypropylene, supplied by TOTAL PETROCHEMICALS, under the trade name Polypropylene PPR 10222.
- The stem is made of High Density Polyethylene, supplied by INEOS Olefins & Polymers Europe, under the trade name Rigidex® HD5226EA.
- The spring is made of Thermoplastic Polyester elastomer, supplied by DSM Product, under the trade name Arnitel® EL250.
- The body is made of Polybutylene Terephthalate, supplied by Ticona - Performance Driven Solutions, under the trade name Celanex® 2500.
- The ring is made of Polypropylene, supplied by TOTAL PETROCHEMICALS, under the trade name Polypropylene PPR 10222.
- The membrane is made of Termoplastic Vulcanizate, supplied by ExxonMobil Chemical, under the trade name SantopreneTM 271-55.
- The seal is made of Expanded polyethylene and Low-density polyethylene, supplied by Action Technology, under the trade name Tri Seal F-217-5.

A 30-month stability study in the final packaging is being performed and results of product-packaging material compatibility will be assessed.

5. Normal and reasonably foreseeable use

Mode of application	The product is rubbed-on the face.
Warnings	-
Comments: -	

6. Exposure to the cosmetic product

Product type	Leave-on
Retention factor	1.00
Site of application	Face
Amount of product applied per application (mg)	1448.40
Duration of use	Undetermined
Normal and reasonably foreseeable exposure route(s)	Topical
Routes of secondary exposure	Ophthalmic
Targeted (or exposed) population(s)	Healthy adults
Possible impacts on exposure due to particle sizes	This product does not contain nanomaterials that can affect human health

Calculation of the Exposure	
mg/day	1448.40
mg/cm2 skin/day	2.56
mg/kg body weight/day	24.14

7. Exposure to the raw materials

		Calculation of the Exposure		
Raw material (trade name)	**Conc. (%)**	**mg/day**	**mg/cm2 skin/day**	**mg/kg body weight/day**
White Oil Light	5.00000	72.4200	0.1280	1.2070
Myritol 318	8.00000	115.8720	0.2048	1.9312
Glycerin 4810	3.00000	43.4520	0.0768	0.7242
Tegin Pellets	8.00000	115.8720	0.2048	1.9312
Goma xantana	0.30000	4.3452	0.0077	0.0724
Água Termal das Termas de Chaves	72.70000	1 052.9868	1.8611	17.5498
Sabowax CS 20	1.00000	14.4840	0.0256	0.2414
1051936 NIVAL	0.10000	1.4484	0.0026	0.0241
Phenonip ME	1.20000	17.3808	0.0307	0.2897
Acido Clorhídrico 37% grado técnico	0.40000	5.7936	0.0102	0.0966
SABONAL C1618 50/50	2.00000	28.9680	0.0512	0.4828

8. Toxicological profile of the substances/raw materials and other information

8.1 Toxicological profile of the substances (INCI name)

Paraffinum Liquidum

REGULATORY RESTRICTIONS
According to the Regulation EC 1223/2009 and respective amendments, there are no restrictions on the use of this ingredient in cosmetic products.

ACUTE TOXICITY

Administration Route	Adverse effects description	LD50	Ref.
Oral	Daily doses of up to 45mL have been administered orally, while doses of up to 120mL have been used as an enema. However, excessive dosage of mineral oil can result in anal seepage and irritation, and its oral use as a laxative is not considered desirable. It may cause diarrhea. If large amounts are ingested, and vomiting occurs, may be aspirated during vomiting, which can cause chemical pneumonitis or pulmonary edema, with serious lung damage, or even death.	(mouse): 22 g/kg; (rat): > 2000 mg/Kg (rabbit) > 5g/Kg	1,2,3,4
Inhalation	The most serious adverse reaction to mineral oil is lipoid pneumonia caused by aspiration of the oil. Mineral oil can enter the bronchial tree without eliciting the cough reflex. Negligible hazard up to 38°C. At temperatures above, it may form vapors irritating and harmful to upper respiratory tract.	-	5,3
Dermal	It is normally considered as not dangerous for the skin.	-	2
Subcutaneous	-	-	

Comments:
Mineral oil is used as an excipient in a wide variety of pharmaceutical formulations. It is also used in cosmetics and in some food products. Therapeutically, mineral oil has been used in the treatment of constipation, as it acts as a lubricant and stool softener when taken orally. Moreover, it is used in ophthalmic formulations for its lubricant properties **(4)** .

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	It shows low toxicity. May cause irritation to sensitive people to the components of the formula.	1,3
Ocular Irritation	It may cause eye irritation.	3
Sensitization	Given its widespread use in many topical products, mineral oil has been associated with few instances of allergic reactions.	4
Dermal Absorption	Data support the view that mineral oil does not effectively penetrate the skin beyond the stratum corneum, resulting in minimal (< 1 %) absorption of white mineral oils after topical exposure.	6

Comments:
-

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.
Oral	Chronic oral consumption of mineral oil may impair the appetite and interfere with the	4

	absorption of fat-soluble vitamins. Prolonged use should be avoided.	
Inhalation	Long term inhalation studies indicate that this oil has a low chronic toxicity. On the other hand, repeated prolonged exposures have resulted in lung inflammatory reactions and lipoid granuloma formation.	7
Dermal	-	

Comments:
May cause drowsiness and loss of consciousness **(1)** .

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY

		Ref.
Carcinogenicity	In groups of 30 rats of strains BDI, BD111, and W (sex unspecified) that received 2% liquid paraffin in the diet (total dose, 136 mg/animal in 500 days), no significant tumor induction was reported.	7
Mutagenicity	There is no data available on the mutagenic effects of this ingredient.	
Teratogenicity	Groups of 25 chickens with 9 day old chicken embryos were exposed to 10 or 20 microL pharmaceutical mineral oil on the eggshell. There were no mortalities or embryos with edema, ascites or liver lesions in either treated group. No histological changes were observed in the livers or kidneys. However embryos exposed to 20 microL mineral oil had slight dilation of the heart. Body wt, liver wt, crown-rump length, and body wt/crown-rump length ratio of the embryos exposed to mineral oil did not differ from those of controls. Hypoprothrombinemia and hemorrhagic disease of the newborn has occurred when mineral oil was chronically administered orally to pregnant women.	7

Comments:
-

PHOTO-INDUCED TOXICITY

There is no data available on the photo-toxic effects of this ingredient.

Ethylparaben

REGULATORY RESTRICTIONS

This ingredient is listed in Regulation EC 1223/2009 annex V (list of preservatives which cosmetic products may contain). According to this Regulation and respective amendments, the use of this paraben in cosmetic products is restricted to a maximum concentration of 0.4% (as acid) for single ester, and 0.8% (as acid) when a mixture of esters is used. CIR (Cosmetic Ingredient Review) considers that this compound is safe when applied in the above-mentioned concentrations.

ACUTE TOXICITY

Administration Route	Adverse effects description	LD50	Ref.
Oral	Ingestion of a 0.03% aqueous ethylparaben solution caused irritation to the intestinal mucosa.	(rat, female): 4.30 g/kg; (rat): 11.0 g/kg; (guinea pig): 2.0 g/kg; (rabbit): 5.0 g/kg; (mouse): 3.0 g/kg; (dog): 5.0 g/kg	8
Inhalation	-	-	
Dermal	It may cause human skin irritation.	(rabbit): 15.0 g/kg	8
Subcutaneous	-	-	

Comments:
Ethylparaben is widely used as an antimicrobial preservative in cosmetics, food products, and pharmaceutical formulations. It may be used either alone or in combination with other paraben esters or with other antimicrobial agents. In cosmetics it is one of the most frequently used preservatives. **(4)** Acute toxicity studies in animals indicate that Parabens are not significantly toxic by various routes of administration. **(9)**

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	Ethylparaben was a skin irritant in man.	8
Ocular Irritation	Ethylparaben at 100% instilled into the eyes of albino rabbits was slightly irritating and at	8

	10% in water produced no signs of irritation. Parabens are often incorporated in creams, lotions and ointments that may be used in the region of the eyes, and occasionally cause redness and swelling of eyelids from allergic contact dermatitis.	
Sensitization	Systemically, no adverse reaction to parabens have been reported, although they have been associated with hypersensitivity reactions, generally of the delayed type and appearing as contact dermatitis. Parabens are capable of inducing cutaneous allergic responses, however, given the widespread use of parabens as preservatives, such reactions are relatively uncommon.	10,4
Dermal Absorption	There are evidences of parabens being rapidly absorbed by animal and human skin. However, available in vitro dermal absorption study results point towards a potential difference in dermal absorption between rat and man. Consequently the rat data as such cannot be simply extrapolated to the human situation without additional supportive data. Nevertheless, until a properly conducted dermal absorption and toxicokinetic study in humans will allow the assignment of a more scientifically solid value, the SCCS will use a dermal absorption value of 3.7% in its margin of safety calculations.	11
Comments: -		

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.
Oral	Chronic oral studies indicate that Parabens are practically non-toxic.	9
Inhalation	-	
Dermal	-	
Comments: -		

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY

		Ref.
Carcinogenicity	Ethylparaben in the diet produced cell proliferation in the forestomach of rats.	9
Mutagenicity	At a concentration of 10 mmol/L, ethylparaben was mutagenic in Escherichia coli. Numerous genotoxicity studies, including Ames testing, dominant lethal assay, host-mediated assay, and cytogenic assays, indicate that Parabens are generally non-mutagenic, although ethylparaben did increase chromosomal aberrations in a Chinese Hamster ovary cell assay.	8,9
Teratogenicity	Ethylparaben was non teratogenic in rats.	9
Comments: -		

PHOTO-INDUCED TOXICITY

In general, parabens do not exhibit significant levels of photo-contact sensitization or photo-toxicity. **(4)**

Methylparaben

REGULATORY RESTRICTIONS

This ingredient is listed in Regulation EC 1223/2009 annex V (list of preservatives which cosmetic products may contain). According to this Regulation and respective amendments, the use of this paraben in cosmetic products is restricted to a maximum concentration of 0.4% (as acid) for single ester, and 0.8% (as acid) when a mixture of esters is used. CIR (Cosmetic Ingredient Review) considers that this compound is safe when applied in the above-mentioned concentrations. CIR (Cosmetic Ingredient Review) considers that this compound is safe when applied in the above-mentioned concentrations.

ACUTE TOXICITY

Administration Route	Adverse effects description	LD50	Ref.
Oral	No toxic effects were observed in animal assays.	(dog): 3.0 g/kg; (dog): 12.2 g/kg; (rabbit): 6 g/kg; (rat): 2.0 g/kg; (mouse):	10,12,4

		> 8 g/kg; (male rat): > 3200 mg/kg; (female rat): > 2280 mg/kg	
Inhalation	-	-	
Dermal	Slightly hazardous in case of skin contact (may cause contact dermatitis).	-	10,4
Subcutaneous	-	(mouse): 1.20 g/kg	4

Comments:
Methylparaben is widely used as an antimicrobial preservative in cosmetics, food products, and oral and topical pharmaceutical formulations. It may be used either alone or in combination with other parabens or with other antimicrobial agents. In cosmetics, methylparaben is the most frequently used antimicrobial preservative **(4)** . Acute toxicity studies in animals indicate that Parabens are not significantly toxic by various routes of administration **(9)** .

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	Parabens are practically non-irritating in the population with normal skin, however, methylparaben (Isocide MP) can cause skin irritation.	12,9
Ocular Irritation	It can cause irritation. Parabens are often incorporated in creams, lotions and ointments that may be used in the region of the eyes, and occasionally cause redness and swelling of eyelids from allergic contact dermatitis.	8,12
Sensitization	When tested on guinea pigs, methylparaben did not induce sensitization effects. No sensitization was reported on a HRIPT (Human Repeated Insult Patch Test) with 50 subjects. Parabens are capable of sensitizing skin and inducing cutaneous allergic responses, although incidence of such reactions is low. Hypersensitivity reactions to parabens, generally of the delayed type and appearing as contact dermatitis, have been reported. However, given the widespread use of parabens as preservatives, such reactions are relatively uncommon.	10,4
Dermal Absorption	There are evidences of parabens being rapidly absorbed by animal and human skin. However, available in vitro dermal absorption study results point towards a potential difference in dermal absorption between rat and man. Consequently the rat data as such cannot be simply extrapolated to the human situation without additional supportive data. Nevertheless, until a properly conducted dermal absorption and toxicokinetic study in humans will allow the assignment of a more scientifically solid value, the SCCS recommends a dermal absorption value of 3.7% in its margin of safety calculation.	11

Comments:
-

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.
Oral	A chronic oral toxicity study in which methylparaben was incorporated into diets at 2 or 8% and the diets fed to groups of 24 rats for 96 weeks was performed. At 2% of the diet, parabens exerted no toxic effect. Rats killed at the conclusion of the feeding test had no treatment related abnormalities. Weanling dogs were dosed 1 g/kg/day methylparaben for 378 to 422 days; and three other dogs, 0.5 g/kg/day methylparaben for 318 to 394 days. No toxicity to the paraben was observed. All animals were in excellent condition throughout the experiment. All tissues were normal. Chronic oral studies indicate that Parabens are practically non-toxic.	10,9
Inhalation	-	
Dermal	-	

Comments:
-

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY

		Ref.
Carcinogenicity	Methylparaben was non-carcinogenic when injected subcutaneously in mice or rats or when administered intravaginally in rats. Although some concern was raised about possible carcinogenic effects of parabens when used in underarms products, the SCCS concluded that there was insufficient data to establish a link between the use of underarm cosmetics and	9,11

	breast cancer.	
Mutagenicity	Numerous genotoxicity studies, including Ames tests, dominant lethal assay, host-mediated assay and cytogenic assays, indicate that Parabens are generally non-mutagenic, although Methylparaben did increase chromosomal aberrations in a Chinese Hamster ovary cell assay.	9
Teratogenicity	Methylparaben was non-teratogenic in rabbits, rats, mice, and hamsters.	9
Comments: -		

PHOTO-INDUCED TOXICITY
In general, parabens do not exhibit significant levels of photo-contact sensitization or photo-toxicity **(4)** .

Phenoxyethanol

REGULATORY RESTRICTIONS
This ingredient is listed in the Regulation EC No. 1223/2009 annex V (List of preservatives which cosmetic products may contain). According to this Regulation and respective amendments the use of this ingredient in cosmetic products is restricted to a maximum concentration of 1%. CIR (Cosmetic Ingredient Review) considers that this ingredient is safe as used up to 1%.

ACUTE TOXICITY

Administration Route	Adverse effects description	LD50	Ref.
Oral	Phenoxyethanol is practically non-toxic when administered orally to rats. Although it may cause gastrointestinal irritation with symptoms like nausea, vomiting and diarrhea.	(rat, male): 1.26 ml/kg; (rat, female): 2.33 ml/kg; (mouse): 933 mg/kg; (rat): 1840 mg/kg	13,14,15,16
Inhalation	At room temperature, exposure to vapor is minimal due to low volatility. Vapor from heated material may cause respiratory tract irritation and other effects.	(rat): 1mg/L (6 hours, aerosol)	14
Dermal	Phenoxyethanol is practically non-toxic when dermally administered to rats. Allergic contact dermatitis to 1% phenoxyethanol could be a rare possibility in patients having an adverse reaction to aqueous creams.	(rabbit): > 545 mg/kg; (rat): > 2250 mg/kg – 14000 mg/kg; (rat): 14391 mg/kg	13,14,15
Subcutaneous	-	-	

Comments:
Phenoxyethanol is an antimicrobial preservative used in cosmetics and topical pharmaceutical formulations at a concentration of 0.5–1.0%. It may also be used as a preservative and antimicrobial agent for vaccines. Therapeutically, a 2.2% solution or 2.0% cream has been used as a desinfectant for superficial wounds, burns, and minor infections of the skin and mucous membranes. Phenoxyethanol produces a local anesthetic effect on the lips, tongue, and other mucous membranes **(4)** .

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	Phenoxyethanol at 2.0% was a slight irritant to rabbit skin, but it was not irritant to guinea pig skin. Phenoxyethanol at 10% in mineral oil is not considered a primary nor a cumulative irritant, but the pure material is a moderate irritant to the skin. Contact urticaria has been reported upon exposure to 2-phenoxyethanolcontaining cosmetics. The US FDA has recommended avoiding at least one topical product containing phenoxyethanol due to concerns over inadvertant exposure to nursing infants.	16,17
Ocular Irritation	Undiluted phenoxyethanol was a strong eye irritant, but was non-irritating when tested at 2.2%. Phenoxyethanol diluted to 5% was applied to the conjunctival sac of rabbits, and induced a mild irritation of the conjunctivae. It may cause moderate eye irritation and moderate corneal injury.	18,14,16
Sensitization	Phenoxyethanol was not a sensitizer to guinea pig skin and did not cause delayed hypersensitivity in clinical studies (HRIPT with 51 subjects, with phenoxyethanol at 10%v/v).	18,14,16

	A modified repeated insult patch test (138 subjects) with phenoxyethanol at 10% and patch tests with the ingredient at 5% indicated no skin reactions consistent with allergic sensitization. It did not cause allergic skin reactions when tested in guinea pigs and in humans.	
Dermal Absorption	It has previously been shown that skin has the capacity for local metabolism of applied chemicals. Therefore, there is a requirement to consider metabolism during dermal absorption of these compounds (glycol ethers) in risk assessment for humans. AFSSAPS (Agence Française de Sécurité Sanitaire des Produits de Santé) considers 80% of dermal absorption of phenoxyethanol in leave-on products and 40% in rinse-off products.	15,16
Comments: -		

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.
Oral	Similar effects to those of acute ingestion are expected.	19
Inhalation	Repeated or prolonged inhalation of vapors may lead to chronic respiratory irritation.	20
Dermal	Phenoxyethanol was applied dermally to 10 female New Zealand White rabbits at a dose of 1000 mg/kg/day for 14 days. Seven of the rabbits died between days 5 and 8 of treatment. The prominent hematologic change noted in these rabbits was indicative of the breakdown of erythrocytes. There were no hematologic changes noted in the three surviving rabbits. In a more recent study, 2000 mg/kg undiluted phenoxyethanol (cosmetic grade) was applied to the shaved and abraded skin of four New Zealand White rabbits, remaining in place for 24 hours, followed by a 14-day observation period and necropsy, no systemic toxicity or adverse effects were noted, except for slight skin irritations on the application site. Excessive exposure may cause hemolysis, thereby impairing the ability of the blood to transport oxygen.	14,15,16

Comments:
Long-term exposure to phenoxyethanol may result in Central Nervous System toxic effects similar to other organic solvents **(4)** .

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY

		Ref.
Carcinogenicity	There is no data available on the carcinogenic effects of this ingredient.	
Mutagenicity	Phenoxyethanol was non-mutagenic in the Ames test, with and without metabolic activation. In vitro genetic toxicity studies were negative. Animal genetic toxicity studies were negative.	18,14,16
Teratogenicity	In dermal treatment studies, phenoxyethanol was neither teratogenic, embryotoxic, nor fetotoxic at doses which were maternally toxic. A fetotoxic and teratogenic evaluation of 2-phenoxyethanol was performed with rabbits following dermal exposure. Dermal application of 1000 mg/kg/day produced maternal toxicity and maternal toxicity was also observed in rabbits treated with 600 mg 2-phenoxyethanol/kg/day but at a lower incidence. No signs of maternal toxicity were seen at 300 mg/kg/day. Examination of rabbit fetuses indicated that, at the dosages tested, 2-phenoxyethanol was not embryotoxic, fetotoxic, or teratogenic. It did not cause birth defects or other effects in the fetus even at doses which caused toxic effects in the mother. Moreover, in animal studies, repeated exposure did not have any effects on reproductive organs.	14,19,16

Comments:
This product may contain an impurity, Phenol, that is Mutagenic Category 2 in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labelling of hazardous substances). This product may contain an impurity, ethylene oxide, that is classified as 1B regarding its Carcinogenic and Mutagenic toxicity in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labelling of hazardous substances).

PHOTO-INDUCED TOXICITY

Phenoxyethanol was not photo-toxic in clinical studies **(16)** .

Caprylic/Capric Triglyceride

REGULATORY RESTRICTIONS

According to the Regulation EC 1223/2009 and respective amendments there are no restrictions on its use. CIR (Cosmetic Ingredient Review) considers that caprylic/capric triglyceride is safe as used up to 84%.

ACUTE TOXICITY

Administration Route	Adverse effects description	LD50	Ref.
Oral	Adverse effects including abdominal pain and diarrhea were reported by patients consuming diets based on medium-chain triglycerides. In one test on mice, lethargy and ataxia occurred within ten minutes after the administration of 25 ml/k 8 and dyspnea was noted in some animals within one hour. All animals appeared asymptomatic at the end of the first day and no deaths were reported. In the second mouse test, ataxia, lethargy, dyspnea, and diuresis occurred within 15 minutes, and in several animals complete loss of activity was observed within two hours. Following the two highest doses, three deaths occurred in 24 to 48 hours. All symptoms disappeared in the survivors by the end of the third day. No necropsy observations were reported from either tests. From the results of these tests it may be concluded that the acute oral LD50 in female mice is higher than 25 ml/kg.	(mouse): 29.6 g/kg; (rat): 33.3 g/kg (rat): 10g/Kg	21,4
Inhalation	Male rats and guinea pigs in groups often each were exposed for six hours in a 40-liter chamber containing an aerosol of Caprylic/Capric Triglyceride. The fraction of the aerosol with particles small enough to be inhaled into the lung. Three controls of each species were sham exposed. Observation during the exposure and for 14 days thereafter revealed no symptoms, abnormal behavior, or effects on body weight. One hour after the exposure, three animals and one control of each species were sacrificed for pathological examination, and the remaining test animals were sacrificed at 14 days. No gross or microscopic defects attributable to the substance were reported. Examination of the respiratory tract for adverse effects, including the detection of accumulated oil droplets, gave negative results.	-	21
Dermal	-	-	
Subcutaneous	-	-	

Comments:
Medium-chain triglycerides are used in a variety of pharmaceutical formulations including oral, parenteral, and topical products, and are generally regarded as essentially non-toxic and non-irritant materials **(4)** . In acute toxicology studies in animals and humans, no irritant or other adverse reactions have been observed **(4)** . In humans, administration of 0.5 g/kg body-weight medium-chain triglycerides to healthy individuals produced no change in blood or serum triglycerides compared to subjects receiving the same dose of the long-chain triglyceride triolein **(4)** .

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	Medium-chain triglycerides were patch-tested on more than 100 individuals and no irritation was produced on either healthy or eczematous skin. It is slightly irritating in guinea pigs.	22,21,4,23
Ocular Irritation	Medium-chain triglycerides are not irritating to the eyes. The product was applied 3 times in a Draize Test. It caused slight redness after the first application, which disappeared within 24 hours after the third application. It is not eye irritant for rabbits. Only very small effects or no effects were found. Therefore, Myritol 318 is at the most only very mild, transient irritant to the eye of rabbit. It is non-irritant for humans.	22,4,23
Sensitization	Medium-chain triglycerides exhibit no capacity for induction of hypersensitivity. It is not a	24,21,23

	sensitizer agent for guinea pigs. One hundred and twenty-eight adult males and females were tested with Caprylic/Capric Triglyceride using a modification of the Draize repeated insult patch test. All subjects had little or no irritation and none was sensitized. One subject had barely perceptible erythema at the first reading immediately following the removal of the first patch which had been applied for 48 hours.	
Dermal Absorption	There is no data available for dermal absorption for Caprylic/Capric Triglyceride, but other Medium-chain triglycerides showed little skin penetration in mice and guinea pigs. The CIR Expert Panel recognizes that, reportedly, Triolein and Tricaprylin can enhance the skin penetration of other chemicals, and recommends that care should be exercised in using these and other Glyceryl Triesters in cosmetic products.	25
Comments: -		

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.
Oral	Chronic toxicology studies in animals have shown no harmful adverse effects associated with medium-chain triglyceride following oral administration. Groups of 15 male and female rats were fed a diet containing 19.6% of a medium-chain triglyceride (75% caprylic acid and 25% capric acid) for 47 weeks. This diet supported normal growth and development, though growth rate was slightly less than that of rats fed conventional dietary fats. At autopsy, the carcass protein, ash levels and organ weights of test rats were similar to those of control rats but there was less carcass fat and smaller epididymal fat pads in the test group. Histological study revealed no abnormalities in intestine and liver.	21,4,23
Inhalation	Chronic toxicology studies in animals have shown no harmful adverse effects associated with medium-chain triglyceride following inhalation administration.	4
Dermal	In dermal irritation testing medium-chain triglycerides exhibit virtually no potential as dermal irritants, even with prolonged skin exposure.	26

Comments:
Six groups of 5 male rats each were injected intraperitoneally with single doses of Caprilic/Capric Triglyceride ranging from 1 to 24mL/Kg. There were no deaths. After doses of 8mL/Kg and higher, the rats showed a lack of appetite and decreased mobility during the first 2 days. Subsequently, the animals became normal in these respects. Necroscopy after 14 days revealed some unabsorbed test material in the stomach area and "slight vascular complications". No histological observations were described. Though no LD50 could be calculated, this test shows that the intraperatonial LD50 of this product in the rat is greater than 24mL/Kg **(23)** .

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY

		Ref.
Carcinogenicity	There is no data available on the carcinogenic effects of this ingredient.	
Mutagenicity	Studies in vivo and in vitro show that this ingredient is not mutagenic. In a S. thyphimurium Reverse Mutation Assay, it did not have mutagenic effects.	22,23
Teratogenicity	There was no evidence that intravenous (iv) or dietary administration of medium-chain triglycerides adversely affected the reproductive performance of rats or resulted in fetal toxicity or teratogenic effects at doses up to 4.28 g/kg body weight/day (iv) or 12500 mg/kg body weight/day (dietary). There was no evidence that dietary administration of medium-chain triglycerides adversely affected the reproductive performance of pigs or resulted in fetal toxicity or teratogenic effects at doses up to 4000 mg/kg body weight/day in the diet.	24

Comments:
In a reproduction study, young adult male and female rats were fed a balanced diet containing 19.6% of a triglyceride of 75% caprylic and 25% capric acid for th tee weeks before mating. Litter size and birth weight of the test animals were similar to those of rats on conventional or low fat diets, but mortality during lactation was somewhat higher, and there was less weight gain due to a smaller volume of milk secreted. After wean in 8, the F1 generation was fed as the F0 generation had been and showed a weight gain comparable to that of control rats on an oleo oil diet **(21)** .

PHOTO-INDUCED TOXICITY

Phototoxic properties were tested on hairless mice with 50% substance. There were no phototoxic properties found **(23)** .

Glycerin

REGULATORY RESTRICTIONS
According to Regulation EC 1223/2009 and respective amendments there are no restrictions on its use in cosmetic products.

ACUTE TOXICITY			
Administration Route	**Adverse effects description**	**LD50**	**Ref.**
Oral	Glycerin is readily absorbed from the intestine and is either metabolized to carbon dioxide and glycogen or used in the synthesis of body fats. Consuming large amounts may cause vomiting, nausea, diarrhea, headache, and hyperglycemia. However, if not ingested in considerable amounts, glycerin presents no hazardous effects on human health.	(mouse): 4100 mg/kg; (guinea pig): 7750 mg/kg; (rat): 12600 mg/kg; (rabbit): 27000 mg/kg	5,27,4
Inhalation	Breathing of small amounts of this material is not likely to cause harmful effects. It may cause irritation of nose, throat and airways.	(rat): > 570 mg/m3 (1 hour)	27
Dermal	It does not cause skin irritation.	(rabbit): > 18700 mg/kg	27
Subcutaneous	Glycerol is more toxic when administered intravenously, intraperitoneally or subcutaneously.	(mouse): 90 mg/kg; (rat): 100 mg/kg	4,28
Comments: This ingredient is used in pharmaceutical oral, topical, ophthalmic and parenteral formulations, besides being also used as a food additive **(4,28)** .			

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY		
		Ref.
Skin Irritation	Not irritant to the skin.	4,28
Ocular Irritation	Glycerin is not irritating to the eyes.	28
Sensitization	Based on the available information, there is no human or animal data that indicates glycerol to be a skin sensitizer. Considering the extensive, widespread dermal exposure to glycerol in preparations repeatedly applied to the skin, the absence of case reports of humans showing skin reactions is consistent with glycerol having a very low skin sensitization potential.	28
Dermal Absorption	This ingredient is absorbed through the skin and is a permeation enhancer.	27,4
Comments: -		

CHRONIC TOXICITY		
Administration Route	**Adverse effects description**	**Ref.**
Oral	Prolonged or repeated ingestion may affect the blood (hemolysis, changes in white blood cell count), endocrine system (changes in adrenal weight), respiratory system, and may cause kidney injury. However, several studies indicate that repeated oral exposure by gavage to glycerol does not induce adverse effects other than local irritation of the gastro-intestinal tract. It was concluded that the NOEL is 10000 mg/kg bw (20% in diet), since at this dose level no systemic or local effects were observed.	5,4,28
Inhalation	In an inhalation study with rats (during 14 days), there was no effect on lung, liver, kidney, brain and heart weight nor any macroscopic findings reported. Histopathologic examination of the respiratory tract, liver, kidneys and heart of controls and high dose animals revealed an increased incidence of minimal to mild squamous metaplasia of the epiglottis in all treated animals. No systemic effects were seen at the highest dose tested 3910 mg/m3. Nevertheless, the NOAEL for local effects on the respiratory tract following exposure by inhalation is 165 mg/m3.	28
Dermal	-	

Comments:
Overexposure to this material has been suggested as a cause of mild reversible liver effects and mild reversible kidney effects (laboratory animals) **(27)** . Preexisting disorders of skin or lung (such as asthma-like conditions) may be aggravated by exposure to this material **(27)** .

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY

		Ref.
Carcinogenicity	Glycerin does not contain any known carcinogenic substance and studies performed previously do not raise concern for carcinogenic potential of this ingredient. This material is not expected to cause cancer in humans since it did not cause cancer in laboratory animals. This material is not listed as a carcinogen by IARC, NTP or OSHA.	27,28
Mutagenicity	In studies performed in vitro, glycerol was negative (Ames tests with and without metabolic activation) and did not induce chromosomal effects in mammalian cells. There is no in vitro or in vivo data that indicates glycerol to have a genotoxic potential.	28
Teratogenicity	Based on the available data, it can be concluded that glycerol does not have any adverse effects on reproductive parameters. There was no evidence of teratogenicity.	28

Comments:
-

PHOTO-INDUCED TOXICITY

There is no data available on the photo-toxic effects of this ingredient.

Glyceryl stearate SE

REGULATORY RESTRICTIONS

According to the Regulation EC 1223/2009 and respective amendments, there are no restrictions on the use of this ingredient in cosmetic products. CIR (Cosmetic Ingredient Review) considers this compound safe as used up to 25%.

ACUTE TOXICITY

Administration Route	Adverse effects description	LD50	Ref.
Oral	Ingestion may cause gastrointestinal damage. In acute oral toxicity studies in rats, glyceryl stearate was slightly toxic.	(rat): > 5 g/kg	29,30,31
Inhalation	It may cause respiratory tract irritation.	-	32
Dermal	-	-	
Subcutaneous	-	-	

Comments:
Glyceryl monostearate is widely used in cosmetics, foods, and oral and topical pharmaceutical formulations, and is generally regarded as a non-toxic and non-irritant material **(4)** . This ingredient is GRAS listed and it is included in the FDA Inactive Ingredients Database (oral capsules and tablets; ophthalmic, optic, rectal, topical, transdermal, and vaginal preparations) **(4)** . Appropriate to use with no known adverse health effects. Since the substance is used for parenteral feeding, it is considered as not harmful to health **(33)** .

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	It may cause skin irritation. Glyceryl Stearate and Glyceryl Stearate/SE at concentrations of up to 100% were reported to be mildly irritating or nonirritating to the skin of rabbits. Nevertheless, single and Repeated Insult Patch Tests showed this ingredient to be non-irritating.	32,31
Ocular Irritation	Primary eye irritation studies, at concentrations up to 100%, were mildly irritating or non-irritating to rabbits.	31
Sensitization	Single and Repeated Insult Patch Tests showed this ingredient to be non-sensitizing.	31
Dermal Absorption	-	

Comments:
-

CHRONIC TOXICITY		
Administration Route	**Adverse effects description**	**Ref.**
Oral	In chronic studies, 15-25% Glyceryl Stearate in the diet of rats for three consecutive generations had no adverse effects. Rats fed a diet containing 25% Glyceryl Stearate for two years developed renal calcifications.	31
Inhalation	-	
Dermal	In sub-chronic and chronic dermal toxicity tests, Glyceryl Stearate was nontoxic to rabbits but it did cause moderate irritation.	31
Comments: -		

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY		
		Ref.
Carcinogenicity	Glyceryl stearate, fed to mice in doses of 50-100 mg/day or 1.5% in the diet until they died, did not induce significant brain or gastric tumor formation, respectively. 5% glyceryl stearate did not promote the carcinogenicity of DMBA in mouse skin.	31
Mutagenicity	There is no data available on the mutagenic effects of this ingredient.	
Teratogenicity	Glyceryl stearate in the diet of rats for three consecutive generations had no adverse effects.	31
Comments: -		

PHOTO-INDUCED TOXICITY
Products containing 2% glyceryl stearate were non-photo-toxic and non-photo-allergenic **(31)** .

Xanthan Gum

REGULATORY RESTRICTIONS
According to the Regulation EC 1223/2009 and respective amendments, there are no restrictions on the use of this ingredient in cosmetic products.

ACUTE TOXICITY			
Administration Route	**Adverse effects description**	**LD50**	**Ref.**
Oral	No known significant effects or critical hazards. The estimated acceptable daily intake for xanthan gum has been set by the WHO at up to 10 mg/kg body-weight.	(rat): 45 g/kg (mouse): 20 g/kg	34,35,17
Inhalation	Exposure to airborne concentrations above statutory or recommended exposure limits may cause irritation of the nose, throat and lungs. Adverse symptoms may include respiratory airways irritation. Excessive inhalation of dust may be annoying and might mechanically prevent breathing. Because of its hygroscopic properties, could form a paste or gel in the airways.	(rat): 21 mg/l (1h)	34,35,17
Dermal	No known significant effects or critical hazards.	-	34
Subcutaneous	-	-	
Comments: Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and food products and is generally regarded as nontoxic and nonirritant at the levels employed as a pharmaceutical excipient. Xanthan gum has been incorporated in an ophthalmic liquid dosage form, and can be used in vaginal formulations **(17)** . This ingrediente is listed as GRAS, and is accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (oral solutions,suspensions, and tablets; rectal and topical preparations) **(17)** .			

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY		
		Ref.
Skin Irritation	It is not irritating to the skin. No skin irritation has been observed in rabbits. Prolonged contact with dust dry may cause skin dryness or cracking.	34,35
Ocular Irritation	Exposure to airborne concentrations above statutory or recommended exposure limits may cause irritation of the eyes, however, no eye irritation has been observed in rabbits.	34,35,4
Sensitization	It is not a skin sensitizer. No skin allergy has been observed in guinea pigs following skin exposure.	34,35
Dermal Absorption	-	
Comments: -		

CHRONIC TOXICITY		
Administration Route	**Adverse effects description**	**Ref.**
Oral	No adverse effects were observed in long term feeding studies with rats (up to 1000 mg/kg/day) and dogs (up to 1000 mg/kg/day).	35,17
Inhalation	Repeated or prolonged inhalation of dust may lead to chronic respiratory irritation.	34
Dermal	-	
Comments: -		

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY		
		Ref.
Carcinogenicity	Not classifiable as a human carcinogen.	34
Mutagenicity	Animal testing did not show any mutagenic effects.	34
Teratogenicity	No adverse effects were observed in a three-generation reproduction study with rats (up to 500 mg/kg/day).	35,17
Comments: This ingredient has an impurity, Lead, classified as 1A regarding its reproductive toxicity in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labelling of hazardous substances). This ingredient has an impurity, Cadmium, classified as 2 regarding its mutagenicity and reproductive toxicity, and it is classified as 1B regarding its carcinogenicity in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labelling of hazardous substances).		

PHOTO-INDUCED TOXICITY
There is no data available on the photo-induced toxicity effects of this ingredient.

Chaves Thermal Water (Chaves Aqua)

REGULATORY RESTRICTIONS
According to Regulation EC no. 1223/2009 and respective amendments there are no restrictions on its use in cosmetic products.

ACUTE TOXICITY			
Administration Route	**Adverse effects description**	**LD50**	**Ref.**
Oral	-	-	
Inhalation	-	-	
Dermal	-	-	
Subcutaneous	-	-	
Comments: -			

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY		
		Ref.
Skin Irritation	-	
Ocular Irritation	-	
Sensitization	-	
Dermal Absorption	-	
Comments: -		

CHRONIC TOXICITY		
Administration Route	**Adverse effects description**	**Ref.**
Oral	-	
Inhalation	-	
Dermal	-	
Comments: -		

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY		
		Ref.
Carcinogenicity	There is no data available on the carcinogenic effects of this ingredient.	
Mutagenicity	There is no data available on the mutagenic effects of this ingredient.	
Teratogenicity	There is no data available on the teratogenic effects of this ingredient.	
Comments: This product has an impurity, Nickel, that is a Carcinogenic Category 2 in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labelling of hazardous substances). This ingredient has an impurity, Cadmium, classified as 2 regarding its mutagenicity and reproductive toxicity, and it is classified as 1B regarding its carcinogenicity in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labelling of hazardous substances). This ingredient has an impurity, Lead, classified as 1A regarding its reproductive toxicity in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labelling of hazardous substances).		

PHOTO-INDUCED TOXICITY
There is no data available on the photo-toxic effects of this ingredient.

Ceteareth-20

REGULATORY RESTRICTIONS
According to the Regulation EC 1223/2009 and respective amendments, there are no restrictions on the use of this ingredient in cosmetic products. CIR (Cosmetic Ingredient Review) considers this ingredient safe in the present practices of use and concentration in cosmetics, when formulated to avoid irritation. CIR refers that Ceteareth-20 is used at 0.02% to 11% in leave-on poducts and 0.008% to 10% in rinse-off products.

ACUTE TOXICITY			
Administration Route	**Adverse effects description**	**LD50**	**Ref.**
Oral	Ingestion of large amounts may cause gastrointestinal tract irritation and discomfort. Toxicity studies with rats, rabbits, and dogs indicate that PEGs have low oral toxicity.	(Rat): >2000 mg/kg (for C12-C18 etoxylated alcohols and C12-C14 fatty acid)	36,37,38,4,39,40
Inhalation	There is not information about the toxicity by inhalation. However, the powder may cause irritation due to mechanical action.	-	36
Dermal	Sporadic contact for a short time will not cause damage.	(rabbit): 800 mg/Kg (rat): >2000 mg/kg (for C12-C18 etoxylated	36,38

		alcohols; (rabbit): >2000 mg/kg (for C12-C14 fatty acid)	
Subcutaneous	-	-	

Comments:
Classified as not expected to be potentially toxic or harmful **(41)** . Polyoxyethylene alkyl ethers are nonionic surfactants widely used in topical pharmaceutical formulations and cosmetics **(4)** . In cosmetics and personal care products, Ceteareth ingredients are used in skin care products, moisturizers, hair conditioners, suntan and indoor tanning products and hair dyes, colors, and tints **(42)** . Ceteareths are the polyethylene glycol (PEG) ethers of Cetearyl Alcohol (q.v.). To supplement the limited available data on Ceteareths, previous findings from the safety assessment of Polyethylene Glycol (PEG), several fatty alcohols (Cetearyl Alcohol, Cetyl Alcohol, and Stearyl Alcohol), and Steareths were considered. These data indicate little evidence of toxicity **(40)** .

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	May cause irritation. May cause slight irritation in rabbits.	36,41,40
Ocular Irritation	May cause moderate irritation.	36,37,41
Sensitization	C12-C18 etoxylated alcohols and C12-C14 fatty acids are not sensitizers (tested on guinea pigs).	38
Dermal Absorption	CIR Panel mentioned that dermal penetration of long-chain alcohols is likely to be low, and the dermal penetration for alkyl PEG ethers is likely to be even lower. This ingredient is an absorption promoter.	43,44

Comments:
-

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.
Oral	Ingestion of large amounts may cause gastrointestinal tract irritation and discomfort.	36
Inhalation	-	
Dermal	Repeated and prolonged contact may cause moderate irritation.	36

Comments:
-

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY

		Ref.
Carcinogenicity	This ingredient is not carcinogenic (animal tests).	36
Mutagenicity	This ingredient is not mutagenic (animal tests). C12-C18 etoxylated alcohols and C12-C14 fatty acids are not mutagenic (Ames Test with Salmonella typhimurium).	41,36
Teratogenicity	No teratogenic effects are expected.	36

Comments:
This product may contain an impurity, ethylene oxide, that is classified as 1B regarding its Carcinogenic and Mutagenic toxicity in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labelling of hazardous substances). This product may contain an impurity, 1,4-Dioxane, that is a Carcinogenic Category 2 in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labelling of hazardous substances).

PHOTO-INDUCED TOXICITY

Photosensitization studies of products containing 1.0% and 4.0% cetyl alcohol were negative **(39)** .

Parfum

REGULATORY RESTRICTIONS

According to the Regulation EC 1223/2009 and respective amendments, there are no restrictions on the use of this ingredient in cosmetic products.

ACUTE TOXICITY			
Administration Route	**Adverse effects description**	**LD50**	**Ref.**
Oral	Male rats (6/dose; strain unspecified) were administered a single dose of benzyl salicylate (present allergen) via oral gavage at 0, 1250, 2500 or 5000 mg/kg and observed for seven days. Mortality was observed at 2500 and 5000 mg/kg.	Concerning to a present allergen: Benzyl salicylate (rat): 2227 mg/kg	45
Inhalation	-	-	
Dermal	-	-	
Subcutaneous	-	-	
Comments:			

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY		
		Ref.
Skin Irritation	This ingredient is a skin irritant.	46
Ocular Irritation	This ingredient is an eye irritant.	46
Sensitization	Sensitization may occur when in contact with the skin. Hexyl cinnamal (the major present allergen) has a low skin-sensitizing potency.	46,47
Dermal Absorption	-	
Comments:		

CHRONIC TOXICITY		
Administration Route	**Adverse effects description**	**Ref.**
Oral	-	
Inhalation	-	
Dermal	-	
Comments: -		

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY		
		Ref.
Carcinogenicity	There is no data available on the carcinogenic effects of this ingredient.	
Mutagenicity	There is no data available on the mutagenic effects of this ingredient.	
Teratogenicity	There is no data available on the teratogenic effects of this ingredient.	
Comments:		

PHOTO-INDUCED TOXICITY
There is no data available on the photo-toxic effects of this ingredient.

Cetearyl alcohol

REGULATORY RESTRICTIONS
According to the Regulation EC 1223/2009 and respective amendments there are no restrictions on its use in cosmetic products. Cosmetic Ingredient Review (CIR) considers that cetearyl alcohol is safe as used up to 25%.

ACUTE TOXICITY			
Administration Route	**Adverse effects description**	**LD50**	**Ref.**
Oral	Swallowing small amounts of this material during normal handling is not likely to cause harmful effects. Swallowing large amounts may be harmful. It may	(rat): > 2000 mg/kg	48,49

	cause stomach or intestinal upset (nausea, vomiting and diarrhea). Cetearyl alcohol is long-chain aliphatic alcohol that is, at most, only slightly toxic when administered orally at doses of 5 g/kg and greater.		
Inhalation	It may cause irritation of nose, throat and respiratory airways.	-	48
Dermal	It may cause skin irritation. Symptoms may include redness, burning, and swelling of skin.	-	48
Subcutaneous	-	-	

Comments:
The Food and Drug Administration (FDA) includes synthetic fatty alcohols including cetyl alcohol and stearyl alcohol on its list of food additives allowed for direct addition to food as multipurpose food additives. Synthetic fatty alcohols are also permitted as indirect food additives, as adjuvants and production aids **(50)** . This material has a low level of toxicity **(48)** . Nevertheless, preexisting lung diseases (for example, asthma-like conditions) may be aggravated by exposure to this material **(48)** .

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	A skin irritation study of a cream containing 3.0% Cetearyl Alcohol was conducted with 6 New Zealand albino rabbits (3 males, 3 females) weighing from 3.5-4.2 kg. The product was applied to intact and abraded skin of each animal during 5 consecutive days. After each application, an occlusive dressing was placed over the test site and removed after an 8-h period. Sites were graded for signs of irritation at 8 and 24 h postapplication. Mean erythema scores for intact skin ranged from 1.0 to 3.0 at 8 h and from 1.17 to 2.67 at 24 h post application. For abraded skin, mean erythema scores ranged from 1.0 to 3.0 at 8 h and from 1.17 to 2.50 at 24 h. It was concluded that the cream was mildly irritating to the skin. In other study this ingredient was non skin irritating to rabbits.	48,49
Ocular Irritation	The dust can cause eye irritation. Symptoms include stinging, tearing, redness, and swelling of eyes. The ocular irritation potential of a cream containing 3.0% Cetearyl Alcohol was assessed in 9 albino rabbits. The product was instilled into one eye of each animal. The eyes of 3 animals were rinsed after instillation. Ocular reactions were scored at 1, 2, 3, 4, and 7 days post instillation. The product was classified as a non-irritant. In other study this ingredient was slightly eye irritating to rabbits.	48,49
Sensitization	In a human skin sensitization study of a cream containing 3.0% cetearyl alcohol, none of the subjects had positive reactions. Although it is not common, some sensitization reactions have been reported. Indeed, there are some reported cases of allergic contact dermatitis derived from the use of this ingredient. There is no evidence of a potential sensitizing effect on the skin.	48,51,49,4
Dermal Absorption	-	

Comments:
-

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.
Oral	-	
Inhalation	Prolonged or repeated breathing of this material may result in chronic bronchitis (inflammation of the airways of the lungs). Symptoms include coughing and shortness of breath. Symptoms are not expected at air concentrations below the recommended exposure limits, if applicable.	48
Dermal	-	

Comments:
-

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY

		Ref.
Carcinogenicity	This material is not listed as a carcinogen by the International Agency for Research on Cancer	48

	(IARC), the National Toxicology Program (NTP) or the Occupational Safety and Health Administration (OSHA).	
Mutagenicity	Ames Test: negative.	48
Teratogenicity	This product does not contain any chemicals known to cause birth defects, or any other reproductive harm (California Prop. 65).	48

Comments:
-

PHOTO-INDUCED TOXICITY

Clinical photosensitization studies of a lipstick product containing 4.0% cetyl alcohol and a skin care preparation containing 1.0% cetyl alcohol resulted in no positive reactions. Identical results were reported moisturizing lotion containing 0.10% myristyl alcohol (related compound) **(49)** .

Hydrochloric acid

REGULATORY RESTRICTIONS

According to the Regulation EC 1223/2009 and respective amendments, there are no restrictions on the use of this ingredient in cosmetic products.

ACUTE TOXICITY

Administration Route	Adverse effects description	LD50	Ref.
Oral	The concentrated solution is corrosive and can cause severe damage if ingested. It can cause burns in gastrointestinal tract. When used diluted, at low concentration, hydrochloric acid is not usually associated with any adverse effects.	(rabbit): 0.9 g/kg	52,4
Inhalation	The inhalation of vapors causes irritation of the airways.	-	52
Dermal	In case of contact with skin it can cause burns.	-	52
Subcutaneous	-	-	

Comments:
LD50 (mouse, IP): 1.4 g/kg **(4)** .

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	It is corrosive to the skin.	53
Ocular Irritation	Severe effects such as burns and irreversible damage of optic nerve can be expected from exposure to the eyes.	53
Sensitization	No skin sensitization has been reported.	53
Dermal Absorption	-	

Comments:
-

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.
Oral	-	
Inhalation	No effects on the gonads were observed in a good quality 90-day inhalation study up to 50 ppm.	53
Dermal	-	

Comments:
For repeated dose toxicity, local irritation effects were observed in the groups of 10 ppm and above in a 90-day inhalation study.

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY		
		Ref.
Carcinogenicity	For carcinogenicity, no pre-neoplastic or neoplastic nasal lesions were observed in a 128-week inhalation study with SD male rats at 10 ppm hydrogen chloride gas. No evidence of treatment related carcinogenicity was observed either in other animal studies performed by inhalation, oral or dermal administration. In humans, no association between hydrogen chloride exposure and tumor incidence was observed.	53
Mutagenicity	For genetic toxicity, a negative result has been shown in the Ames test. A positive result, which is considered to be an artifact due to the low pH, has been obtained in a chromosome aberration test using Hamster ovary cells. The effects of low pH in in vitro studies are not a problem in vivo as the proton level is regulated systemically.	53
Teratogenicity	No reliable studies have been reported regarding toxicity to reproduction and development in animals after oral, dermal or inhalation exposure to hydrogen chloride/hydrochloric acid.	53
Comments: -		

PHOTO-INDUCED TOXICITY
There is no data available on the photo-toxic effects of this ingredient.

8.2 Toxicological profile of the mixtures

Phenonip ME

REGULATORY RESTRICTIONS
According to Regulation EC No. 1223/2009 and respective amendments there are no restrictions on the use of this mixture in cosmetic products. The regulatory restrictions of the substances present in this mixture are presented in: section 8.1.

ACUTE TOXICITY			
Administration Route	**Adverse effects description**	**LD50**	**Ref.**
Oral	-	-	
Inhalation	Inhalation of vapours causes irritation of the respiratory system and mucous membranes, headache, nausea, dizziness, vomiting.	-	54
Dermal	-	-	
Subcutaneous	-	-	
Comments:-			

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY		
		Ref.
Skin Irritation	-	
Ocular Irritation	-	
Sensitization	Sensitization effects are not known.	54
Dermal Absorption	-	
Comments: -		

CHRONIC TOXICITY		
Administration Route	**Adverse effects description**	**Ref.**
Oral	-	

Inhalation	-	
Dermal	-	
Comments: -		

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY		
		Ref.
Carcinogenicity	There is no data available on the carcinogenic effects of this mixture.	
Mutagenicity	There is no data available on the mutagenic effects of this mixture.	
Teratogenicity	There is no data available on the teratogenic effects of this mixture.	
Comments: -		

PHOTO-INDUCED TOXICITY
There is no data available on the photo-toxic effects of this ingredient.

Acido Clorhídrico 37% grado técnico

REGULATORY RESTRICTIONS
According to Regulation EC No. 1223/2009 and respective amendments there are no restrictions on the use of this mixture in cosmetic products. The regulatory restrictions of the substances present in this mixture are presented in: section 8.1.

ACUTE TOXICITY			
Administration Route	**Adverse effects description**	**LD50**	**Ref.**
Oral	If ingested, this mixture can cause burns in digestive tract. It can cause intestinal and esophageal perforation.	(rabbit): 0.9 g/kg	55
Inhalation	This mixture can cause irritation to the respiratory tract.	-	55
Dermal	This mixture is very corrosive to the skin.	-	55
Subcutaneous	-	-	
Comments:-			

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY		
		Ref.
Skin Irritation	This mixture is very corrosive to the skin.	55
Ocular Irritation	When in contact with eyes, the mixture can cause burns, blindness and irreversible lesions to the ocular nerve.	55
Sensitization	-	
Dermal Absorption	-	
Comments: -		

CHRONIC TOXICITY		
Administration Route	**Adverse effects description**	**Ref.**
Oral	-	
Inhalation	-	
Dermal	-	
Comments: -		

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY		
		Ref.
Carcinogenicity	There is no data available on the carcinogenic effects of this mixture.	
Mutagenicity	There is no data available on the mutagenic effects of this mixture.	
Teratogenicity	There is no data available on the teratogenic effects of this mixture.	
Comments: -		

PHOTO-INDUCED TOXICITY
There is no data available on the photo-toxic effects of this mixture.

8.3 Data for calculation of systemic exposure dosage and margin of safety of the substances (INCI name)

Paraffinum Liquidum

Dermal absorption (%)	Justification of dermal absorption value			Ref.
1.00	Data support the view that mineral oil does not effectively penetrate the skin beyond the stratum corneum, resulting in minimal (< 1 %) absorption of white mineral oils after topical exposure.			6
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	56
	900.000	rat	Dermal, 8-week developmental toxicity study	

Ethylparaben

Dermal absorption (%)	Justification of dermal absorption value			Ref.
3.70	The SCCS will use a dermal absorption value of 3.7%.			11
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	11
	2.000	rats	subcutaneous, 17 days	

Methylparaben

Dermal absorption (%)	Justification of dermal absorption value			Ref.
3.70	The SCCS recommends a dermal absorption value of 3.7%.			11
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	11
	2.000	rats	subcutaneous, 17 days	

Phenoxyethanol

Dermal absorption (%)	Justification of dermal absorption value			Ref.
80.00	The AFSSAPS considers 80% of dermal absorption of phenoxyethanol in leave-on products and 40% in rinse-off products.			15
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	15
	164.000	rat	90-day sub-chronic oral study	

Caprylic/Capric Triglyceride

Dermal absorption (%)	Justification of dermal absorption value			Ref.
10.00	There is no data available for dermal absorption for Caprylic/Capric Triglyceride, but other Medium-chain triglycerides showed little skin penetration in mice and guinea pigs.			25
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	26
	1000.000	rabbit	maternal toxicity of rabbit; intravenous administration	

Glycerin

Dermal absorption (%)	Justification of dermal absorption value			Ref.
100.00	Glycerin is absorbed into skin.			4
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	28
	950.000	dog	3 days oral toxicity study in dogs	

Glyceryl stearate SE

Dermal absorption (%)	Justification of dermal absorption value			Ref.
100.00	Since its molecular weight is lower than 500 g/mol (358.6 g/mol), it is assumed that glyceryl stearate is 100% absorbed into skin.			57
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	-
	unknown	-	-	

Xanthan Gum

Dermal absorption (%)	Justification of dermal absorption value			Ref.
10.00	The molecular weight is higher than 500 g/mol (2 to 50E6 Da), so a dermal absorption of 10% will be considered.			4
ADI	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	4
	10.000	Human	-	

Chaves Thermal Water (Chaves Aqua)

Dermal absorption (%)	Justification of dermal absorption value			Ref.
100.00	Considering the low molecular weight of the molecule, a 100% dermal absoprtion will be considered			57
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	-
	unknown	-	-	

Ceteareth-20

Dermal absorption (%)	Justification of dermal absorption value			Ref.
10.00	As dermal penetration for alkyl PEG ethers is likely to be lower, a dermal absorption of 10% will be assumed.			44
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	-
	unknown	-	-	

Parfum

Dermal absorption (%)	Justification of dermal absorption value			Ref.
100.00	As there is no available data on dermal absorption of this ingredient, it will be assumed a dermal absorption of 100% for calculation of systemic exposure.			
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	-
	unknown	-	-	

Cetearyl alcohol

Dermal absorption (%)	Justification of dermal absorption value			Ref.
10.00	Although the molecular weights of cetyl alcohol and stearyl alcohol are lower than 500 g/mol, the partition coefficients of these compounds that constitute the ingredient cetearyl alcohol are higher than 4, so a 10% of dermal absorption will be assumed.			57
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	-
	unknown	-	-	

Hydrochloric acid

Dermal absorption (%)	Justification of dermal absorption value			Ref.
100.00	Since this ingredient presents a low molecular weight (36.46 g/mol) a dermal absorption of 100% will be assumed.			57
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	53
	20.000	Rat and mice	90-day inhalation study	

8.4 Exposure to the substances, calculation of respective systemic exposure and margin of safety

Substance (INCI)	Total Conc. of the Substance in the Cosmetic Product (%)	mg/kg body weight/ day	Dermal absorption (%)	Systemic Exposure (mg/kg/day)	NOAEL or Other Parameter	Margin of Safety	Margin of Safety /2 *
Caprylic/Capric Triglyceride	8.00	1.9312	10	0.1931	1000	5178	n.a.
Ceteareth-20	1.00	0.2414	10	0.0241	-	-	-
Cetearyl alcohol	2.00	0.4828	10	0.0483	-	-	-
Chaves Thermal Water (Chaves Aqua)	72.70	17.5498	100	17.5498	-	-	-
Ethylparaben	0.15	0.0362	3.7	0.0013	2	1493	n.a.
Glycerin	3.00	0.7242	100	0.7242	950	1312	656
Glyceryl stearate SE	8.00	1.9312	100	1.9312	-	-	-
Hydrochloric acid	0.156	0.0377	100	0.0377	20	531	n.a.
Methylparaben	0.15	0.0362	3.7	0.0013	2	1493	n.a.
Paraffinum Liquidum	5.00	1.207	1	0.0121	900	74565	n.a.
Parfum	0.10	0.0241	100	0.0241	-	-	-
Phenoxyethanol	0.90	0.2173	80	0.1738	164	944	472
Xanthan Gum	0.324	0.0782	10	0.0078	10	1279	640

** Additional factor applied for substances for which the Margin of Safety was calculated taking into account NOAEL obtained from oral studies.*

8.5 Possible impacts on the toxicological profile due to particle sizes (including nanomaterials), impurities and interaction of the substances

The cosmetic product does not contain nanomaterials and interactions between its substances are not expected to occur. This product contains allergens that according to the Annex III of the Regulation EC 1223/2009 are substances which cosmetic products must not contain except subject to some restrictions. This Annex III of the Regulation EC no. 1223/2009 states that these substances must be labeled in the final product if their concentration in the cosmetic product exceeds 0.01% in rinse-off products and 0.001% on leave-on products. In this leave-on product the allergens which must be labeled are: Alpha-Isomethyl Ionone, Benzyl Alcohol, Benzyl Salicylate, Butylphenyl Methylpropional, Citronellol, Coumarin, Eugenol, Geraniol, Hexyl Cinnamal, Hydroxycitronellal and Linalool. The presence of these allergens in the final cosmetic product can cause sensitization reactions in individuals with more sensitive skin. However, as it can be seen on the table below, the margins of safety of these allergens were calculated. The margins of safety calculated for the allergens Alpha-Isomethyl Ionone, Benzyl Alcohol, Benzyl Salicylate, Butylphenyl Methylpropional, Coumarin, Eugenol, Geraniol, Hexyl Cinnamal, Hydroxycitronellal allergens are 42270, 2589064, 2448, 13243, 12630, 621375, 6575400, 77984 and 271106, respectively (based on oral studies performed in animal species), which are values greater than 100 (which is the reference value considered as minimum to assume the ingredients' use as safe when long term animal studies are considered). Considering the allergens Citronellol and Linalool, the margins of safety calculated are 9501 and 345, respectively (based on oral studies performed in humans), which are values greater than 10 (which is the reference value considered as minimum to assume the ingredients' use as safe when long term human studies are considered). Hence, there are no significant systemic risks to human health associated to the presence of these substances, under normal conditions of use of the final product.

Substance (INCI)	Total Conc. of the Substance in the Cosmetic Product (%)	mg/kg body weight/ day	Dermal absorption (%)	Systemic Exposure (mg/kg/ day)	NOAEL or Other Parameter	Margin of Safety	Margin of Safety /2 *
Alpha-Isomethyl Ionone	0.0049	0.00118286	100	0.00118286	50	42270	n.a.
Benzyl Alcohol	0.001	0.0002414	32	0.000077248	400	5178128	2589064
Benzyl Salicylate	0.00423	0.001021122	100	0.001021122	5	4897	2448
Butylphenyl Methylpropional	0.00391	0.000943874	100	0.000943874	25	26487	13243
Citronellol	0.00109	0.000263126	10	2.63126E-05	0.5	19002	9501
Coumarin	0.00164	0.000395896	100	0.000395896	10	25259	12630
Eugenol	0.001	0.0002414	100	0.0002414	300	1242751	621375
Geraniol	0.00315	0.00076041	10	0.000076041	1000	13150800	6575400
Hexyl Cinnamal	0.00664	0.001602896	100	0.001602896	125	77984	n.a.
Hydroxycitronellal	0.00191	0.000461074	100	0.000461074	250	542212	271106

Linalool	0.003	0.0007242	100	0.0007242	0.5	690	345

** Additional factor applied for substances for which the Margin of Safety was calculated taking into account NOAEL obtained from oral studies.*

This cosmetic product contains diethylene glycol as trace impurity of the raw material Glycerin 4810. According to Regulation (EC) 1223/2009, diethylene glycol is allowed at a maximum concentration of 0.1% as traces in ingredients. The concentration of diethylene glycol in this cosmetic product is 0.003% therefore it is in compliance with the Regulation.

The raw materials used on this product contain some other impurities (as listed in section 4.1), but their respective concentrations in the finished product are very low. Therefore, under normal conditions of use, no significant harmful reactions or adverse effects to human health are expected due to these impurities.

9. Undesirable effects and serious undesirable effects

This cosmetic product is not on the market yet therefore no undesirable effects or serious undesirable effects have been reported.

10. Information on the cosmetic product

A study to evaluate the moisturizing efficacy of the product DERMOCOSMÉTICA TERMAL AQUAE CREME HIDRATANTE ROSTO was performed. This test was performed in a similar formula, under the name Loção Hidratante (FR01A/P054B11 from Inovapotek), which is not the same as the one to which this report refers. Nevertheless, the differences differences between the formulas are minimal, therefore the results of this Efficacy Test can be considered valid. In this test, 20 voluntees were included, with ages between 18 to 60 years. The test product was applied in the volar part of the arms and the measurements of the moisturizing level were performed before, and after 2, 4 and 8 hours of products application. Before the use of Loção Hidratante, the average value for the moisturizing level was 33.06 (arbitrary units), 2 hours after application the value increased to 47.86, 4 hours after application the value increased to 50.51 and 8 hours after application the average value was 47.27. The differences between before and after 2, 4 and 8 hours of product application were +46.4%, +52.9% and +43.2%, respectively. There was an increase of moisturizing effect in 100% of volunteers, at all time-points of evaluation. These differences were statistically significant ($p<0.05$).

PART B – Cosmetic Product Safety Assessment

1. Assessment conclusion

The Safety Assessment of the cosmetic product "**DERMOCOSMÉTICA TERMAL AQUAE CREME HIDRATANTE ROSTO"** was performed according to Regulation (EC) 1223/2009 and respective amendments. It was concluded that this cosmetic product is safe for human health under normal or reasonably foreseeable conditions of use taking into account its presentation, labeling, instructions for use and disposal and warnings, as long as:

- It passes the 30-month stability/product-packaging material compatibility study under course.

2. Labeled warnings and instructions of use

The information that must be printed on cosmetic product labels (containers and packaging) is regulated under Article 19 of the Regulation (EC) 1223/2009. The following items are compulsory labelling requirements of the Regulation:

- Name or registered name and the address of the responsible person
- Country of origin for cosmetic products imported into the EU
- Nominal content at the time of packaging by weight or by volume.
- Date of minimum durability preceded by the symbol  or the words: „best used before the end of". - Indication of the date of minimum durability is not mandatory for products with a minimum durability of more than 30 months. For such products except where the concept of durability after opening is not relevant an indication of the period of time after opening has to be indicated for which the product is safe and can be used without any harm to the consumer. This information shall be indicated by the symbol  followed by the period (in months and/or years, but usually in months as "x M")
- Information regarding possible precautions to be observed in use. Note especially the compulsory information listed in Annexes III to VI. In the case of this cosmetic product, there are no mandatory warnings to be included in the labelling.
- Batch number or reference to identify the final cosmetic product. When products are too small, such information only need to appear on the secondary packaging.
- Function of the cosmetic product, unless it is clear from its presentation.
- List of ingredients (INCI)- May be indicated on the packaging only, must be preceded by the term „ingredients" - the full INCI list of this cosmetic product (including allergens) is presented in section "1.3 Quantitative and qualitative composition of the cosmetic product by INCI name".

3. Reasoning

Paraffinum liquidum, also known as mineral oil, is used as an excipient in a wide variety of pharmaceutical formulations. It is also used in cosmetics and in some food products. It is to point out that mineral oil displays acute and chronic toxicity effects if ingested and inhaled as well as it may cause eye irritation. On the other hand, it is normally considered as not dangerous for the skin as it shows low dermal toxicity. Subchronic or chronic topical exposure to refined white mineral oils in mice, rats and rabbits results in no histopathological changes in any internal organ or at the site of application (i.e. skin) but given to its widespread use in many topical products, mineral oil has been associated with few instances of allergic reactions. According to the Regulation EC 1223/2009 and respective amendments, there are no restrictions on the use of this ingredient in cosmetic products. The margin of safety calculated for this ingredient is 74565 (based on dermal studies performed in animal species), which is a value greater than 300 (which is the reference value considered as minimum to assume the ingredients' use as safe when short term animal studies are considered). Hence, there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

Caprylic/capric triglyceride is included in the chemical group of medium-chain triglycerides, which are used in a variety of pharmaceutical formulations including oral, parenteral and topical products, and which are generally regarded as essentially non-toxic and non-irritant materials. It is not expected that caprylic/capric triglyceride cause irritation to the skin or to the eyes neither reactions of hypersensitivity. Medium chain triglycerides showed little skin penetration in mice and guinea pigs, however, some of these triglycerides can enhance the skin penetration of other chemicals, so CIR Expert Panel recommends that care should be exercised in using these triglycerides in cosmetic products. According to the Regulation EC 1223/2009 and respective amendments there are no restrictions on its use in cosmetic products. The CIR expert panel evaluated the scientific data and concluded that caprylic/capric triglyceride is safe for use as cosmetic ingredient at concentrations up to 84%. The concentration of this ingredient in the cosmetic product – 8% - is according to the CIR Expert Panel recommendation. The margin of safety calculated for this ingredient is 5178 (based on intravenous studies performed in animal species), which is a value greater than 300 (which is the reference value considered as minimum to assume the ingredients' use as safe when animal studies of unknown duration are considered). Hence, there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

Glycerin is used in pharmaceutical oral, topical, ophthalmic and parenteral formulations, besides being also used as a food additive. The consumption of large amounts of glycerin may cause vomiting, nausea, diarrhea, headache, and hyperglycemia. Moreover, it may cause irritation of nose, throat and airways but does not cause skin irritation. It is to point out that glycerin is more toxic when administered intravenously, intraperitoneally or subcutaneously. Considering the extensive, widespread dermal exposure to glycerol in preparations repeatedly applied to the skin, the absence of case reports of humans showing skin reactions is consistent with glycerol having a very low skin sensitization potential. According to Regulation EC 1223/2009 and respective amendments there are no restrictions on its use in cosmetic products. The margin of safety calculated for this ingredient is 656 (based on oral studies performed in animal species), which is a value greater than 300 (which is the reference value considered as minimum to assume the ingredients' use as

safe when short term animal studies are considered). Hence, there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

Glyceryl stearate SE is generally regarded as a non-toxic and non-irritant material. However, it may display acute toxicity effects by oral, inhalation and dermal administration routes as well as chronic dermal toxicity effects (skin irritation). It is non-irritating to the skin and it is a non-sensitizer agent. Moreover, at concentrations up to 100%, it is mildly irritating or non-irritating to the eyes (rabbit). According to the Regulation EC 1223/2009 and respective amendments, there are no restrictions on the use of this ingredient in cosmetic products. CIR considers this compound safe as used up to 25%. The concentration of this ingredient in the cosmetic product – 8% - is according to the CIR Expert Panel recommendation. As NOAEL for this ingredient is unknown, it is not possible to determine its margin of safety under normal conditions of use. Based on its toxicological profile - is non-irritating to the skin and it is a non-sensitizer agent there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and food products and is generally regarded as safe, also regarded as nontoxic and nonirritant at the levels employed as a pharmaceutical excipient. Xanthan gum is a nonirritating agent to the skin and it does not cause eye irritation, unless its statutory or recommended exposure limits are exceeded. In addition, xanthan gum is not a skin sensitizer. Exposure to airborne concentrations above statutory or recommended exposure limits may cause irritation of the nose, throat and lungs. According to the Regulation EC 1223/2009 and respective amendments there are no restrictions on its use in cosmetic products. The margin of safety calculated for this ingredient is 640 (based on oral studies performed in humans), which is a value greater than 10 (which is the reference value considered as minimum to assume the ingredients' use as safe when long term human studies are considered). Hence, there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

Chaves Thermal Water (Chaves Aqua) is has been widely used since the Roman times for the treatment of musculoskeletal, digestive and respiratory tract ailments therefore no toxicological risk is expected. Moreover, no skin reactions have been reported from its use. According to Regulation EC no. 1223/2009 and respective amendments there are no restrictions on the use of Chaves Thermal Water (Chaves Aqua) in cosmetic products.

Ceteareth-20 (one of polyoxyethylene alkyl ethers) is a nonionic surfactant widely used in topical pharmaceutical formulations and cosmetics and it is classified as not expected to be potentially toxic or harmful. In addition, it is not expected that this compound acts like a sensitizer. Nevertheless, ceteareth-20 is a skin and eye irritant agent. According to the Regulation EC 1223/2009 and respective amendments, there are no restrictions on the use of this ingredient in cosmetic products. CIR (Cosmetic Ingredient Review) considers this ingredient safe in the present practices of use and concentration in cosmetics, when formulated to avoid irritation. CIR refers that Ceteareth-20 is used at 0.02% to 11% in leave-on poducts and 0.008% to 10% in rinse-off products. The concentration of this ingredient in this leave-on cosmetic product – 1% - is according to the CIR Expert Panel recommendation. As NOAEL for this ingredient is unknown, it is not possible to determine its margin of safety under normal conditions of use. Based on its low systemic exposure value (0.0241 mg/kg/day), there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

1051936 NIVAL is a perfume that the exact composition is not known. The main allergens are Hexyl Cinnamal, Alpha-isomethyl ionone and Benzyl Salicylate. This ingredient is a skin and eye irritant and sensitization may occur when in contact with the skin. Benzyl salicylate (present allergen) via oral gavage showed mortality levels observed at 2500 and 5000 mg/kg. Hexyl cinnamal (the major present allergen) has a low skin-sensitizing potency. According to the Regulation EC 1223/2009 and respective amendments, there are no restrictions on the use of this ingredient in cosmetic products. As NOAEL for this ingredient is unknown, it is not possible to determine its margin of safety under normal conditions of use. This product contains allergens that according to the Annex III of the Regulation EC 1223/2009 are substances which cosmetic products must not contain except subject to some restrictions. This Annex III of the Regulation EC no. 1223/2009 states that these substances must be labeled in the final product if their concentration in the cosmetic product exceeds 0.01% in rinse-off products and 0.001% on leave-on products. In this leave-on product the allergens which must be labeled are: Alpha-Isomethyl Ionone, Benzyl Alcohol, Benzyl Salicylate, Butylphenyl Methylpropional, Citronellol, Coumarin, Eugenol, Geraniol, Hexyl Cinnamal, Hydroxycitronellal and Linalool. The presence of these allergens in the final cosmetic product can cause sensitization reactions in individuals with more sensitive skin. However, the margins of safety of these allergens were calculated. The margins of safety calculated for the allergens Alpha-Isomethyl Ionone, Benzyl Alcohol, Benzyl Salicylate, Butylphenyl Methylpropional, Coumarin, Eugenol, Geraniol, Hexyl Cinnamal, Hydroxycitronellal allergens are 42270, 2589064, 2448, 13243, 12630, 621375, 6575400, 77984 and 271106, respectively (based on oral studies performed in animal species), which are values greater than 100 (which is the reference value considered as minimum to assume the ingredients' use as safe when long term animal studies are considered). Considering the allergens Citronellol and Linalool, the margins of safety calculated are 9501 and 345, respectively (based on oral studies performed in humans), which are values greater than 10 (which is the reference value considered as minimum to assume the ingredients' use as safe when long term human studies are considered). Hence, there are no significant systemic risks to human health associated to the presence of these substances, under normal conditions of use of the final product.

Ethylparaben and Methylparaben are widely used in cosmetics, food products, and oral and topical pharmaceutical formulations. In general, parabens are practically non-irritating and non-sensitizing in the population with normal skin and they do not exhibit significant levels of photo-contact sensitization or photo-toxicity. Moreover, chronic oral studies indicate that parabens are practically non-toxic. On the other hand, parabens are often incorporated in creams, lotions and ointments that may be used in the region of the eyes, and occasionally cause redness and swelling of eyelids. Ethylparaben and Methylparaben are listed in Regulation EC 1223/2009 annex V (list of preservatives which cosmetic products may contain). According to this Regulation and respective amendments, the use of these parabens in cosmetic products is restricted to a maximum concentration of 0.4% (as acid) for single ester, and 0.8% (as acid) when a mixture of esters is used. CIR (Cosmetic Ingredient Review) considers that this compound is safe when applied in the above-mentioned concentrations. The concentration of the individual parabens (0.15% for ethylparaben and 0.15% for methylparaben) and the sum of concentrations of all parabens present in the cosmetic product – 0.30% - is according to the Regulation EC 1223/2009 and also according to CIR Expert Panel recommendation. The margins of safety calculated for ethylparaben and methylparaben are 1493 and 1493 respectively (based on subcutaneous studies performed in animal species), which are values greater than 300 (which is the reference value considered as minimum to assume the ingredients' use as safe when short term animal studies are considered). Hence, there are no significant systemic risks to human health associated to the use of these substances, under normal conditions of use of the final product.

Phenoxyethanol is an antimicrobial preservative used in cosmetics and topical pharmaceutical formulations, including vaccines. It has also been used at approximately 2% in superficial wounds, burns and minor skin infections as a

disinfectant. Phenoxyethanol is practically non-toxic when oral administered (animal data), but it is able to cause respiratory tract irritation if inhaled, and moderate eye irritation. Moreover, Phenoxyethanol at 10% in mineral oil is not considered a primary or a cumulative irritant, but the pure material is a moderate irritant to the skin. It is not a sensitizer or a photo-toxic agent, although mild skin irritation or contact urticaria due to phenoxyethanol have been reported. This substance is listed in the Regulation EC 1223/2009 as a preservative that can be used in cosmetic productsts up to a maximum concentration of 1%. CIR also considers that this ingredient is safe as used up to 1%. The concentration of this ingredient in the cosmetic product – 0.9% - is according to the Regulation EC 1223/2009 and also according to CIR Expert Panel recommendation. The margin of safety calculated for this ingredient is 472 (based on oral studies performed in animal species), which is a value greater than 100 (which is the reference value considered as minimum to assume the ingredients' use as safe when long term animal studies are considered). Hence, there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

Hydrochloric acid, in a concentrated solution, is corrosive and can cause severe damage if ingested. It can cause burns in gastrointestinal tract. The inhalation of vapors causes irritation of the airways. In case of contact with skin it can cause burns. Severe effects such as burns and irreversible damage of optic nerve can be expected from exposure to the eyes. When used diluted, at low concentration, hydrochloric acid is not usually associated with any adverse effects. According to the Regulation EC 1223/2009 and respective amendments, there are no restrictions on the use of this ingredient in cosmetic products. The margin of safety calculated for this ingredient is 531 (based on inhalation studies performed in animal species), which is a value greater than 100 (which is the reference value considered as minimum to assume the ingredients' use as safe when long term animal studies are considered). Hence, there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

Cetearyl alcohol is a long-chain aliphatic alcohol that is, at most, only slightly toxic when administered orally at doses of 5 g/kg and greater. It may cause irritation of nose, throat and respiratory airways. It may cause mild skin irritation with redness, burning, and swelling of skin to no irritation at all. The Food and Drug Administration (FDA) includes synthetic fatty alcohols including cetyl alcohol and stearyl alcohol on its list of food additives allowed for direct addition to food as multipurpose food additives. Although, there are some reported cases of allergic contact dermatitis derived from the use of this ingredient, there is no evidence of a potential sensitizing effect on the skin. Concerning ocular irritation, this ingredient demonstrated to be non to slightly eye irritating in rabbits. Regarding to its chronic toxicity effects, it can be mentioned that prolonged or repeated breathing of this compound may result in chronic bronchitis. According to the Regulation EC 1223/2009 and respective amendments there are no restrictions on its use in cosmetic products. Cosmetic Ingredient Review (CIR) considers that cetearyl alcohol is safe as used up to 25%. The concentration of this ingredient in the cosmetic product – 2% - is according to the CIR Expert Panel recommendation. As NOAEL for this ingredient is unknown, it is not possible to determine its margin of safety under normal conditions of use. Based on its low systemic exposure value (0.0483 mg/kg/day), there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

Phenonip ME is a mixture containing Phenoxyethanol, Methylparaben and Ethylparaben. Inhalation of vapours causes irritation of the respiratory system and mucous membranes, headache, nausea, dizziness, vomiting. Sensitization effects are not known. According to Regulation EC No. 1223/2009 and respective amendments there are no restrictions on the

use of this mixture in cosmetic products. The regulatory restrictions of the substances present in this mixture are presented in: section 8.1. and their toxicological profiles and margins of safety are presented above.

Acido Clorhídrico 37% grado técnico is a mixture of Hydrochloric acid and Aqua. This mixture can cause irritation to the respiratory tract. This mixture is very corrosive to the skin. When in contact with eyes, the mixture can cause burns, blindness and irreversible lesions to the ocular nerve. If ingested, this mixture can cause burns in digestive tract. It can cause intestinal and esophageal perforation. According to Regulation EC No. 1223/2009 and respective amendments there are no restrictions on the use of this mixture in cosmetic products. The regulatory restrictions of the substances present in this mixture are presented in: section 8.1. and their toxicological profiles and margins of safety are presented above.

Considering the type of formulation, the composition, and the fact that no interactions between the substances are expected, it is unlikely that physico-chemical degradation occurs, putting in risk human health. At the time of this report, a long term stability study is under course, as well as the experimental determination of PAO.

Considering the microbiological stability as well as the results of the challenge test, performed on a similar formula of DERMOCOSMÉTICA TERMAL AQUAE CREME HIDRATANTE ROSTO, it can be concluded that this cosmetic product contains adequate preservatives so it is not expected that its microbial contamination (which can be threat to human health) occurs.

Considering the packaging material used in the cosmetic product it is not expected that any risk to human health can be triggered due to the packaging selected. At the time of this report, a long term stability study is under course, where the product-packaging compatibility will alsobe evaluated.

There are no mandatory warnings to be included in the labelling of this cosmetic product.

The Safety Assessment of the cosmetic product "**DERMOCOSMÉTICA TERMAL AQUAE CREME HIDRATANTE ROSTO"** was performed according to Regulation (EC) 1223/2009 and respective amendments. It was concluded that this cosmetic product is safe for human health under normal or reasonably foreseeable conditions of use taking into account its presentation, labeling, instructions for use and disposal and warnings, as long as:

- It passes the 30-month stability/product-packaging material compatibility study under course.

4. Assessor's credentials and approval of part B

Name of the Safety Assessor	Marta Alexandra de Oliveira Ferreira	
Address	INOVAPOTEK. Pharmaceutical Research and Development Lda UPTEC. Parque de Ciência e Tecnologia da Universidade do Porto, Rua Alfredo Allen n.º455/461 4200-135, Porto Portugal	
Qualifications of the safety assessor	Master in Pharmaceutical Sciences	
Approval of Part B	**Signature**	
	Date	30-10-2015

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inovapotek
PHARMACEUTICAL RESEARCH AND DEVELOPMENT

CURRICULUM VITAE

Personal ID

Name: Marta Alexandra de Oliveira Ferreira
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Birthday date: 02/07/1980
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CV Summary

Is currently the General Manager and Technical Director of inovapotek, a spin-off company of Oporto University proving R&D, testing and consulting services to the cosmetics and pharmaceutical industry. Holds a master's degree in Pharmaceutical Sciences and a master's degree in Pharmaceutical Technology and has now more than 10 years of experience in cosmetics product development, testing and regulatory affairs.

Professional experience

Founder, General Manager and Technical Director, *Inovapotek, Pharmaceutical Research and Development Lda. (since October 2008)*

Activities:

- Coordination of all Technical Department activities such as:
    - Safety assessment according with EU regulation
    - Safety and tolerance testing
    - Efficacy testing
    - Formulation development
    - Stability studies
    - New methods development and validation
    - Study plans design
- Coordination of Marketing/Sales Department
- Human resources management
- Coordination of Financial & Administrative Department

Consultant, *Fluidinova, Engenharia de Fluidos, SA (2008)*

Activities: definition of a R&D project in the cosmetic area, including definition of activities and tasks, planning and resources.

R&D manager of the project "Development of cosmetic products with S. Pedro do Sul Spring water", *Termalistur – Termas de São Pedro do Sul EM, in partnership with the Faculty of Pharmacy of Oporto University (2005-2008)*

Activities: Development of a new range of cosmetic products, including formulation, stability, safety and efficacy studies of the products. Responsible for the implementation of a new microbiological laboratory for the quality control of the spring water.

Invited Teacher of the Master of Pharmaceutical Technology , *Faculty of Pharmacy of Oporto University (2006 e 2007)*

Researcher at the Medicines Technologic Centre, *Pharmacies National Association (2005)*
Activities: Development of several monographs of semi-solid products for the Portuguese National formulary.

Pharmacist (Health assistant), *Hospital São João de Deus S.A., Vila Nova de Famalicão (2005)*

Pharmacist, *Farmácia Marques, Braga (2004 a 2005)*

Researcher at the Pharmaceutical Technology Department, *Faculty of Pharmacy of Oporto University (2002 a 2003)*
Activities: Planning and implementation of a R&D project for the development of a pediatric syrup.

Researcher at the Organic Chemistry, Phytochemistry and Pharmacology Studies Centre, Organic Chemistry Department, *Faculty of Pharmacy of Oporto University (2000 a 2002)*
Activities: Collaboration of a research project that aimed the development and selection of PLA-PEG nanocapsules for the incorporation and xanthonic compounds.

Education and Training

Good Laboratory Practices Principles Training, Eng.ª Helena Loureiro (2014)

I Course Good Clinical Practices, Lisbon Faculty of Medicine (2012)

Integrated Audits of Quality, Environment and Health and Safety, Process Advice (2010)

Master in Pharmaceutical Sciences, *Faculty of Pharmacy of Oporto University* (2009)

Master in Pharmaceutical Technology (classification: very good), *Faculty of Pharmacy of Oporto University* (2008)

Post-graduation in Pharmacotechnics (classification: 16/20), *Faculty of Pharmacy of Oporto University* (2007)

Advanced Program in Entrepreneurship, Business Creation and Business Development, National Association of Young Entrepreneurs, Porto (2005)

Primary Compounding Course, Professional Compounding Centres of America, Houston (2005)

Degree in Pharmaceutical Sciences (classification: 16/20), *Faculty of Pharmacy of Oporto University* (1998-2004)

Scientific curriculum

Thesis

1. Ferreira M.O. Efficacy testing of cosmetic products in human volunteers using objective instrumental methods. *Faculty of Pharmacy of Oporto University*, Porto, Portugal, 2009.
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7. Ferreira M.O., Amaral M.H., Pereira T., Costa P., Bahía M.F., Evaluation of the skin compatibility of new cosmetic products. 2nd National Congress of Dermatocosmetic Sciences (1st congress of the Portuguese society of Cosmetic Sciences), Lisbon (Portugal), 27th March, 2009.
8. Neto P., Ferreira M., Evaluation of a new active complex in decreasing *vellus* hairs ratio, 21st EADV Congress, Prague, 2012.
9. Neto P., Ferreira M., Evaluation of a new active complex for increasing hair thickness in alopecia, 21st EADV Congress, Prague, 2012.
10. Neto P., Ferreira M., Efficacy evaluation of a new active complex for hair loss, 21st EADV Congress, Prague, 2012.

Oral presentations

1. Ferreira M.O. Cosmetic products development, Panel "Quality, Efficacy and Acceptability of Cosmetic Products", Dermatology and Cosmetology – health to promote well-being Congress, Porto (Portugal), 18-19th April, 2007.
2. Ferreira M.O., Costa P., Bahía M.F. Water and skin: the S. Pedro do Sul thermal water cutaneous effects, Panel "Dermatological and Allergic Studies", 36th Congress of the International Society of Medical Hydrology & Climatology, Porto (Portugal), 25-28th June, 2008.
3. Ferreira M.O. Development of the 1st Cosmetic Products with a Portuguese Thermal Water, Aquameeting – Health and Well-being International Seminar, Porto (Portugal), 19-21th September, 2008.
4. Ferreira M.O. Dermocosmetic Products with a Portuguese Thermal Water. 2nd National Congress of Dermatocosmetic Sciences (1st congress of the Portuguese society of Cosmetic Sciences), Lisbon (Portugal), 27th March, 2009.
5. Ferreira M.O. Cosmetic Products Development: quality, efficacy and safety aspects. Dermatocosmetic Workshop, Health School of the Bragança Polytechnic Institute, Bragança (Portugal), 5th June, 2009.
6. Ferreira M.O. How to prepare for importing to Europe. European Cosmetics Regulation Seminar (Ecore), Tel aviv, 3rd-5th February 2013
7. Ferreira M.O. Cosmetics Testing – compliance with the new regulation. European Cosmetics Regulation Seminar (Ecore), Cosmoprof Bologne, 10th March 2013
8. Ferreira M.O. Systemic Exposure of the Human Body to Cosmetic Ingredients and the Influence on Product. Safety European Cosmetics Regulation Workshop, Istanbul, 2nd October 2013
9. Ferreira M.O. Formulation principles & R&D exercises. Safety European Cosmetics Regulation Workshop, Istambul, 3rd October 2013
10. Ferreira M.O. Safety Assessment. Israeli Cosmetics Conference. Tel aviv, 12nd November 2013
11. Ferreira M.O. PIF = Product Information File. Israeli Cosmetics Conference. Tel aviv, 12nd November 2013
12. Ferreira M.O. Formulation principles & R&D exercises. European Cosmetics Regulation Workshop, Athens, 7th May 2014
13. Ferreira M.O. Safety Assessment (Opinion 1501/12) MoS Calculation - Practical Aspects on How to Make the MoS Calculations. European Cosmetics Regulation Workshop, Athens, 7th May 2014

14. Ferreira M.O. Safety Assessment for Different Types of Products & Examples. European Cosmetics Regulation Workshop, Athens, 7th May 2014
15. Ferreira M.O. PIF = Product Information File. European Cosmetics Regulation Seminar (Ecore), Tel aviv, 16th June 2014

Awards

1. Winner of the Portuguese Galenic Formulary Award (2004).
2. Winner of the "Best Communication" Award at the *II Congresso Nacional de Ciências Dermatocosméticas* (2009).

Presence in seminaries and scientific congresses

1. Skin and Formulation, 2nd Symposium, Versailles (France), 9-10th October, 2006.
2. Dermatology and Cosmetology – health to promote well-being Congress, Porto (Portugal), 18-19th April, 2007.
3. 36th Congress of the International Society of Medical Hydrology & Climatology, Porto (Portugal), 25-28th June, 2008.
4. 2008 Cosmetic Science Conference (CSC), In-cosmetics, Amsterdam (Netherlands), 2008.
5. Aquameeting – Health and Well-being International Seminar, Porto (Portugal), 19-21th September, 2008.
6. 2nd National Congress of Dermatocosmetic Sciences (1st congress of the Portuguese society of Cosmetic Sciences), Lisbon (Portugal), 27th March, 2009.
7. 2009 Cosmetic Science Conference (CSC), In-cosmetics, Munich (Germany), 22-23rd April, 2009.
8. SME's go Health International Information and Training Workshop, Istanbul (Turkey), 27th April, 2009.
9. 7th Framework Programme – Opportunities to SME's, 1st European Week of SME's 2009, Porto (Portugal), 7th May, 2009.
10. 3rd National Congress of Dermatocosmetic Sciences (2nd congress of the Portuguese society of Cosmetic Sciences), Lisbon (Portugal), 18th March, 2011.
11. 20th European Academy of Dermatology and Venereology Congress, Lisbon (Portugal), 20-24th October 2011
12. Day of the imaging technologies for the skin, 4th edition, DIIP Association, Tours (France), 27th September 2012.
13. European Cosmetics Regulation Seminar (Ecore), Tel aviv, 3rd-5th February 2013
14. European Cosmetics Regulation Seminar (Ecore), Cosmoprof Bologne, 10th March 2013
15. European Cosmetics Regulation Workshop, Istanbul, 30th September 2013 - 4th October 2013
16. Israeli Cosmetics Conference. Tel aviv, 12nd November 2013
17. European Cosmetics Regulation Workshop, Athens, 5th-9th May 2014
18. Cosmetics Europe Conference: Cosmetics at the Crossroads of Science and Regulation, 10-11th June 2014
19. European Cosmetics Regulation Seminar (Ecore), Tel aviv, 16th June 2014
20. III Cosmetology Innovation Workshop, Faculty of Pharmacy of Oporto University, 22nd May 2014

Personal skills

Language skills

English: excellent knowledge (860 points at *TOEIC*).
Spanish: good knowledge.
French: medium knowledge.

Informatics skills

Microsoft Word, Microsoft Excel, Microsoft Power Point, SPSS, EndNote

Additional information

Member of the following societies:
International Society for Biophysics and Imaging of the Skin (ISBS)
European Responsible Person Association (ERPA)
Portuguese Society of Cosmetic Sciences (SPCC)
OF

CERTIFICATE

Master's Degree

ISABEL GLÓRIA PEREIRA GUIMARÃES, Head of the Administration Office of the Faculty of Pharmacy of the University of Porto
Hereby certifies that

Marta Alexandra de Oliveira Ferreira

holder of identity Card number 11658756, of portuguese nationality, completed at this University, on the 08th of September 2008, the MSc in Pharmaceutical Technology - Scientific Area in Pharmacotecnics, with the final grade of very good.
This degree was registered under number 11004863M050604002.
This Document is authenticated with the embossed seal of this Faculty.
Academic Services of the Faculty, 23rd of August 2010.

Isabel Guimarães

Emit. BRUNO
Emol. € 15,00
Cont. 16.

CERTIFICATE

Master's Degree

ISABEL GLÓRIA PEREIRA GUIMARÃES, Head of the Administration Office of the Faculty of Pharmacy of the University of Porto
Hereby certifies that

Marta Alexandra de Oliveira Ferreira
holder of Identity Card number 11658756, of portuguese nationality, completed at this University, on the 04th of September 2009, the MSc in Pharmaceutical Sciences, with the final grade of Sixteen (out of 20), corresponding to grade A on the European grading scale
This degree was registered under number 11009494M080601284.
This Document is authenticated with the embossed seal of this Faculty.
Academic Services of the Faculty, 23rd of August 2010.

ADMINISTRATIVE RESPONSIBLE

Isabel Guimarães

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PHARMACEUTICAL RESEARCH AND DEVELOPMENT

Safety Assessment Report

Report number FR09A/P135B13

Cosmetic Product Safety Report of the cosmetic product
DERMOCOSMÉTICA TERMAL AQUAE CREME DE MÃOS

30-10-2015

Promoter:
Município de Chaves

All information contained herein is confidential and will not be disclosed, whole or in part, without the proper written consent of the promoter.

CIDADE DE CHAVES
COOPERACIÓN TRANSFRONTERIZA ESPAÑA – PORTUGAL COOPERAÇÃO TRANSFRONTEIRIÇA
União Europeia
Fundo Europeu de Desenvolvimento Regional
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CHAVES TERMAS&SPA

Identification of the study

Proposal Number	P135B13
Report number	FR09A/P135B13
Safety Assessment Report	Cosmetic Product Safety Report of the cosmetic product DERMOCOSMÉTICA TERMAL AQUAE CREME DE MÃOS
Beginning Date	24-08-2015
Report Date	30-10-2015

Identification of the study responsible personnel

Promoter	**Name**	Município de Chaves
	Address	Câmara Municipal de Chaves Praça de Camões, 5400-150 Chaves
Proponent	**Name**	INOVAPOTEK, Pharmaceutical Research and Development Lda
	Address	UPTEC, Parque de Ciência e Tecnologia da Universidade do Porto, Rua Alfredo Allen, n.º 455/461 4200-135 Porto – PORTUGAL
Safety Assessor	**Name**	Marta Alexandra de Oliveira Ferreira
	Qualifications of the safety assessor	Master in Pharmaceutical Sciences

History of the document

Version	Alterations	Date
A	First version	30-10-2015

Part A. Cosmetic Product Safety Information

1. Quantitative and qualitative composition of the cosmetic product

1.1 By trade name

Raw material (trade name)	Supplier	Function	Conc. (%)
Glycerin 4810	Oleon NV	Humectant	10.00000
Saboderm G20	SABO SpA	Emollient	1.00000
Água Termal das Termas de Chaves	Termas de Chaves	Solvent	64.70000
Refined Shea Butter	The Savannah Fruits Company Ltd.	Skin conditioning	4.00000
Sabowax CS 20	SABO SpA	Thickener	3.00000
Ecorol 68/50P	Ecogreen Oleochemicals GmbH	Emulsifying	2.00000
Sabonal C16	SABO SpA	Emollient	2.00000
Radia 7730 (Miristato Isopropilo EP)	Oleon NV	Emollient	2.00000
Pristerene 4900 (Flake)	Croda Europe Limited	Emulsifying	3.00000
1051936 NIVAL	Iberchem, S.A.	Perfuming	0.10000
Carbopol 940 - 2%	COSLAB - Laboratórios	Thickener	7.00000
Phenonip ME	Clariant	Preservative	1.20000

1.2 By trade name and respective INCI name

Raw material (trade name)	INCI	IUPAC	CAS	EINECS/ELINCS	Function	Conc. of the substance in the raw material (%)	Conc. of the substance in the cosmetic product (%)
Glycerin 4810	Glycerin	Glycerol	56-81-5	200-289-5	Humectant	100.00000	10.00000
Saboderm G20	Octyldodecanol	2-Octyldodecan-1-ol	5333-42-6	226-242-9	Emollient	100.00000	1.00000
Água Termal das Termas de Chaves	Chaves Thermal Water (Chaves Aqua)	-	7732-18-5	231-791-2	Solvent	100.00000	64.70000
Refined Shea Butter	Butyrospermum parkii Butter	-	194043-92-0 - 91080-23-8	293-515-7	Skin conditioning	100.00000	4.00000
Sabowax CS 20	Ceteareth-20	-	68439-49-6	-	Thickener	100.00000	3.00000
Ecorol 68/50P	Cetearyl alcohol	-	67762-27-0 / 8005-44-5	267-008-6 / -	Emulsifying	100.00000	2.00000
Sabonal C16	Cetyl Alcohol	Hexadecan-1-ol	36653-82-4	253-149-0	Emollient	100.00000	2.00000
Radia 7730 (Miristato Isopropilo EP)	Isopropyl Myristate	Tetradecanoic acid, isopropyl ester	110-27-0	203-751-4	Emollient	100.00000	2.00000
Pristerene 4900 (Flake)	Stearic acid	Stearic acid	57-11-4	200-313-4	Emulsifying	100.00000	3.00000
1051936 NIVAL	Parfum	-	-	-	Perfuming	100.00000	0.10000
Carbopol 940 - 2%	Aqua	-	7732-18-5	231-791-2	Solvent	93.25000	6.52750
	Triethanolamine	2,2',2''-Nitrilotriethanol	102-71-6	203-049-8	Buffering	0.10000	0.00700
	Carbomer	-	9007-20-9/9003-01-	-	Thickener	1.65000	0.11550

			4/76050-42-5/9062-04-8/9007-16-3/9007-17-4				
	Alcohol denat. (with Diethyl phthalate and Denatonium benzoate)	-	-	-	Solvent;Viscosity controlling	5.00000	0.35000
Phenonip ME	Ethylparaben	Ethyl 4-hydroxybenzoate	120-47-8	204-399-4	Preservative	12.50000	0.15000
	Methylparaben	Methyl 4-hydroxybenzoate	99-76-3	202-785-7		12.50000	0.15000
	Phenoxyethanol	2-phenoxyethanol	122-99-6	204-589-7		75.00000	0.90000

1.3 By INCI name

INCI	Total Concentration In The Final Product (%)
Chaves Thermal Water (Chaves Aqua)	64.700000000000
Glycerin	10.000000000000
Aqua	6.527500000000
Butyrospermum parkii Butter	4.000000000000
Ceteareth-20	3.000000000000
Stearic acid	3.000000000000
Cetearyl alcohol	2.000000000000
Cetyl Alcohol	2.000000000000
Isopropyl Myristate	2.000000000000
Octyldodecanol	1.000000000000
Phenoxyethanol	0.900000000000
Alcohol denat. (with Diethyl phthalate and Denatonium benzoate)	0.350000000000
Ethylparaben	0.150000000000
Methylparaben	0.150000000000
Carbomer	0.115500000000
Parfum	0.100000000000
Triethanolamine	0.007000000000
Hexyl Cinnamal	0.006640000000
Alpha-Isomethyl Ionone	0.004900000000
Benzyl Salicylate	0.004230000000
Butylphenyl Methylpropional	0.003910000000
Geraniol	0.003150000000
Linalool	0.003000000000
Hydroxycitronellal	0.001910000000
Coumarin	0.001640000000
Citronellol	0.001090000000
Eugenol	0.001000000000
Benzyl Alcohol	0.001000000000

2. Physical/chemical characteristics and stability of the cosmetic product

2.1 Physical/chemical characteristics of the raw materials

Glycerin 4810

CHEMICAL AND PHYSICAL COMPOSITION			
Composition	**Conc. (%)**	**CAS**	**EINECS**
Glycerin	99.5-100	56-81-5	200-289-5
Comments: -			

CHEMICAL AND PHYSICAL SPECIFICATIONS	
Molecular Weight	92.09 g/mol
Physical State	Liquid
Organoleptic Properties	Clear, colorless syrupy liquid
Solubility	Completely soluble in water and ethanol; Slightly soluble in acetone. Solubility in ether: 0.2g/100 mL
Partition coefficient (Log Pow)	-1.76
pH	-
Nanomaterials	NO

Comments:

Water content: max.: 0.5%

Other impurities eluating before glycerol % <0.1

Total impurities eluating after glycerol % <0.5

IMPURITIES AND/OR ALLERGEN SUBSTANCES	
Impurity/Allergen substance	**Concentration (%)**
Halogenated compounds	0-0.0030
Chlorides	0-0.0010
Heavy metals	0-0.0005
diethylene glycol	0-0.1

Saboderm G20

CHEMICAL AND PHYSICAL COMPOSITION			
Composition	**Conc. (%)**	**CAS**	**EINECS**
Octyldodecanol	90-100	5333-42-6	226-242-9
Comments: -			

CHEMICAL AND PHYSICAL SPECIFICATIONS	
Molecular Weight	298.55 g/mol
Physical State	Liquid
Organoleptic Properties	Clear, almost colorless liquid.
Solubility	Insoluble in water.
Partition coefficient (Log Pow)	9.2
pH	-
Nanomaterials	NO

Comments:

Boiling point: > 200 °C

Flashpoint: > 150 °C

Relative density: 0.836

Acidity value: max 0.5

K.F. water: max 0.5%

IMPURITIES AND/OR ALLERGEN SUBSTANCES

This ingredient does not contain impurities and/or allergen substances.

Água Termal das Termas de Chaves

CHEMICAL AND PHYSICAL COMPOSITION

Composition	Conc. (%)	CAS	EINECS
Chaves Thermal Water (Chaves Aqua)	100	7732-18-5	231-791-2

Comments:

The majority components of the analysed thermal water are described below.

Water hole AC1

Anions:

Fluoride (F^-): 7.8 mg/L

Chloride (Cl^-): 40.0 mg/L

Hydrogen carbonate (HCO_3^-): 1624 mg/L

Carbonate (CO_3^{2-}): -

Hydrogen sulfide (HS^-): -

Sulfate (SO_4^{2-}): 25.9 mg/L

Silicate ($H_3SiO_4^-$): -

Phosphate ($H_2PO_4^-$): 0.42 mg/L

Nitrate (NO_3^-): 0.31 mg/L

Nitrite (NO_2^-): < 0.01mg/L

Cyanide (CN^-): < 1.0 microg/L

Bromide (Br^-): 0.26 mg/L

Bromate (BrO_3-): < 0.20

Iodide (I^-): 6 microg/L

Cations:

Lithium (Li^+): 2.4 mg/L

Sodium (Na^+): 581 mg/L

Potassium (K^+): 59.7 mg/L

Magnesium (Mg^{2+}): 5.2 mg/L

Calcium (Ca^{2+}): 21.6 mg/L

Iron (Fe^{2+}): 0.19 mg/L

Iron (Fe^{3+}): 0.03 mg/L

Ammonium (NH_4^+): 1.2 mg/L

Strontium(Sr^{2+}): 0.37 mg/L

Water hole AC2

Anions:

Fluoride (F^-): 8.2 mg/L

Chloride (Cl^-): 38.5 mg/L

Hydrogen carbonate (HCO_3^-): 1760 mg/L

Carbonate (CO_3^{2-}): -

Hydrogen sulfide (HS^-): -

Sulfate (SO_4^{2-}): 18.8 mg/L

Silicate ($H_3SiO_4^-$): -

Phosphate ($H_2PO_4^-$): 0.13 mg/L

Nitrate (NO_3^-): 0.30 mg/L

Nitrite (NO_2^-): < 0.01mg/L

Cyanide (CN^-): < 1.0 microg/L

Bromide (Br^-): 0.23 mg/L

Bromate (BrO_3^-): < 0.20

Iodide (I^-): 6 microg/L

Cations:

Lithium (Li^+): 2.6 mg/L

Sodium (Na^+): 630 mg/L

Potassium (K^+): 61.1 mg/L

Magnesium (Mg^{2+}): 5.1 mg/L

Calcium (Ca^{2+}): 21.2 mg/L

Iron (Fe^{2+}): 0.19 mg/L

Iron (Fe^{3+}): 0.02 mg/L

Ammonium (NH_4^+): 1.2 mg/L

Strontium(Sr^{2+}): 0.4 mg/L

CHEMICAL AND PHYSICAL SPECIFICATIONS	
Molecular Weight	18 g/mol
Physical State	Liquid
Organoleptic Properties	Clear, colorless liquid with sulfuric odor
Solubility	-
Partition coefficient (Log Pow)	-
pH	8.86 (21.2 °C)
Nanomaterials	NO

Comments:

Water hole AC1

Anions: 1698 mg/L

Cations: 672 mg/L

Silica: 79.5 mg/L

Conductivity (20 °C): 2150 µS/cm

Alkalinity: 266.2 (mL/L de HCl 0.1M)

Total hardness: 7.5 p.p. 10^5 $CaCO_3$

Total CO_2 : - (mmol/L de CO_2)

Total sulfidation: - (mL/L I_2 0.01N)

Dry residue (180ºC): 1606 mg/L

Water hole AC2

Anions: 1826 mg/L

Cations: 722 mg/L

Silica: 84.6 mg/L

Conductivity (20 °C): 2300 µS/cm

Alkalinity: 288.6 (mL/L de HCl 0.1M)

Total hardness: 7.4 p.p. 10^5 $CaCO_3$

Total CO_2 : - (mmol/L de CO_2)

Total sulfidation: - (mL/L I_2 0.01N)

Dry residue (180ºC): 1722 mg/L

IMPURITIES AND/OR ALLERGEN SUBSTANCES

Impurity/Allergen substance	Concentration (%)
Aluminium	0.00000146
Arsenic	0.0000128
Lead	0-0.000000006
Mercury	0-0.000000054
Selenium	0-0.00000149
Silver	0-0.000000012
Boron	0.0000729
Barium	0.0000431
Beryllium	0.00000144
Cadmium	0-0.000000015
Cobalt	0.000000073
Chromium	0.00000076
Copper	0-0.000000039
Cesium	0.0000407
Manganese	0.00000429
Molybdenum	0.00000014
Nickel	0-0.00000076
Rubidium	0.0000492
Antimony	0.00000032
Tin	0-0.000000026
Tantalum	0-0.000000001
Tellurium	0-0.00000011
Thallium	0.00000078

Uranium	0.000000025
Vanadium	0.000000054
Tungsten	0.00000347
Zinc	0.00000213
Zirconium	0-0.00000019
Bismuth	0-0.000000005
yttrium	0-0.000000001
niobium	0-0.000000005

Refined Shea Butter

CHEMICAL AND PHYSICAL COMPOSITION

Composition	Conc. (%)	CAS	EINECS
Butyrospermum parkii Butter	-	194043-92-0 - 91080-23-8	293-515-7

Comments:

This product is constituted by the following fatty acids:

Fatty Acid	Concentration (%)
Oleic Acid (C18:1)	45.4
Stearic Acid (C18:0)	43.3
Palmitic Acid (C16:0)	4.4
Linoleic Acid (C18:2)	5.5
Arachidic acid (C20:0)	1.4

CHEMICAL AND PHYSICAL SPECIFICATIONS

Molecular Weight	-
Physical State	Solid
Organoleptic Properties	Off-white to ivory soft solid with a faint, characteristic odour
Solubility	Insoluble in water. Soluble in oils and organic solvents
Partition coefficient (Log Pow)	-
pH	-
Nanomaterials	NO

Comments:

Contains Vitamin E

Free fatty acid (as Oleic acid): 1.00 % maximum

Peroxide Value: 5.0 meq/kg maximum

Moisture Content: 0.10% maximum

Unsaponifiables: 4.0 - 9.0 %

Fatty Acid	Molecular weight (g/mol)	Partition coefficient
Oleic Acid (C18:1)	282.46	7.73
Stearic Acid (C18:0)	284.48	8.23
Palmitic Acid (C16:0)	256.42	-
Linoleic Acid (C18:2)	280.45	-
Arachidic acid (C20:0)	312.53	-

IMPURITIES AND/OR ALLERGEN SUBSTANCES

This ingredient does not contain impurities and/or allergen substances.

Sabowax CS 20

CHEMICAL AND PHYSICAL COMPOSITION

Composition	Conc. (%)	CAS	EINECS
Ceteareth-20	99-100	68439-49-6	-

Comments: -

CHEMICAL AND PHYSICAL SPECIFICATIONS

Molecular Weight	-
Physical State	Solid
Organoleptic Properties	White, waxy, flakes
Solubility	Soluble in water and alcohol. Insoluble in paraffinic oils
Partition coefficient (Log Pow)	-
pH	at 5%: 5.5 - 7.5
Nanomaterials	NO

Comments:

Moisture: 1% max

IMPURITIES AND/OR ALLERGEN SUBSTANCES

Impurity/Allergen substance	Concentration (%)
1,4-Dioxane	0
Ethylene oxide	0

Ecorol 68/50P

CHEMICAL AND PHYSICAL COMPOSITION

Composition	Conc. (%)	CAS	EINECS
Cetearyl alcohol	100	67762-27-0 / 8005-44-5	267-008-6 / -

Comments:

<= C14: maximum 1.5 %

C16: 46 - 53 %

C18: 44 - 53 %

>= C20: maximum 1.5 %

CHEMICAL AND PHYSICAL SPECIFICATIONS	
Molecular Weight	512.93 g/mol
Physical State	Solid
Organoleptic Properties	White solid with characteristic odour
Solubility	Insoluble in water
Partition coefficient (Log Pow)	-
pH	-
Nanomaterials	NO

Comments:
Melting point: 48-52 °C
Density: 0.81 g/cm3 (20 °C)

This ingredient is mainly constituted by two compounds, which molecular weights and partition coefficients are represented in the table below:

Compound	Molecular weight (g/mol)	Partition Coefficient
Stearyl alcohol	270.49	8.4
Cetyl alcohol	242.44	7.3

IMPURITIES AND/OR ALLERGEN SUBSTANCES

This ingredient does not contain impurities and/or allergen substances.

Sabonal C16

CHEMICAL AND PHYSICAL COMPOSITION

Composition	Conc. (%)	CAS	EINECS
Cetyl Alcohol	95-100	36653-82-4	253-149-0

Comments:

The generical composition on fatty acids of this ingredient is described below:

Chain distribution	Concentration (%)
Myristic acid (C 14)	<= 3.0
Palmitic acid (C 16)	>= 95.0
Stearic acid (C 18)	<= 5.0

CHEMICAL AND PHYSICAL SPECIFICATIONS	
Molecular Weight	242.45 g/mol
Physical State	Solid (20°C)
Organoleptic Properties	White wax
Solubility	Insoluble in water at 20°C
Partition coefficient (Log Pow)	7.3
pH	-
Nanomaterials	NO

Comments:

Water content: <= 0.3%

Hydrocarbons: <= 0.5%

IMPURITIES AND/OR ALLERGEN SUBSTANCES

This ingredient does not contain impurities and/or allergen substances.

Radia 7730 (Miristato Isopropilo EP)

CHEMICAL AND PHYSICAL COMPOSITION

Composition	Conc. (%)	CAS	EINECS
Isopropyl Myristate	100	110-27-0	203-751-4

Comments:

The main fatty acids that generally constitute this raw ingredient :

Composition	Concentration (%)
Myristic acid	>= 98
Palmitic acid	<= 0.5
Stearic acid	<= 0.5

CHEMICAL AND PHYSICAL SPECIFICATIONS

Molecular Weight	270.5 g/mol
Physical State	Liquid
Organoleptic Properties	Colourless to yellowish amber, odourless to oil
Solubility	Imiscible in water, glycerol or propyleneglycol. Easily soluble in alcohol 90%.
Partition coefficient (Log Pow)	7.17
pH	-
Nanomaterials	NO

Comments:

Water content: maximum 0.1 %

Ashes: maximum 0.1 %

Viscosity: 5 - 6 mPa.s (20 °C)

Density: 0.850 - 0.855 g/mL (20 °C)

Composition	Molecular Weight (g/mol)	Partition Coefficient
Myristic Acid	228.37	-
Palmitic Acid	256.42	-
Stearic Acid	284.48	8.23

IMPURITIES AND/OR ALLERGEN SUBSTANCES

This ingredient does not contain impurities and/or allergen substances.

Pristerene 4900 (Flake)

CHEMICAL AND PHYSICAL COMPOSITION

Composition	Conc. (%)	CAS	EINECS
Stearic acid	100	57-11-4	200-313-4

Comments:

This product is derived from palm oil and palm seed oil. According to its specifications, the fatty acid composition is:

Fatty Acid	Concentration (%)
Myristic acid	0.0 - 5.0
Palmitic acid	43.0 - 52.0
Stearic acid	40.0 - 56.0
Oleic acid	0.0 - 1.0

CHEMICAL AND PHYSICAL SPECIFICATIONS

Molecular Weight	284.47 g/mol
Physical State	Solid
Organoleptic Properties	White solid with a faint odour
Solubility	Insoluble in water. Soluble in many organic solvents. Solubility in ethanol: 50 g/l
Partition coefficient (Log Pow)	8.23
pH	-
Nanomaterials	NO

Comments:

Fatty Acid	Molecular Weight (g/mol)	Partition Coefficient (Log Pow)
Myristic acid	228.37	-
Palmitic acid	256.42	7.17
Stearic acid	284.48	8.23
Oleic acid	282.46	-

Autoignition temperature: ~350 °C

Melting point: 53 - 63 °C

Boiling point: 200 - 240 °C

IMPURITIES AND/OR ALLERGEN SUBSTANCES

This ingredient does not contain impurities and/or allergen substances.

1051936 NIVAL

CHEMICAL AND PHYSICAL COMPOSITION

Composition	Conc. (%)	CAS	EINECS
Parfum	-	-	-

Comments:

It is not known the exact composition of the perfume. This perfume is a mixture of natural and synthetic odour compounds, without ethanol. The following table shows the hazardous components for human health and their content, present in this perfume.

Compound	CAS	EINECS	Concentration (%)
4-tert-Butylcyclohexyl Acetate	32210-23-4	250-954-9	10 - 25
Linalyl Acetate	115-95-7	204-116-4	1 -5
Tricyclodecenyl Propionate	17511-60-3	241-514-7	1 - 5
Phenethyl acetate	103-45-7	203-113-5	1 - 5
Terpineol	8000-41-7	232-268-1	1 - 5
Coumarin	91-64-5	202-086-7	1 - 5
a-terpinyl acetate	80-26-2	201-265-7	1 - 5
Nerol	106-25-2	203-378-7	1 - 5
2,6-dimethyl-7-octen-2-ol	18479-58-8	242-362-4	1 - 5
Undecylenal	112-45-8	203-973-1	1 - 5
Citronellyl acetate	150-84-5	205-775-0	0.1 - 1
Geranyl acetate	105-87-3	203-341-5	0.1 - 1

CHEMICAL AND PHYSICAL SPECIFICATIONS

Molecular Weight	-
Physical State	Liquid
Organoleptic Properties	Transparent, yellow liquid with a floral-aldehyde characteristic odour
Solubility	-
Partition coefficient (Log Pow)	-
pH	-
Nanomaterials	NO

Comments:

Flashpoint: > 100 °C

Density: 0.9740 - 1.0140 g/cc (20 °C)

IMPURITIES AND/OR ALLERGEN SUBSTANCES

Impurity/Allergen substance	Concentration (%)
Alpha-Isomethyl Ionone	4.9050
Benzyl Alcohol	1.0021
Benzyl Benzoate	0.0128
Benzyl Salicylate	4.23
Butylphenyl Methylpropional	3.9091
Citral	0.0014
Citronellol	1.0909
Coumarin	1.6364
Eugenol	1

Geraniol	3.1547
Hexyl Cinnamal	6.6364
Hydroxycitronellal	1.9091
Hydroxyisohexyl 3-Cyclohexene Carboxaldehyde	0.5455
Isoeugenol	0.9091
Linalool	3
Limonene	0.0036

Carbopol 940 - 2%

CHEMICAL AND PHYSICAL COMPOSITION

Composition	Conc. (%)	CAS	EINECS
Aqua	93.25	7732-18-5	231-791-2
Triethanolamine	0.1	102-71-6	203-049-8
Carbomer	1.65	9007-20-9/9003-01-4/76050-42-5/9062-04-8/9007-16-3/9007-17-4	-
Alcohol denat. (with Diethyl phthalate and Denatonium benzoate)	5	-	-

Comments:

CHEMICAL AND PHYSICAL SPECIFICATIONS

Molecular Weight	-
Physical State	-
Organoleptic Properties	-
Solubility	-
Partition coefficient (Log Pow)	-
pH	-
Nanomaterials	NO

Comments:

Compound	Trade name/ Supplier	Molecular weight (g/mol)	Partition coefficient
Carbomer	Flogel 1000/SNF S.A.S.	500000 to 4000000	-
Aqua	-	18	-
Alcohol denat.	Soluções de Etanol/AGA – Álcool e Géneros Alimentares, S.A.	46.07 g/mol (ethanol)	-
Triethanolamine	Trietanolamina / Fagron	149.19	-2.3

IMPURITIES AND/OR ALLERGEN SUBSTANCES

Impurity/Allergen substance	Concentration (%)
iron	0-0.00005
Aldehydes	0-0.001
Methanol	0-0.01
Methylene Chloride	0-0.165
Bitrex (Denatonium Benzoate)	0.0002

Diethyl Phthalate	0.3

Phenonip ME

CHEMICAL AND PHYSICAL COMPOSITION

Composition	Conc. (%)	CAS	EINECS
Ethylparaben	12.5	120-47-8	204-399-4
Methylparaben	12.5	99-76-3	202-785-7
Phenoxyethanol	75	122-99-6	204-589-7

Comments:

CHEMICAL AND PHYSICAL SPECIFICATIONS

Molecular Weight	-
Physical State	Liquid
Organoleptic Properties	Colourless to light straw viscous liquid with a characteristic odour
Solubility	Solubility: water (approx. 0.7 %), ethanol/water 50/50 (> 95 %), Liquid Paraffin (< 0.1 %), Glycerol (approx. 8 %). Soluble in Ethanol. Miscible in Isopropanol, Acetone, Propylene Glycol and Sodium Laureth Sulfate (28 %)
Partition coefficient (Log Pow)	-
pH	-
Nanomaterials	NO

Comments:

Compound	Molecular Weight (g/mol)	Partition coefficent
Ethylparaben	166.17	2.47
Methylparaben	152.15	1.96
Phenoxyethanol	138.16	1.16

IMPURITIES AND/OR ALLERGEN SUBSTANCES

This ingredient does not contain impurities and/or allergen substances.

2.2 Stability and reactivity of the raw materials

Glycerin 4810

Stability and Reactivity
Store at room temperature in a clean and aerated place. For bulk storage, it is recommended to keep the product in nitrogen flushed tanks. This ingredient is hygroscopic. It decomposes by temperature rise, releasing corrosive, toxic vapors (acrolein). It may form CO and CO2 in case of combustion. It can polymerize by increase of temperature. Reacts violently with (strong) oxidizing agents and with (some) acids (increased) with risk of fire or explosion. Avoid heat sources, oxidizing agents, strong acids and strong alkalis. The container must be kept in a well-ventilated space at room temperature and protected from direct sun light. Storage material: steel, aluminium, iron or glass.

Saboderm G20

Stability and Reactivity
This ingredient is stable under normal conditions. The container must be kept in a well-ventilated area. In the original unopened containers the product can be stored for at least 18 months, protected from moisture at below 35°C.

Água Termal das Termas de Chaves

Stability and Reactivity
This water is stable for one month after its abstraction, when kept in a tightly closed HDPE bottle, at room temperature.

Refined Shea Butter

Stability and Reactivity
Avoid contact with strong oxidizing agents. When heated, toxic fumes (carbon dioxide and carbon monoxide) may be formed.

Sabowax CS 20

Stability and Reactivity
No decomposition if used according to specifications. The contact with strong acids, oxidizers and bases must be avoided. Suitable materials are: polyethylene (PE) resin, phenol-epoxy EHD0022, Oven-varnish R 78433 and High density polyethylene (HDPE). Store at temperatures below 30 °C, protected from moisture. The product melts above 35 °C. Should be kept away from heat, sparks, open flames and hot surfaces. It has to be stored in a cool place in closed original container.Depending on the temperature, the pH value may decrease during storage. However, the product quality is not negatively influenced above a pH value of 4.0.

Ecorol 68/50P

Stability and Reactivity
This ingredient is stable under normal conditions. It may emit noxious fumes of CO. The contact with strong oxidizing agents and strong mineral acids must be avoided.

Sabonal C16

Stability and Reactivity
Stable under normal storage and handling conditions. It is a combustible substance: avoid contact with direct heating, open flames, dirt, chemical contamination, sunlight, Ultra-Violet or ionizing radiation. Hazardous decomposition products in case of fire. No decomposition if used according to specifications. Store at temperatures less then 30°C. Avoid moisture. At temperatures higher than 40°C the product may melt and re-solidify upon cooling to form larger agglomerates or lumps.

Radia 7730 (Miristato Isopropilo EP)

Stability and Reactivity
Keep well-closed in the original packaging in a well-ventilated, cool and dry area, away from light. It is incompatible with oxidizing agents. Hazard decomposition products are: carbon monoxide and carbon dioxide.

Pristerene 4900 (Flake)

Stability and Reactivity
Keep closed in the same container as the original material and in a dry, ventilated and cool place. Strong acids, strong bases, strong oxidizing and reducing agents should be avoided. Avoid direct fire. When exposed to high temperature, as in case of fire, it originates carbon oxides. Thermal decomposition will evolve irritant vapours.

1051936 NIVAL

Stability and Reactivity
Keep the product in a tightly closed container, in a dry and well-ventilated place. Keep the product away from ignition sources and protected from light. Incompatible with strong reducing agents, azo and diazo compounds, hydrazines, nitrides, caustics, strong oxidizing agents, epoxides and acids. During combustion, carbon monoxide and unidentified organic compounds may be formed.

Carbopol 940 - 2%

Stability and Reactivity
The stability and reactivity of this mixture are not known.

Phenonip ME

Stability and Reactivity
Phenonip ME remains fully stable over a wide pH range from 3- 8. The product must be protected from excessively high temperatures during storage. This mixture may react with oxidant agents and strong oxidant agents.

2.3 Physical/chemical characteristics of the cosmetic product

	Specifications	**Method**
Organoleptic Properties	White and bright homogeneous emulsion with characteristic odour	Sensorial analysis
pH	5.5-6.5	Potentiometer
Viscosity	65000 - 85000 cps	Brookfield LVDV-E, Spindle S64/ 5 rpm
Specific gravity	-	-
Comments: -		

2.4 Stability of the cosmetic product

The product DERMOCOSMÉTICA TERMAL AQUAE CREME DE MÃOS was submitted to an accelerated stability test where samples were stored for 3 months in the final packaging and in a control packaging, at room temperature, at 40ºC±2ºC and at 4ºC±2ºC. Samples stored in the final packaging and in control package were also exposed to sunlight for 1 month.

After 3 months of stability, the organoleptic characteristics remained unchanged. There were no significant changes in the pH values, which remained within the established specifications for samples stored in the final packaging and in the control packaging. Regarding the viscosity, after 3 months, a tendency to increase in all storage conditions was observed, surpassing the established specifications for the samples stored at 4ºC. However, these changes did not affect the cosmeticity of the product. These fluctuations may be related with the maturation period of the emulsion. The microbiological properties of the product remained within the limits established by SCCS (Scientific Committee on Consumer Safety) for category 2 cosmetics (Total aerobic count ≤ 10^3 CFU/mL) before and after 3 months at the differents conditions. The final packaging showed no changes regarding the appearence, colour, integrity and the weight control showed that the selected type of packaging is suitable.

According to the obtained results, it was possible to conclude that the product DERMOCOSMÉTICA TERMAL AQUAE CREME DE MÃOS is stable after 3 months of accelerated stability study and it is compatible with the selected packaging.

Based on these results, as well as the Challenge test results, a Date of Minimum Durability (DDM) of 24 months was established.

At the time of this report, a long term stability study is under course to confirm the established date of minimum durability of the product DERMOCOSMÉTICA TERMAL AQUAE CREME DE MÃOS. Samples will be stored at room temperature in the final packaging for 30 months and physical-chemical analysis will be performed after 3 months, 6 months and 30 months. Moreover, the experimental determination of PAO is also being performed to confirm the theoretically estimated value of 13 months. The theoretical estimation of the PAO of the product was performed according to the guidelines "Recommandations relatives a l'estimation de la Period Apres Ouverture (PAO)", from the "Agence Française de securité sanitaire de produits de santé".

3. Microbiological quality

3.1 Microbiological specifications of the raw materials

Glycerin 4810

The microbiological specifications for this ingredient are unknown.

Saboderm G20

The microbiological specifications for this ingredient are unknown.

Água Termal das Termas de Chaves

The microbiological specifications for this ingredient are:

Clostridium sulfite reducers: 0 CFU / 50 mL

Fecal coliforms: 0 CFU / 250 mL

Total coliforms: 0 CFU / 250 mL

Enterococci: 0 CFU / 250 mL

Escherichia coli: 0 CFU / 250 mL

Total viable count (22 ° C): < 100 CFU/ml

Total viable count (36 ° C): < 20 CFU/ml

Pseudomonas aeruginosa: 0 CFU / 250 mL

Staphylococcus Coagulase (+): 0 CFU / 100 mL

Refined Shea Butter

The microbiological specifications for this ingredient are unknown.

Sabowax CS 20

The microbiological specifications of this ingredient are not known.

Ecorol 68/50P

The microbiological specifications for this ingredient are unknown.

Sabonal C16

The microbiological specifications for this ingredient are unknown.

Radia 7730 (Miristato Isopropilo EP)

The microbiological specifications for this ingredient are not known.

Pristerene 4900 (Flake)

The microbiological specifications of this ingredient are unknown.

1051936 NIVAL

The microbiological specifications for this ingredient are unknown.

Carbopol 940 - 2%

The microbiological specifications for this mixture are unknown

Phenonip ME

The microbiological specifications for this ingredient are not known. However, once it is a preservative agent, microbiological contamination is not expected to occur.

3.2 Microbiological characteristics of the final cosmetic product

The microbiological specifications for this product are:
- Bacteria: < 1000 CFU/g;
- Yeast and Mold: < 1000 CFU/g;
- *Candida albicans*: absent;
- *Staphilococcus aureus*: absent;
- *Pseudomonas aeroginosa*: absent

3.3 Results of preservation challenge test

A challenge test according to European Pharmacopoeia 8 was performed to evaluate the efficacy of the preservative system of the cosmetic product DERMOCOSMÉTICA TERMAL AQUAE CREME DE MÃOS.

The following microorganisms were included in the assay and incubated in the coditions as described:

Staphylococcus aureus ATCC 6538 - 35º C, 2 days
Pseudomonas aeruginosa ATCC 9027 - 35º C, 2 days
Candida albicans ATCC 10231 - 25º C, 2 days
Aspergillus brasiliensis ATCC 16404 - 25º C, 5 days

The test product was inoculated separately with each one of the test microorganisms at a ratio of 200 µL calibrated cell suspension to 20 g of test product. The results of the challenge test are shown in the table below:

Microrganisms	**2 days (UFC)**	**2 days (Δlog)**	**7 days (UFC)**	**7 days (Δlog)**	**14 days (UFC)**	**14 days (Δlog)**	**28 days (UFC)**	**28 days (Δlog)**	**Criteria**
S. aureus ATCC 6538	1.47E+03	2.75	0	5.92; N/I *	0	5.92; N/I *	0	5.92; N/I	A
P. aeruginosa ATCC 9027	0	6.09	0	6.09; N/I *	0	6.09; N/I *	0	6.09; N/I	A
C. albicans ATCC 10231	---	---	---	---	0	5.28; N/I *	0	5.28; N/I	A
A. brasiliensis ATCC 16404	---	---	---	---	1.50E+03	1.68	0	4.85; N/I	B

* N/I – No increase

The study performed with the sample of product "DERMOCOSMÉTICA TERMAL AQUAE CREME DE MÃOS" allows to conclude that the product meets criteria B of European Pharmacopoeia 8.

4. Impurities, traces, information about the packaging material

4.1 Impurities of the Raw Materials

Besides the possible impurities that this cosmetic product may contain, it is also included in this section all its allergen substances.

IMPURITIES AND/OR ALLERGEN SUBSTANCES	
Impurity/Allergen substance	**Total Concentration (%)**
iron	0.000004
Halogenated compounds	0.00030
Chlorides	0.00010
1,4-Dioxane	unknown
Heavy metals	0.00005
Ethylene oxide	unknown
Alpha-Isomethyl Ionone	0.00490
Benzyl Alcohol	0.00100
Benzyl Benzoate	0.00001
Benzyl Salicylate	0.00423
Butylphenyl Methylpropional	0.00391
Citral	0.000001
Citronellol	0.00109
Coumarin	0.00164
Eugenol	0.00100
Geraniol	0.00315
Hexyl Cinnamal	0.00664
Hydroxycitronellal	0.00191
Hydroxyisohexyl 3-Cyclohexene Carboxaldehyde	0.00055
Isoeugenol	0.00091
Linalool	0.00300
Aluminium	0.000001
Arsenic	0.00001
Lead	0.000000004
Mercury	0.00000003
Limonene	0.000004
Aldehydes	0.00007
Selenium	0.000001
Methanol	0.00070
Silver	0.00000001
Boron	0.00005
Barium	0.00003
Beryllium	0.000001
Cadmium	0.00000001
Cobalt	0.00000005
Chromium	0.0000005
Copper	0.00000003
Cesium	0.00003
Manganese	0.000003
Molybdenum	0.0000001
Nickel	0.0000005

Rubidium	0.00003
Antimony	0.0000002
Tin	0.00000002
Tantalum	0.000000001
Tellurium	0.0000001
Thallium	0.000001
Uranium	0.00000002
Vanadium	0.00000003
Tungsten	0.000002
Zinc	0.000001
Zirconium	0.0000001
Diethylene glycol	0.01000
Bismuth	0.000000003
Yttrium	0.000000001
Niobium	0.000000003
Methylene Chloride	0.01155
Bitrex (Denatonium Benzoate)	0.00001
Diethyl Phthalate	0.02100

4.2 Traces of prohibited compounds in the cosmetic product

Some impurities present in this product are in the list of substances prohibited in cosmetic products (Annex II of the Regulation EC 1223/2009). However, according the article 17 of the same regulation, the non-intended presence of a small quantity of a prohibited substance, stemming from impurities of natural or synthetic ingredients, the manufacturing process, storage, migration from packaging, which is technically unavoidable in good manufacturing practice, shall be permitted provided that such presence is in conformity with Article 3, when used under normal or reasonably foreseeable conditions of use. The presence of these traces is technically unavoidable, even following good manufacturing practices, because they are impurities of raw materials used and they are: Diethylene glycol (present in Glycerin 4810); Methylene Chloride (present in Carbopol 940 - 2%); Arsenic, Lead, Mercury, Selenium, Beryllium, Cadmium, Chromium, Nickel, Antimony, Thallium and Zirconium (present in Água Termal das Termas de Chaves).

The substances 1,4-dioxane and Ethylene Oxide may be present in the raw material Sabowax CS 20, although it is not mentioned by the supplier.

It is also important to point out that one of these substances has carcinogenic, mutagenic or reproductive potential, being listed in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labeling of hazardous substances):

- 1,4-Dioxane - Carcinogenic Category 2
- Ethylene Oxide - Mutagenicity toxicity and Carcinogenic Category 1B
- Methylene Chloride - Carcinogenic Category 2
- Lead - Reproductive toxicity Category 1A
- Mercury – Reproductive toxicity Category 1B
- Beryllium - Carcinogenic Category 1B
- Cadmium - Mutagenicity and reproductive toxicity Category 2
- Nickel - Carcinogenic Category 2

4.3 Characteristics of the packaging material

According to the information provided, the packaging of this product which is in contact with the cosmetic product is composed of: a cap, provided by Eurovetrocap S.r.L, under the trade name Cappuccio SK A; an adapter provided by Eurovetrocap S.r.L, under the trade name Riduttore SK Diametro 12/Foro 2.5; and a tube provided by Eurovetrocap S.r.L, under the trade name Tubo SK 100ml Int. Bocca Per Riduttore 11.20.

The cap is made of Polypropylene, supplied by Total Research & Technology Feluy (under the trade name POLYPROPYLENE PPH 10012) and TOTAL PETROCHEMICALS & REFINING SA/NV (under the trade name TOTAL POLYPROPYLENE HOMOPOLYMER).

The adapter is made of Polyethylene (PE), supplied by SABIC SALES Europe B.V. or any of its Affiliates under the trade name SABIC® LDPE - granular.

The tube is made of High Density Polyethylene (HDPE), supplied by SABIC SALES Europe B.V. or any of its Affiliates under the trade names SABIC® HDPE, SABIC® Vestolen A – granular and SABIC® HDPE B5421.

An accelareted stability/product-packaging compatibility study was performed with the product DERMOCOSMÉTICA TERMAL AQUAE CREME DE MÃOS (see 2.4 Stability of the cosmetic product), and it was concluded that the product is stable after 3 months of accelerated stability study and it is compatible with the selected packaging.

At the time of this report, a long term stability study is under course, to confirm the shelf life stability and product-packaging compatibility of the product DERMOCOSMÉTICA TERMAL AQUAE CREME DE MÃOS.

5. Normal and reasonably foreseeable use

Mode of application	The product is rubbed-on the hands
Warnings	-
Comments: -	

6. Exposure to the cosmetic product

Product type	Leave-on
Retention factor	1.00
Site of application	Hands
Amount of product applied per application (mg)	1962.00
Duration of use	Undetermined
Normal and reasonably foreseeable exposure route(s)	Topical
Routes of secondary exposure	-
Targeted (or exposed) population(s)	Healthy adults
Possible impacts on exposure due to particle sizes	This product does not contain nanomaterials that can affect human health

Calculation of the Exposure	
mg/day	1962.00
mg/cm2 skin/day	2.28
mg/kg body weight/day	32.70

7. Exposure to the raw materials

		Calculation of the Exposure		
Raw material (trade name)	**Conc. (%)**	**mg/day**	**mg/cm2 skin/day**	**mg/kg body weight/day**
Glycerin 4810	10.00000	196.2000	0.2280	3.2700
Saboderm G20	1.00000	19.6200	0.0228	0.3270
Água Termal das Termas de Chaves	64.70000	1 269.4140	1.4752	21.1569
Refined Shea Butter	4.00000	78.4800	0.0912	1.3080
Sabowax CS 20	3.00000	58.8600	0.0684	0.9810
Ecorol 68/50P	2.00000	39.2400	0.0456	0.6540
Sabonal C16	2.00000	39.2400	0.0456	0.6540
Radia 7730 (Miristato Isopropilo EP)	2.00000	39.2400	0.0456	0.6540
Pristerene 4900 (Flake)	3.00000	58.8600	0.0684	0.9810
1051936 NIVAL	0.10000	1.9620	0.0023	0.0327
Carbopol 940 - 2%	7.00000	137.3400	0.1596	2.2890
Phenonip ME	1.20000	23.5440	0.0274	0.3924

8. Toxicological profile of the substances/raw materials and other information

8.1 Toxicological profile of the substances (INCI name)

Ethylparaben

REGULATORY RESTRICTIONS
This ingredient is listed in Regulation EC 1223/2009 annex V (list of preservatives which cosmetic products may contain). According to this Regulation and respective amendments, the use of this paraben in cosmetic products is restricted to a maximum concentration of 0.4% (as acid) for single ester, and 0.8% (as acid) when a mixture of esters is used. CIR (Cosmetic Ingredient Review) considers that this compound is safe when applied in the above-mentioned concentrations.

ACUTE TOXICITY

Administration Route	Adverse effects description	LD50	Ref.
Oral	Ingestion of a 0.03% aqueous ethylparaben solution caused irritation to the intestinal mucosa.	(rat, female): 4.30 g/kg; (rat): 11.0 g/kg; (guinea pig): 2.0 g/kg; (rabbit): 5.0 g/kg; (mouse): 3.0 g/kg; (dog): 5.0 g/kg	1
Inhalation	-	-	
Dermal	It may cause human skin irritation.	(rabbit): 15.0 g/kg	1
Subcutaneous	-	-	

Comments:
Ethylparaben is widely used as an antimicrobial preservative in cosmetics, food products, and pharmaceutical formulations. It may be used either alone or in combination with other paraben esters or with other antimicrobial agents. In cosmetics it is one of the most frequently used preservatives. **(2)** Acute toxicity studies in animals indicate that Parabens are not significantly toxic by various routes of administration. **(3)**

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	Ethylparaben was a skin irritant in man.	1
Ocular Irritation	Ethylparaben at 100% instilled into the eyes of albino rabbits was slightly irritating and at 10% in water produced no signs of irritation. Parabens are often incorporated in creams, lotions and ointments that may be used in the region of the eyes, and occasionally cause redness and swelling of eyelids from allergic contact dermatitis.	1
Sensitization	Systemically, no adverse reaction to parabens have been reported, although they have been associated with hypersensitivity reactions, generally of the delayed type and appearing as contact dermatitis. Parabens are capable of inducing cutaneous allergic responses, however, given the widespread use of parabens as preservatives, such reactions are relatively uncommon.	4,2
Dermal Absorption	There are evidences of parabens being rapidly absorbed by animal and human skin. However, available in vitro dermal absorption study results point towards a potential difference in dermal absorption between rat and man. Consequently the rat data as such cannot be simply extrapolated to the human situation without additional supportive data. Nevertheless, until a properly conducted dermal absorption and toxicokinetic study in humans will allow the assignment of a more scientifically solid value, the SCCS will use a dermal absorption value of 3.7% in its margin of safety calculations.	5

Comments:
-

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.
Oral	Chronic oral studies indicate that Parabens are practically non-toxic.	3

Inhalation	-	
Dermal	-	
Comments: -		

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY		
		Ref.
Carcinogenicity	Ethylparaben in the diet produced cell proliferation in the forestomach of rats.	3
Mutagenicity	At a concentration of 10 mmol/L, ethylparaben was mutagenic in Escherichia coli. Numerous genotoxicity studies, including Ames testing, dominant lethal assay, host-mediated assay, and cytogenic assays, indicate that Parabens are generally non-mutagenic, although ethylparaben did increase chromosomal aberrations in a Chinese Hamster ovary cell assay.	1,3
Teratogenicity	Ethylparaben was non teratogenic in rats.	3
Comments: -		

PHOTO-INDUCED TOXICITY
In general, parabens do not exhibit significant levels of photo-contact sensitization or photo-toxicity. **(2)**

Methylparaben

REGULATORY RESTRICTIONS
This ingredient is listed in Regulation EC 1223/2009 annex V (list of preservatives which cosmetic products may contain). According to this Regulation and respective amendments, the use of this paraben in cosmetic products is restricted to a maximum concentration of 0.4% (as acid) for single ester, and 0.8% (as acid) when a mixture of esters is used. CIR (Cosmetic Ingredient Review) considers that this compound is safe when applied in the above-mentioned concentrations. CIR (Cosmetic Ingredient Review) considers that this compound is safe when applied in the above-mentioned concentrations.

ACUTE TOXICITY			
Administration Route	**Adverse effects description**	**LD50**	**Ref.**
Oral	No toxic effects were observed in animal assays.	(dog): 3.0 g/kg; (dog): 12.2 g/kg; (rabbit): 6 g/kg; (rat): 2.0 g/kg; (mouse): > 8 g/kg; (male rat): > 3200 mg/kg; (female rat): > 2280 mg/kg	4,6,2
Inhalation	-	-	
Dermal	Slightly hazardous in case of skin contact (may cause contact dermatitis).	-	4,2
Subcutaneous	-	(mouse): 1.20 g/kg	2
Comments: Methylparaben is widely used as an antimicrobial preservative in cosmetics, food products, and oral and topical pharmaceutical formulations. It may be used either alone or in combination with other parabens or with other antimicrobial agents. In cosmetics, methylparaben is the most frequently used antimicrobial preservative **(2)** . Acute toxicity studies in animals indicate that Parabens are not significantly toxic by various routes of administration **(3)** .			

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY		
		Ref.
Skin Irritation	Parabens are practically non-irritating in the population with normal skin, however, methylparaben (Isocide MP) can cause skin irritation.	6,3
Ocular Irritation	It can cause irritation. Parabens are often incorporated in creams, lotions and ointments that may be used in the region of the eyes, and occasionally cause redness and swelling of eyelids from allergic contact dermatitis.	1,6
Sensitization	When tested on guinea pigs, methylparaben did not induce sensitization effects. No sensitization was reported on a HRIPT (Human Repeated Insult Patch Test) with 50 subjects. Parabens are capable of sensitizing skin and inducing cutaneous allergic	4,2

	responses, although incidence of such reactions is low. Hypersensitivity reactions to parabens, generally of the delayed type and appearing as contact dermatitis, have been reported. However, given the widespread use of parabens as preservatives, such reactions are relatively uncommon.	
Dermal Absorption	There are evidences of parabens being rapidly absorbed by animal and human skin. However, available in vitro dermal absorption study results point towards a potential difference in dermal absorption between rat and man. Consequently the rat data as such cannot be simply extrapolated to the human situation without additional supportive data. Nevertheless, until a properly conducted dermal absorption and toxicokinetic study in humans will allow the assignment of a more scientifically solid value, the SCCS recommends a dermal absorption value of 3.7% in its margin of safety calculation.	5
Comments: -		

CHRONIC TOXICITY		
Administration Route	**Adverse effects description**	**Ref.**
Oral	A chronic oral toxicity study in which methylparaben was incorporated into diets at 2 or 8% and the diets fed to groups of 24 rats for 96 weeks was performed. At 2% of the diet, parabens exerted no toxic effect. Rats killed at the conclusion of the feeding test had no treatment related abnormalities. Weanling dogs were dosed 1 g/kg/day methylparaben for 378 to 422 days; and three other dogs, 0.5 g/kg/day methylparaben for 318 to 394 days. No toxicity to the paraben was observed. All animals were in excellent condition throughout the experiment. All tissues were normal. Chronic oral studies indicate that Parabens are practically non-toxic.	4,3
Inhalation	-	
Dermal	-	
Comments: -		

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY		
		Ref.
Carcinogenicity	Methylparaben was non-carcinogenic when injected subcutaneously in mice or rats or when administered intravaginally in rats. Although some concern was raised about possible carcinogenic effects of parabens when used in underarms products, the SCCS concluded that there was insufficient data to establish a link between the use of underarm cosmetics and breast cancer.	3,5
Mutagenicity	Numerous genotoxicity studies, including Ames tests, dominant lethal assay, host-mediated assay and cytogenic assays, indicate that Parabens are generally non-mutagenic, although Methylparaben did increase chromosomal aberrations in a Chinese Hamster ovary cell assay.	3
Teratogenicity	Methylparaben was non-teratogenic in rabbits, rats, mice, and hamsters.	3
Comments: -		

PHOTO-INDUCED TOXICITY
In general, parabens do not exhibit significant levels of photo-contact sensitization or photo-toxicity **(2)** .

Triethanolamine

REGULATORY RESTRICTIONS
According to Regulation EC 1223/2009 this ingredient is listed in Annex III (list of substances that cosmetic products must not contain except subject to restrictions) under the group of trialkylamines, trialkanolamines and their salts. According to this Regulation and respective amendments, the use of trialkylamines, trialkanolamines and their salts can be used in rinse-off products with no concentration restriction but is restricted in leave-on products to a maximum concentration of 2.5%. The use of this ingredient in cosmetic products is conditioned by the following restrictions: do not use with nitrosating systems; minimum purity: 99%; maximum secondary amine content: 0.5% (applies to raw materials); maximum nitrosamine content: 50 microg/kg; keep in nitrite-free containers. CIR (Cosmetic Ingredient Review) considers this

ingredient safe in the present practices of use and concentration (up to 6% in leave-on products and up to 19% in other cosmetic products), when formulated to be non-irritating and it should not be used in products in which N-nitroso compounds can be formed.

ACUTE TOXICITY

Administration Route	Adverse effects description	LD50	Ref.
Oral	It may cause slight irritation in mouth, throat and esophagus, gastrointestinal irritation and diarrhea. Triethanolamine may also cause injuries in kidneys and liver. The effects observed in rats and guinea pigs in an acute oral study were confined to the gastrointestinal tract. Toxic effects were probably from the alkaline irritation, because larger doses of the neutralized material produced no symptoms at levels where the free base would cause 100% mortality. In single-dose oral toxicity for rats, triethanolamine was practically non-toxic to slightly toxic. It may cause stomach or intestinal upset (nausea, vomiting and diarrhea) and central nervous system depression (dizziness, drowsiness, weakness, fatigue, nausea, headache, unconsciousness).	(rabbit): 2200 mg/kg; (guinea pig): 2200 mg/kg; (mouse): 5846 mg/kg; (rat): 8000 mg/kg	7,8,9,10,11
Inhalation	Inhalation of vapor may be harmful. It may cause irritation of nose, throat and airways.	-	9,11
Dermal	Triethanolamine showed little potential for rabbit skin irritation in acute skin irritation tests. In single-contact, triethanolamine was practically non-toxic.	(rabbit): > 2000 mg/kg; (rat): > 5000 g/kg	10,11
Subcutaneous	-	-	

Comments:
Triethanolamine is widely used in topical pharmaceutical formulations, primarily in the formation of emulsions. Triethanolamine is also used in salt formation for injectable solutions and in topical analgesic preparations. It is also used in sunscreen preparations **(11)** . Following concern about the possible production of nitrosamines in the stomach, the Swiss authorities have restricted the use of triethanolamine to preparations intended for external use. The lethal human oral dose of triethanolamine is estimated to be 5-15 g/kg body-weight **(11)** .

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	Applications of 5 or 10% solution to rabbit or rat skin did not produce irritation. However, clinical skin testing of triethanolamine and cosmetic products containing triethanolamine showed mild skin irritation in concentrations above 5%. Triethanolamine appeared to induce no irritating effects at concentration below 5% in most people. Undiluted triethanolamine is slight to moderately irritating to the skin. This ingredient is generally regarded as a non-toxic material, nevertheless it may cause hypersensitivity or it may be irritant to the skin when present in formulated products. Symptoms may include redness and burning of skin.	8,9,10,11,12
Ocular Irritation	It causes ocular irritation. Symptoms include stinging, tearing, redness, and swelling of eyes. Undiluted triethanolamine and concentrated solutions have an irritating action on the eyes, but only slight transient or no corneal injury would be expected.	7,8,9
Sensitization	It may cause hypersensitivity and allergic skin reaction. Triethanolamine has been identified as causing contact dermatitis and allergic contact dermatitis, erythematous vesicular lesions, eczema, and irritation in workers exposed to triethanolamine in their occupations.	13,10,11
Dermal Absorption	Studies performed in rats showed a dermal absorption rate up to 95%.	13

Comments:
-

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.

Oral	Long-term oral ingestion of the ethanolamines by rats and guinea pigs produced lesions limited mainly to the liver and kidney.	10
Inhalation	-	
Dermal	It may cause skin dryness and irritation or dermatitis. Triethanolamine has been identified as causing allergic contact dermatitis, erythematous vesicular lesions, eczema, contact dermatitis, and irritation in workers exposed to triethanolamine in their occupations. A burn may result from prolonged and repeated contact (undiluted triethanolamine). Long-term cutaneous applications to animals of the ethanolamines also produced evidence of hepatic and renal damage.	8,13,10
Comments: Overexposure to this material (or its components) has been suggested as a cause of the following effects in laboratory animals: anemia, testis damage, heart damage, central nervous system damage, kidney damage and liver damage **(9)** .		

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY		
		Ref.
Carcinogenicity	Triethanolamine was adequately tested for carcinogenicity in mice and in rats by oral administration in the drinking-water. No increase in the incidence of tumors was observed. It was also tested by dermal application in rats and no increase in the incidence of tumors was found. In a Tg.AC transgenic mouse model, dermal application of triethanolamine produced no increase in tumors. Triethanolamine had no carcinogenic or co-carcinogenic activity when dermally applied to mice for 18 months. Triethanolamine is not listed as carcinogenic by the International Agency for Research on Cancer (IARC), the National Toxicology Program (NTP), or the Occupational Safety and Health Administration (OSHA). There is inadequate evidence in humans for the carcinogenicity of triethanolamine. Thereby, triethanolamine is not classifiable as to its carcinogenicity to humans (Group 3). ACGIH designates Triethanolamine as A3 – confirmed animal carcinogen with unknown relevance to humans.	9,14,10,12
Mutagenicity	Triethanolamine did not induce mutations in bacteria, unless nitrite was also present. It did not influence the frequency of micronuclei in mouse peripheral blood in vivo after dermal application. Triethanolamine did not induce unscheduled DNA synthesis, sister chromatid exchange, chromosomal aberrations or cell transformation in rodent cells in vitro. Triethanolamine had no effect on sex-linked recessive lethal mutations in Drosophila melanogaster or on gene conversion in Saccharomyces cerevisiae. The ethanolamines were non-mutagenic in the Ames test and triethanolamine is also non-mutagenic to Bacillus subtilis.	10,12
Teratogenicity	No reproductive or developmental effects were produced when rats and mice were exposed by topical administration. This material (or a component) has been shown to cause harm to the fetus in laboratory animal studies. Harm to the fetus occurs only at exposure levels that harm the pregnant animal. The relevance of these findings to humans is uncertain. Limited data from animal studies does not indicate that Triethanolamine is a developmental toxin.	9,10,12,14
Comments: Limited data from animal studies does not indicate that Triethanolamine is a reproductive toxin **(14)** .		

PHOTO-INDUCED TOXICITY
There were no photo-toxicity or photo-sensitization reactions with products containing up to 20.04% triethanolamine **(10)** .

Phenoxyethanol

REGULATORY RESTRICTIONS
This ingredient is listed in the Regulation EC No. 1223/2009 annex V (List of preservatives which cosmetic products may contain). According to this Regulation and respective amendments the use of this ingredient in cosmetic products is restricted to a maximum concentration of 1%. CIR (Cosmetic Ingredient Review) considers that this ingredient is safe as used up to 1%.

ACUTE TOXICITY			
Administration Route	**Adverse effects description**	**LD50**	**Ref.**
Oral	Phenoxyethanol is practically non-toxic when administered orally to rats. Although it may cause	(rat, male): 1.26 ml/kg; (rat, female): 2.33 ml/kg; (mouse): 933 mg/kg; (rat):	15,16,17,18

	gastrointestinal irritation with symptoms like nausea, vomiting and diarrhea.	1840 mg/kg	
Inhalation	At room temperature, exposure to vapor is minimal due to low volatility. Vapor from heated material may cause respiratory tract irritation and other effects.	(rat): 1mg/L (6 hours, aerosol)	16
Dermal	Phenoxyethanol is practically non-toxic when dermally administered to rats. Allergic contact dermatitis to 1% phenoxyethanol could be a rare possibility in patients having an adverse reaction to aqueous creams.	(rabbit): > 545 mg/kg; (rat): > 2250 mg/kg – 14000 mg/kg; (rat): 14391 mg/kg	15,16,17
Subcutaneous	-	-	

Comments:
Phenoxyethanol is an antimicrobial preservative used in cosmetics and topical pharmaceutical formulations at a concentration of 0.5–1.0%. It may also be used as a preservative and antimicrobial agent for vaccines. Therapeutically, a 2.2% solution or 2.0% cream has been used as a desinfectant for superficial wounds, burns, and minor infections of the skin and mucous membranes. Phenoxyethanol produces a local anesthetic effect on the lips, tongue, and other mucous membranes **(2)** .

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	Phenoxyethanol at 2.0% was a slight irritant to rabbit skin, but it was not irritant to guinea pig skin. Phenoxyethanol at 10% in mineral oil is not considered a primary nor a cumulative irritant, but the pure material is a moderate irritant to the skin. Contact urticaria has been reported upon exposure to 2-phenoxyethanolcontaining cosmetics. The US FDA has recommended avoiding at least one topical product containing phenoxyethanol due to concerns over inadvertant exposure to nursing infants.	18,19
Ocular Irritation	Undiluted phenoxyethanol was a strong eye irritant, but was non-irritating when tested at 2.2%. Phenoxyethanol diluted to 5% was applied to the conjunctival sac of rabbits, and induced a mild irritation of the conjunctivae. It may cause moderate eye irritation and moderate corneal injury.	20,16,18
Sensitization	Phenoxyethanol was not a sensitizer to guinea pig skin and did not cause delayed hypersensitivity in clinical studies (HRIPT with 51 subjects, with phenoxyethanol at 10%v/v). A modified repeated insult patch test (138 subjects) with phenoxyethanol at 10% and patch tests with the ingredient at 5% indicated no skin reactions consistent with allergic sensitization. It did not cause allergic skin reactions when tested in guinea pigs and in humans.	20,16,18
Dermal Absorption	It has previously been shown that skin has the capacity for local metabolism of applied chemicals. Therefore, there is a requirement to consider metabolism during dermal absorption of these compounds (glycol ethers) in risk assessment for humans. AFSSAPS (Agence Française de Sécurité Sanitaire des Produits de Santé) considers 80% of dermal absorption of phenoxyethanol in leave-on products and 40% in rinse-off products.	17,18

Comments:
-

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.
Oral	Similar effects to those of acute ingestion are expected.	21
Inhalation	Repeated or prolonged inhalation of vapors may lead to chronic respiratory irritation.	22
Dermal	Phenoxyethanol was applied dermally to 10 female New Zealand White rabbits at a dose of 1000 mg/kg/day for 14 days. Seven of the rabbits died between days 5 and 8 of treatment. The prominent hematologic change noted in these rabbits was indicative of the breakdown of erythrocytes. There were no hematologic changes noted in the three surviving rabbits. In a more recent study, 2000 mg/kg undiluted phenoxyethanol (cosmetic grade) was applied to the shaved and abraded skin of four New Zealand White rabbits, remaining in place for 24 hours, followed by a 14-day observation period and necropsy, no systemic toxicity or adverse effects were noted, except for slight skin irritations on the application site. Excessive exposure may cause hemolysis, thereby impairing the ability of	16,17,18

	the blood to transport oxygen.	

Comments:
Long-term exposure to phenoxyethanol may result in Central Nervous System toxic effects similar to other organic solvents **(2)** .

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY		
		Ref.
Carcinogenicity	There is no data available on the carcinogenic effects of this ingredient.	
Mutagenicity	Phenoxyethanol was non-mutagenic in the Ames test, with and without metabolic activation. In vitro genetic toxicity studies were negative. Animal genetic toxicity studies were negative.	20,16,18
Teratogenicity	In dermal treatment studies, phenoxyethanol was neither teratogenic, embryotoxic, nor fetotoxic at doses which were maternally toxic. A fetotoxic and teratogenic evaluation of 2-phenoxyethanol was performed with rabbits following dermal exposure. Dermal application of 1000 mg/kg/day produced maternal toxicity and maternal toxicity was also observed in rabbits treated with 600 mg 2-phenoxyethanol/kg/day but at a lower incidence. No signs of maternal toxicity were seen at 300 mg/kg/day. Examination of rabbit fetuses indicated that, at the dosages tested, 2-phenoxyethanol was not embryotoxic, fetotoxic, or teratogenic. It did not cause birth defects or other effects in the fetus even at doses which caused toxic effects in the mother. Moreover, in animal studies, repeated exposure did not have any effects on reproductive organs.	16,21,18

Comments:
This product may contain an impurity, Phenol, that is Mutagenic Category 2 in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labelling of hazardous substances). This product may contain an impurity, ethylene oxide, that is classified as 1B regarding its Carcinogenic and Mutagenic toxicity in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labelling of hazardous substances).

PHOTO-INDUCED TOXICITY
Phenoxyethanol was not photo-toxic in clinical studies **(18)** .

Carbomer

REGULATORY RESTRICTIONS
According to the Regulation EC 1223/2009 and respective amendments there are no restrictions on its use in cosmetic products. CIR considers that Carbomer-910, -962 are not in current use (were the ingredient to be used in the future, the expectation is that it would be used at concentrations comparable to others in the group) and Carbomer-934, -934P, -940, -941 are safe as used up to 2 %.

ACUTE TOXICITY			
Administration Route	**Adverse effects description**	**LD50**	**Ref.**
Oral	Low oral toxicity. It may cause vomiting and diarrhea. Acute oral animal studies showed that Carbomers-910, -934, -934P, -940, and -941 have low toxicities when ingested. There is no evidence of systemic absorption of carbomer polymers following oral administration.	(rat): > 1000 mg/kg; (rat): 2000-5000 mg/kg	23,24,25,2
Inhalation	If material is misted or if vapors are generated from heating, exposure may cause irritation of mucous membranes and the upper respiratory tract. Breathing of dust may cause coughing, mucous production and shortness of breath. Animal studies indicated that the inhalation of respirable polyacrylate dust may cause inflammatory changes in the lung.	-	24
Dermal	It may cause skin irritation.	(rabbit): > 2000 mg/kg/day (rat): > 2000 mg/kg	26,24
Subcutaneous	-	-	

Comments:
Carbomers are used extensively in non-parenteral products, particularly topical liquid and semisolid preparations. Carbomers are generally regarded as essentially non-toxic and non-irritant materials **(2)** .

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY		
		Ref.
Skin Irritation	It may cause skin irritation. Rabbits showed minimal skin irritation when tested with Carbomers-910 and -934. Clinical studies with Carbomers showed that these polymers have low potential for skin irritation at concentrations up to 100%.	24,25
Ocular Irritation	It is a weak to moderate eye irritant. Particulates may cause mechanical irritation and solid particles (powder or dust) on the eye may cause pain and irritation. Rabbits showed zero to moderate eye irritation when tested with Carbomers-910 and -934.	24,25
Sensitization	Clinical studies with Carbomers showed that these polymers have low potential for sensitization at concentrations up to 100%. It is not expected to cause skin sensitization. Indeed, there is no evidence in humans of hypersensitivity reactions to carbomers used topically.	24,25,2
Dermal Absorption	-	
Comments: -		

CHRONIC TOXICITY		
Administration Route	**Adverse effects description**	**Ref.**
Oral	Dogs chronically fed with Carbomer-934P manifested gastrointestinal irritation and marked pigment deposition within Kupffer cells of the liver. Sub-chronic feeding of rats and dogs with Carbomer-934 in the diet resulted in lower than normal body weights, but no pathological changes were observed.	25
Inhalation	Adverse lung effects were observed in rats receiving life-long inhalation exposure to respirable polyacrylate dust. Effects included inflammation, hyperplasia, fibrosis and alveolar abnormalities. Pre-existing respiratory conditions may be aggravated by prolonged or repeated exposure.	26,24
Dermal	Contact dermatitis may occur in sensitive individuals under extreme and unusual conditions of prolonged and repeated contact, such as high exposure accompanied by elevated temperature and occlusion by clothing. Pre-existing skin conditions may be aggravated by prolonged or repeated exposure.	26,24
Comments: -		

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY		
		Ref.
Carcinogenicity	No evidence of carcinogenicity in humans. A life-time (2-year) inhalation study in rats exposed to respirable polyacrylate dust resulted in tumors (besides inflammation). However, the tumorigenic response may be a "rat specific" finding and thus not relevant to humans. Not listed as a carcinogen by NTP, IARC or OSHA.	23,26,24
Mutagenicity	Up to 0.1% it is not genotoxic neither mutagenic.	24
Teratogenicity	Up to 0.1% it does not cause birth defects and does not present reproductive toxicity.	24
Comments: This ingredient may contain an impurity, Benzene, that is a Carcinogenic Category 1A and Mutagenic Category 1B in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonised classification and labelling of hazardous substances).		

PHOTO-INDUCED TOXICITY
Carbomer-934 demonstrated low potential for photo-toxicity and photo-contact allergenicity **(25)** .

Glycerin

REGULATORY RESTRICTIONS
According to Regulation EC 1223/2009 and respective amendments there are no restrictions on its use in cosmetic products.

ACUTE TOXICITY

Administration Route	Adverse effects description	LD50	Ref.
Oral	Glycerin is readily absorbed from the intestine and is either metabolized to carbon dioxide and glycogen or used in the synthesis of body fats. Consuming large amounts may cause vomiting, nausea, diarrhea, headache, and hyperglycemia. However, if not ingested in considerable amounts, glycerin presents no hazardous effects on human health.	(mouse): 4100 mg/kg; (guinea pig): 7750 mg/kg; (rat): 12600 mg/kg; (rabbit): 27000 mg/kg	27,28,2
Inhalation	Breathing of small amounts of this material is not likely to cause harmful effects. It may cause irritation of nose, throat and airways.	(rat): > 570 mg/m3 (1 hour)	28
Dermal	It does not cause skin irritation.	(rabbit): > 18700 mg/kg	28
Subcutaneous	Glycerol is more toxic when administered intravenously, intraperitoneally or subcutaneously.	(mouse): 90 mg/kg; (rat): 100 mg/kg	2,29

Comments:
This ingredient is used in pharmaceutical oral, topical, ophthalmic and parenteral formulations, besides being also used as a food additive **(2,29)** .

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	Not irritant to the skin.	2,29
Ocular Irritation	Glycerin is not irritating to the eyes.	29
Sensitization	Based on the available information, there is no human or animal data that indicates glycerol to be a skin sensitizer. Considering the extensive, widespread dermal exposure to glycerol in preparations repeatedly applied to the skin, the absence of case reports of humans showing skin reactions is consistent with glycerol having a very low skin sensitization potential.	29
Dermal Absorption	This ingredient is absorbed through the skin and is a permeation enhancer.	28,2

Comments:
-

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.
Oral	Prolonged or repeated ingestion may affect the blood (hemolysis, changes in white blood cell count), endocrine system (changes in adrenal weight), respiratory system, and may cause kidney injury. However, several studies indicate that repeated oral exposure by gavage to glycerol does not induce adverse effects other than local irritation of the gastro-intestinal tract. It was concluded that the NOEL is 10000 mg/kg bw (20% in diet), since at this dose level no systemic or local effects were observed.	27,2,29
Inhalation	In an inhalation study with rats (during 14 days), there was no effect on lung, liver, kidney, brain and heart weight nor any macroscopic findings reported. Histopathologic examination of the respiratory tract, liver, kidneys and heart of controls and high dose animals revealed an increased incidence of minimal to mild squamous metaplasia of the epiglottis in all treated animals. No systemic effects were seen at the highest dose tested 3910 mg/m3. Nevertheless, the NOAEL for local effects on the respiratory tract following exposure by inhalation is 165 mg/m3.	29
Dermal	-	

Comments:
Overexposure to this material has been suggested as a cause of mild reversible liver effects and mild reversible kidney

effects (laboratory animals) **(28)** . Preexisting disorders of skin or lung (such as asthma-like conditions) may be aggravated by exposure to this material **(28)** .

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY		
		Ref.
Carcinogenicity	Glycerin does not contain any known carcinogenic substance and studies performed previously do not raise concern for carcinogenic potential of this ingredient. This material is not expected to cause cancer in humans since it did not cause cancer in laboratory animals. This material is not listed as a carcinogen by IARC, NTP or OSHA.	28,29
Mutagenicity	In studies performed in vitro, glycerol was negative (Ames tests with and without metabolic activation) and did not induce chromosomal effects in mammalian cells. There is no in vitro or in vivo data that indicates glycerol to have a genotoxic potential.	29
Teratogenicity	Based on the available data, it can be concluded that glycerol does not have any adverse effects on reproductive parameters. There was no evidence of teratogenicity.	29
Comments: -		

PHOTO-INDUCED TOXICITY
There is no data available on the photo-toxic effects of this ingredient.

Octyldodecanol

REGULATORY RESTRICTIONS
According to Regulation (EC) No. 1223/2009 and respective amendments there are no restrictions on its use. Cosmetic Ingredient Review (CIR) considers this ingredient safe as used up to 85%.

ACUTE TOXICITY			
Administration Route	**Adverse effects description**	**LD50**	**Ref.**
Oral	Ingestion of small amounts may cause nausea and vomit. In an acute oral toxicity study in rats fed with 5 g/kg of undiluted Octyldodecanol no deaths were observed. The results of acute oral toxicity studies in rats of undiluted Octyldodecanol and of products containing Octyldodecanol at concentrations up to 20% indicate a very low order of toxicity.	(rat): >5000 mg/Kg	30,31,32,2
Inhalation	Its vapors in high concentrations may cause irritation on the respiratory tract.	-	31
Dermal	In a study of acute dermal toxicity, areas abraded and intact skin of guinea pigs were treated with 3 g/kg of undiluted Octyldodecanol under occlusive patch, no deaths and no serious skin lesions were observed.	(guinea pig): >5000 mg/Kg	31,32,2
Subcutaneous	-	-	
Comments: Octyldodecanol is widely used in cosmetic and pharmaceutical applications as an emulsifier and opacifying agent. It is mainly used in topical applications for its emollient and lubricating properties **(2)** . This ingredient is generally regarded as nontoxic and nonirritant at the levels employed as an excipient **(2)** . Results of percutaneous toxicity studies with 100% Octyldodecanol also indicate a low order of toxicity. **(31,32)**			

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY		
		Ref.
Skin Irritation	A skin irritation test with Octyldodecanol at 30% produced no irritation in rabbits. In animal studies with low doses of Octyldodecanol slight skin irritation was induced. When formulated in cosmetic and pharmaceutical products it is generally classified as non-irritant.	33,34,32,35

Ocular Irritation	It may induce eye irritation when in direct contact. Octyldodecanol caused no or minimal ocular, transient irritation in the eyes of rabbits, when tested in 3 to 10.2%.	33,35,2
Sensitization	A study conducted on a lipstick formulation containing 10.2% of Octyl Dodecanol indicated no sensitization. Several studies of screening patch test for contact sensitization in large populations had rates of 6 cases of skin irritation of 1664 (0.36 percent) for Octyldodecanol at 30% in petrolatum. Studies indicated a very low order of sensitization.	30,32
Dermal Absorption	Studies to estimate the permeability coefficient of Octyldodecanol suggested that this ingredient might be an enhancer for the skin permeation.	2
Comments: -		

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.
Oral	-	
Inhalation	Chronic toxicity inhalation effects are described only when high concentrations of the product are used.	34,31
Dermal	Prolonged contact with the skin may induce irritation.	34,31,35
Comments:		

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY

		Ref.
Carcinogenicity	There is no data available for carcinogenic effects.	
Mutagenicity	No in vitro or in vivo mutagenic effects were described for this ingredient.	33,34,31,35
Teratogenicity	This ingredient is classified as not expected to be potentially teratogenic in studies with rats.	33,31

Comments:
Due to the chemical nature and benign biological activity of these compounds, they are not suspected of significant potential for reproductive or developmental effects **(33)** .

PHOTO-INDUCED TOXICITY

A repeated insult photosensitization test using 23 subjects was conducted on a lipstick formulation containing 10.2% of Octyl Dodecanol. There were no reactions and thus no evidence of phototoxicity or photoallergenicity **(32)** .

Chaves Thermal Water (Chaves Aqua)

REGULATORY RESTRICTIONS

According to Regulation EC no. 1223/2009 and respective amendments there are no restrictions on its use in cosmetic products.

ACUTE TOXICITY

Administration Route	Adverse effects description	LD50	Ref.
Oral	-	-	
Inhalation	-	-	
Dermal	-	-	
Subcutaneous	-	-	
Comments: -			

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	-	
Ocular Irritation	-	

Sensitization	-	
Dermal Absorption	-	
Comments: -		

CHRONIC TOXICITY		
Administration Route	**Adverse effects description**	**Ref.**
Oral	-	
Inhalation	-	
Dermal	-	
Comments: -		

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY		
		Ref.
Carcinogenicity	There is no data available on the carcinogenic effects of this ingredient.	
Mutagenicity	There is no data available on the mutagenic effects of this ingredient.	
Teratogenicity	There is no data available on the teratogenic effects of this ingredient.	
Comments: This product has an impurity, Nickel, that is a Carcinogenic Category 2 in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labelling of hazardous substances). This ingredient has an impurity, Cadmium, classified as 2 regarding its mutagenicity and reproductive toxicity, and it is classified as 1B regarding its carcinogenicity in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labelling of hazardous substances). This ingredient has an impurity, Lead, classified as 1A regarding its reproductive toxicity in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labelling of hazardous substances).		

PHOTO-INDUCED TOXICITY
There is no data available on the photo-toxic effects of this ingredient.

Butyrospermum parkii Butter

REGULATORY RESTRICTIONS
According to the Regulation EC 1223/2009 and respective amendments there are no restrictions on its use in cosmetic products. Cosmetic Ingredients Review (CIR) considers that Butyrospermum parkii (shea) butter is safe as used up to 60%.

ACUTE TOXICITY			
Administration Route	**Adverse effects description**	**LD50**	**Ref.**
Oral	No toxic effects are expected. No harmful effects expected in amounts likely to be ingested by accident.	> 2000 mg/kg	36,37
Inhalation	If accidentally inhaled, no irritation to the mucosa is expected.	-	38,37
Dermal	It may cause slight skin irritation (rabbit). In an acute dermal irritation study, 3 New Zealand White male rabbits received 0.5 ml of Butyrospermum parkii butter (concentration not reported) under a patch on the shaved doro-lumbar region of each rabbit. The occluded patches were left in place for 4 hours. Very slight erythema with or without very slight edema was observed in 2 rabbits. These reactions were resolved on days 3 or 4. No reactions were observed in the 3rd rabbit.	-	39
Subcutaneous	-	-	

Comments:
Shea Butter is used in many types of cosmetics and personal care products including bath products, cleansing products, eye makeup, lotions and creams, suntan products, lipstick and hair care products **(40)** . It is regarded as non-toxic ingredient and as safe for human consumption **(37)** . The product is a refined food grade vegetable fat **(41)** .

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	CIR considers that this ingredient is not a dermal irritant. In a study it was slightly irritant to the skin.	36,39
Ocular Irritation	It is classified as non-irritating to the eye (rabbit). In one study, undiluted Butyrospermum parkii butter was tested for acute ocular irritation in 3 male rabbits. Approximately 0.1 ml of test material was instilled into the conjunctival sac of the right eye and left for 24 hours. The left eye served as control. Conjunctival reactions were mild and disappeared completely within 24 hours. No corneal lesions or irital reactions were observed during the test. Butyrospermum parkii butter was classified as not irritation to mucous membranes in this study.	39
Sensitization	This ingredient does not cause skin sensitization reactions. However, rare cases of allergic reactions have been reported. Based on a history of safe use in food, CIR considers that this ingredient is not a sensitizer.	37,42,39
Dermal Absorption	Stearic acid: has poor ability to penetrate skin or mucous membranes.	43

Comments:
-

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.
Oral	-	
Inhalation	-	
Dermal	-	

Comments:
Toxic effects by long-term exposure were not reported. Just some rare allergy cases to the ingredient may occur **(37,42)** .

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY

		Ref.
Carcinogenicity	There is no data available on the carcinogenic effects of this ingredient.	
Mutagenicity	It does not show mutagenicity (method: OECD 471).	44
Teratogenicity	There is no data available on the teratogenic effects of this ingredient.	

Comments:
-

PHOTO-INDUCED TOXICITY

Photo-induced toxicity is not observed. In a photo-toxicity study, 15 female Pirbright white guinea pigs were treated with 50 µl of 10% and 20% Butyrospermum parkii butter diluted in acetone on shaved skin. The guinea pigs also received the positive control, 5% 8-methoxypsoralen in acetone. Another site was left untouched and served as negative control. Ten guinea pigs were then irradiated with UV-B light for 80 seconds followed by UV-A light for 80 min. The five guinea pigs that were not irradiated served as controls. The positive controls yielded expected results. No skin reactions were observed in animals that received the test material and were irradiated. It was concluded that Butyrospermum parkii butter was not phototoxic. **(39) (42)** .

Ceteareth-20

REGULATORY RESTRICTIONS

According to the Regulation EC 1223/2009 and respective amendments, there are no restrictions on the use of this ingredient in cosmetic products. CIR (Cosmetic Ingredient Review) considers this ingredient safe in the present practices of use and concentration in cosmetics, when formulated to avoid irritation. CIR refers that Ceteareth-20 is used at 0.02% to 11% in leave-on poducts and 0.008% to 10% in rinse-off products.

ACUTE TOXICITY

Administration Route	Adverse effects description	LD50	Ref.
Oral	Ingestion of large amounts may cause gastrointestinal tract irritation and discomfort. Toxicity studies with rats, rabbits, and dogs indicate that PEGs have low oral toxicity.	(Rat): >2000 mg/kg (for C12-C18 etoxylated alcohols and C12-C14 fatty acid)	45,46,47,2,48,49
Inhalation	There is not information about the toxicity by inhalation. However, the powder may cause irritation due to mechanical action.	-	45
Dermal	Sporadic contact for a short time will not cause damage.	(rabbit): 800 mg/Kg (rat): >2000 mg/kg (for C12-C18 etoxylated alcohols; (rabbit): >2000 mg/kg (for C12-C14 fatty acid)	45,47
Subcutaneous	-	-	

Comments:
Classified as not expected to be potentially toxic or harmful **(50)** . Polyoxyethylene alkyl ethers are nonionic surfactants widely used in topical pharmaceutical formulations and cosmetics **(2)** . In cosmetics and personal care products, Ceteareth ingredients are used in skin care products, moisturizers, hair conditioners, suntan and indoor tanning products and hair dyes, colors, and tints **(51)** . Ceteareths are the polyethylene glycol (PEG) ethers of Cetearyl Alcohol (q.v.). To supplement the limited available data on Ceteareths, previous findings from the safety assessment of Polyethylene Glycol (PEG), several fatty alcohols (Cetearyl Alcohol, Cetyl Alcohol, and Stearyl Alcohol), and Steareths were considered. These data indicate little evidence of toxicity **(49)** .

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	May cause irritation. May cause slight irritation in rabbits.	45,50,49
Ocular Irritation	May cause moderate irritation.	45,46,50
Sensitization	C12-C18 etoxylated alcohols and C12-C14 fatty acids are not sensitizers (tested on guinea pigs).	47
Dermal Absorption	CIR Panel mentioned that dermal penetration of long-chain alcohols is likely to be low, and the dermal penetration for alkyl PEG ethers is likely to be even lower. This ingredient is an absorption promoter.	52,53

Comments:
-

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.
Oral	Ingestion of large amounts may cause gastrointestinal tract irritation and discomfort.	45
Inhalation	-	
Dermal	Repeated and prolonged contact may cause moderate irritation.	45

Comments:
-

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY

		Ref.
Carcinogenicity	This ingredient is not carcinogenic (animal tests).	45
Mutagenicity	This ingredient is not mutagenic (animal tests). C12-C18 etoxylated alcohols and C12-C14 fatty acids are not mutagenic (Ames Test with Salmonella typhimurium).	50,45
Teratogenicity	No teratogenic effects are expected.	45

Comments:
This product may contain an impurity, ethylene oxide, that is classified as 1B regarding its Carcinogenic and Mutagenic toxicity in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labelling of hazardous substances). This product may contain an impurity, 1,4-Dioxane, that is a Carcinogenic Category 2 in Annex

VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labelling of hazardous substances).

PHOTO-INDUCED TOXICITY
Photosensitization studies of products containing 1.0% and 4.0% cetyl alcohol were negative **(48)** .

Cetearyl alcohol

REGULATORY RESTRICTIONS
According to the Regulation EC 1223/2009 and respective amendments there are no restrictions on its use in cosmetic products. Cosmetic Ingredient Review (CIR) considers that cetearyl alcohol is safe as used up to 25%.

ACUTE TOXICITY

Administration Route	Adverse effects description	LD50	Ref.
Oral	Swallowing small amounts of this material during normal handling is not likely to cause harmful effects. Swallowing large amounts may be harmful. It may cause stomach or intestinal upset (nausea, vomiting and diarrhea). Cetearyl alcohol is long-chain aliphatic alcohol that is, at most, only slightly toxic when administered orally at doses of 5 g/kg and greater.	(rat): > 2000 mg/kg	54,55
Inhalation	It may cause irritation of nose, throat and respiratory airways.	-	54
Dermal	It may cause skin irritation. Symptoms may include redness, burning, and swelling of skin.	-	54
Subcutaneous	-	-	

Comments:
The Food and Drug Administration (FDA) includes synthetic fatty alcohols including cetyl alcohol and stearyl alcohol on its list of food additives allowed for direct addition to food as multipurpose food additives. Synthetic fatty alcohols are also permitted as indirect food additives, as adjuvants and production aids **(56)** . This material has a low level of toxicity **(54)** . Nevertheless, preexisting lung diseases (for example, asthma-like conditions) may be aggravated by exposure to this material **(54)** .

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	A skin irritation study of a cream containing 3.0% Cetearyl Alcohol was conducted with 6 New Zealand albino rabbits (3 males, 3 females) weighing from 3.5-4.2 kg. The product was applied to intact and abraded skin of each animal during 5 consecutive days. After each application, an occlusive dressing was placed over the test site and removed after an 8-h period. Sites were graded for signs of irritation at 8 and 24 h postapplication. Mean erythema scores for intact skin ranged from 1.0 to 3.0 at 8 h and from 1.17 to 2.67 at 24 h post application. For abraded skin, mean erythema scores ranged from 1.0 to 3.0 at 8 h and from 1.17 to 2.50 at 24 h. It was concluded that the cream was mildly irritating to the skin. In other study this ingredient was non skin irritating to rabbits.	54,55
Ocular Irritation	The dust can cause eye irritation. Symptoms include stinging, tearing, redness, and swelling of eyes. The ocular irritation potential of a cream containing 3.0% Cetearyl Alcohol was assessed in 9 albino rabbits. The product was instilled into one eye of each animal. The eyes of 3 animals were rinsed after instillation. Ocular reactions were scored at 1, 2, 3, 4, and 7 days post instillation. The product was classified as a non-irritant. In other study this ingredient was slightly eye irritating to rabbits.	54,55
Sensitization	In a human skin sensitization study of a cream containing 3.0% cetearyl alcohol, none of the subjects had positive reactions. Although it is not common, some sensitization reactions have been reported. Indeed, there are some reported cases of allergic contact dermatitis derived from the use of this ingredient. There is no evidence of a potential sensitizing effect on the skin.	54,57,55,2
Dermal Absorption	-	

Comments:
-

CHRONIC TOXICITY		
Administration Route	**Adverse effects description**	**Ref.**
Oral	-	
Inhalation	Prolonged or repeated breathing of this material may result in chronic bronchitis (inflammation of the airways of the lungs). Symptoms include coughing and shortness of breath. Symptoms are not expected at air concentrations below the recommended exposure limits, if applicable.	54
Dermal	-	
Comments: -		

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY		
		Ref.
Carcinogenicity	This material is not listed as a carcinogen by the International Agency for Research on Cancer (IARC), the National Toxicology Program (NTP) or the Occupational Safety and Health Administration (OSHA).	54
Mutagenicity	Ames Test: negative.	54
Teratogenicity	This product does not contain any chemicals known to cause birth defects, or any other reproductive harm (California Prop. 65).	54
Comments: -		

PHOTO-INDUCED TOXICITY
Clinical photosensitization studies of a lipstick product containing 4.0% cetyl alcohol and a skin care preparation containing 1.0% cetyl alcohol resulted in no positive reactions. Identical results were reported moisturizing lotion containing 0.10% myristyl alcohol (related compound) **(55)** .

Cetyl Alcohol

REGULATORY RESTRICTIONS
According to the Regulation EC 1223/2009 and respective amendments there are no restrictions on its use. CIR (Cosmetic Ingredient Review) considers this ingredient safe as used up to 50%.

ACUTE TOXICITY			
Administration Route	**Adverse effects description**	**LD50**	**Ref.**
Oral	Swallowing small amounts of this material during normal handling is not likely to cause harmful effects. Ingestion of this ingredient may cause hypermotility, vomiting and diarrhea and may also affect the cardiovascular system, respiratory system and central nervous system. Components of the product may be absorbed into the body by ingestion. In acute oral toxicity studies (rats) of formulations containing 2.0, 3.25, and 4.0% Cetyl Alcohol, there were predominantly no toxic effects.	(mouse): > 3200 mg/kg (rat): > 2000 mg/kg	58,59,60,61,55,2
Inhalation	No adverse effects are expected from inhalation of this ingredient. However, this material may produce dust and may cause respiratory tract irritation, dizziness and headaches. A study involving a single 6 hour exposure of groups of 10 mice, rats, and guinea pigs to Cetyl Alcohol vapors, followed by a 24 hour holding period, was	1-Tetradecanol (analogous substance) (rat): > 1,5 mg/l (1 h)	58,59,55

	reported. Necropsies were performed on the animals at the end of the holding period. Local irritation due to the alcohol vapor was slight and involved the mucous membranes of the eyes, nose, throat, and respiratory passages. There were no signs of systemic toxicity, and no deaths were reported. In a second inhalation study, groups of 10 rats and 10 guinea pigs were exposed to Cetyl Alcohol vapor every 30 min for a period of 4 h. A comparable control group was exposed to room air for the same period. Half of the animals were killed immediately after the exposures, and the rest were killed after a 14-day holding period. The lungs of some of the exposed animals had lesions indicative of chronic respiratory disease (rats) and interstitial or bronchial pneumonia (guinea pigs). The incidence and severity of these changes were comparable to such observations in the control group. No effects related to Cetyl Alcohol exposure were noted. Alternatively, in other study, the inhalation of 2220 mg/m3 of synthetic Cetyl Alcohol for 6 hours had resulted in the death of all exposed rats.		
Dermal	1-Tetradecanol, a related substance cause erythema, emaciation and weakness. Cetyl Alcohol was applied full-strength to the clipped intact abdominal skin of 16 albino rabbits. The animals were divided equally into four treatment groups: 0.10, 0.316, 1.00, and 3.16 ml/kg doses. Each exposed area was covered with an occlusive binding that remained in place for 24 hours. Observations for signs of toxicity were made for a total of 7 days post application. The LD50 was reported to be greater than 2.6 g/kg. One of the four animals in the 3.16 ml/kg group had decreased activity and labored respiration.	(rabbit): > 2600 mg/kg	58,55,2
Subcutaneous	-	-	
Comments: The substance is not classified as an intoxicant of an organ target after single exposure **(58)** .			

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY		
		Ref.
Skin Irritation	According to Draize test this ingredient may be slightly skin irritating. The skin irritation potential of Cetyl Alcohol (100.0%) was evaluated in 20 subjects. No erythematous reactions were elicited by the test substance. A topical tolerance study involving an 11.5% Cetyl Alcohol cream base was conducted with 80 male subjects. The cream base was applied to the left forearm and to the left lower facial region, including the left side of the lips. The preparations were applied five times daily for 10 days. One subject had erythema, folliculitis, and pustule formation (forearm site). In another study, the skin cumulative irritation potential of a cream containing 6.0% Cetyl Alcohol was evaluated in 12 female subjects. The total irritation score (for all panelists) indicate mild cumulative irritation. Clinical skin irritation studies of product formulations containing 8.4%, 6.36%, 6.0%, 4.0%, 3.3%, 3.25%, 3.0%, 2.85, 2.0%, and 1.0% Cetyl Alcohol produced no substantial evidence of irritation. Studies in rabbits considered this ingredient a non-skin irritant (at 50.0%). However, in another study, the skin irritation potential of a cream containing 2.0% Cetyl Alcohol caused well-defined erythema and mild edema. This ingredient caused no irritation in genital mucosa of rabbits.	58,60,61,55,2
Ocular Irritation	Studies showed that this ingredient produces only slight transient eye irritation to no irritation in rabbits. The ocular irritation potential of 100% Cetyl Alcohol was evaluated in rabbits and the test material was practically non-irritating. In a similar study of Cetyl Alcohol, the test substance was either minimally irritating or non-irritating. According to	58,59,61,55

	Draize test it might be slightly irritating to the eyes.	
Sensitization	In a human skin sensitization study of Cetyl Alcohol (30.0% in petrolatum), sensitization reactions were observed in 11.0% of the subjects. Human sensitization studies of product formulations containing 5.0%, 4.78%, 4.5%, 2.59%, and 2.0% Cetyl Alcohol revealed no positive reactions in any of the subjects. Cross-sensitization with cetostearyl alcohol, lanolin, and stearyl alcohol has been reported. Cetyl alcohol has been associated with allergic delayed-type hypersensitivity reactions in patients with stasis dermatitis. Cetyl alcohol is not sensitizing to the skin of guinea pigs.	59,4,55,2
Dermal Absorption	-	

Comments:
-

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.
Oral	-	
Inhalation	-	
Dermal	Prolonged skin contact may cause removal of natural fat from the skin and irritation of the skin.	59

Comments:
The substance is not classified as an intoxicant to a target organ by repeated exposure **(58)** . A heated Cetyl Alcohol mixture (30% Cetyl Alcohol in methyl alcohol and propylene glycol) was massaged into a depilated area on the right flanks of female albino rabbits. The animals were treated daily for 30 days. Microscopic alterations (after 10 days) were infiltrates of lymphomononuclear cells and histiocytes in superficial portions of the dermis. In another study, 400 mglkg of a cream base containing 11.5% Cetyl Alcohol was applied to a 5 cm diameter area in the lumbar region of the backs of 48 New Zealand rabbits. The rabbits developed exfoliative dermatitis within 2 to 3 days of treatment **(55)** .

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY

		Ref.
Carcinogenicity	This ingredient is not expected to be a carcinogenic agent. The tumor promoting activity of n-hexadecanol was studied by applying it three times weekly for 60 weeks to the skin of 40 mice that had previously received an initiating dose of dimethylbenzanthracene. One papilloma appeared after 53 weeks of treatment.	4
Mutagenicity	No mutagenic effects were reported on the Ames test and in vivo and in vitro tests. Mutagenicity tests for Cetyl Alcohol were conducted with five mutant strains of Salmonella typhimurium. Results indicate that Cetyl Alcohol was not mutagenic to any of the strains in the presence or absence of metabolic activation.	61,4,55
Teratogenicity	No teratogenic or developmental effects were reported.	58

Comments:
Reproductive toxicity of hexane-1-ol (analogous substance):rat; oral; 90 days, NOAEL (parents): 1127 mg / kg (in reference to body weight and day). Dodecane-1-ol (analogous compound): rat; oral; 55 days, NOAEL (pregnant female): 2000 mg / kg (in reference to body weight and day) **(58)** .

PHOTO-INDUCED TOXICITY

The photosensitization potential of a lipstick product containing 4.0% Cetyl Alcohol was evaluated in 52 subjects. The experimental procedure was not stated. Photosensitization reactions were not noted in any of the subjects. In another study, a skin care preparation containing 1.0% Cetyl Alcohol did not induce photosensitization in the 407 subjects tested. The experimental procedure was not stated **(55)** .

Isopropyl Myristate

REGULATORY RESTRICTIONS

According to Regulation EC No. 1223/2009 and respective amendments there are no restrictions on the use of this mixture in cosmetic products. CIR (Cosmetic Ingredient Review) considers this ingredient safe as used up to 82%.

ACUTE TOXICITY

Administration Route	Adverse effects description	LD50	Ref.
Oral	This ingredient can cause irritation of the digestive tract. If ingested in large amounts can cause nausea, vomiting and diarrhea.	(rat): 49.7 g/kg; (rat): 2000 mg/kg	62
Inhalation	Does not apply at room temperature.	-	62
Dermal	A face mask with 15% isopropyl myristate was applied in a total of 38 individuals for a period of 24 hours. The results indicated doubtful erythema development. In another study, doses of approximately 0.3 ml of an oil bath containing isopropyl myristate and 42.9% were repeatedly applied under occlusion in six men and four women. After applying daily for a period of 10 days, there was no irritating effect. It was concluded that this ingredient can cause slight irritation in individuals at risk.	(rabbit): 5 g/Kg	62
Subcutaneous	-	-	

Comments:
-

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	It may cause slight irritation in some susceptible individuals.	62
Ocular Irritation	May cause irritation when in direct contact with eyes.	62
Sensitization	In four separate studies of human sensibility an antiperspirant concentrate containing isopropyl myristate to 52-58%, produced no reactions indicative of sensitization.	62
Dermal Absorption	Isopropyl myristate, as a non-polar penetration enhancer, is largely retained in the stratum corneum. It was not detected in the receptor fluid of flow-through diffusion cells in in vitro skin permeation experiments using human epidermis (stratum corneum and viable epidermis) and dermis (varying thickness).	63

Comments:
-

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.
Oral	-	
Inhalation	-	
Dermal	May cause irritation by long exposure time.	62

Comments:
The isopropyl myristate is widely used in cosmetic and topical pharmaceutical formulations and is generally regarded as nontoxic **(62)** .

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY

		Ref.
Carcinogenicity	There is no data available on the carcinogenic effects of this ingredient.	
Mutagenicity	There is no data available on the mutagenic effects of this ingredient.	
Teratogenicity	There is no data available on the teratogenic effects of this ingredient.	

Comments:
-

PHOTO-INDUCED TOXICITY

In a study of a formulation containing phototoxicity oil bath with 42.9% isopropyl myristate was applied in men and nine women. The body sites where application of the oil was effected were irradiated after 6 and 24 hours, with a 15 W solar simulator equipped with GP355 Schott filter to remove UVB, UVA giving a total of 25-30 mW/cm2. No phototoxic effects

were observed **(62)** .

Stearic acid

REGULATORY RESTRICTIONS

According to Regulation EC no. 1223/2009 and respective amendments there are no restrictions on its use. CIR (Cosmetic Ingredient Review) considers this compound safe for use even at concentrations > 50%.

ACUTE TOXICITY

Administration Route	Adverse effects description	LD50	Ref.
Oral	Little acute toxicity was observed when Stearic Acid or cosmetic formulations containing this fatty acid were given to rats orally at doses of 15-19 g/kg body weight. Ingestion of large amounts may cause gastrointestinal tract irritation, bowel obstruction or diarrhea, nausea and vomiting.	(mouse): > 2000 mg/kg; (rat): > 5000 mg/kg; (human): 14286 mg/kg	64,65,66,67,68,2
Inhalation	Can lead to respiratory tract irritation and coughing, although its inhalation at room temperature is difficult.	-	66,67
Dermal	After two hours of exposure, slight erythema was observed and oedema was not detected in albino rats. Results from topical application of Stearic Acid to the skin of mice, rabbits, and guinea pigs produced little or no apparent toxicity.	(rabbit): > 2000 mg/kg	65,67,68,69
Subcutaneous	-	-	

Comments:
Stearic acid is widely used in oral and topical pharmaceutical formulations. It is also used in cosmetics and food products. Stearic acid is generally regarded as a non-toxic and non-irritant material. However, consumption of excessive amounts may be harmful **(2)** . Stearic acid is recognized as safe by FDA. It is also accepted as a food additive up to 4000 ppm **(69)** . LC50, 4h (rat, inhalation): > 0.1621 mg/L **(65)**

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	It causes skin irritation, redness and pain.	67
Ocular Irritation	It may cause irritation. Tests were performed on albino rabbits only with stearic acid and stearic acid incorporated in cosmetic formulations (1 to 19.4%). After daily contact during 14 days, it was not observed ocular irritation or was observed minimal irritation (mild conjunctival oedema). It may cause mild conjunctivitis that disappears in 72 hours. CIR does not consider this acid as an eye irritant.	66,68,69
Sensitization	Tests with 5% solution of stearic acid in petrolatum show no sensitization reactions in 25 human subjects.	69
Dermal Absorption	This ingredient has poor ability to penetrate skin.	70

Comments:
-

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.
Oral	-	
Inhalation	-	
Dermal	-	

Comments:
-

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY

		Ref.
Carcinogenicity	There are no available data on the carcinogenicity of stearic acid.	
Mutagenicity	It has no mutagenic activity (Ames test with Salmonella typhimurium).	69
Teratogenicity	No reproductive toxicity was reported.	71
Comments: -		

PHOTO-INDUCED TOXICITY
Studies using product formulations containing Oleic and Stearic acids indicate that they are not photosensitizing agents **(68)** .

Parfum

REGULATORY RESTRICTIONS
According to the Regulation EC 1223/2009 and respective amendments, there are no restrictions on the use of this ingredient in cosmetic products.

ACUTE TOXICITY

Administration Route	Adverse effects description	LD50	Ref.
Oral	Male rats (6/dose; strain unspecified) were administered a single dose of benzyl salicylate (present allergen) via oral gavage at 0, 1250, 2500 or 5000 mg/kg and observed for seven days. Mortality was observed at 2500 and 5000 mg/kg.	Concerning to a present allergen: Benzyl salicylate (rat): 2227 mg/kg	72
Inhalation	-	-	
Dermal	-	-	
Subcutaneous	-	-	
Comments:			

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	This ingredient is a skin irritant.	73
Ocular Irritation	This ingredient is an eye irritant.	73
Sensitization	Sensitization may occur when in contact with the skin. Hexyl cinnamal (the major present allergen) has a low skin-sensitizing potency.	73,74
Dermal Absorption	-	
Comments:		

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.
Oral	-	
Inhalation	-	
Dermal	-	
Comments: -		

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY

		Ref.
Carcinogenicity	There is no data available on the carcinogenic effects of this ingredient.	
Mutagenicity	There is no data available on the mutagenic effects of this ingredient.	
Teratogenicity	There is no data available on the teratogenic effects of this ingredient.	

Comments:

PHOTO-INDUCED TOXICITY
There is no data available on the photo-toxic effects of this ingredient.

Alcohol denat. (with Diethyl phthalate and Denatonium benzoate)

REGULATORY RESTRICTIONS
According to Regulation EC No. 1223/2009 and respective amendments there are no restrictions on its use.

ACUTE TOXICITY

Administration Route	Adverse effects description	LD50	Ref.
Oral	Alcohol is a central nervous system depressant and ingestion of low to moderate quantities can lead to symptoms of intoxication including muscle incoordination, visual impairment and slurred speech. Ingestion of higher concentrations may cause depression of medullary action, lethargy, amnesia, hypothermia, hypoglycemia, stupor, coma, respiratory depression, and cardiovascular collapse. The lethal human blood alcohol concentration is generally estimated to be 400–500 mg/100 mL.	(rat): 7060 mg/kg (Alcohol) (mouse): 3450 mg/kg (Alcohol) (male rats): 640 mg/kg (Denatonium Benzoate) (female rats): 584 mg/kg (Denatonium Benzoate) (male rabbits): 508 mg/kg (Denatonium Benzoate) (female rabbits):640 mg/kg (Denatonium Benzoate) (rabbit:): 1.0 g/kg	75,76,19
Inhalation	Inhalation of high concentrations of alcohol may cause central nervous system effects characterized by nausea, headache, dizziness, unconsciousness and coma. It also causes respiratory tract irritation. May cause narcotic effects in high concentration. Denatonium Benzoate (0.1%) did not show adverse effects in 10 rats in an acute inhalation toxicity test.	(rat): 66000mg/l; 4h (ethanol)	77,78,75
Dermal	Alcohol may cause skin irritation and cyanosis of the extremities.	-	78
Subcutaneous	-	(mouse): 8285 mg/kg (alcohol)	13

Comments:
Alcohol and aqueous alcohol solutions are widely used in a variety of pharmaceutical formulations and cosmetics **(19)** . Alcohol denat. is the generic term used by the cosmetics industry to describe denatured alcohol. Alcohol denat. and various specially denatured (SD) alcohols are used as cosmetic ingredients in a wide variety of products **(75)** . In cosmetics and personal care products, Alcohol denat. is used in many product types including makeup, lotions, fragrance, shaving, oral care, skin care and hair care products **(79)** . Denatonium Benzoate is one of the most bitter substances. It is added to a wide variety of products at required low levels, but does not interfere with the mode of action of the product. It is detectable by taste at concentrations as low as 10 ppb, discernibly bitter at 50 ppb, and at 10 ppm it is unpleasantly bitter **(75)** .

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	Preparations containing more than 50% v/v alcohol may cause skin irritation. It also may cause mucous membranes irritation.	13
Ocular Irritation	Alcohol may be irritant and cause watering of the eyes, but there appear to be no reports of eye injury from industrial exposure. Splashes of SD Alcohol 40-B (related compound) may cause temporary pain and blurred vision. 0.005% to 0.05% Denatonium Benzoate was nonirritating to ocular mucosa in 6 albino rabbits. Undiluted Diethyl Phthalate was instilled into the eyes of rabbits and irritation was minimal.	80,13,75,76,19
Sensitization	It did not result in dermal sensitization. In fact, many RIPTs were conducted using SD Alcohol 40-B (denatured with Denatonium Benzoate). The materials tested in these studies were a deodorant spray: 98% SD Alcohol 40-B; a night cream: 61.3% SD Alcohol 40-B; other shaving preparation: 82% SD Alcohol 40-B (95%); a gel formula: 29% SD Alcohol 40-B; and a spray formula: 12.0% SD Alcohol 40-B. In all of the tests performed, there was no evidence of dermal sensitization.	79,75

Dermal Absorption	Alcohol is an absorption enhancer. It is absorbed into skin (repeated exposure). The distribution of topically applied lidocaine, a topical anesthetic chemically related to Denatonium Benzoate demonstrated that virtually no lidocaine appears in the plasma, suggesting that the larger Denatonium Benzoate molecule also would have little or no systemic exposure. Labeled Diethyl Phthalate (14C) was absorbed through the skin of rabbits, and the radioactivity was distributed throughout the body and excreted in the urine.	81,75,76,19
Comments: A spray formula containing 12% SD Alcohol 40-B (related compound) was found to be nonirritating when evaluated for vaginal mucosal irritation in New Zealand white rabbits **(75)** .		

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.
Oral	In two chronic toxicity studies, Denatonium Benzoate was administered (by gavage) at 1.6, 8, and 16 mg/kg/day, one using cynomologus monkeys and the other rats, resulted in no compound-related toxicity. The toxicity of SD Alcohols has also been tested, with implications for the particular denaturant used.	75
Inhalation	Repeated and prolonged alcohol inhalation may cause respiratory tract irritation and may cause central nervous system effects characterized by nausea, headache, dizziness, unconsciousness and coma.	78
Dermal	Repeated and prolonged skin contact with alcohol causes irritation. SD denatured alcohol 40B may cause irritation, cracking, flaking and defatting of skin on prolonged contact.	80,78
Comments: -		

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY

		Ref.
Carcinogenicity	Alcohol is not classifiable as a human carcinogen. Denatonium Benzoate is not listed by ACGIH, IARC, NIOSH, NTP, or OSHA.	80,13
Mutagenicity	Alcohol is not classified as a human mutagen. Diethyl Phthalate was not mutagenic for E. coli.	13,76
Teratogenicity	Prenatal exposure to alcohol (as alcoholic beverages) is associated with a distinct pattern of congenital malformations that have been collectively termed the fetal alcohol syndrome. Among the characteristics of this syndrome are intrauterine and postnatal growth deficiency, a distinctive pattern of physical malformations, including microcephaly, shortened palpebral fissures, joint, limb, and cardiac anomalies, and behavioral/cognitive impairment such as fine motor dysfunction and mental retardation. This syndrome has been associated with alcoholic women who drank heavily and chronically during pregnancy.	13
Comments:		

PHOTO-INDUCED TOXICITY

Concerning to a related compound: A gel formula containing 29% SD Alcohol 40-B and a spray liquid containing 12% SD Alcohol 40-B did not induce photoallergy or phototoxic response in human subjects **(75)** .

8.2 Toxicological profile of the mixtures

Carbopol 940 - 2%

REGULATORY RESTRICTIONS

According to the Regulation EC 1223/2009 and respective amendments there are no restrictions on the use of this mixture in cosmetic products. The regulatory restrictions of the substances present in this mixture are presented in section 8.1.

ACUTE TOXICITY			
Administration Route	**Adverse effects description**	**LD50**	**Ref.**
Oral	-	-	
Inhalation	-	-	
Dermal	-	-	
Subcutaneous	-	-	
Comments:			

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY		
		Ref.
Skin Irritation	-	
Ocular Irritation	-	
Sensitization	-	
Dermal Absorption	-	
Comments:		

CHRONIC TOXICITY		
Administration Route	**Adverse effects description**	**Ref.**
Oral	-	
Inhalation	-	
Dermal	-	
Comments:		

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY		
		Ref.
Carcinogenicity	There is no data available for carcinogenic effects.	
Mutagenicity	There is no data available for mutagenic effects.	
Teratogenicity	There is no data available for teratogenic effects.	
Comments: This product has an impurity, Methylene Chloride, that is a Carcinogenic Category 2 in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labelling of hazardous substances).		

PHOTO-INDUCED TOXICITY
There is no data available for photo-induced toxic effects.

Phenonip ME

REGULATORY RESTRICTIONS
According to Regulation EC No. 1223/2009 and respective amendments there are no restrictions on the use of this mixture in cosmetic products. The regulatory restrictions of the substances present in this mixture are presented in: section 8.1.

ACUTE TOXICITY			
Administration Route	**Adverse effects description**	**LD50**	**Ref.**
Oral	-	-	
Inhalation	Inhalation of vapours causes irritation of the respiratory system and mucous membranes, headache, nausea, dizziness, vomiting.	-	82
Dermal	-	-	
Subcutaneous	-	-	

Comments:-

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY		
		Ref.
Skin Irritation	-	
Ocular Irritation	-	
Sensitization	Sensitization effects are not known.	82
Dermal Absorption	-	
Comments: -		

CHRONIC TOXICITY		
Administration Route	**Adverse effects description**	**Ref.**
Oral	-	
Inhalation	-	
Dermal	-	
Comments: -		

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY		
		Ref.
Carcinogenicity	There is no data available on the carcinogenic effects of this mixture.	
Mutagenicity	There is no data available on the mutagenic effects of this mixture.	
Teratogenicity	There is no data available on the teratogenic effects of this mixture.	
Comments: -		

PHOTO-INDUCED TOXICITY
There is no data available on the photo-toxic effects of this ingredient.

8.3 Data for calculation of systemic exposure dosage and margin of safety of the substances (INCI name)

Ethylparaben

Dermal absorption (%)	**Justification of dermal absorption value**			**Ref.**
3.70	The SCCS will use a dermal absorption value of 3.7%.			5
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	5
	2.000	rats	subcutaneous, 17 days	

Methylparaben

Dermal absorption (%)	**Justification of dermal absorption value**			**Ref.**
3.70	The SCCS recommends a dermal absorption value of 3.7%.			5
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	5
	2.000	rats	subcutaneous, 17 days	

Triethanolamine

Dermal absorption (%)	**Justification of dermal absorption value**			**Ref.**
95.00	Studies performed in rats showed a dermal absorption rate up to 95%.			13
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	83
	80.000	rat	90-day oral study	

Phenoxyethanol

Dermal absorption (%)	Justification of dermal absorption value			Ref.
80.00	The AFSSAPS considers 80% of dermal absorption of phenoxyethanol in leave-on products and 40% in rinse-off products.			17
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	17
	164.000	rat	90-day oral study	

Carbomer

Dermal absorption (%)	Justification of dermal absorption value			Ref.
1.00	Considering the very high molecular weight of these molecules (50000 to 4000000), 1% dermal absorption will be assumed			84
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	2
	1500.000	rat/dog	oral administration, carbomer homopolymer type B.	

Glycerin

Dermal absorption (%)	Justification of dermal absorption value			Ref.
100.00	Glycerin is absorbed into skin.			2
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	29
	950.000	dog	3 days oral toxicity study in dogs	

Octyldodecanol

Dermal absorption (%)	Justification of dermal absorption value			Ref.
10.00	Due to its high partition coefficient (9.2), it is assumed that the Octyldodecanol is 10% dermal absorbed.			84
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	35
	840.000	Rats	-	

Chaves Thermal Water (Chaves Aqua)

Dermal absorption (%)	Justification of dermal absorption value			Ref.
100.00	Considering the low molecular weight of the molecule, a 100% dermal absoprtion will be considered			84
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	-
	unknown	-	-	

Butyrospermum parkii Butter

Dermal absorption (%)	Justification of dermal absorption value			Ref.
10.00	Although the molecular weights of the main compounds of this ingredient (oleic and stearic acid) are lower than 500 g/mol (282.45 and 284.48 g/mol respectively), the partition coefficient of oleic and steari acid are 7.64 and 8.23 respectively. For this reason, it is assumed that this ingredient may be 10% absorbed into skin.			43,85,84
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	69
	7500.000	rat	24-week oral toxicity study of oleic acid	

Ceteareth-20

Dermal absorption (%)	Justification of dermal absorption value			Ref.
10.00	As dermal penetration for alkyl PEG ethers is likely to be lower, a dermal absorption of 10% will be assumed.			53
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	-
	unknown	-	-	

Cetearyl alcohol

Dermal absorption (%)	Justification of dermal absorption value			Ref.
10.00	Although the molecular weights of cetyl alcohol and stearyl alcohol are lower than 500 g/mol, the partition coefficients of these compounds that constitute the ingredient cetearyl alcohol are higher than 4, so a 10% of dermal absorption will be assumed.			84
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	-
	unknown	-	-	

Cetyl Alcohol

Dermal absorption (%)	Justification of dermal absorption value			Ref.
10.00	Once the partition coefficient is higher than 4, it will be assumed that there is 10% of dermal absorption.			84
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	58
	4000.000	rat	Repeated dose oral toxicity (rat, subchronic)	

Isopropyl Myristate

Dermal absorption (%)	Justification of dermal absorption value			Ref.
10.00	Once the partition coefficient is higher than 4 (7.17), it will be assumed 10% of dermal absorption.			84
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	-
	unknown	-	-	

Stearic acid

Dermal absorption (%)	Justification of dermal absorption value			Ref.
10.00	This ingredient has poor ability to penetrate skin and its partition coefficient is high (7.05-8.23).			65
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	69
	7500.000	rat	18 weeks oral toxicity study	

Parfum

Dermal absorption (%)	Justification of dermal absorption value			Ref.
100.00	As there is no available data on dermal absorption of this ingredient, it will be assumed a dermal absorption of 100% for calculation of systemic exposure.			
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	-
	unknown	-	-	

Alcohol denat. (with Diethyl phthalate and Denatonium benzoate)

Dermal absorption (%)	Justification of dermal absorption value			Ref.
100.00	Alcohol is absorbed through the skin. Since the molecular weights of Alcohol and Denatonium Benzoate (one of the present denaturant) are lower than 500 g/mol and the partition coefficients are between -1 and 4, a 100 % dermal absorption will be assumed.			81,84
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	86
	2400.000	rats	90 days oral feed study (regarding alcohol denat. with denatonium benzoate)	

8.4 Exposure to the substances, calculation of respective systemic exposure and margin of safety

Substance (INCI)	Total Conc. of the Substance in the Cosmetic Product (%)	mg/kg body weight/ day	Dermal absorption (%)	Systemic Exposure (mg/kg/day)	NOAEL or Other Parameter	Margin of Safety	Margin of Safety /2 *
Alcohol denat. (with Diethyl phthalate and Denatonium benzoate)	0.35	0.1144	100	0.1144	2400	20970	10485
Butyrospermum parkii Butter	4.00	1.308	10	0.1308	7500	57339	28670
Carbomer	0.1155	0.0378	1	0.0004	1500	3971564	1985782
Ceteareth-20	3.00	0.981	10	0.0981	-	-	-
Cetearyl alcohol	2.00	0.654	10	0.0654	-	-	-
Cetyl Alcohol	2.00	0.654	10	0.0654	4000	61162	30581
Chaves Thermal Water (Chaves Aqua)	64.7	21.1569	100	21.1569	-	-	-
Ethylparaben	0.15	0.049	3.7	0.0018	2	1102	n.a.
Glycerin	10.0	3.27	100	3.27	950	291	146
Isopropyl Myristate	2.0	0.654	10	0.0654	-	-	-
Methylparaben	0.15	0.049	3.7	0.0018	2	1102	n.a.
Octyldodecanol	1.0	0.327	10	0.0327	840	25688	12844
Parfum	0.1	0.0327	100	0.0327	-	-	-
Phenoxyethanol	0.9	0.2943	80	0.2354	164	697	349
Stearic acid	3.0	0.981	10	0.0981	7500	76453	38227
Triethanolamine	0.007	0.0023	95	0.0022	80	36789	18395

** Additional factor applied for substances for which the Margin of Safety was calculated taking into account NOAEL obtained from oral studies.*

8.5 Possible impacts on the toxicological profile due to particle sizes (including nanomaterials), impurities and interaction of the substances

The cosmetic product does not contain nanomaterials. Reaction between stearic acid and triethanolamine may occur, leading to the formation of Triethanolamine Stearate.

This product contains allergens that according to the Annex III of the Regulation EC 1223/2009 are substances which cosmetic products must not contain except subject to some restrictions. This Annex III of the Regulation EC no. 1223/2009 states that these substances must be labeled in the final product if their concentration in the cosmetic product exceeds 0.01% in rinse-off products and 0.001% on leave-on products. In this leave-on product the allergens which must be labeled are: Alpha-Isomethyl Ionone, Benzyl Alcohol, Benzyl Salicylate, Butylphenyl Methylpropional, Citronellol, Coumarin, Eugenol, Geraniol, Hexyl Cinnamal, Hydroxycitronellal and Linalool. The presence of these allergens in the final cosmetic product can cause sensitization reactions in individuals with more sensitive skin. However, as it can be seen on the table below, the margins of safety of the allergens Alpha-Isomethyl Ionone, Benzyl Alcohol, Benzyl Salicylate, Butylphenyl Methylpropional, Coumarin, Eugenol, Geraniol, Hexyl Cinnamal and Hydroxycitronellal were calculated. The margins of safety calculated for these allergens are 31205, 1911315, 1807, 9777, 9323, 458716, 4854133, 57570 and 200138, respectively (based on oral studies performed in animal species), which are values greater than 100 (which is the reference value considered as minimum to assume the ingredients' use as safe when long term animal studies are considered). Considering the allergens Citronellol and Linalool, the margins of safety calculated are 7014 and 255, respectively (based on oral studies performed in humans), which is a value greater than 10 (which is the reference value considered as minimum to assume the ingredients' use as safe when long term human studies are considered).Hence, there are no significant systemic risks to human health associated to the presence of these substances, under normal conditions of use of the final product.

Substance (INCI)	Total Conc. of the Substance in the Cosmetic Product (%)	mg/kg body weight/ day	Dermal absorption (%)	Systemic Exposure (mg/kg/ day)	NOAEL or Other Parameter	Margin of Safety	Margin of Safety /2 *
Alpha-Isomethyl Ionone	0.0049	0.0016023	100	0.0016023	50	31205	n.a.
Benzyl Alcohol	0.001	0.000327	32	0.00010464	400	3822630	1911315
Benzyl Salicylate	0.00423	0.00138321	100	0.00138321	5	3615	1807
Butylphenyl Methylpropional	0.00391	0.00127857	100	0.00127857	25	19553	9777
Citronellol	0.00109	0.00035643	10	0.000035643	0.5	14028	7014
Coumarin	0.00164	0.00053628	100	0.00053628	10	18647	9323

Eugenol	0.001	0.000327	100	0.000327	300	917431	458716
Geraniol	0.00315	0.00103005	10	0.000103005	1000	9708267	4854133
Hexyl Cinnamal	0.00664	0.00217128	100	0.00217128	125	57570	n.a.
Hydroxycitronellal	0.00191	0.00062457	100	0.00062457	250	400275	200138
Linalool	0.003	0.000981	100	0.000981	0.5	510	255

** Additional factor applied for substances for which the Margin of Safety was calculated taking into account NOAEL obtained from oral studies.*

This cosmetic product contains diethylene glycol as trace impurity of the raw material Glycerin 4810. According to Regulation (EC) 1223/2009, diethylene glycol is allowed at a maximum concentration of 0.1% as traces in ingredients. The concentration of diethylene glycol in this cosmetic product is 0.01% therefore it is in compliance with the Regulation.

The raw materials used on this product contain some other impurities (as listed in section 4.1), but their respective concentrations in the finished product are very low. Therefore, under normal conditions of use, no significant harmful reactions or adverse effects to human health are expected due to these impurities.

9. Undesirable effects and serious undesirable effects

This cosmetic product is not on the market yet, therefore no undesirable effects or serious undesirable effects have been reported.

10. Information on the cosmetic product

No relevant information (including studies form human volunteers) are available.

PART B – Cosmetic Product Safety Assessment

1. Assessment conclusion

The Safety Assessment of the cosmetic product " **DERMOCOSMÉTICA TERMAL AQUAE CREME DE MÃOS"** was performed according to Regulation (EC) 1223/2009 and respective amendments. It was concluded that this cosmetic product is safe for human health under normal or reasonably foreseeable conditions of use taking into account its presentation, labeling, instructions for use and disposal and warnings.

2. Labeled warnings and instructions of use

The information that must be printed on cosmetic product labels (containers and packaging) is regulated under Article 19 of the Regulation (EC) 1223/2009. The following items are compulsory labelling requirements of the Regulation:

- Name or registered name and the address of the responsible person
- Country of origin for cosmetic products imported into the EU
- Nominal content at the time of packaging by weight or by volume.
- Date of minimum durability preceded by the symbol  or the words: „best used before the end of". - Indication of the date of minimum durability is not mandatory for products with a minimum durability of more than 30 months. For such products except where the concept of durability after opening is not relevant an indication of the period of time after opening has to be indicated for which the product is safe and can be used without any harm to the consumer. This information shall be indicated by the symbol  followed by the period (in months and/or years, but usually in months as "x M")
- Information regarding possible precautions to be observed in use. Note especially the compulsory information listed in Annexes III to VI. In the case of this cosmetic product, there are no mandatory warnings to be included in the labelling.
- Batch number or reference to identify the final cosmetic product. When products are too small, such information only need to appear on the secondary packaging.
- Function of the cosmetic product, unless it is clear from its presentation.
- List of ingredients (INCI)- May be indicated on the packaging only, must be preceded by the term „ingredients" - the full INCI list of this cosmetic product (including allergens) is presented in section "1.3 Quantitative and qualitative composition of the cosmetic product by INCI name".

3. Reasoning

Glycerin is used in pharmaceutical oral, topical, ophthalmic and parenteral formulations, besides being also used as a food additive. The consumption of large amounts of glycerin may cause vomiting, nausea, diarrhea, headache, and hyperglycemia. Moreover, it may cause irritation of nose, throat and airways but does not cause skin irritation. It is to point out that glycerin is more toxic when administered intravenously, intraperitoneally or subcutaneously. Considering the extensive, widespread dermal exposure to glycerol in preparations repeatedly applied to the skin, the absence of case reports of humans showing skin reactions is consistent with glycerol having a very low skin sensitization potential. According to Regulation EC 1223/2009 and respective amendments there are no restrictions on its use in cosmetic products. The margin of safety calculated for this ingredient is 146 (based on oral studies performed in animal species), which is a value lower than 300 (which is the reference value considered as minimum to assume the ingredients' use as safe when short term animal studies are considered). Nevertheless, glycerin does not cause skin irritation and it is considered to have a very low skin sensitization potential hence it can be assumed that there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

Octyldodecanol undiluted and products containing Octyldodecanol at concentrations up to 20% indicate a very low order of toxicity in acute oral toxicity studies in rats. Its vapors in high concentrations may cause irritation on the respiratory tract. A skin irritation test with Octyldodecanol at 30% produced no irritation in rabbits. Octyldodecanol caused no or minimal ocular, transient irritation in the eyes of rabbits, when tested in 3 to 10.2%. Studies indicated a very low order of sensitization; a study conducted on a lipstick formulation containing 10.2% of Octyl Dodecanol indicated no sensitization. There is no evidence of phototoxicity or photoallergenicity. According to Regulation (EC) No. 1223/2009 and respective amendments there are no restrictions on its use. Cosmetic Ingredient Review (CIR) considers this ingredient safe as used up to 85%. The concentration of this ingredient in the cosmetic product – 1% - is according to the CIR Expert Panel recommendation. The margin of safety calculated for this ingredient is 12844 (based on oral studies performed in animal species), which is a value greater than 300 (which is the reference value considered as minimum to assume the ingredients' use as safe when short term animal studies are considered). Hence, there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

Chaves Thermal Water (Chaves Aqua) has been widely used since the Roman times for the treatment of musculoskeletal, digestive and respiratory tract ailments, therefore no toxicological risk is expected. Moreover, no skin reactions have been reported from its use. According to Regulation EC no. 1223/2009 and respective amendments there are no restrictions on the use of Chaves Thermal Water (Chaves Aqua) in cosmetic products.

Butyrospermum parkii butter is used in many types of cosmetics and personal care products including bath products, cleansing products, eye makeup, lotions and creams, suntan products, lipstick and hair care products and it is regarded as non-toxic ingredient as well as safe for human consumption. Actually, no toxic effects are expected if it is ingested and inhaled. Moreover, this ingredient is not a dermal irritant; it is classified as non-irritating to the eye (rabbit) and it does not cause sensitization reactions and its photo-induced toxicity is not observed. According to the Regulation EC 1223/2009 and respective amendments there are no restrictions on its use in cosmetic products. CIR considers that

Butyrospermum parkii (shea) butter is safe as used up to 60%. The concentration of this ingredient in the cosmetic product – 4% - is according to the CIR Expert Panel recommendation. The margin of safety calculated for this ingredient is 28670 (based on oral studies performed in animal species), which is a value greater than 100 (which is the reference value considered as minimum to assume the ingredients' use as safe when long term animal studies are considered). Hence, there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

Ceteareth-20 (one of polyoxyethylene alkyl ethers) is a nonionic surfactant widely used in topical pharmaceutical formulations and cosmetics and it is classified as not expected to be potentially toxic or harmful. In addition, it is not expected that this compound acts like a sensitizer. Nevertheless, ceteareth-20 is a skin and eye irritant agent. According to the Regulation EC 1223/2009 and respective amendments, there are no restrictions on the use of this ingredient in cosmetic products. CIR (Cosmetic Ingredient Review) considers this ingredient safe in the present practices of use and concentration in cosmetics, when formulated to avoid irritation. CIR refers that Ceteareth-20 is used at 0.02% to 11% in leave-on poducts and 0.008% to 10% in rinse-off products. The concentration of this ingredient in this leave-on cosmetic product – 3% - is according to the CIR Expert Panel recommendation. As NOAEL for this ingredient is unknown, it is not possible to determine its margin of safety under normal conditions of use. Based on its low systemic exposure value (0.0981 mg/kg/day), there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

Cetearyl alcohol is a long-chain aliphatic alcohol that is, at most, only slightly toxic when administered orally at doses of 5 g/kg and greater. It may cause irritation of nose, throat and respiratory airways. It may cause mild skin irritation with redness, burning, and swelling of skin to no irritation at all. The Food and Drug Administration (FDA) includes synthetic fatty alcohols including cetyl alcohol and stearyl alcohol on its list of food additives allowed for direct addition to food as multipurpose food additives. Although, there are some reported cases of allergic contact dermatitis derived from the use of this ingredient, there is no evidence of a potential sensitizing effect on the skin. Concerning ocular irritation, this ingredient demonstrated to be non to slightly eye irritating in rabbits. Regarding to its chronic toxicity effects, it can be mentioned that prolonged or repeated breathing of this compound may result in chronic bronchitis. According to the Regulation EC 1223/2009 and respective amendments there are no restrictions on its use in cosmetic products. Cosmetic Ingredient Review (CIR) considers that cetearyl alcohol is safe as used up to 25%. The concentration of this ingredient in the cosmetic product – 2% - is according to the CIR Expert Panel recommendation. As NOAEL for this ingredient is unknown, it is not possible to determine its margin of safety under normal conditions of use. Based on its low systemic exposure value (0.0654 mg/kg/day), there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

Cetyl Alcohol ingestion may cause hypermotility, vomiting and diarrhea and may also affect the cardiovascular system, respiratory system and central nervous system. This ingredient may cause respiratory tract irritation, dizziness and headaches. Dermal acute toxicity effects in rabbits caused decreased activity and labored respiration. The skin irritation potential of Cetyl Alcohol (at 100.0%) caused no erythematous reactions. In another study Cetyl Alcohol demonstrated mild cumulative irritation; it is a slight skin irritant. This ingredient at 100% produces only slight transient eye irritation to no irritation in rabbits. In a human skin sensitization study of Cetyl Alcohol sensitization reactions were observed in 11.0% of the subjects and in another study Cetyl Alcohol revealed no positive reactions in any of the subjects. Cross-sensitization with cetostearyl alcohol, lanolin, and stearyl alcohol has been reported. Prolonged skin contact may cause removal of natural fat from the skin and irritation. Subchronic dermal exposure to Cetyl Alcohol in rabbits caused infiltration of

lymphomononuclear cells and histiocytes in superficial portions of the dermis and exfoliative dermatitis. The substance is not classified as an intoxicant to a target organ by repeated exposure. This ingredient is not a photosensitizer. According to the Regulation EC 1223/2009 and respective amendments there are no restrictions on its use. CIR (Cosmetic Ingredient Review) considers this ingredient safe as used up to 50%. The concentration of this ingredient in the cosmetic product – 2% - is according to the CIR Expert Panel recommendation. The margin of safety calculated for this ingredient is 30581 (based on oral studies performed in animal species), which is a value greater than 300 (which is the reference value considered as minimum to assume the ingredients' use as safe when short term animal studies are considered). Hence, there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

Isopropyl myristate is widely used in cosmetic and topical pharmaceutical formulations and is generally regarded as nontoxic. However, this ingredient can cause irritation of the digestive tract. If ingested in large amounts can cause nausea, vomiting and diarrhea, moreover it can be irritating to the skin and the eye but is not a skin sensitizing agent. It is an enhancer of dermal absorption. According to Regulation EC No. 1223/2009 and respective amendments there are no restrictions on the use of this mixture in cosmetic products. CIR (Cosmetic Ingredient Review) considers this ingredient safe as used up to 82%. The concentration of this ingredient in the cosmetic product – 2% - is according to the CIR Expert Panel recommendation. As NOAEL for this ingredient is unknown, it is not possible to determine its margin of safety under normal conditions of use. Based on its low systemic exposure value (0.0654 mg/kg/day), there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

Stearic acid is widely used in oral and topical pharmaceutical formulations, being also incorporated in cosmetics and food products. This fatty acid is generally regarded as a non-toxic and non-irritant material. Moreover, it does not cause sensitization reactions neither photosensitizing effects. On the other hand, it may cause skin irritation as well as some acute toxicity effects if inhaled. According to Regulation EC no. 1223/2009 and respective amendments there are no restrictions on its use. CIR considers this compound safe for use even at concentrations > 50%. The concentration of this ingredient in the cosmetic product – 3% - is according to the CIR Expert Panel recommendation. The margin of safety calculated for this ingredient is 38227 (based on oral studies performed in animal species), which is a value greater than 300 (which is the reference value considered as minimum to assume the ingredients' use as safe when short term animal studies are considered). Hence, there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

1051936 NIVAL is a perfume that the exact composition is not known. The main allergens are Hexyl Cinnamal, Alpha-isomethyl ionone and Benzyl Salicylate. This ingredient is a skin and eye irritant and sensitization may occur when in contact with the skin. Benzyl salicylate (present allergen) via oral gavage showed mortality levels observed at 2500 and 5000 mg/kg. Hexyl cinnamal (the major present allergen) has a low skin-sensitizing potency. According to the Regulation EC 1223/2009 and respective amendments, there are no restrictions on the use of this ingredient in cosmetic products. As NOAEL for this ingredient is unknown, it is not possible to determine its margin of safety under normal conditions of use. This ingredient contains allergens that according to the Annex III of the Regulation EC 1223/2009 are substances which cosmetic products must not contain except subject to some restrictions. This Annex III of the Regulation EC no. 1223/2009 states that these substances must be labeled in the final product if their concentration in the cosmetic product exceeds 0.01% in rinse-off products and 0.001% on leave-on products. In this leave-on product the allergens which must be labeled are: Alpha-Isomethyl Ionone, Benzyl Alcohol, Benzyl Salicylate, Butylphenyl Methylpropional, Citronellol, Coumarin, Eugenol, Geraniol, Hexyl Cinnamal, Hydroxycitronellal and Linalool. The presence of these allergens in the

final cosmetic product can cause sensitization reactions in individuals with more sensitive skin. The margins of safety calculated for the allergens Alpha-Isomethyl Ionone, Benzyl Alcohol, Benzyl Salicylate, Butylphenyl Methylpropional, Coumarin, Eugenol, Geraniol, Hexyl Cinnamal, Hydroxycitronellal are 31205, 1911315, 1807, 9777, 9323, 458716, 4854133, 57570 and 200138, respectively (based on oral studies performed in animal species), which are values greater than 100 (which is the reference value considered as minimum to assume the ingredients' use as safe when long term animal studies are considered). Considering the allergens Citronellol and Linalool, the margins of safety calculated are 7014 and 255, respectively (based on oral studies performed in humans), which is a value greater than 10 (which is the reference value considered as minimum to assume the ingredients' use as safe when long term human studies are considered).Hence, there are no significant systemic risks to human health associated to the presence of these substances, under normal conditions of use of the final product.

Triethanolamine is widely used in topical pharmaceutical formulations, primarily in the formation of emulsions. It is also used in sunscreen preparations and in salt formation for injectable solutions and in topical analgesic preparations. Although this ingredient is generally regarded as a non-toxic material, it displays acute (oral and inhalation) and chronic (oral and dermal) toxicity effects. Moreover, it may cause hypersensitivity and it may be irritating to the skin when present in formulated products, with symptoms like redness and burning. Moreover, this ingredient has been identified as causing contact dermatitis and allergic contact dermatitis, erythematous vesicular lesions, eczema, and irritation in workers exposed to triethanolamine in their occupations. Triethanolamine also causes ocular irritation, expressed by stinging, tearing, redness, and swelling of eyes. According to Regulation EC 1223/2009 this ingredient is listed in Annex III (list of substances that cosmetic products must not contain except subject to restrictions) under the group of trialkylamines, trialkanolamines and their salts. According to this Regulation and respective amendments, the use of trialkylamines, trialkanolamines and their salts can be used in rinse-off products with no concentration restriction but is restricted in leave-on products to a maximum concentration of 2.5%. The use of this ingredient in cosmetic products is conditioned by the following restrictions: do not use with nitrosating systems; minimum purity: 99%; maximum secondary amine content: 0.5% (applies to raw materials); maximum nitrosamine content: 50 microg/kg; keep in nitrite-free containers. CIR (Cosmetic Ingredient Review) considers this ingredient safe in the present practices of use and concentration (up to 6% in leave-on products and up to 19% in other cosmetic products), when formulated to be non-irritating and it should not be used in products in which N-nitroso compounds can be formed. The concentration of this ingredient in the cosmetic product – 0.007% - is according to the Regulation EC 1223/2009. Triethanolamine is present in this cosmetic product as part of a mixture and there is no information regarding the nitrosamine content or secondary amine content, nevertheless, the concentration of triethanolmine in the cosmetic product is very low (70 ppm) and therefore it can be assumed that the concentrations of secondary amine and/or nitrosamines (if present) will also be very low. The final packaging of this cosmetic product is nitrite-free and no nitrosating agents are present, The margin of safety calculated for this ingredient is 18395 (based on oral studies performed in animal species), which is a value greater than 100 (which is the reference value considered as minimum to assume the ingredients' use as safe when long term animal studies are considered). Hence, there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

Carbomer is extensively used in non-parenteral products, particularly topical liquid and semisolid preparations and it is generally regarded as essentially nontoxic and nonirritant material. It has low oral toxicity but it is able to cause inflammatory changes in the lung if inhaled and it is a weak to moderate eye irritant. Clinical studies with carbomers showed that these polymers have low potential for skin irritation and sensitization at concentrations up to 100%. According to the Regulation EC 1223/2009 and respective amendments there are no restrictions on its use in cosmetic

products. CIR considers this ingredient safe as used up to 2%. The concentration of this ingredient in the cosmetic product – 0.1155% - is according to the CIR Expert Panel recommendation. The margin of safety calculated for this ingredient is 1985782 (based on oral studies performed in animal species), which is a value greater than 300 (which is the reference value considered as minimum to assume the ingredients' use as safe when short term animal studies are considered). Hence, there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

Alcohol denat. is used in many product types including makeup, lotions, fragrance, shaving, oral care, skin care and hair care products. Alcohol is a central nervous system depressant and ingestion of low to moderate quantities can lead to symptoms of intoxication. Inhalation of high concentrations of alcohol may cause central nervous system effects. Alcohol may also cause skin irritation. Splashes of SD Alcohol 40-B (related compound) may cause temporary pain and blurred vision. Many RIPTs were conducted using SD Alcohol 40-B (denatured with Denatonium Benzoate) and, in all of the tests performed, there was no evidence of dermal sensitization. 0.005% to 0.05% Denatonium Benzoate was nonirritating to ocular mucosa in rabbits. Undiluted Diethyl Phthalate (the other denaturan present) was instilled into the eyes of rabbits and irritation was minimal. Labeled Diethyl Phthalate (14C) was absorbed through the skin of rabbits, and the radioactivity was distributed throughout the body and excreted in the urine. According to Regulation EC No. 1223/2009 and respective amendments there are no restrictions on its use. The margin of safety calculated for this ingredient is 10485 (based on oral studies performed in animal species), which is a value greater than 100 (which is the reference value considered as minimum to assume the ingredients' use as safe when long term animal studies are considered). Hence, there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

Ethylparaben and Methylparaben are widely used in cosmetics, food products, and oral and topical pharmaceutical formulations. In general, parabens are practically non-irritating and non-sensitizing in the population with normal skin and they do not exhibit significant levels of photo-contact sensitization or photo-toxicity. Moreover, chronic oral studies indicate that parabens are practically non-toxic. On the other hand, parabens are often incorporated in creams, lotions and ointments that may be used in the region of the eyes, and occasionally cause redness and swelling of eyelids. Ethylparaben is listed in Regulation EC 1223/2009 annex V (list of preservatives which cosmetic products may contain). According to this Regulation and respective amendments, the use of these parabens in cosmetic products is restricted to a maximum concentration of 0.4% (as acid) for single ester, and 0.8% (as acid) when a mixture of esters is used. CIR (Cosmetic Ingredient Review) considers that this compound is safe when applied in the above-mentioned concentrations. The concentration of the individual parabens (0.15% for ethylparaben and 0.15% for methylparaben) and the sum of concentrations of all parabens present in the cosmetic product – 0.30% - is according to the Regulation EC 1223/2009 and also according to CIR Expert Panel recommendation. The margins of safety calculated for ethylparaben and methylparaben are 1102 and 1102 respectively (based on subcutaneous studies performed in animal species), which are values greater than 300 (which is the reference value considered as minimum to assume the ingredients' use as safe when short term animal studies are considered). Hence, there are no significant systemic risks to human health associated to the use of these substances, under normal conditions of use of the final product.

Phenoxyethanol is an antimicrobial preservative used in cosmetics and topical pharmaceutical formulations, including vaccines. It has also been used at approximately 2% in superficial wounds, burns and minor skin infections as a disinfectant. Phenoxyethanol is practically non-toxic when oral administered (animal data), but it is able to cause respiratory tract irritation if inhaled, and moderate eye irritation. Moreover, Phenoxyethanol at 10% in mineral oil is not

considered a primary or a cumulative irritant, but the pure material is a moderate irritant to the skin. It is not a sensitizer or a photo-toxic agent, although mild skin irritation or contact urticaria due to phenoxyethanol have been reported. This substance is listed in the Regulation EC 1223/2009 as a preservative that can be used in cosmetic products up to a maximum concentration of 1%. CIR also considers that this ingredient is safe as used up to 1%. The concentration of this ingredient in the cosmetic product – 0.9% - is according to the Regulation EC 1223/2009 and also according to CIR Expert Panel recommendation. The margin of safety calculated for this ingredient is 349 (based on oral studies performed in animal species), which is a value greater than 100 (which is the reference value considered as minimum to assume the ingredients' use as safe when long term animal studies are considered). Hence, there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

Carbopol 940 - 2% is a mixture containing Aqua, Carbomer, Alcohol denat. and Triethanolamine. According to Regulation EC No. 1223/2009 and respective amendments there are no restrictions on the use of this mixture in cosmetic products. The regulatory restrictions of the substances present in this mixture are presented in: section 8.1. and their toxicological profiles and margins of safety are presented above.

Phenonip ME is a mixture containing Phenoxyethanol, Methylparaben and Ethylparaben. Inhalation of vapours causes irritation of the respiratory system and mucous membranes, headache, nausea, dizziness, vomiting. Sensitization effects are not known. According to Regulation EC No. 1223/2009 and respective amendments there are no restrictions on the use of this mixture in cosmetic products. The regulatory restrictions of the substances present in this mixture are presented in: section 8.1. and their toxicological profiles and margins of safety are presented above.

Considering the type of formulation, the composition and the stability results, it is unlikely that physico-chemical degradation occurs, putting in risk human health. Interaction between stearic and triethanolamine can occur, leading to the formation of triethanolaine stearate. Nevertheless, this product would be formed to a very low extent and therefore it would not have impact on the stability of the product.

Considering the microbiological stability as well as the results of the challenge test, it can be concluded that this cosmetic product contains adequate preservative. Therefore, it is not expected that its microbial contamination (which can be a threat to human health) occurs.

Considering the packaging material used in the cosmetic product as well as the results of compatibility test packaging material-cosmetic product it is not expected that any risk to human health can be triggered due to the packaging selected.

There are no mandatory warnings to be included in the labelling of this cosmetic product.

The Safety Assessment of the cosmetic product " **DERMOCOSMÉTICA TERMAL AQUAE CREME DE MÃOS"** was performed according to Regulation (EC) 1223/2009 and respective amendments. It was concluded that this cosmetic product is safe for human health under normal or reasonably foreseeable conditions of use taking into account its presentation, labeling, instructions for use and disposal and warnings

4. Assessor's credentials and approval of part B

Name of the Safety Assessor	Marta Alexandra de Oliveira Ferreira	
Address	INOVAPOTEK. Pharmaceutical Research and Development Lda UPTEC. Parque de Ciência e Tecnologia da Universidade do Porto, Rua Alfredo Allen n.º455/461 4200-135, Porto Portugal	
Qualifications of the safety assessor	Master in Pharmaceutical Sciences	
Approval of Part B	**Signature**	
	Date	30-10-2015

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CV Summary

Is currently the General Manager and Technical Director of inovapotek, a spin-off company of Oporto University proving R&D, testing and consulting services to the cosmetics and pharmaceutical industry. Holds a master's degree in Pharmaceutical Sciences and a master's degree in Pharmaceutical Technology and has now more than 10 years of experience in cosmetics product development, testing and regulatory affairs.

Professional experience

Founder, General Manager and Technical Director, *Inovapotek, Pharmaceutical Research and Development Lda. (since October 2008)*

Activities:

- Coordination of all Technical Department activities such as:
    - Safety assessment according with EU regulation
    - Safety and tolerance testing
    - Efficacy testing
    - Formulation development
    - Stability studies
    - New methods development and validation
    - Study plans design
- Coordination of Marketing/Sales Department
- Human resources management
- Coordination of Financial & Administrative Department

Consultant, *Fluidinova, Engenharia de Fluidos, SA (2008)*

Activities: definition of a R&D project in the cosmetic area, including definition of activities and tasks, planning and resources.

R&D manager of the project "Development of cosmetic products with S. Pedro do Sul Spring water", *Termalistur – Termas de São Pedro do Sul EM, in partnership with the Faculty of Pharmacy of Oporto University (2005-2008)*

Activities: Development of a new range of cosmetic products, including formulation, stability, safety and efficacy studies of the products. Responsible for the implementation of a new microbiological laboratory for the quality control of the spring water.

Invited Teacher of the Master of Pharmaceutical Technology , *Faculty of Pharmacy of Oporto University (2006 e 2007)*

Researcher at the Medicines Technologic Centre, *Pharmacies National Association (2005)*
Activities: Development of several monographs of semi-solid products for the Portuguese National formulary.

Pharmacist (Health assistant), *Hospital São João de Deus S.A., Vila Nova de Famalicão (2005)*

Pharmacist, *Farmácia Marques, Braga (2004 a 2005)*

Researcher at the Pharmaceutical Technology Department, *Faculty of Pharmacy of Oporto University (2002 a 2003)*
Activities: Planning and implementation of a R&D project for the development of a pediatric syrup.

Researcher at the Organic Chemistry, Phytochemistry and Pharmacology Studies Centre, Organic Chemistry Department, *Faculty of Pharmacy of Oporto University (2000 a 2002)*
Activities: Collaboration of a research project that aimed the development and selection of PLA-PEG nanocapsules for the incorporation and xanthonic compounds.

Education and Training

Good Laboratory Practices Principles Training, Eng.ª Helena Loureiro (2014)

I Course Good Clinical Practices, Lisbon Faculty of Medicine (2012)

Integrated Audits of Quality, Environment and Health and Safety, Process Advice (2010)

Master in Pharmaceutical Sciences, *Faculty of Pharmacy of Oporto University* (2009)

Master in Pharmaceutical Technology (classification: very good), *Faculty of Pharmacy of Oporto University* (2008)

Post-graduation in Pharmacotechnics (classification: 16/20), *Faculty of Pharmacy of Oporto University* (2007)

Advanced Program in Entrepreneurship, Business Creation and Business Development, National Association of Young Entrepreneurs, Porto (2005)

Primary Compounding Course, Professional Compounding Centres of America, Houston (2005)

Degree in Pharmaceutical Sciences (classification: 16/20), *Faculty of Pharmacy of Oporto University* (1998-2004)

Scientific curriculum

Thesis

1. Ferreira M.O. Efficacy testing of cosmetic products in human volunteers using objective instrumental methods. *Faculty of Pharmacy of Oporto University*, Porto, Portugal, 2009.
2. Ferreira M.O. Cutaneous effect of S. Pedro do Sul Spring water. *Faculty of Pharmacy of Oporto University*, Porto, Portugal, 2008.
3. Ferreira M.O. Bio-identical hormone replacement therapy. *Faculty of Pharmacy of Oporto University*, Porto, Portugal, 2007.

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8. Figueiredo R. P., Costa P. C. and Ferreira M. O. Non-Invasive Skin Imaging Techniques. Skin Research and Technology (article in press)

Presentations in poster

1. Ferreira M.O., Almeida I.F., Bahía M.F., Costa P. Study of the effect of several thermal waters in skin surface hydration. Skin and Formulation, 2nd Symposium, Versailles (France), 9-10th October, 2006.
2. Ferreira M.O., Mota A.F., Oliveira A.Z., Ximenes C.S., Ribeiro A.M., Almeida I.F., Bahía M.F., Costa P. Mechanical characterization of an oleogel/hydrogel mixture. Skin and Formulation, 2nd Symposium, Versailles (France), 9-10th October, 2006.
3. L. Carvalho, A. J. Chambe, K. Krambeck, A. F. Lemos, S. Oliveira, M.O. Ferreira, P.C. Costa. Evaluation of the cutaneous hydration induced by O/W creams with different glycerin concentrations. 9th Annual Meeting of Skin Fórum, London (United Kingdom), 25-26th June, 2008.
4. Isabel F. Almeida, M.O. Ferreira, Paulo C. Costa, M. Fernanda Bahia. In vitro evaluation of the antioxidant activity of a semisolid formulation incorporating a plant extract. 9th Annual Meeting of Skin Fórum, London (United Kingdom), 25-26th June, 2008.

5. Ferreira M.O., Amaral M.H., Costa P., Bahía M.F., Assessment of age-related differences in skin surface, hydration, sebum and pH. Building Cosmetics: Research, Technology & Culture, 25th IFSCC Congress, Barcelona (Spain), 6-9th October, 2008.
6. Ferreira M.O., Amaral M.H., Costa P., Bahía M.F., Study of the inter-relations between skin surface parameters, hydration, sebum and pH. Building Cosmetics: Research, Technology & Culture, 25th IFSCC Congress, Barcelona (Spain), 6-9th October, 2008.
7. Ferreira M.O., Amaral M.H., Pereira T., Costa P., Bahía M.F., Evaluation of the skin compatibility of new cosmetic products. 2nd National Congress of Dermatocosmetic Sciences (1st congress of the Portuguese society of Cosmetic Sciences), Lisbon (Portugal), 27th March, 2009.
8. Neto P., Ferreira M., Evaluation of a new active complex in decreasing *vellus* hairs ratio, 21st EADV Congress, Prague, 2012.
9. Neto P., Ferreira M., Evaluation of a new active complex for increasing hair thickness in alopecia, 21st EADV Congress, Prague, 2012.
10. Neto P., Ferreira M., Efficacy evaluation of a new active complex for hair loss, 21st EADV Congress, Prague, 2012.

Oral presentations

1. Ferreira M.O. Cosmetic products development, Panel "Quality, Efficacy and Acceptability of Cosmetic Products", Dermatology and Cosmetology – health to promote well-being Congress, Porto (Portugal), 18-19th April, 2007.
2. Ferreira M.O., Costa P., Bahía M.F. Water and skin: the S. Pedro do Sul thermal water cutaneous effects, Panel "Dermatological and Allergic Studies", 36th Congress of the International Society of Medical Hydrology & Climatology, Porto (Portugal), 25-28th June, 2008.
3. Ferreira M.O. Development of the 1st Cosmetic Products with a Portuguese Thermal Water, Aquameeting – Health and Well-being International Seminar, Porto (Portugal), 19-21th September, 2008.
4. Ferreira M.O. Dermocosmetic Products with a Portuguese Thermal Water. 2nd National Congress of Dermatocosmetic Sciences (1st congress of the Portuguese society of Cosmetic Sciences), Lisbon (Portugal), 27th March, 2009.
5. Ferreira M.O. Cosmetic Products Development: quality, efficacy and safety aspects. Dermatocosmetic Workshop, Health School of the Bragança Polytechnic Institute, Bragança (Portugal), 5th June, 2009.
6. Ferreira M.O. How to prepare for importing to Europe. European Cosmetics Regulation Seminar (Ecore), Tel aviv, 3rd-5th February 2013
7. Ferreira M.O. Cosmetics Testing – compliance with the new regulation. European Cosmetics Regulation Seminar (Ecore), Cosmoprof Bologne, 10th March 2013
8. Ferreira M.O. Systemic Exposure of the Human Body to Cosmetic Ingredients and the Influence on Product. Safety European Cosmetics Regulation Workshop, Istanbul, 2nd October 2013
9. Ferreira M.O. Formulation principles & R&D exercises. Safety European Cosmetics Regulation Workshop, Istambul, 3rd October 2013
10. Ferreira M.O. Safety Assessment. Israeli Cosmetics Conference. Tel aviv, 12nd November 2013
11. Ferreira M.O. PIF = Product Information File. Israeli Cosmetics Conference. Tel aviv, 12nd November 2013
12. Ferreira M.O. Formulation principles & R&D exercises. European Cosmetics Regulation Workshop, Athens, 7th May 2014
13. Ferreira M.O. Safety Assessment (Opinion 1501/12) MoS Calculation - Practical Aspects on How to Make the MoS Calculations. European Cosmetics Regulation Workshop, Athens, 7th May 2014

14. Ferreira M.O. Safety Assessment for Different Types of Products & Examples. European Cosmetics Regulation Workshop, Athens, 7th May 2014
15. Ferreira M.O. PIF = Product Information File. European Cosmetics Regulation Seminar (Ecore), Tel aviv, 16th June 2014

Awards

1. Winner of the Portuguese Galenic Formulary Award (2004).
2. Winner of the "Best Communication" Award at the *II Congresso Nacional de Ciências Dermatocosméticas* (2009).

Presence in seminaries and scientific congresses

1. Skin and Formulation, 2nd Symposium, Versailles (France), 9-10th October, 2006.
2. Dermatology and Cosmetology – health to promote well-being Congress, Porto (Portugal), 18-19th April, 2007.
3. 36th Congress of the International Society of Medical Hydrology & Climatology, Porto (Portugal), 25-28th June, 2008.
4. 2008 Cosmetic Science Conference (CSC), In-cosmetics, Amsterdam (Netherlands), 2008.
5. Aquameeting – Health and Well-being International Seminar, Porto (Portugal), 19-21th September, 2008.
6. 2nd National Congress of Dermatocosmetic Sciences (1st congress of the Portuguese society of Cosmetic Sciences), Lisbon (Portugal), 27th March, 2009.
7. 2009 Cosmetic Science Conference (CSC), In-cosmetics, Munich (Germany), 22-23rd April, 2009.
8. SME's go Health International Information and Training Workshop, Istanbul (Turkey), 27th April, 2009.
9. 7th Framework Programme – Opportunities to SME's, 1st European Week of SME's 2009, Porto (Portugal), 7th May, 2009.
10. 3rd National Congress of Dermatocosmetic Sciences (2nd congress of the Portuguese society of Cosmetic Sciences), Lisbon (Portugal), 18th March, 2011.
11. 20th European Academy of Dermatology and Venereology Congress, Lisbon (Portugal), 20-24th October 2011
12. Day of the imaging technologies for the skin, 4th edition, DIIP Association, Tours (France), 27th September 2012.
13. European Cosmetics Regulation Seminar (Ecore), Tel aviv, 3rd-5th February 2013
14. European Cosmetics Regulation Seminar (Ecore), Cosmoprof Bologne, 10th March 2013
15. European Cosmetics Regulation Workshop, Istanbul, 30th September 2013 - 4th October 2013
16. Israeli Cosmetics Conference. Tel aviv, 12nd November 2013
17. European Cosmetics Regulation Workshop, Athens, 5th-9th May 2014
18. Cosmetics Europe Conference: Cosmetics at the Crossroads of Science and Regulation, 10-11th June 2014
19. European Cosmetics Regulation Seminar (Ecore), Tel aviv, 16th June 2014
20. III Cosmetology Innovation Workshop, Faculty of Pharmacy of Oporto University, 22nd May 2014

Personal skills

Language skills

English: excellent knowledge (860 points at *TOEIC*).
Spanish: good knowledge.
French: medium knowledge.

Informatics skills

Microsoft Word, Microsoft Excel, Microsoft Power Point, SPSS, EndNote

Additional information

Member of the following societies:
International Society for Biophysics and Imaging of the Skin (ISBS)
European Responsible Person Association (ERPA)
Portuguese Society of Cosmetic Sciences (SPCC)
OF

CERTIFICATE

Master's Degree

ISABEL GLÓRIA PEREIRA GUIMARÃES, Head of the Administration Office of the Faculty of Pharmacy of the University of Porto
Hereby certifies that

Marta Alexandra de Oliveira Ferreira

holder of identity Card number 11658756, of portuguese nationality, completed at this University, on the 08th of September 2008, the MSc in Pharmaceutical Technology - Scientific Area in Pharmacotecnics, with the final grade of very good.
This degree was registered under number 11004863M050604002.
This Document is authenticated with the embossed seal of this Faculty.
Academic Services of the Faculty, 23rd of August 2010.

Isabel Guimarães

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Cont. 16.

CERTIFICATE

Master's Degree

ISABEL GLÓRIA PEREIRA GUIMARÃES, Head of the Administration Office of the Faculty of Pharmacy of the University of Porto
Hereby certifies that

Marta Alexandra de Oliveira Ferreira
holder of Identity Card number 11658756, of portuguese nationality, completed at this University, on the 04th of September 2009, the MSc in Pharmaceutical Sciences, with the final grade of Sixteen (out of 20), corresponding to grade A on the European grading scale
This degree was registered under number 11009494M080601284.
This Document is authenticated with the embossed seal of this Faculty.
Academic Services of the Faculty, 23rd of August 2010.

ADMINISTRATIVE RESPONSIBLE

Isabel Guimarães

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PHARMACEUTICAL RESEARCH AND DEVELOPMENT

Cosmetic Product Safety Report

Report number FR10A/P135B13

Cosmetic Product Safety Report of the cosmetic product
DERMOCOSMÉTICA TERMAL AQUAE CREME HIDRATANTE CORPORAL

30-10-2015

Promoter:
Município de Chaves

All information contained herein is confidential and will not be disclosed, whole or in part, without the proper written consent of the promoter.

CIDADE DE CHAVES
PROGRAMA COOPERACIÓN TRANSFRONTERIZA ESPAÑA - PORTUGAL COOPERAÇÃO TRANSFRONTEIRIÇA 2007-2013
União Europeia
Fundo Europeu de Desenvolvimento Regional
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CHAVES TERMAS&SPA

Identification of the study

Proposal Number	P135B13
Report number	FR10A/P135B13
Safety Assessment Report	Cosmetic Product Safety Report of the cosmetic product DERMOCOSMÉTICA TERMAL AQUAE CREME HIDRATANTE CORPORAL
Beginning Date	13-10-2015
Report Date	30-10-2015

Identification of the study responsible personnel

Promoter	**Name**	Município de Chaves
	Address	Câmara Municipal de Chaves Praça de Camões, 5400-150 Chaves
Proponent	**Name**	INOVAPOTEK, Pharmaceutical Research and Development Lda
	Address	UPTEC, Parque de Ciência e Tecnologia da Universidade do Porto,Rua Alfredo Allen, n.º 455/461 4200-135 Porto – PORTUGAL
Safety Assessor	**Name**	Marta Alexandra de Oliveira Ferreira
	Qualifications of the safety assessor	Master in Pharmaceutical Sciences

History of the document

Version	Alterations	Date
A	First version	30-10-2015

Part A. Cosmetic Product Safety Information

1. Quantitative and qualitative composition of the cosmetic product

1.1 By trade name

Raw material (trade name)	Supplier	Function	Conc. (%)
White Oil Light	Mosselman	Emollient; skin protecting	5.00000
Myritol 318	COGNIS	Emollient; skin conditioning	8.00000
Glycerin 4810	Oleon NV	Humectant	3.00000
Tegin Pellets	Evonik Industries AG	Emulsifying	8.00000
Goma xantana	Guinama	Emulsion Stabilising;Viscosity Controlling	0.30000
Água Termal das Termas de Chaves	Termas de Chaves	Solvent	72.70000
Sabowax CS 20	SABO SpA	Emulsifying	1.00000
1051936 NIVAL	Iberchem, S.A.	Fragrance	0.10000
Phenonip ME	Clariant	Preservative	1.20000
Acido Clorhídrico 37% grado técnico	Panreac AppliChem	Buffering	0.40000
SABONAL C1618 50/50	SABO SpA	Emulsifying	2.00000

1.2 By trade name and respective INCI name

Raw material (trade name)	INCI	IUPAC	CAS	EINECS/ELINCS	Function	Conc. of the substance in the raw material (%)	Conc. of the substance in the cosmetic product (%)
White Oil Light	Paraffinum Liquidum	Paraffin oils. Liquid hydrocarbons from petroleum	8012-95-1/8042-47-5	232-384-2/232-455-8	Emollient; skin protecting	100.00000	5.00000
Myritol 318	Caprylic/Capric Triglyceride	-	73398-61-5/65381-09-1	277-452-2/265-724-3	Emollient; skin conditioning	100.00000	8.00000
Glycerin 4810	Glycerin	Glycerol	56-81-5	200-289-5	Humectant	100.00000	3.00000
Tegin Pellets	Glyceryl stearate SE	Octadecanoic acid, reaction products with 1,2,3-propanetriol (1:1), neutralized	11099-07-3	234-325-6	Emulsifying	100.00000	8.00000
Goma xantana	Xanthan Gum	-	11138-66-2	234-394-2	Emulsion Stabilising Viscosity Controlling	108.00000	0.32400
Água Termal das Termas de Chaves	Chaves Thermal Water (Chaves Aqua)	-	7732-18-5	231-791-2	Solvent	100.00000	72.70000
Sabowax CS 20	Ceteareth-20	-	68439-49-6	-	Emulsifying	100.00000	1.00000
1051936 NIVAL	Parfum	-	-	-	Perfuming	100.00000	0.10000
Phenonip ME	Ethylparaben	Ethyl 4-hydroxybenzoate	120-47-8	204-399-4	Preservative	12.50000	0.15000
	Methylparaben	Methyl 4-hydroxybenzoate	99-76-3	202-785-7	Preservative	12.50000	0.15000
	Phenoxyethanol	2-phenoxyethanol	122-99-6	204-589-7	Preservative	75.00000	0.90000

Acido Clorhídrico 37% grado técnico	Hydrochloric acid	Hydrogen chloride	7647-01-0	231-595-7	Buffering	39.00000	0.15600
	Aqua	-	7732-18-5	231-791-2		63.50000	0.25400
SABONAL C1618 50/50	Cetearyl alcohol	-	67762-27-0 / 8005-44-5	267-008-6 / -	Emulsifying	100.00000	2.00000

1.3 By INCI name

INCI	Total Concentration In The Final Product (%)
Chaves Thermal Water (Chaves Aqua)	72.700000000000
Caprylic/Capric Triglyceride	8.000000000000
Glyceryl stearate SE	8.000000000000
Paraffinum Liquidum	5.000000000000
Glycerin	3.000000000000
Cetearyl alcohol	2.000000000000
Ceteareth-20	1.000000000000
Phenoxyethanol	0.900000000000
Xanthan Gum	0.324000000000
Aqua	0.254000000000
Hydrochloric acid	0.156000000000
Ethylparaben	0.150000000000
Methylparaben	0.150000000000
Parfum	0.100000000000
Hexyl Cinnamal	0.006640000000
Alpha-Isomethyl Ionone	0.004900000000
Benzyl Salicylate	0.004230000000
Butylphenyl Methylpropional	0.003910000000
Geraniol	0.003150000000
Linalool	0.003000000000
Hydroxycitronellal	0.001910000000
Coumarin	0.001640000000
Citronellol	0.001090000000
Eugenol	0.001000000000
Benzyl Alcohol	0.001000000000

2. Physical/chemical characteristics and stability of the cosmetic product

2.1 Physical/chemical characteristics of the raw materials

White Oil Light

CHEMICAL AND PHYSICAL COMPOSITION			
Composition	**Conc. (%)**	**CAS**	**EINECS**
Paraffinum Liquidum	100	8012-95-1/8042-47-5	232-384-2/232-455-8

Comments:

It is described as white mineral oil (petroleum) a highly refined petroleum mineral oil consisting of a complex combination of hydrocarbons obtained from the intensive treatment of a petroleum fraction with sulfuric acid and oleum, or by hydrogenation, or by a combination of hydrogenation and acid treatment. Additional washing and treating steps may be included in the processing operation. It consists of saturated hydrocarbons having carbon numbers predominantly in the range of C15 through C50. Mineral oil (US).

CHEMICAL AND PHYSICAL SPECIFICATIONS	
Molecular Weight	-
Physical State	Liquid
Organoleptic Properties	Colorless and odorless viscous liquid.
Solubility	Practically insoluble in ethanol (95%), glycerin, and water. Soluble in acetone, benzene, chloroform, carbon disulfide, ether, and petroleum ether. Miscible with volatile oils and fixed oils with the exception of castor oil.
Partition coefficient (Log Pow)	-
pH	-
Nanomaterials	NO

Comments:

IMPURITIES AND/OR ALLERGEN SUBSTANCES

This ingredient does not contain impurities and/or allergen substances.

Myritol 318

CHEMICAL AND PHYSICAL COMPOSITION			
Composition	**Conc. (%)**	**CAS**	**EINECS**
Caprylic/Capric Triglyceride	-	73398-61-5/65381-09-1	277-452-2/265-724-3

Comments:

It is medium-chain triglycerides (a mixed triester of glycerin and caprylic and capric acids).

Fatty Acid	Concentration
C6	0.1%
C8	55.8%
C10	44.1%

The Ph. Eur. 6.0 describes medium-chain triglycerides as the fixed oil extracted from

the hard, dried fraction of the endosperm of *Cocos nucifera* L. or from the dried endosperm of *Elaeis guineenis* Jacq. They consist of a mixture of triglycerides of saturated fatty acids, mainly of caprylic acid and of capric acid. They contain not less than 95% of saturated fatty acids.	
CHEMICAL AND PHYSICAL SPECIFICATIONS	
Molecular Weight	408.57 g/mol
Physical State	Liquid
Organoleptic Properties	Clear, colorless oil with characteristic odour
Solubility	Soluble in acetone, chloroform, dichloromethane, ethanol and ether. Insoluble in water.
Partition coefficient (Log Pow)	8.2 - 10.9
pH	-
Nanomaterials	NO
Comments: Density: 0.945-0.949g/cm3 Viscosity: 27-33mPas (20°C) Acid number: maximum 0.1 Saponification Value: 335-350 Hydroxyl Number: maximum 5 Iodine Number: maximum 0.5 Unsaponification content: maximum 0.5%.	
IMPURITIES AND/OR ALLERGEN SUBSTANCES	
This ingredient does not contain impurities and/or allergen substances.	

Glycerin 4810

CHEMICAL AND PHYSICAL COMPOSITION			
Composition	**Conc. (%)**	**CAS**	**EINECS**
Glycerin	99.5-100	56-81-5	200-289-5
Comments: -			

CHEMICAL AND PHYSICAL SPECIFICATIONS	
Molecular Weight	92.09 g/mol
Physical State	Liquid
Organoleptic Properties	Clear, colorless syrupy liquid
Solubility	Completely soluble in water and ethanol; Slightly soluble in acetone. Solubility in ether: 0.2g/100 mL
Partition coefficient (Log Pow)	-1.76
pH	-
Nanomaterials	NO
Comments: Water content: max.: 0.5%	

Other impurity eluating before glycerol % <0.1 Total impurity eluating after glycerol % <0.5

IMPURITIES AND/OR ALLERGEN SUBSTANCES	
Impurity/Allergen substance	**Concentration (%)**
Halogenated compounds	0-0.0030
Chlorides	0-0.0010
Heavy metals	0-0.0005
diethylene glycol	0-0.1

Tegin Pellets

CHEMICAL AND PHYSICAL COMPOSITION			
Composition	**Conc. (%)**	**CAS**	**EINECS**
Glyceryl stearate SE	-	11099-07-3	234-325-6
Comments: Stearic acid, monoester with glycerol			

CHEMICAL AND PHYSICAL SPECIFICATIONS	
Molecular Weight	358.6 g/mol
Physical State	Solid
Organoleptic Properties	Ivory pellets with a slight characteristic odor.
Solubility	Dispersible in water.
Partition coefficient (Log Pow)	-
pH	5-7.5 (100 g/L)
Nanomaterials	NO
Comments: Melting point: 57-60°C Ignition point: >200°C Total monoester content: 32-40% Free Glycerol: 5.0-8.0% Iodine value: <= 3.00 g I/100g Acid Value: 32.00-36.00 mg KOH/g Melting point: 56.0-61.0 °C Saponification value: 145.0-160.0 mg KOH/g	

IMPURITIES AND/OR ALLERGEN SUBSTANCES
This ingredient does not contain impurities and/or allergen substances.

Goma xantana

CHEMICAL AND PHYSICAL COMPOSITION

Composition	Conc. (%)	CAS	EINECS
Xanthan Gum	91 - 108	11138-66-2	234-394-2

Comments:

Xanthan gum is purified by extraction with ethanol or isopropyl alcohol and then dried therefore, traces of this component may be found on its composition.

CHEMICAL AND PHYSICAL SPECIFICATIONS

Molecular Weight	2-50x106 Da
Physical State	Solid
Organoleptic Properties	Creamy-white odourless free-flow powder
Solubility	Soluble in water giving a highly viscous solution practically insoluble in organic solvents.
Partition coefficient (Log Pow)	-
pH	6.0-8.0
Nanomaterials	NO

Comments:
Viscosity: 1400-1600 mPas (1% in KCl 1%, 60 rpm, 25 °C)

Loss on drying: max 12%.

Granulometry:

- < 80 mesh (0.180 mm) = 100%

- < 200 mesh (0.075 mm) = 92 %

Ash: 6.5%-16%

Pyruvic acid: min 1.5%

IMPURITIES AND/OR ALLERGEN SUBSTANCES

Impurity/Allergen substance	Concentration (%)
Heavy metals	0-0.0020
Arsenic	0-0.0002
Lead	0-0.0002
Mercury	0-0.0001
Nitrogen	0-1.5
Cadmium	0-0.0001
Isopropanol	0-0.0500

Água Termal das Termas de Chaves

CHEMICAL AND PHYSICAL COMPOSITION

Composition	Conc. (%)	CAS	EINECS
Chaves Thermal Water (Chaves Aqua)	100	7732-18-5	231-791-2

Comments:

The majority components of the analysed thermal water are described below.

Water hole AC1

Anions:

Fluoride (F^-): 7.8 mg/L

Chloride (Cl^-): 40.0 mg/L

Hydrogen carbonate (HCO_3^-): 1624 mg/L

Carbonate (CO_3^{2-}): -

Hydrogen sulfide (HS^-): -

Sulfate (SO_4^{2-}): 25.9 mg/L

Silicate ($H_3SiO_4^-$): -

Phosphate ($H_2PO_4^-$): 0.42 mg/L

Nitrate (NO_3^-): 0.31 mg/L

Nitrite (NO_2^-): < 0.01mg/L

Cyanide (CN^-): < 1.0 microg/L

Bromide (Br^-): 0.26 mg/L

Bromate (BrO_3-): < 0.20

Iodide (I^-): 6 microg/L

Cations:

Lithium (Li^+): 2.4 mg/L

Sodium (Na^+): 581 mg/L

Potassium (K^+): 59.7 mg/L

Magnesium (Mg^{2+}): 5.2 mg/L

Calcium (Ca^{2+}): 21.6 mg/L

Iron (Fe^{2+}): 0.19 mg/L

Iron (Fe^{3+}): 0.03 mg/L

Ammonium (NH_4^+): 1.2 mg/L

Strontium(Sr^{2+}): 0.37 mg/L

Water hole AC2

Anions:

Fluoride (F^-): 8.2 mg/L

Chloride (Cl^-): 38.5 mg/L

Hydrogen carbonate (HCO_3^-): 1760 mg/L

Carbonate (CO_3^{2-}): -

Hydrogen sulfide (HS^-): -

Sulfate (SO_4^{2-}): 18.8 mg/L

Silicate ($H_3SiO_4^-$): -

Phosphate ($H_2PO_4^-$): 0.13 mg/L

Nitrate (NO_3^-): 0.30 mg/L

Nitrite (NO_2^-): < 0.01mg/L

Cyanide (CN^-): < 1.0 microg/L

Bromide (Br^-): 0.23 mg/L

Bromate (BrO_3^-): < 0.20

Iodide (I^-): 6 microg/L

Cations:

Lithium (Li^+): 2.6 mg/L

Sodium (Na^+): 630 mg/L

Potassium (K^+): 61.1 mg/L

Magnesium (Mg^{2+}): 5.1 mg/L

Calcium (Ca^{2+}): 21.2 mg/L

Iron (Fe^{2+}): 0.19 mg/L

Iron (Fe^{3+}): 0.02 mg/L

Ammonium (NH_4^+): 1.2 mg/L

Strontium(Sr^{2+}): 0.4 mg/L

CHEMICAL AND PHYSICAL SPECIFICATIONS	
Molecular Weight	18 g/mol
Physical State	Liquid
Organoleptic Properties	Clear, colorless liquid with sulfuric odor
Solubility	-
Partition coefficient (Log Pow)	-
pH	8.86 (21.2 °C)
Nanomaterials	NO

Comments:

Water hole AC1

Anions: 1698 mg/L

Cations: 672 mg/L

Silica: 79.5 mg/L

Conductivity (20 °C): 2150 µS/cm

Alkalinity: 266.2 (mL/L de HCl 0.1M)

Total hardness: 7.5 p.p. 10^5 $CaCO_3$

Total CO_2 : - (mmol/L de CO_2)

Total sulfidation: - (mL/L I_2 0.01N)

Dry residue (180°C): 1606 mg/L

Water hole AC2

Anions: 1826 mg/L

Cations: 722 mg/L

Silica: 84.6 mg/L

Conductivity (20 °C): 2300 µS/cm

Alkalinity: 288.6 (mL/L de HCl 0.1M)

Total hardness: 7.4 p.p. 10^5 $CaCO_3$

Total CO_2 : - (mmol/L de CO_2)

Total sulfidation: - (mL/L I_2 0.01N) Dry residue (180°C): 1722 mg/L

IMPURITIES AND/OR ALLERGEN SUBSTANCES

Impurity/Allergen substance	Concentration (%)
Aluminium	0.00000146
Arsenic	0.0000128
Lead	0-0.000000006
Mercury	0-0.000000054
Selenium	0-0.00000149
Silver	0-0.000000012
Boron	0.0000729
Barium	0.0000431
Beryllium	0.00000144
Cadmium	0-0.000000015
Cobalt	0.000000073
Chromium	0.00000076
Copper	0-0.000000039
Cesium	0.0000407
Manganese	0.00000429
Molybdenum	0.00000014
Nickel	0-0.00000076
Rubidium	0.0000492
Antimony	0.00000032
Tin	0-0.000000026
Tantalum	0-0.000000001
Tellurium	0-0.00000011
Thallium	0.00000078
Uranium	0.000000025
Vanadium	0.000000054
Tungsten	0.00000347
Zinc	0.00000213
Zirconium	0-0.00000019
Bismuth	0-0.000000005
yttrium	0-0.000000001
niobium	0-0.000000005

Sabowax CS 20

CHEMICAL AND PHYSICAL COMPOSITION			
Composition	**Conc. (%)**	**CAS**	**EINECS**
Ceteareth-20	99-100	68439-49-6	-
Comments: -			

CHEMICAL AND PHYSICAL SPECIFICATIONS	
Molecular Weight	-
Physical State	Solid
Organoleptic Properties	White, waxy, flakes
Solubility	Soluble in water and alcohol. Insoluble in paraffinic oils
Partition coefficient (Log Pow)	-
pH	at 5%: 5.5 - 7.5
Nanomaterials	NO
Comments: Moisture: 1% max	

IMPURITIES AND/OR ALLERGEN SUBSTANCES	
Impurity/Allergen substance	**Concentration (%)**
1,4-Dioxane	0
Ethylene oxide	0

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CHEMICAL AND PHYSICAL COMPOSITION			
Composition	**Conc. (%)**	**CAS**	**EINECS**
Parfum	-	-	-

Comments:

It is not known the exact composition of the perfume. This perfume is a mixture of natural and synthetic odour compounds, without ethanol. The following table shows the hazardous components for human health and their content, present in this perfume.

Compound	CAS	EINECS	Concentration (%)
4-tert-Butylcyclohexyl Acetate	32210-23-4	250-954-9	10 - 25
Linalyl Acetate	115-95-7	204-116-4	1 -5
Tricyclodecenyl Propionate	17511-60-3	241-514-7	1 - 5
Phenethyl acetate	103-45-7	203-113-5	1 - 5
Terpineol	8000-41-7	232-268-1	1 - 5
Coumarin	91-64-5	202-086-7	1 - 5
a-terpinyl acetate	80-26-2	201-265-7	1 - 5
Nerol	106-25-2	203-378-7	1 - 5
2,6-dimethyl-7-octen-2-ol	18479-58-8	242-362-4	1 - 5
Undecylenal	112-45-8	203-973-1	1 - 5
Citronellyl acetate	150-84-5	205-775-0	0.1 - 1
Geranyl acetate	105-87-3	203-341-5	0.1 - 1

CHEMICAL AND PHYSICAL SPECIFICATIONS	
Molecular Weight	-

Physical State	Liquid
Organoleptic Properties	Transparent, yellow liquid with a floral-aldehyde characteristic odour
Solubility	-
Partition coefficient (Log Pow)	-
pH	-
Nanomaterials	NO
Comments: Flashpoint: > 100 °C Density: 0.9740 - 1.0140 g/cc (20 °C)	

IMPURITIES AND/OR ALLERGEN SUBSTANCES

Impurity/Allergen substance	Concentration (%)
Alpha-Isomethyl Ionone	4.9050
Benzyl Alcohol	1.0021
Benzyl Benzoate	0.0128
Benzyl Salicylate	4.23
Butylphenyl Methylpropional	3.9091
Citral	0.0014
Citronellol	1.0909
Coumarin	1.6364
Eugenol	1
Geraniol	3.1547
Hexyl Cinnamal	6.6364
Hydroxycitronellal	1.9091
Hydroxyisohexyl 3-Cyclohexene Carboxaldehyde	0.5455
Isoeugenol	0.9091
Linalool	3
Limonene	0.0036

Phenonip ME

CHEMICAL AND PHYSICAL COMPOSITION

Composition	Conc. (%)	CAS	EINECS
Ethylparaben	12.5	120-47-8	204-399-4
Methylparaben	12.5	99-76-3	202-785-7
Phenoxyethanol	75	122-99-6	204-589-7

Comments: -

CHEMICAL AND PHYSICAL SPECIFICATIONS

Molecular Weight	-
Physical State	Liquid
Organoleptic Properties	Colourless to light straw viscous liquid with a characteristic odour
Solubility	Solubility: water (approx. 0.7 %), ethanol/water 50/50 (> 95 %), Liquid Paraffin (< 0.1 %), Glycerol (approx. 8 %). Soluble in Ethanol. Miscible in Isopropanol, Acetone, Propylene Glycol and Sodium Laureth Sulfate (28 %)
Partition coefficient (Log Pow)	-
pH	-

Nanomaterials	NO

Comments:

Compound	Molecular Weight (g/mol)	Partition coefficent
Ethylparaben	166.17	2.47
Methylparaben	152.15	1.96
Phenoxyethanol	138.16	1.16

IMPURITIES AND/OR ALLERGEN SUBSTANCES

This ingredient does not contain impurities and/or allergen substances.

Acido Clorhídrico 37% grado técnico

CHEMICAL AND PHYSICAL COMPOSITION

Composition	Conc. (%)	CAS	EINECS
Hydrochloric acid	36.5-39	7647-01-0	231-595-7
Aqua	61-63.5	7732-18-5	231-791-2

Comments:

CHEMICAL AND PHYSICAL SPECIFICATIONS

Molecular Weight	36.46 g/mol
Physical State	Liquid
Organoleptic Properties	Colorless liquid with characteristic odor.
Solubility	Miscible in water.
Partition coefficient (Log Pow)	-
pH	-
Nanomaterials	NO

Comments:

Relative density: 1.185 - 1.195

Compound	Molecular weight (g/mol)	Partition Coefficient
Water	18.01528	-0.5
Hydrochloric acid	36.46	-

IMPURITIES AND/OR ALLERGEN SUBSTANCES

Impurity/Allergen substance	Concentration (%)
iron	0.005
Sulfate	0.005
Arsenic	0.0003
Lead	0.005
Ammonium	0.005

SABONAL C1618 50/50

CHEMICAL AND PHYSICAL COMPOSITION

Composition	Conc. (%)	CAS	EINECS
Cetearyl alcohol	100	67762-27-0 / 8005-44-5	267-008-6 / -

Comments:

C16 (Cetyl alcohol) content: 45% - 55%

C18 (Stearyl alcohol) content: 45% - 55%

CHEMICAL AND PHYSICAL SPECIFICATIONS	
Molecular Weight	512.93 g/mol
Physical State	Solid
Organoleptic Properties	White flakes (at 20°C)
Solubility	Insoluble in water
Partition coefficient (Log Pow)	-
pH	-
Nanomaterials	NO

Comments:
This ingredient is mainly constituted by two compounds, which molecular weights and partition coefficients are represented in the table below:

Compound	Molecular weight (g/mol)	Partition Coefficient
Stearyl alcohol	270.49	8.4
Cetyl alcohol	242.44	7.3

IMPURITIES AND/OR ALLERGEN SUBSTANCES
This ingredient does not contain impurities and/or allergen substances.

2.2 Stability and reactivity of the raw materials

White Oil Light

Stability and Reactivity
Mineral oil should be stored in an airtight container, protected from light, in a cool, dry place. The contact with strong oxidizing agents, O_2 and Cl_2 should be avoided. Mineral oil undergoes oxidation when exposed to heat and light. Oxidation begins with the formation of peroxides, exhibiting an "induction period". Under ordinary conditions, the induction period may take months or years. However, once a trace of peroxide is formed, further oxidation is autocatalytic and proceeds very rapidly. Oxidation results in the formation of aldehydes and organic acids, which impart taste and odor. Stabilizers may be added to retard oxidation, being butylated hydroxyanisole, butylated hydroxytoluene and alpha tocopherol the most commonly used antioxidants.

Myritol 318

Stability and Reactivity
This substance is stable under normal conditions of use. Should be stored in well-closed recipients, protected from moisture, in well-ventilated place at temperatures below 30°C.

Glycerin 4810

Stability and Reactivity
Store at room temperature in a clean and aerated place. For bulk storage, it is recommended to keep the product in nitrogen flushed tanks. This ingredient is hygroscopic. It decomposes by temperature rise, releasing corrosive, toxic vapors (acrolein). It may form CO and CO2 in case of combustion. It can polymerize by increase of temperature. Reacts violently with (strong) oxidizing agents and with (some) acids (increased) with risk of fire or explosion. Avoid heat sources, oxidizing agents, strong acids and strong alkalis. The container must be kept in a well-ventilated space at room temperature and protected from direct sun light. Storage material: steel, aluminium, iron or glass.

Tegin Pellets

Stability and Reactivity
It is stable under normal conditions. No hazardous reactions or decomposition products when properly stored and handled.

Goma xantana

Stability and Reactivity
Stable under normal storage and handling conditions. Aqueous solutions are stable over a wide pH range (pH 3–12), although they demonstrate maximum stability at pH 4–10 and temperatures of 10–60°C. Xanthan gum solutions of less than 1% w/v concentration may be adversely affected by higher than ambient temperatures: for example, viscosity is reduced. Xanthan gum provides the same thickening, stabilizing, and suspending properties during long-term storage at elevated temperatures as it does at ambient conditions. In addition, it ensures excellent freeze–thaw stability. Solutions are also stable in the presence of enzymes, salts, acids, and bases. Xanthan gum is an anionic material and is not usually compatible with cationic surfactants, polymers, or preservatives, as precipitation occurs. Anionic and amphoteric surfactants at concentrations above 15% w/v cause precipitation of xanthan gum from a solution. Under highly alkaline conditions, polyvalent metal ions such as calcium cause gelation or precipitation; this may be inhibited by the addition of a glucoheptonate sequestrant. The presence of low levels of borates (Store in a covered, well-ventilated place in the original packaging unopened. This ingredient will not undergo hazardous polymerization. Avoid the formation of dust when handling and avoid head, sparks and all possible sources of ignition (spark or flame). Take precautionary measures against electrostatic discharges. To avoid fire or explosion, dissipate static electricity during transfer by grounding and bonding containers and equipment before transferring material. Prevent dust accumulation. Reactive or incompatible with the following materials: oxidizing materials. There is the risk of combustion when in contact with: carbon dioxide and carbon monoxide. Avoid draining containers in the presence or near flammable vapors.

Água Termal das Termas de Chaves

Stability and Reactivity
This water is stable for one month after its abstraction, when kept in a tightly closed HDPE bottle, at room temperature

Sabowax CS 20

Stability and Reactivity
No decomposition if used according to specifications. The contact with strong acids, oxidizers and bases must be avoided. Suitable materials are: polyethylene (PE) resin, phenol-epoxy EHD0022, Oven-varnish R 78433 and High density polyethylene (HDPE). Store at temperatures below 30 °C, protected from moisture. The product melts above 35 °C. Should be kept away from heat, sparks, open flames and hot surfaces. It has to be stored in a cool place in closed original container. Depending on the temperature, the pH value may decrease during storage. However, the product quality is not negatively influenced above a pH value of 4.0.

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Stability and Reactivity
Keep the product in a tightly closed container, in a dry and well-ventilated place. Keep the product away from ignition sources and protected from light. Incompatible with strong reducing agents, azo and diazo compounds, hydrazines, nitrides, caustics, strong oxidizing agents, epoxides and acids. During combustion, carbon monoxide and unidentified

organic compounds may be formed.

Phenonip ME

Stability and Reactivity
Phenonip ME remains fully stable over a wide pH range from 3- 8. The product must be protected from excessively high temperatures during storage. This mixture may react with oxidant agents and strong oxidant agents.

Acido Clorhídrico 37% grado técnico

Stability and Reactivity
This mixture is stable under normal conditions. Store in well-closed recipients at room temperature, in well-ventilated area. Do not store in metallic recipients. The contact with several materials must be avoided: aluminium, amines, carbons, fluor, alkaline metals, strong bases, halogenates, concentrated sulfuric acid, metalloid oxides. aldehydes.

SABONAL C1618 50/50

Stability and Reactivity
Store in a cool, dry and well ventilated area. Hazardous polymerization will not occur. Incompatible with strong oxidizing materials. Hazardous decomposition products are oxides of carbon (CO, CO2).

2.3 Physical/chemical characteristics of the cosmetic product

	Specifications	**Method**
Organoleptic Properties	White homogeneous emulsion with characteristic odour of the fragrance	Sensorial analysis
pH	5.5 - 6.0	Potentiometer
Viscosity	20000 – 30000 cP	Viscometer (T=25º; t=1min; v=12RPM; Spindle R5)
Specific gravity	-	-
Comments: No Comments		

2.4 Stability of the cosmetic product

At the time of this report, a long term stability study of the product DERMOCOSMÉTICA TERMAL AQUAE CREME HIDRATANTE ROSTO is under course. This product has the same formula of the product under evaluation in this report, DERMOCOSMÉTICA TERMAL AQUAE CREME HIDRATANTE CORPORAL. Samples will be stored at room temperature in the final packaging for 30 months and physical-chemical analysis will be performed after 3 months, 6 months and 30 months. Moreover, the experimental determination of PAO is also being performed to confirm the theoretically estimated value of 14 months. The theoretical estimation of the PAO of the product was performed according to the guidelines "Recommandations relatives a l'estimation de la Period Apres Ouverture (PAO)", from the "Agence Française de securité sanitaire de produits de santé".

3. Microbiological quality

3.1 Microbiological specifications of the raw materials

White Oil Light

The microbiological specifications for this ingredient are not known.

Myritol 318

The microbiological specifications for this ingredient are unknown.

Glycerin 4810

The microbiological specifications for this ingredient are unknown.

Tegin Pellets

The microbiological specifications for this ingredient are unknown.

Goma xantana

The microbiological specifications for this ingredient are:

Total Plate Count: 1000/g maximum

E. Coli: negative/25g

Coliforms: negative per MPN

Salmonella: negative/25g

Pseudomonas aeruginosa: negative/g

Staphylococcus aureus: negative/g

Enterococcus faecalis: negative/ g

Moulds: maximum 50 CFU/g

Yeasts: 50 /g CFU maximum

Xanthomonas campestris: negative/ g

Água Termal das Termas de Chaves

The microbiological specifications for this ingredient are:

Clostridium sulfite reducers: 0 CFU / 50 mL

Fecal coliforms: 0 CFU / 250 mL

Total coliforms: 0 CFU / 250 mL

Enterococci: 0 CFU / 250 mL

Escherichia coli: 0 CFU / 250 mL

Total viable count (22 ° C): < 100 CFU/ml

Total viable count (36 ° C): < 20 CFU/ml

Pseudomonas aeruginosa: 0 CFU / 250 mL

Staphylococcus Coagulase (+): 0 CFU / 100 mL

Sabowax CS 20

The microbiological specifications of this ingredient are not known.

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The microbiological specifications for this ingredient are unknown.

Phenonip ME

The microbiological specifications for this ingredient are not known. However, once it is a preservative agent, microbiological contamination is not expected to occur.

Acido Clorhídrico 37% grado técnico

The microbiological specifications for this mixture are not known. Nevertheless, the pH of this raw material is very low, therefore microbial contamination is unlikely to occur.

SABONAL C1618 50/50

The microbiological specifications for this ingredient are not known.

3.2 Microbiological characteristics of the final cosmetic product

The microbiological specifications for this product are:
- Bacteria: < 50 CFU/g;
- Yeast and Mold: < 50 CFU/g;
- *Candida albicans*: absent;
- *Staphilococus aureus*: absent;
- *Pseudomonas aeroginosa*: absent

3.3 Results of preservation challenge test

The formula of the product DERMOCOSMÉTICA TERMAL AQUAE CREME HIDRATANTE CORPORAL is the same as the formula of DERMOCOSMÉTICA TERMAL AQUAE CREME HIDRATANTE ROSTO. A challenge test according to European Pharmacopoeia 8 was performed to evaluate the efficacy of the preservative system of the cosmetic product Creme de Rosto, which was not the final formula of DERMOCOSMÉTICA TERMAL AQUAE CREME HIDRATANTE ROSTO. Nevertheless, the preservative system was not altered and the differences in the other ingredients are minimal, therefore the results of this Challenge Test can be considered valid.

The following microorganisms were included in the assay and incubated in the coditions as described:

Staphylococcus aureus ATCC 6538 - 35º C, 2 days
Pseudomonas aeruginosa ATCC 9027 - 35º C, 2 days
Candida albicans ATCC 10231 - 25º C, 2 days
Aspergillus brasiliensis ATCC 16404 - 25º C, 5 days

The test product was inoculated separately with each one of the test microorganisms at a ratio of 200 µL calibrated cell suspension to 20 g of test product. The results of the challenge test are shown in the table below:

Microorganisms	**2 days (CFU)**	**2 days (Δlog)**	**7 days (CFU)**	**7 days (Δlog)**	**14 days (CFU)**	**14 days (Δlog)**	**28 days (CFU)**	**28 days (Δlog)**	**Criteria**
S. aureus ATCC 6538	4.72E+05	0.24	4.46E+04	1.27; N/I *	0	5.92; N/I*	0	5.92; N/I*	B
P. aeruginosa ATCC 9027	0	6.09	0	6.09; N/I *	0	6.09; N/I*	0	6.09; N/I*	A
C. albicans ATCC 10231	---	---	---	---	0	5.28; N/I*	0	5.28; N/I*	A
A. brasiliensis ATCC 16404	---	---	---	---	0	4.85	0	4.85; N/I*	A

- N/I – No increase

The study performed with the sample of product "Creme de Rosto" allows to conclude that the product meets criteria B of European Pharmacopoeia 8, and therefore the product is protected against microbial proliferation which could pose a potential risk for the consumer. Since the formula of DERMOCOSMÉTICA TERMAL AQUAE CREME HIDRATANTE CORPORAL is equivalent, it can be assumed that it will have the same profile.

4. Impurities, traces, information about the packaging material

4.1 Impurities of the Raw Materials

Besides the possible impurities that this cosmetic product may contain, it is also included in this section all its allergen substances.

IMPURITIES AND/OR ALLERGEN SUBSTANCES	
Impurity/Allergen substance	**Total Concentration (%)**
iron	0.00002
Halogenated compounds	0.00009
Chlorides	0.00003
Sulfate	0.00002
1,4-Dioxane	unknown
Heavy metals	0.00002
Ethylene oxide	unknown
Alpha-Isomethyl Ionone	0.00490
Benzyl Alcohol	0.00100
Benzyl Benzoate	0.00001
Benzyl Salicylate	0.00423
Butylphenyl Methylpropional	0.00391
Citral	0.000001
Citronellol	0.00109
Coumarin	0.00164
Eugenol	0.00100
Geraniol	0.00315
Hexyl Cinnamal	0.00664
Hydroxycitronellal	0.00191
Hydroxyisohexyl 3-Cyclohexene Carboxaldehyde	0.00055
Isoeugenol	0.00091
Linalool	0.00300
Aluminium	0.000001
Arsenic	0.00001
Lead	0.00002
Mercury	0.0000003
Limonene	0.000004
Selenium	0.000001
Nitrogen	0.00450
Silver	0.00000001
Boron	0.00005
Barium	0.00003
Beryllium	0.000001
Cadmium	0.0000003
Cobalt	0.0000001
Chromium	0.000001
Copper	0.00000003
Cesium	0.00003
Manganese	0.000003

Molybdenum	0.0000001
Nickel	0.000001
Rubidium	0.00004
Antimony	0.0000002
Tin	0.00000002
Tantalum	0.000000001
Tellurium	0.0000001
Thallium	0.000001
Uranium	0.00000002
Vanadium	0.00000004
Tungsten	0.000003
Zinc	0.000002
Zirconium	0.0000001
Ammonium	0.00002
Isopropanol	0.00015
Diethylene glycol	0.00300
Bismuth	0.000000004
Yttrium	0.000000001
Niobium	0.000000004

4.2 Traces of prohibited compounds in the cosmetic product

Some impurities present in this product are in the list of substances prohibited in cosmetic products (Annex II of the Regulation EC 1223/2009). However, according the article 17 of the same regulation, the non-intended presence of a small quantity of a prohibited substance, stemming from impurities of natural or synthetic ingredients, the manufacturing process, storage, migration from packaging, which is technically unavoidable in good manufacturing practice, shall be permitted provided that such presence is in conformity with Article 3, when used under normal or reasonably foreseeable conditions of use. The presence of these traces is technically unavoidable, even following good manufacturing practices, because they are impurities of raw materials used and they are: Arsenic (present in Goma xantana, Água Termal das Termas de Chaves and Acido Clorhídrico 37% grado técnico); Lead (present in Goma xantana, Água Termal das Termas de Chaves and Acido Clorhídrico 37% grado técnico); Mercury (present in Goma xantana and Água Termal das Termas de Chaves); Cadmium (present in Goma xantana and Água Termal das Termas de Chaves); Diethylene glycol (present in Glycerin 4810); Selenium, Beryllium, Chromium, Nickel, Antimony, Thallium and Zirconium (present in Água Termal das Termas de Chaves).

The substances 1,4-dioxane and Ethylene Oxide may be present in the raw material Sabowax CS 20, although it is not mentioned by the supplier.

It is also important to point out that one of these substances has carcinogenic, mutagenic or reproductive potential, being listed in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labeling of hazardous substances):

- 1,4-Dioxane - Carcinogenic Category 2
- Ethylene Oxide - Mutagenicity toxicity and Carcinogenic Category 1B
- Lead - Reproductive toxicity Category 1A
- Mercury – Reproductive toxicity Category 1B
- Beryllium - Carcinogenic Category 1B

- Cadmium - Mutagenicity and reproductive toxicity Category 2
- Nickel - Carcinogenic Category 2.

4.3 Characteristics of the packaging material

According to the information provided, the packaging of this product which is in contact with the cosmetic product is composed of: a flask, provided by Eurovetrocap S.r.l., under the trade name Cllindro Alto 200 ml Bocca 24/410 EV; a dispenser, provided by Eurovetrocap S.r.l., under the trade name Erogatore Svizzero Per Pompe 24/410 & 24-M 500 mcl and a pump, provided by Eurovetrocap S.r.l., under the trade name Pompa 24-M 500 mcl Plastica Assieme.

The tube is made of HPDE (High Density Polyethylene), supplied by SABIC SALES Europe B.V., under the trade name SABIC® HDPE, SABIC® Vestolen A - granular and SABIC® HDPE B5421.

The cap is made of SAN (Styrene Acrylonitrile copolymer), supplied by Versalis S.p.A., under the trade name Kostil B 266.

The dispenser is made of PP (Polypropylene), supplied by Carmel Olefins Ltd., under the trade name Capilene QT 80 A.

The pump is composed of several parts as follows:

Stem	POM
Spring	TPE
Sphere	Stainless Steel
Seal	EPE / PE-EVA

The stem is made of Polyoxymethylene, supplied by Ticona, under the trade name HOSTAFORM C27021, CF2001, NATURAL.

The spring is made of stainless steel with coated surface, supplied by Trafilerie Brambilla, under the trade name ST 302 SGB.

The sphere is made of Stainless steel, supplied by R.G.P. International S.r.l., under the trade name AISI 304.

The seal is made of Expanded polyethylene and Ethylene vinyl acetate copolymer, supplied by Tekni-Plex Europe N.V., under the trade name Tri Seal F-217-4.

A 30-month stability study in the final packaging is being performed and results of product-packaging material compatibility will be assessed.

5. Normal and reasonably foreseeable use

Mode of application	The product is rubbed-on the body
Warnings	-
Comments: -	

6. Exposure to the cosmetic product

Product type	Leave-on
Retention factor	1.00
Site of application	Body
Amount of product applied per application (mg)	7392.00
Duration of use	Undetermined
Normal and reasonably foreseeable exposure route(s)	Topical
Routes of secondary exposure	-
Targeted (or exposed) population(s)	Healthy adults
Possible impacts on exposure due to particle sizes	This product does not contain nanomaterials that can affect human health

Calculation of the Exposure	
mg/day	7392.00
mg/cm2 skin/day	0.47
mg/kg body weight/day	123.20

7. Exposure to the raw materials

		Calculation of the Exposure		
Raw material (trade name)	**Conc. (%)**	**mg/day**	**mg/cm2 skin/day**	**mg/kg body weight/day**
White Oil Light	5.00000	369.6000	0.0235	6.1600
Myritol 318	8.00000	591.3600	0.0376	9.8560
Glycerin 4810	3.00000	221.7600	0.0141	3.6960
Tegin Pellets	8.00000	591.3600	0.0376	9.8560
Goma xantana	0.30000	22.1760	0.0014	0.3696
Água Termal das Termas de Chaves	72.70000	5 373.9840	0.3417	89.5664
Sabowax CS 20	1.00000	73.9200	0.0047	1.2320
1051936 NIVAL	0.10000	7.3920	0.0005	0.1232
Phenonip ME	1.20000	88.7040	0.0056	1.4784
Acido Clorhídrico 37% grado técnico	0.40000	29.5680	0.0019	0.4928
SABONAL C1618 50/50	2.00000	147.8400	0.0094	2.4640

8. Toxicological profile of the substances/raw materials and other information

8.1 Toxicological profile of the substances (INCI name)

Paraffinum Liquidum

REGULATORY RESTRICTIONS
According to the Regulation EC 1223/2009 and respective amendments, there are no restrictions on the use of this ingredient in cosmetic products.

ACUTE TOXICITY

Administration Route	Adverse effects description	LD50	Ref.
Oral	Daily doses of up to 45mL have been administered orally, while doses of up to 120mL have been used as an enema. However, excessive dosage of mineral oil can result in anal seepage and irritation, and its oral use as a laxative is not considered desirable. It may cause diarrhea. If large amounts are ingested, and vomiting occurs, may be aspirated during vomiting, which can cause chemical pneumonitis or pulmonary edema, with serious lung damage, or even death.	(mouse): 22 g/kg; (rat): > 2000 mg/Kg (rabbit) > 5g/Kg	1,2,3,4
Inhalation	The most serious adverse reaction to mineral oil is lipoid pneumonia caused by aspiration of the oil. Mineral oil can enter the bronchial tree without eliciting the cough reflex. Negligible hazard up to 38°C. At temperatures above, it may form vapors irritating and harmful to upper respiratory tract.	-	5,3
Dermal	It is normally considered as not dangerous for the skin.	-	2
Subcutaneous	-	-	

Comments:
Mineral oil is used as an excipient in a wide variety of pharmaceutical formulations. It is also used in cosmetics and in some food products. Therapeutically, mineral oil has been used in the treatment of constipation, as it acts as a lubricant and stool softener when taken orally. Moreover, it is used in ophthalmic formulations for its lubricant properties **(4)** .

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	It shows low toxicity. May cause irritation to sensitive people to the components of the formula.	1,3
Ocular Irritation	It may cause eye irritation.	3
Sensitization	Given its widespread use in many topical products, mineral oil has been associated with few instances of allergic reactions.	4
Dermal Absorption	Data support the view that mineral oil does not effectively penetrate the skin beyond the stratum corneum, resulting in minimal (< 1 %) absorption of white mineral oils after topical exposure.	6

Comments:
-

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.
Oral	Chronic oral consumption of mineral oil may impair the appetite and interfere with the	4

	absorption of fat-soluble vitamins. Prolonged use should be avoided.	
Inhalation	Long term inhalation studies indicate that this oil has a low chronic toxicity. On the other hand, repeated prolonged exposures have resulted in lung inflammatory reactions and lipoid granuloma formation.	7
Dermal	-	

Comments:
May cause drowsiness and loss of consciousness **(1)** .

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY

		Ref.
Carcinogenicity	In groups of 30 rats of strains BDI, BD111, and W (sex unspecified) that received 2% liquid paraffin in the diet (total dose, 136 mg/animal in 500 days), no significant tumor induction was reported.	7
Mutagenicity	There is no data available on the mutagenic effects of this ingredient.	
Teratogenicity	Groups of 25 chickens with 9 day old chicken embryos were exposed to 10 or 20 microL pharmaceutical mineral oil on the eggshell. There were no mortalities or embryos with edema, ascites or liver lesions in either treated group. No histological changes were observed in the livers or kidneys. However embryos exposed to 20 microL mineral oil had slight dilation of the heart. Body wt, liver wt, crown-rump length, and body wt/crown-rump length ratio of the embryos exposed to mineral oil did not differ from those of controls. Hypoprothrombinemia and hemorrhagic disease of the newborn has occurred when mineral oil was chronically administered orally to pregnant women.	7

Comments:
-

PHOTO-INDUCED TOXICITY

There is no data available on the photo-toxic effects of this ingredient.

Ethylparaben

REGULATORY RESTRICTIONS

This ingredient is listed in Regulation EC 1223/2009 annex V (list of preservatives which cosmetic products may contain). According to this Regulation and respective amendments, the use of this paraben in cosmetic products is restricted to a maximum concentration of 0.4% (as acid) for single ester, and 0.8% (as acid) when a mixture of esters is used. CIR (Cosmetic Ingredient Review) considers that this compound is safe when applied in the above-mentioned concentrations.

ACUTE TOXICITY

Administration Route	Adverse effects description	LD50	Ref.
Oral	Ingestion of a 0.03% aqueous ethylparaben solution caused irritation to the intestinal mucosa.	(rat, female): 4.30 g/kg; (rat): 11.0 g/kg; (guinea pig): 2.0 g/kg; (rabbit): 5.0 g/kg; (mouse): 3.0 g/kg; (dog): 5.0 g/kg	8
Inhalation	-	-	
Dermal	It may cause human skin irritation.	(rabbit): 15.0 g/kg	8
Subcutaneous	-	-	

Comments:
Ethylparaben is widely used as an antimicrobial preservative in cosmetics, food products, and pharmaceutical formulations. It may be used either alone or in combination with other paraben esters or with other antimicrobial agents. In cosmetics it is one of the most frequently used preservatives. **(4)** Acute toxicity studies in animals indicate that Parabens are not significantly toxic by various routes of administration. **(9)**

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	Ethylparaben was a skin irritant in man.	8
Ocular Irritation	Ethylparaben at 100% instilled into the eyes of albino rabbits was slightly irritating and at	8

	10% in water produced no signs of irritation. Parabens are often incorporated in creams, lotions and ointments that may be used in the region of the eyes, and occasionally cause redness and swelling of eyelids from allergic contact dermatitis.	
Sensitization	Systemically, no adverse reaction to parabens have been reported, although they have been associated with hypersensitivity reactions, generally of the delayed type and appearing as contact dermatitis. Parabens are capable of inducing cutaneous allergic responses, however, given the widespread use of parabens as preservatives, such reactions are relatively uncommon.	10,4
Dermal Absorption	There are evidences of parabens being rapidly absorbed by animal and human skin. However, available in vitro dermal absorption study results point towards a potential difference in dermal absorption between rat and man. Consequently the rat data as such cannot be simply extrapolated to the human situation without additional supportive data. Nevertheless, until a properly conducted dermal absorption and toxicokinetic study in humans will allow the assignment of a more scientifically solid value, the SCCS will use a dermal absorption value of 3.7% in its margin of safety calculations.	11
Comments: -		

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.
Oral	Chronic oral studies indicate that Parabens are practically non-toxic.	9
Inhalation	-	
Dermal	-	
Comments: -		

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY

		Ref.
Carcinogenicity	Ethylparaben in the diet produced cell proliferation in the forestomach of rats.	9
Mutagenicity	At a concentration of 10 mmol/L, ethylparaben was mutagenic in Escherichia coli. Numerous genotoxicity studies, including Ames testing, dominant lethal assay, host-mediated assay, and cytogenic assays, indicate that Parabens are generally non-mutagenic, although ethylparaben did increase chromosomal aberrations in a Chinese Hamster ovary cell assay.	8,9
Teratogenicity	Ethylparaben was non teratogenic in rats.	9
Comments: -		

PHOTO-INDUCED TOXICITY

In general, parabens do not exhibit significant levels of photo-contact sensitization or photo-toxicity. **(4)**

Methylparaben

REGULATORY RESTRICTIONS

This ingredient is listed in Regulation EC 1223/2009 annex V (list of preservatives which cosmetic products may contain). According to this Regulation and respective amendments, the use of this paraben in cosmetic products is restricted to a maximum concentration of 0.4% (as acid) for single ester, and 0.8% (as acid) when a mixture of esters is used. CIR (Cosmetic Ingredient Review) considers that this compound is safe when applied in the above-mentioned concentrations. CIR (Cosmetic Ingredient Review) considers that this compound is safe when applied in the above-mentioned concentrations.

ACUTE TOXICITY

Administration Route	Adverse effects description	LD50	Ref.
Oral	No toxic effects were observed in animal assays.	(dog): 3.0 g/kg; (dog): 12.2 g/kg; (rabbit): 6 g/kg; (rat): 2.0 g/kg; (mouse):	10,12,4

		> 8 g/kg; (male rat): > 3200 mg/kg; (female rat): > 2280 mg/kg	
Inhalation	-	-	
Dermal	Slightly hazardous in case of skin contact (may cause contact dermatitis).	-	10,4
Subcutaneous	-	(mouse): 1.20 g/kg	4

Comments:
Methylparaben is widely used as an antimicrobial preservative in cosmetics, food products, and oral and topical pharmaceutical formulations. It may be used either alone or in combination with other parabens or with other antimicrobial agents. In cosmetics, methylparaben is the most frequently used antimicrobial preservative **(4)** . Acute toxicity studies in animals indicate that Parabens are not significantly toxic by various routes of administration **(9)** .

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	Parabens are practically non-irritating in the population with normal skin, however, methylparaben (Isocide MP) can cause skin irritation.	12,9
Ocular Irritation	It can cause irritation. Parabens are often incorporated in creams, lotions and ointments that may be used in the region of the eyes, and occasionally cause redness and swelling of eyelids from allergic contact dermatitis.	8,12
Sensitization	When tested on guinea pigs, methylparaben did not induce sensitization effects. No sensitization was reported on a HRIPT (Human Repeated Insult Patch Test) with 50 subjects. Parabens are capable of sensitizing skin and inducing cutaneous allergic responses, although incidence of such reactions is low. Hypersensitivity reactions to parabens, generally of the delayed type and appearing as contact dermatitis, have been reported. However, given the widespread use of parabens as preservatives, such reactions are relatively uncommon.	10,4
Dermal Absorption	There are evidences of parabens being rapidly absorbed by animal and human skin. However, available in vitro dermal absorption study results point towards a potential difference in dermal absorption between rat and man. Consequently the rat data as such cannot be simply extrapolated to the human situation without additional supportive data. Nevertheless, until a properly conducted dermal absorption and toxicokinetic study in humans will allow the assignment of a more scientifically solid value, the SCCS recommends a dermal absorption value of 3.7% in its margin of safety calculation.	11

Comments:
-

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.
Oral	A chronic oral toxicity study in which methylparaben was incorporated into diets at 2 or 8% and the diets fed to groups of 24 rats for 96 weeks was performed. At 2% of the diet, parabens exerted no toxic effect. Rats killed at the conclusion of the feeding test had no treatment related abnormalities. Weanling dogs were dosed 1 g/kg/day methylparaben for 378 to 422 days; and three other dogs, 0.5 g/kg/day methylparaben for 318 to 394 days. No toxicity to the paraben was observed. All animals were in excellent condition throughout the experiment. All tissues were normal. Chronic oral studies indicate that Parabens are practically non-toxic.	10,9
Inhalation	-	
Dermal	-	

Comments:
-

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY

		Ref.
Carcinogenicity	Methylparaben was non-carcinogenic when injected subcutaneously in mice or rats or when administered intravaginally in rats. Although some concern was raised about possible carcinogenic effects of parabens when used in underarms products, the SCCS concluded that there was insufficient data to establish a link between the use of underarm cosmetics and	9,11

	breast cancer.	
Mutagenicity	Numerous genotoxicity studies, including Ames tests, dominant lethal assay, host-mediated assay and cytogenic assays, indicate that Parabens are generally non-mutagenic, although Methylparaben did increase chromosomal aberrations in a Chinese Hamster ovary cell assay.	9
Teratogenicity	Methylparaben was non-teratogenic in rabbits, rats, mice, and hamsters.	9
Comments: -		

PHOTO-INDUCED TOXICITY
In general, parabens do not exhibit significant levels of photo-contact sensitization or photo-toxicity **(4)** .

Phenoxyethanol

REGULATORY RESTRICTIONS
This ingredient is listed in the Regulation EC No. 1223/2009 annex V (List of preservatives which cosmetic products may contain). According to this Regulation and respective amendments the use of this ingredient in cosmetic products is restricted to a maximum concentration of 1%. CIR (Cosmetic Ingredient Review) considers that this ingredient is safe as used up to 1%.

ACUTE TOXICITY

Administration Route	Adverse effects description	LD50	Ref.
Oral	Phenoxyethanol is practically non-toxic when administered orally to rats. Although it may cause gastrointestinal irritation with symptoms like nausea, vomiting and diarrhea.	(rat, male): 1.26 ml/kg; (rat, female): 2.33 ml/kg; (mouse): 933 mg/kg; (rat): 1840 mg/kg	13,14,15,16
Inhalation	At room temperature, exposure to vapor is minimal due to low volatility. Vapor from heated material may cause respiratory tract irritation and other effects.	(rat): 1mg/L (6 hours, aerosol)	14
Dermal	Phenoxyethanol is practically non-toxic when dermally administered to rats. Allergic contact dermatitis to 1% phenoxyethanol could be a rare possibility in patients having an adverse reaction to aqueous creams.	(rabbit): > 545 mg/kg; (rat): > 2250 mg/kg – 14000 mg/kg; (rat): 14391 mg/kg	13,14,15
Subcutaneous	-	-	

Comments:
Phenoxyethanol is an antimicrobial preservative used in cosmetics and topical pharmaceutical formulations at a concentration of 0.5–1.0%. It may also be used as a preservative and antimicrobial agent for vaccines. Therapeutically, a 2.2% solution or 2.0% cream has been used as a desinfectant for superficial wounds, burns, and minor infections of the skin and mucous membranes. Phenoxyethanol produces a local anesthetic effect on the lips, tongue, and other mucous membranes **(4)** .

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	Phenoxyethanol at 2.0% was a slight irritant to rabbit skin, but it was not irritant to guinea pig skin. Phenoxyethanol at 10% in mineral oil is not considered a primary nor a cumulative irritant, but the pure material is a moderate irritant to the skin. Contact urticaria has been reported upon exposure to 2-phenoxyethanolcontaining cosmetics. The US FDA has recommended avoiding at least one topical product containing phenoxyethanol due to concerns over inadvertant exposure to nursing infants.	16,17
Ocular Irritation	Undiluted phenoxyethanol was a strong eye irritant, but was non-irritating when tested at 2.2%. Phenoxyethanol diluted to 5% was applied to the conjunctival sac of rabbits, and induced a mild irritation of the conjunctivae. It may cause moderate eye irritation and moderate corneal injury.	18,14,16
Sensitization	Phenoxyethanol was not a sensitizer to guinea pig skin and did not cause delayed hypersensitivity in clinical studies (HRIPT with 51 subjects, with phenoxyethanol at 10%v/v).	18,14,16

	A modified repeated insult patch test (138 subjects) with phenoxyethanol at 10% and patch tests with the ingredient at 5% indicated no skin reactions consistent with allergic sensitization. It did not cause allergic skin reactions when tested in guinea pigs and in humans.	
Dermal Absorption	It has previously been shown that skin has the capacity for local metabolism of applied chemicals. Therefore, there is a requirement to consider metabolism during dermal absorption of these compounds (glycol ethers) in risk assessment for humans. AFSSAPS (Agence Française de Sécurité Sanitaire des Produits de Santé) considers 80% of dermal absorption of phenoxyethanol in leave-on products and 40% in rinse-off products.	15,16
Comments: -		

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.
Oral	Similar effects to those of acute ingestion are expected.	19
Inhalation	Repeated or prolonged inhalation of vapors may lead to chronic respiratory irritation.	20
Dermal	Phenoxyethanol was applied dermally to 10 female New Zealand White rabbits at a dose of 1000 mg/kg/day for 14 days. Seven of the rabbits died between days 5 and 8 of treatment. The prominent hematologic change noted in these rabbits was indicative of the breakdown of erythrocytes. There were no hematologic changes noted in the three surviving rabbits. In a more recent study, 2000 mg/kg undiluted phenoxyethanol (cosmetic grade) was applied to the shaved and abraded skin of four New Zealand White rabbits, remaining in place for 24 hours, followed by a 14-day observation period and necropsy, no systemic toxicity or adverse effects were noted, except for slight skin irritations on the application site. Excessive exposure may cause hemolysis, thereby impairing the ability of the blood to transport oxygen.	14,15,16

Comments:
Long-term exposure to phenoxyethanol may result in Central Nervous System toxic effects similar to other organic solvents **(4)** .

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY

		Ref.
Carcinogenicity	There is no data available on the carcinogenic effects of this ingredient.	
Mutagenicity	Phenoxyethanol was non-mutagenic in the Ames test, with and without metabolic activation. In vitro genetic toxicity studies were negative. Animal genetic toxicity studies were negative.	18,14,16
Teratogenicity	In dermal treatment studies, phenoxyethanol was neither teratogenic, embryotoxic, nor fetotoxic at doses which were maternally toxic. A fetotoxic and teratogenic evaluation of 2-phenoxyethanol was performed with rabbits following dermal exposure. Dermal application of 1000 mg/kg/day produced maternal toxicity and maternal toxicity was also observed in rabbits treated with 600 mg 2-phenoxyethanol/kg/day but at a lower incidence. No signs of maternal toxicity were seen at 300 mg/kg/day. Examination of rabbit fetuses indicated that, at the dosages tested, 2-phenoxyethanol was not embryotoxic, fetotoxic, or teratogenic. It did not cause birth defects or other effects in the fetus even at doses which caused toxic effects in the mother. Moreover, in animal studies, repeated exposure did not have any effects on reproductive organs.	14,19,16

Comments:
This product may contain an impurity, Phenol, that is Mutagenic Category 2 in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labelling of hazardous substances). This product may contain an impurity, ethylene oxide, that is classified as 1B regarding its Carcinogenic and Mutagenic toxicity in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labelling of hazardous substances).

PHOTO-INDUCED TOXICITY

Phenoxyethanol was not photo-toxic in clinical studies **(16)** .

Caprylic/Capric Triglyceride

REGULATORY RESTRICTIONS

According to the Regulation EC 1223/2009 and respective amendments there are no restrictions on its use. CIR (Cosmetic Ingredient Review) considers that caprylic/capric triglyceride is safe as used up to 84%.

ACUTE TOXICITY

Administration Route	Adverse effects description	LD50	Ref.
Oral	Adverse effects including abdominal pain and diarrhea were reported by patients consuming diets based on medium-chain triglycerides. In one test on mice, lethargy and ataxia occurred within ten minutes after the administration of 25 ml/k 8 and dyspnea was noted in some animals within one hour. All animals appeared asymptomatic at the end of the first day and no deaths were reported. In the second mouse test, ataxia, lethargy, dyspnea, and diuresis occurred within 15 minutes, and in several animals complete loss of activity was observed within two hours. Following the two highest doses, three deaths occurred in 24 to 48 hours. All symptoms disappeared in the survivors by the end of the third day. No necropsy observations were reported from either tests. From the results of these tests it may be concluded that the acute oral LD50 in female mice is higher than 25 ml/kg.	(mouse): 29.6 g/kg; (rat): 33.3 g/kg (rat): 10g/Kg	21,4
Inhalation	Male rats and guinea pigs in groups often each were exposed for six hours in a 40-liter chamber containing an aerosol of Caprylic/Capric Triglyceride. The fraction of the aerosol with particles small enough to be inhaled into the lung. Three controls of each species were sham exposed. Observation during the exposure and for 14 days thereafter revealed no symptoms, abnormal behavior, or effects on body weight. One hour after the exposure, three animals and one control of each species were sacrificed for pathological examination, and the remaining test animals were sacrificed at 14 days. No gross or microscopic defects attributable to the substance were reported. Examination of the respiratory tract for adverse effects, including the detection of accumulated oil droplets, gave negative results.	-	21
Dermal	-	-	
Subcutaneous	-	-	

Comments:
Medium-chain triglycerides are used in a variety of pharmaceutical formulations including oral, parenteral, and topical products, and are generally regarded as essentially non-toxic and non-irritant materials **(4)** . In acute toxicology studies in animals and humans, no irritant or other adverse reactions have been observed **(4)** . In humans, administration of 0.5 g/kg body-weight medium-chain triglycerides to healthy individuals produced no change in blood or serum triglycerides compared to subjects receiving the same dose of the long-chain triglyceride triolein **(4)** .

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	Medium-chain triglycerides were patch-tested on more than 100 individuals and no irritation was produced on either healthy or eczematous skin. It is slightly irritating in guinea pigs.	22,21,4,23
Ocular Irritation	Medium-chain triglycerides are not irritating to the eyes. The product was applied 3 times in a Draize Test. It caused slight redness after the first application, which disappeared within 24 hours after the third application. It is not eye irritant for rabbits. Only very small effects or no effects were found. Therefore, Myritol 318 is at the most only very mild, transient irritant to the eye of rabbit. It is non-irritant for humans.	22,4,23
Sensitization	Medium-chain triglycerides exhibit no capacity for induction of hypersensitivity. It is not a	24,21,23

	sensitizer agent for guinea pigs. One hundred and twenty-eight adult males and females were tested with Caprylic/Capric Triglyceride using a modification of the Draize repeated insult patch test. All subjects had little or no irritation and none was sensitized. One subject had barely perceptible erythema at the first reading immediately following the removal of the first patch which had been applied for 48 hours.	
Dermal Absorption	There is no data available for dermal absorption for Caprylic/Capric Triglyceride, but other Medium-chain triglycerides showed little skin penetration in mice and guinea pigs. The CIR Expert Panel recognizes that, reportedly, Triolein and Tricaprylin can enhance the skin penetration of other chemicals, and recommends that care should be exercised in using these and other Glyceryl Triesters in cosmetic products.	25
Comments: -		

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.
Oral	Chronic toxicology studies in animals have shown no harmful adverse effects associated with medium-chain triglyceride following oral administration. Groups of 15 male and female rats were fed a diet containing 19.6% of a medium-chain triglyceride (75% caprylic acid and 25% capric acid) for 47 weeks. This diet supported normal growth and development, though growth rate was slightly less than that of rats fed conventional dietary fats. At autopsy, the carcass protein, ash levels and organ weights of test rats were similar to those of control rats but there was less carcass fat and smaller epididymal fat pads in the test group. Histological study revealed no abnormalities in intestine and liver.	21,4,23
Inhalation	Chronic toxicology studies in animals have shown no harmful adverse effects associated with medium-chain triglyceride following inhalation administration.	4
Dermal	In dermal irritation testing medium-chain triglycerides exhibit virtually no potential as dermal irritants, even with prolonged skin exposure.	26

Comments:
Six groups of 5 male rats each were injected intraperitoneally with single doses of Caprilic/Capric Triglyceride ranging from 1 to 24mL/Kg. There were no deaths. After doses of 8mL/Kg and higher, the rats showed a lack of appetite and decreased mobility during the first 2 days. Subsequently, the animals became normal in these respects. Necroscopy after 14 days revealed some unabsorbed test material in the stomach area and "slight vascular complications". No histological observations were described. Though no LD50 could be calculated, this test shows that the intraperatonial LD50 of this product in the rat is greater than 24mL/Kg **(23)** .

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY

		Ref.
Carcinogenicity	There is no data available on the carcinogenic effects of this ingredient.	
Mutagenicity	Studies in vivo and in vitro show that this ingredient is not mutagenic. In a S. thyphimurium Reverse Mutation Assay, it did not have mutagenic effects.	22,23
Teratogenicity	There was no evidence that intravenous (iv) or dietary administration of medium-chain triglycerides adversely affected the reproductive performance of rats or resulted in fetal toxicity or teratogenic effects at doses up to 4.28 g/kg body weight/day (iv) or 12500 mg/kg body weight/day (dietary). There was no evidence that dietary administration of medium-chain triglycerides adversely affected the reproductive performance of pigs or resulted in fetal toxicity or teratogenic effects at doses up to 4000 mg/kg body weight/day in the diet.	24

Comments:
In a reproduction study, young adult male and female rats were fed a balanced diet containing 19.6% of a triglyceride of 75% caprylic and 25% capric acid for th tee weeks before mating. Litter size and birth weight of the test animals were similar to those of rats on conventional or low fat diets, but mortality during lactation was somewhat higher, and there was less weight gain due to a smaller volume of milk secreted. After wean in 8, the F1 generation was fed as the F0 generation had been and showed a weight gain comparable to that of control rats on an oleo oil diet **(21)** .

PHOTO-INDUCED TOXICITY

Phototoxic properties were tested on hairless mice with 50% substance. There were no phototoxic properties found **(23)** .

Glycerin

REGULATORY RESTRICTIONS
According to Regulation EC 1223/2009 and respective amendments there are no restrictions on its use in cosmetic products.

ACUTE TOXICITY			
Administration Route	**Adverse effects description**	**LD50**	**Ref.**
Oral	Glycerin is readily absorbed from the intestine and is either metabolized to carbon dioxide and glycogen or used in the synthesis of body fats. Consuming large amounts may cause vomiting, nausea, diarrhea, headache, and hyperglycemia. However, if not ingested in considerable amounts, glycerin presents no hazardous effects on human health.	(mouse): 4100 mg/kg; (guinea pig): 7750 mg/kg; (rat): 12600 mg/kg; (rabbit): 27000 mg/kg	5,27,4
Inhalation	Breathing of small amounts of this material is not likely to cause harmful effects. It may cause irritation of nose, throat and airways.	(rat): > 570 mg/m3 (1 hour)	27
Dermal	It does not cause skin irritation.	(rabbit): > 18700 mg/kg	27
Subcutaneous	Glycerol is more toxic when administered intravenously, intraperitoneally or subcutaneously.	(mouse): 90 mg/kg; (rat): 100 mg/kg	4,28
Comments: This ingredient is used in pharmaceutical oral, topical, ophthalmic and parenteral formulations, besides being also used as a food additive **(4,28)** .			

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY		
		Ref.
Skin Irritation	Not irritant to the skin.	4,28
Ocular Irritation	Glycerin is not irritating to the eyes.	28
Sensitization	Based on the available information, there is no human or animal data that indicates glycerol to be a skin sensitizer. Considering the extensive, widespread dermal exposure to glycerol in preparations repeatedly applied to the skin, the absence of case reports of humans showing skin reactions is consistent with glycerol having a very low skin sensitization potential.	28
Dermal Absorption	This ingredient is absorbed through the skin and is a permeation enhancer.	27,4
Comments: -		

CHRONIC TOXICITY		
Administration Route	**Adverse effects description**	**Ref.**
Oral	Prolonged or repeated ingestion may affect the blood (hemolysis, changes in white blood cell count), endocrine system (changes in adrenal weight), respiratory system, and may cause kidney injury. However, several studies indicate that repeated oral exposure by gavage to glycerol does not induce adverse effects other than local irritation of the gastro-intestinal tract. It was concluded that the NOEL is 10000 mg/kg bw (20% in diet), since at this dose level no systemic or local effects were observed.	5,4,28
Inhalation	In an inhalation study with rats (during 14 days), there was no effect on lung, liver, kidney, brain and heart weight nor any macroscopic findings reported. Histopathologic examination of the respiratory tract, liver, kidneys and heart of controls and high dose animals revealed an increased incidence of minimal to mild squamous metaplasia of the epiglottis in all treated animals. No systemic effects were seen at the highest dose tested 3910 mg/m3. Nevertheless, the NOAEL for local effects on the respiratory tract following exposure by inhalation is 165 mg/m3.	28
Dermal	-	

Comments:
Overexposure to this material has been suggested as a cause of mild reversible liver effects and mild reversible kidney effects (laboratory animals) **(27)** . Preexisting disorders of skin or lung (such as asthma-like conditions) may be aggravated by exposure to this material **(27)** .

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY

		Ref.
Carcinogenicity	Glycerin does not contain any known carcinogenic substance and studies performed previously do not raise concern for carcinogenic potential of this ingredient. This material is not expected to cause cancer in humans since it did not cause cancer in laboratory animals. This material is not listed as a carcinogen by IARC, NTP or OSHA.	27,28
Mutagenicity	In studies performed in vitro, glycerol was negative (Ames tests with and without metabolic activation) and did not induce chromosomal effects in mammalian cells. There is no in vitro or in vivo data that indicates glycerol to have a genotoxic potential.	28
Teratogenicity	Based on the available data, it can be concluded that glycerol does not have any adverse effects on reproductive parameters. There was no evidence of teratogenicity.	28

Comments:
-

PHOTO-INDUCED TOXICITY

There is no data available on the photo-toxic effects of this ingredient.

Glyceryl stearate SE

REGULATORY RESTRICTIONS

According to the Regulation EC 1223/2009 and respective amendments, there are no restrictions on the use of this ingredient in cosmetic products. CIR (Cosmetic Ingredient Review) considers this compound safe as used up to 25%.

ACUTE TOXICITY

Administration Route	Adverse effects description	LD50	Ref.
Oral	Ingestion may cause gastrointestinal damage. In acute oral toxicity studies in rats, glyceryl stearate was slightly toxic.	(rat): > 5 g/kg	29,30,31
Inhalation	It may cause respiratory tract irritation.	-	32
Dermal	-	-	
Subcutaneous	-	-	

Comments:
Glyceryl monostearate is widely used in cosmetics, foods, and oral and topical pharmaceutical formulations, and is generally regarded as a non-toxic and non-irritant material **(4)** . This ingredient is GRAS listed and it is included in the FDA Inactive Ingredients Database (oral capsules and tablets; ophthalmic, optic, rectal, topical, transdermal, and vaginal preparations) **(4)** . Appropriate to use with no known adverse health effects. Since the substance is used for parenteral feeding, it is considered as not harmful to health **(33)** .

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	It may cause skin irritation. Glyceryl Stearate and Glyceryl Stearate/SE at concentrations of up to 100% were reported to be mildly irritating or nonirritating to the skin of rabbits. Nevertheless, single and Repeated Insult Patch Tests showed this ingredient to be non-irritating.	32,31
Ocular Irritation	Primary eye irritation studies, at concentrations up to 100%, were mildly irritating or non-irritating to rabbits.	31
Sensitization	Single and Repeated Insult Patch Tests showed this ingredient to be non-sensitizing.	31
Dermal Absorption	-	

Comments:
-

CHRONIC TOXICITY		
Administration Route	**Adverse effects description**	**Ref.**
Oral	In chronic studies, 15-25% Glyceryl Stearate in the diet of rats for three consecutive generations had no adverse effects. Rats fed a diet containing 25% Glyceryl Stearate for two years developed renal calcifications.	31
Inhalation	-	
Dermal	In sub-chronic and chronic dermal toxicity tests, Glyceryl Stearate was nontoxic to rabbits but it did cause moderate irritation.	31
Comments: -		

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY		
		Ref.
Carcinogenicity	Glyceryl stearate, fed to mice in doses of 50-100 mg/day or 1.5% in the diet until they died, did not induce significant brain or gastric tumor formation, respectively. 5% glyceryl stearate did not promote the carcinogenicity of DMBA in mouse skin.	31
Mutagenicity	There is no data available on the mutagenic effects of this ingredient.	
Teratogenicity	Glyceryl stearate in the diet of rats for three consecutive generations had no adverse effects.	31
Comments: -		

PHOTO-INDUCED TOXICITY
Products containing 2% glyceryl stearate were non-photo-toxic and non-photo-allergenic **(31)** .

Xanthan Gum

REGULATORY RESTRICTIONS
According to the Regulation EC 1223/2009 and respective amendments, there are no restrictions on the use of this ingredient in cosmetic products.

ACUTE TOXICITY			
Administration Route	**Adverse effects description**	**LD50**	**Ref.**
Oral	No known significant effects or critical hazards. The estimated acceptable daily intake for xanthan gum has been set by the WHO at up to 10 mg/kg body-weight.	(rat): 45 g/kg (mouse): 20 g/kg	34,35,17
Inhalation	Exposure to airborne concentrations above statutory or recommended exposure limits may cause irritation of the nose, throat and lungs. Adverse symptoms may include respiratory airways irritation. Excessive inhalation of dust may be annoying and might mechanically prevent breathing. Because of its hygroscopic properties, could form a paste or gel in the airways.	(rat): 21 mg/l (1h)	34,35,17
Dermal	No known significant effects or critical hazards.	-	34
Subcutaneous	-	-	
Comments: Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and food products and is generally regarded as nontoxic and nonirritant at the levels employed as a pharmaceutical excipient. Xanthan gum has been incorporated in an ophthalmic liquid dosage form, and can be used in vaginal formulations **(17)** . This ingrediente is listed as GRAS, and is accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (oral solutions,suspensions, and tablets; rectal and topical preparations) **(17)** .			

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY		
		Ref.
Skin Irritation	It is not irritating to the skin. No skin irritation has been observed in rabbits. Prolonged contact with dust dry may cause skin dryness or cracking.	34,35
Ocular Irritation	Exposure to airborne concentrations above statutory or recommended exposure limits may cause irritation of the eyes, however, no eye irritation has been observed in rabbits.	34,35,4
Sensitization	It is not a skin sensitizer. No skin allergy has been observed in guinea pigs following skin exposure.	34,35
Dermal Absorption	-	
Comments: -		

CHRONIC TOXICITY		
Administration Route	**Adverse effects description**	**Ref.**
Oral	No adverse effects were observed in long term feeding studies with rats (up to 1000 mg/kg/day) and dogs (up to 1000 mg/kg/day).	35,17
Inhalation	Repeated or prolonged inhalation of dust may lead to chronic respiratory irritation.	34
Dermal	-	
Comments: -		

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY		
		Ref.
Carcinogenicity	Not classifiable as a human carcinogen.	34
Mutagenicity	Animal testing did not show any mutagenic effects.	34
Teratogenicity	No adverse effects were observed in a three-generation reproduction study with rats (up to 500 mg/kg/day).	35,17
Comments: This ingredient has an impurity, Lead, classified as 1A regarding its reproductive toxicity in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labelling of hazardous substances). This ingredient has an impurity, Cadmium, classified as 2 regarding its mutagenicity and reproductive toxicity, and it is classified as 1B regarding its carcinogenicity in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labelling of hazardous substances).		

PHOTO-INDUCED TOXICITY
There is no data available on the photo-induced toxicity effects of this ingredient.

Chaves Thermal Water (Chaves Aqua)

REGULATORY RESTRICTIONS
According to Regulation EC no. 1223/2009 and respective amendments there are no restrictions on its use in cosmetic products.

ACUTE TOXICITY			
Administration Route	**Adverse effects description**	**LD50**	**Ref.**
Oral	-	-	
Inhalation	-	-	
Dermal	-	-	
Subcutaneous	-	-	
Comments: -			

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY		
		Ref.
Skin Irritation	-	
Ocular Irritation	-	
Sensitization	-	
Dermal Absorption	-	
Comments: -		

CHRONIC TOXICITY		
Administration Route	**Adverse effects description**	**Ref.**
Oral	-	
Inhalation	-	
Dermal	-	
Comments: -		

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY		
		Ref.
Carcinogenicity	There is no data available on the carcinogenic effects of this ingredient.	
Mutagenicity	There is no data available on the mutagenic effects of this ingredient.	
Teratogenicity	There is no data available on the teratogenic effects of this ingredient.	
Comments: This product has an impurity, Nickel, that is a Carcinogenic Category 2 in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labelling of hazardous substances). This ingredient has an impurity, Cadmium, classified as 2 regarding its mutagenicity and reproductive toxicity, and it is classified as 1B regarding its carcinogenicity in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labelling of hazardous substances). This ingredient has an impurity, Lead, classified as 1A regarding its reproductive toxicity in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labelling of hazardous substances).		

PHOTO-INDUCED TOXICITY
There is no data available on the photo-toxic effects of this ingredient.

Ceteareth-20

REGULATORY RESTRICTIONS
According to the Regulation EC 1223/2009 and respective amendments, there are no restrictions on the use of this ingredient in cosmetic products. CIR (Cosmetic Ingredient Review) considers this ingredient safe in the present practices of use and concentration in cosmetics, when formulated to avoid irritation. CIR refers that Ceteareth-20 is used at 0.02% to 11% in leave-on poducts and 0.008% to 10% in rinse-off products.

ACUTE TOXICITY			
Administration Route	**Adverse effects description**	**LD50**	**Ref.**
Oral	Ingestion of large amounts may cause gastrointestinal tract irritation and discomfort. Toxicity studies with rats, rabbits, and dogs indicate that PEGs have low oral toxicity.	(Rat): >2000 mg/kg (for C12-C18 etoxylated alcohols and C12-C14 fatty acid)	36,37,38,4,39,40
Inhalation	There is not information about the toxicity by inhalation. However, the powder may cause irritation due to mechanical action.	-	36
Dermal	Sporadic contact for a short time will not cause damage.	(rabbit): 800 mg/Kg (rat): >2000 mg/kg (for C12-C18 etoxylated	36,38

		alcohols; (rabbit): >2000 mg/kg (for C12-C14 fatty acid)	
Subcutaneous	-	-	

Comments:
Classified as not expected to be potentially toxic or harmful **(41)** . Polyoxyethylene alkyl ethers are nonionic surfactants widely used in topical pharmaceutical formulations and cosmetics **(4)** . In cosmetics and personal care products, Ceteareth ingredients are used in skin care products, moisturizers, hair conditioners, suntan and indoor tanning products and hair dyes, colors, and tints **(42)** . Ceteareths are the polyethylene glycol (PEG) ethers of Cetearyl Alcohol (q.v.). To supplement the limited available data on Ceteareths, previous findings from the safety assessment of Polyethylene Glycol (PEG), several fatty alcohols (Cetearyl Alcohol, Cetyl Alcohol, and Stearyl Alcohol), and Steareths were considered. These data indicate little evidence of toxicity **(40)** .

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	May cause irritation. May cause slight irritation in rabbits.	36,41,40
Ocular Irritation	May cause moderate irritation.	36,37,41
Sensitization	C12-C18 etoxylated alcohols and C12-C14 fatty acids are not sensitizers (tested on guinea pigs).	38
Dermal Absorption	CIR Panel mentioned that dermal penetration of long-chain alcohols is likely to be low, and the dermal penetration for alkyl PEG ethers is likely to be even lower. This ingredient is an absorption promoter.	43,44

Comments:
-

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.
Oral	Ingestion of large amounts may cause gastrointestinal tract irritation and discomfort.	36
Inhalation	-	
Dermal	Repeated and prolonged contact may cause moderate irritation.	36

Comments:
-

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY

		Ref.
Carcinogenicity	This ingredient is not carcinogenic (animal tests).	36
Mutagenicity	This ingredient is not mutagenic (animal tests). C12-C18 etoxylated alcohols and C12-C14 fatty acids are not mutagenic (Ames Test with Salmonella typhimurium).	41,36
Teratogenicity	No teratogenic effects are expected.	36

Comments:
This product may contain an impurity, ethylene oxide, that is classified as 1B regarding its Carcinogenic and Mutagenic toxicity in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labelling of hazardous substances). This product may contain an impurity, 1,4-Dioxane, that is a Carcinogenic Category 2 in Annex VI, part 3, Table 3.1 of Regulation (EC) No. 1272/2008 (list of harmonized classification and labelling of hazardous substances).

PHOTO-INDUCED TOXICITY

Photosensitization studies of products containing 1.0% and 4.0% cetyl alcohol were negative **(39)** .

Parfum

REGULATORY RESTRICTIONS

According to the Regulation EC 1223/2009 and respective amendments, there are no restrictions on the use of this ingredient in cosmetic products.

ACUTE TOXICITY			
Administration Route	**Adverse effects description**	**LD50**	**Ref.**
Oral	Male rats (6/dose; strain unspecified) were administered a single dose of benzyl salicylate (present allergen) via oral gavage at 0, 1250, 2500 or 5000 mg/kg and observed for seven days. Mortality was observed at 2500 and 5000 mg/kg.	Concerning to a present allergen: Benzyl salicylate (rat): 2227 mg/kg	45
Inhalation	-	-	
Dermal	-	-	
Subcutaneous	-	-	
Comments:			

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY		
		Ref.
Skin Irritation	This ingredient is a skin irritant.	46
Ocular Irritation	This ingredient is an eye irritant.	46
Sensitization	Sensitization may occur when in contact with the skin. Hexyl cinnamal (the major present allergen) has a low skin-sensitizing potency.	46,47
Dermal Absorption	-	
Comments:		

CHRONIC TOXICITY		
Administration Route	**Adverse effects description**	**Ref.**
Oral	-	
Inhalation	-	
Dermal	-	
Comments: -		

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY		
		Ref.
Carcinogenicity	There is no data available on the carcinogenic effects of this ingredient.	
Mutagenicity	There is no data available on the mutagenic effects of this ingredient.	
Teratogenicity	There is no data available on the teratogenic effects of this ingredient.	
Comments:		

PHOTO-INDUCED TOXICITY
There is no data available on the photo-toxic effects of this ingredient.

Cetearyl alcohol

REGULATORY RESTRICTIONS
According to the Regulation EC 1223/2009 and respective amendments there are no restrictions on its use in cosmetic products. Cosmetic Ingredient Review (CIR) considers that cetearyl alcohol is safe as used up to 25%.

ACUTE TOXICITY			
Administration Route	**Adverse effects description**	**LD50**	**Ref.**
Oral	Swallowing small amounts of this material during normal handling is not likely to cause harmful effects. Swallowing large amounts may be harmful. It may	(rat): > 2000 mg/kg	48,49

	cause stomach or intestinal upset (nausea, vomiting and diarrhea). Cetearyl alcohol is long-chain aliphatic alcohol that is, at most, only slightly toxic when administered orally at doses of 5 g/kg and greater.		
Inhalation	It may cause irritation of nose, throat and respiratory airways.	-	48
Dermal	It may cause skin irritation. Symptoms may include redness, burning, and swelling of skin.	-	48
Subcutaneous	-	-	

Comments:
The Food and Drug Administration (FDA) includes synthetic fatty alcohols including cetyl alcohol and stearyl alcohol on its list of food additives allowed for direct addition to food as multipurpose food additives. Synthetic fatty alcohols are also permitted as indirect food additives, as adjuvants and production aids **(50)** . This material has a low level of toxicity **(48)** . Nevertheless, preexisting lung diseases (for example, asthma-like conditions) may be aggravated by exposure to this material **(48)** .

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	A skin irritation study of a cream containing 3.0% Cetearyl Alcohol was conducted with 6 New Zealand albino rabbits (3 males, 3 females) weighing from 3.5-4.2 kg. The product was applied to intact and abraded skin of each animal during 5 consecutive days. After each application, an occlusive dressing was placed over the test site and removed after an 8-h period. Sites were graded for signs of irritation at 8 and 24 h postapplication. Mean erythema scores for intact skin ranged from 1.0 to 3.0 at 8 h and from 1.17 to 2.67 at 24 h post application. For abraded skin, mean erythema scores ranged from 1.0 to 3.0 at 8 h and from 1.17 to 2.50 at 24 h. It was concluded that the cream was mildly irritating to the skin. In other study this ingredient was non skin irritating to rabbits.	48,49
Ocular Irritation	The dust can cause eye irritation. Symptoms include stinging, tearing, redness, and swelling of eyes. The ocular irritation potential of a cream containing 3.0% Cetearyl Alcohol was assessed in 9 albino rabbits. The product was instilled into one eye of each animal. The eyes of 3 animals were rinsed after instillation. Ocular reactions were scored at 1, 2, 3, 4, and 7 days post instillation. The product was classified as a non-irritant. In other study this ingredient was slightly eye irritating to rabbits.	48,49
Sensitization	In a human skin sensitization study of a cream containing 3.0% cetearyl alcohol, none of the subjects had positive reactions. Although it is not common, some sensitization reactions have been reported. Indeed, there are some reported cases of allergic contact dermatitis derived from the use of this ingredient. There is no evidence of a potential sensitizing effect on the skin.	48,51,49,4
Dermal Absorption	-	

Comments:
-

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.
Oral	-	
Inhalation	Prolonged or repeated breathing of this material may result in chronic bronchitis (inflammation of the airways of the lungs). Symptoms include coughing and shortness of breath. Symptoms are not expected at air concentrations below the recommended exposure limits, if applicable.	48
Dermal	-	

Comments:
-

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY

		Ref.
Carcinogenicity	This material is not listed as a carcinogen by the International Agency for Research on Cancer	48

	(IARC), the National Toxicology Program (NTP) or the Occupational Safety and Health Administration (OSHA).	
Mutagenicity	Ames Test: negative.	48
Teratogenicity	This product does not contain any chemicals known to cause birth defects, or any other reproductive harm (California Prop. 65).	48

Comments:
-

PHOTO-INDUCED TOXICITY

Clinical photosensitization studies of a lipstick product containing 4.0% cetyl alcohol and a skin care preparation containing 1.0% cetyl alcohol resulted in no positive reactions. Identical results were reported moisturizing lotion containing 0.10% myristyl alcohol (related compound) **(49)** .

Hydrochloric acid

REGULATORY RESTRICTIONS

According to the Regulation EC 1223/2009 and respective amendments, there are no restrictions on the use of this ingredient in cosmetic products.

ACUTE TOXICITY

Administration Route	Adverse effects description	LD50	Ref.
Oral	The concentrated solution is corrosive and can cause severe damage if ingested. It can cause burns in gastrointestinal tract. When used diluted, at low concentration, hydrochloric acid is not usually associated with any adverse effects.	(rabbit): 0.9 g/kg	52,4
Inhalation	The inhalation of vapors causes irritation of the airways.	-	52
Dermal	In case of contact with skin it can cause burns.	-	52
Subcutaneous	-	-	

Comments:
LD50 (mouse, IP): 1.4 g/kg **(4)** .

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY

		Ref.
Skin Irritation	It is corrosive to the skin.	53
Ocular Irritation	Severe effects such as burns and irreversible damage of optic nerve can be expected from exposure to the eyes.	53
Sensitization	No skin sensitization has been reported.	53
Dermal Absorption	-	

Comments:
-

CHRONIC TOXICITY

Administration Route	Adverse effects description	Ref.
Oral	-	
Inhalation	No effects on the gonads were observed in a good quality 90-day inhalation study up to 50 ppm.	53
Dermal	-	

Comments:
For repeated dose toxicity, local irritation effects were observed in the groups of 10 ppm and above in a 90-day inhalation study.

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY		
		Ref.
Carcinogenicity	For carcinogenicity, no pre-neoplastic or neoplastic nasal lesions were observed in a 128-week inhalation study with SD male rats at 10 ppm hydrogen chloride gas. No evidence of treatment related carcinogenicity was observed either in other animal studies performed by inhalation, oral or dermal administration. In humans, no association between hydrogen chloride exposure and tumor incidence was observed.	53
Mutagenicity	For genetic toxicity, a negative result has been shown in the Ames test. A positive result, which is considered to be an artifact due to the low pH, has been obtained in a chromosome aberration test using Hamster ovary cells. The effects of low pH in in vitro studies are not a problem in vivo as the proton level is regulated systemically.	53
Teratogenicity	No reliable studies have been reported regarding toxicity to reproduction and development in animals after oral, dermal or inhalation exposure to hydrogen chloride/hydrochloric acid.	53
Comments: -		

PHOTO-INDUCED TOXICITY
There is no data available on the photo-toxic effects of this ingredient.

8.2 Toxicological profile of the mixtures

Phenonip ME

REGULATORY RESTRICTIONS
According to Regulation EC No. 1223/2009 and respective amendments there are no restrictions on the use of this mixture in cosmetic products. The regulatory restrictions of the substances present in this mixture are presented in: section 8.1.

ACUTE TOXICITY			
Administration Route	**Adverse effects description**	**LD50**	**Ref.**
Oral	-	-	
Inhalation	Inhalation of vapours causes irritation of the respiratory system and mucous membranes, headache, nausea, dizziness, vomiting.	-	54
Dermal	-	-	
Subcutaneous	-	-	
Comments:-			

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY		
		Ref.
Skin Irritation	-	
Ocular Irritation	-	
Sensitization	Sensitization effects are not known.	54
Dermal Absorption	-	
Comments: -		

CHRONIC TOXICITY		
Administration Route	**Adverse effects description**	**Ref.**
Oral	-	

Inhalation	-	
Dermal	-	
Comments: -		

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY		
		Ref.
Carcinogenicity	There is no data available on the carcinogenic effects of this mixture.	
Mutagenicity	There is no data available on the mutagenic effects of this mixture.	
Teratogenicity	There is no data available on the teratogenic effects of this mixture.	
Comments: -		

PHOTO-INDUCED TOXICITY
There is no data available on the photo-toxic effects of this ingredient.

Acido Clorhídrico 37% grado técnico

REGULATORY RESTRICTIONS
According to Regulation EC No. 1223/2009 and respective amendments there are no restrictions on the use of this mixture in cosmetic products. The regulatory restrictions of the substances present in this mixture are presented in: section 8.1.

ACUTE TOXICITY			
Administration Route	**Adverse effects description**	**LD50**	**Ref.**
Oral	If ingested, this mixture can cause burns in digestive tract. It can cause intestinal and esophageal perforation.	(rabbit): 0.9 g/kg	55
Inhalation	This mixture can cause irritation to the respiratory tract.	-	55
Dermal	This mixture is very corrosive to the skin.	-	55
Subcutaneous	-	-	
Comments:-			

SKIN SENSITIZATION, IRRITATION AND CORROSIVITY		
		Ref.
Skin Irritation	This mixture is very corrosive to the skin.	55
Ocular Irritation	When in contact with eyes, the mixture can cause burns, blindness and irreversible lesions to the ocular nerve.	55
Sensitization	-	
Dermal Absorption	-	
Comments: -		

CHRONIC TOXICITY		
Administration Route	**Adverse effects description**	**Ref.**
Oral	-	
Inhalation	-	
Dermal	-	
Comments: -		

CARCINOGENIC, MUTAGENIC EFFECTS AND REPRODUCTIVE TOXICITY		
		Ref.
Carcinogenicity	There is no data available on the carcinogenic effects of this mixture.	
Mutagenicity	There is no data available on the mutagenic effects of this mixture.	
Teratogenicity	There is no data available on the teratogenic effects of this mixture.	
Comments: -		

PHOTO-INDUCED TOXICITY
There is no data available on the photo-toxic effects of this mixture.

8.3 Data for calculation of systemic exposure dosage and margin of safety of the substances (INCI name)

Paraffinum Liquidum

Dermal absorption (%)	Justification of dermal absorption value			Ref.
1.00	Data support the view that mineral oil does not effectively penetrate the skin beyond the stratum corneum, resulting in minimal (< 1 %) absorption of white mineral oils after topical exposure.			6
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	56
	900.000	rat	Dermal, 8-week developmental toxicity study	

Ethylparaben

Dermal absorption (%)	Justification of dermal absorption value			Ref.
3.70	The SCCS will use a dermal absorption value of 3.7%.			11
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	11
	2.000	rats	subcutaneous, 17 days	

Methylparaben

Dermal absorption (%)	Justification of dermal absorption value			Ref.
3.70	The SCCS recommends a dermal absorption value of 3.7%.			11
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	11
	2.000	rats	subcutaneous, 17 days	

Phenoxyethanol

Dermal absorption (%)	Justification of dermal absorption value			Ref.
80.00	The AFSSAPS considers 80% of dermal absorption of phenoxyethanol in leave-on products and 40% in rinse-off products.			15
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	15
	164.000	rat	90-day sub-chronic oral study	

Caprylic/Capric Triglyceride

Dermal absorption (%)	Justification of dermal absorption value			Ref.
10.00	There is no data available for dermal absorption for Caprylic/Capric Triglyceride, but other Medium-chain triglycerides showed little skin penetration in mice and guinea pigs.			25
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	26
	1000.000	rabbit	maternal toxicity of rabbit; intravenous administration	

Glycerin

Dermal absorption (%)	Justification of dermal absorption value			Ref.
100.00	Glycerin is absorbed into skin.			4
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	28
	950.000	dog	3 days oral toxicity study in dogs	

Glyceryl stearate SE

Dermal absorption (%)	Justification of dermal absorption value			Ref.
100.00	Since its molecular weight is lower than 500 g/mol (358.6 g/mol), it is assumed that glyceryl stearate is 100% absorbed into skin.			57
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	-
	unknown	-	-	

Xanthan Gum

Dermal absorption (%)	Justification of dermal absorption value			Ref.
10.00	The molecular weight is higher than 500 g/mol (2 to 50E6 Da), so a dermal absorption of 10% will be considered.			4
ADI	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	4
	10.000	Human	-	

Chaves Thermal Water (Chaves Aqua)

Dermal absorption (%)	Justification of dermal absorption value			Ref.
100.00	Considering the low molecular weight of the molecule, a 100% dermal absoprtion will be considered			57
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	-
	unknown	-	-	

Ceteareth-20

Dermal absorption (%)	Justification of dermal absorption value			Ref.
10.00	As dermal penetration for alkyl PEG ethers is likely to be lower, a dermal absorption of 10% will be assumed.			44
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	-
	unknown	-	-	

Parfum

Dermal absorption (%)	Justification of dermal absorption value			Ref.
100.00	As there is no available data on dermal absorption of this ingredient, it will be assumed a dermal absorption of 100% for calculation of systemic exposure.			
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	-
	unknown	-	-	

Cetearyl alcohol

Dermal absorption (%)	Justification of dermal absorption value			Ref.
10.00	Although the molecular weights of cetyl alcohol and stearyl alcohol are lower than 500 g/mol, the partition coefficients of these compounds that constitute the ingredient cetearyl alcohol are higher than 4, so a 10% of dermal absorption will be assumed.			57
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	-
	unknown	-	-	

Hydrochloric acid

Dermal absorption (%)	Justification of dermal absorption value			Ref.
100.00	Since this ingredient presents a low molecular weight (36.46 g/mol) a dermal absorption of 100% will be assumed.			57
NOAEL	**Value (mg/kg/day)**	**Specie(s)**	**Type of Study**	53
	20.000	Rat and mice	90-day inhalation study	

8.4 Exposure to the substances, calculation of respective systemic exposure and margin of safety

Substance (INCI)	Total Conc. of the Substance in the Cosmetic Product (%)	mg/kg body weight/ day	Dermal absorption (%)	Systemic Exposure (mg/kg/day)	NOAEL or Other Parameter	Margin of Safety	Margin of Safety /2 *
Caprylic/Capric Triglyceride	8.00	9.856	10	0.9856	1000	1015	n.a.
Ceteareth-20	1.00	1.232	10	0.1232	-	-	-
Cetearyl alcohol	2.00	2.464	10	0.2464	-	-	-
Chaves Thermal Water (Chaves Aqua)	72.70	89.5664	100	89.5664	-	-	-
Ethylparaben	0.15	0.1848	3.7	0.0068	2	293	n.a.
Glycerin	3.00	3.696	100	3.696	950	257	129
Glyceryl stearate SE	8.00	9.856	100	9.856	-	-	-
Hydrochloric acid	0.156	0.1922	100	0.1922	20	104	n.a.
Methylparaben	0.15	0.1848	3.7	0.0068	2	293	n.a.
Paraffinum Liquidum	5.00	6.16	1	0.0616	900	14610	n.a.
Parfum	0.10	0.1232	100	0.1232	-	-	-
Phenoxyethanol	0.90	1.1088	80	0.887	164	185	93
Xanthan Gum	0.324	0.3992	10	0.0399	10	251	126

** Additional factor applied for substances for which the Margin of Safety was calculated taking into account NOAEL obtained from oral studies.*

8.5 Possible impacts on the toxicological profile due to particle sizes (including nanomaterials), impurities and interaction of the substances

The cosmetic product does not contain nanomaterials and interactions between its substances are not expected to occur. This product contains allergens that according to the Annex III of the Regulation EC 1223/2009 are substances which cosmetic products must not contain except subject to some restrictions. This Annex III of the Regulation EC no. 1223/2009 states that these substances must be labeled in the final product if their concentration in the cosmetic product exceeds 0.01% in rinse-off products and 0.001% on leave-on products. In this leave-on product the allergens which must be labeled are: Alpha-Isomethyl Ionone, Benzyl Alcohol, Benzyl Salicylate, Butylphenyl Methylpropional, Citronellol, Coumarin, Eugenol, Geraniol, Hexyl Cinnamal, Hydroxycitronellal and Linalool. The presence of these allergens in the final cosmetic product can cause sensitization reactions in individuals with more sensitive skin. However, as it can be seen on the table below, the margins of safety of these allergens were calculated. The margins of safety calculated for the allergens Alpha-Isomethyl Ionone, Benzyl Alcohol, Benzyl Salicylate, Butylphenyl Methylpropional, Coumarin, Eugenol, Geraniol, Hexyl Cinnamal, Hydroxycitronellal allergens are 828253, 50730519, 47972, 259491, 247466, 12175325, 128839415, 1528028 and 5312096, respectively (based on oral studies performed in animal species), which are values greater than 100 (which is the reference value considered as minimum to assume the ingredients' use as safe when long term animal studies are considered). Considering the allergens Citronellol and Linalool, the margins of safety calculated are 186167 and 6764, respectively (based on oral studies performed in humans), which are values greater than 10 (which is the reference value considered as minimum to assume the ingredients' use as safe when long term human studies are considered). Hence, there are no significant systemic risks to human health associated to the presence of these substances, under normal conditions of use of the final product.

Substance (INCI)	Total Conc. of the Substance in the Cosmetic Product (%)	mg/kg body weight/day	Dermal absorption (%)	Systemic Exposure (mg/kg/day)	NOAEL or Other Parameter	Margin of Safety	Margin of Safety /2 *
Alpha-Isomethyl Ionone	0.0049	0.0060368	100	0.0000604	50	828253	n.a.
Benzyl Alcohol	0.001	0.001232	32	0.0000039	400	101461039	50730519
Benzyl Salicylate	0.00423	0.00521136	100	0.0000521	5	95944	47972
Butylphenyl Methylpropional	0.00391	0.00481712	100	0.0000482	25	518982	259491
Citronellol	0.00109	0.00134288	10	0.0000013	0.5	372334	186167
Coumarin	0.00164	0.00202048	100	0.0000202	10	494932	247466
Eugenol	0.001	0.001232	100	0.0000123	300	24350649	12175325
Geraniol	0.00315	0.0038808	10	0.0000039	1000	257678829	128839415
Hexyl Cinnamal	0.00664	0.00818048	100	0.0000818	125	1528028	n.a.
Hydroxycitronellal	0.00191	0.00235312	100	0.0000235	250	10624193	5312096
Linalool	0.003	0.003696	100	0.0000370	0.5	13528	6764

** Additional factor applied for substances for which the Margin of Safety was calculated taking into account NOAEL obtained from oral studies.*

This cosmetic product contains diethylene glycol as trace impurity of the raw material Glycerin 4810. According to Regulation (EC) 1223/2009, diethylene glycol is allowed at a maximum concentration of 0.1% as traces in ingredients. The concentration of diethylene glycol in this cosmetic product is 0.003% therefore it is in compliance with the Regulation.

The raw materials used on this product contain some other impurities (as listed in section 4.1), but their respective concentrations in the finished product are very low. Therefore, under normal conditions of use, no significant harmful reactions or adverse effects to human health are expected due to these impurities.

9. Undesirable effects and serious undesirable effects

This cosmetic product is not on the market yet, therefore no undesirable effects or serious undesirable effects have been reported.

10. Information on the cosmetic product

A study to evaluate the moisturizing efficacy of the product DERMOCOSMÉTICA TERMAL AQUAE CREME HIDRATANTE CORPORAL was performed. This test was performed in a similar formula, under the name Loção Hidratante (FR01A/P054B11 from Inovapotek), which is not the same as the one to which this report refers. Nevertheless, the differences between the formulas are minimal, therefore the results of this Efficacy Test can be considered valid. In this test, 20 voluntees were included, with ages between 18 to 60 years. The test product was applied in the volar part of the arms and the measurements of the moisturizing level were performed before, and after 2, 4 and 8 hours of products application. Before the use of Loção Hidratante, the average value for the moisturizing level was 33.06 (arbitrary units), 2 hours after application the value increased to 47.86, 4 hours after application the value increased to 50.51 and 8 hours after application the average value was 47.27. The differences between before and after 2, 4 and 8 hours of product application were +46.4%, +52.9% and +43.2%, respectively. There was an increase of moisturizing effect in 100% of volunteers, at all time-points of evaluation. These differences were statistically significant ($p<0.05$).

PART B – Cosmetic Product Safety Assessment

1. Assessment conclusion

The Safety Assessment of the cosmetic product "**DERMOCOSMÉTICA TERMAL AQUAE CREME HIDRATANTE CORPORAL"** was performed according to Regulation (EC) 1223/2009 and respective amendments. It was concluded that this cosmetic product is safe for human health under normal or reasonably foreseeable conditions of use taking into account its presentation, labeling, instructions for use and disposal and warnings, as long as:

- It passes the 30-month stability/product-packaging material compatibility study under course.

2. Labeled warnings and instructions of use

The information that must be printed on cosmetic product labels (containers and packaging) is regulated under Article 19 of the Regulation (EC) 1223/2009. The following items are compulsory labelling requirements of the Regulation:

- Name or registered name and the address of the responsible person
- Country of origin for cosmetic products imported into the EU
- Nominal content at the time of packaging by weight or by volume.
- Date of minimum durability preceded by the symbol  or the words: „best used before the end of". - Indication of the date of minimum durability is not mandatory for products with a minimum durability of more than 30 months. For such products except where the concept of durability after opening is not relevant an indication of the period of time after opening has to be indicated for which the product is safe and can be used without any harm to the consumer. This information shall be indicated by the symbol  followed by the period (in months and/or years, but usually in months as "x M")
- Information regarding possible precautions to be observed in use. Note especially the compulsory information listed in Annexes III to VI. In the case of this cosmetic product, there are no mandatory warnings to be included in the labelling.
- Batch number or reference to identify the final cosmetic product. When products are too small, such information only need to appear on the secondary packaging.
- Function of the cosmetic product, unless it is clear from its presentation.
- List of ingredients (INCI)- May be indicated on the packaging only, must be preceded by the term „ingredients" - the full INCI list of this cosmetic product (including allergens) is presented in section "1.3 Quantitative and qualitative composition of the cosmetic product by INCI name".

3. Reasoning

Paraffinum liquidum, also known as mineral oil, is used as an excipient in a wide variety of pharmaceutical formulations. It is also used in cosmetics and in some food products. It is to point out that mineral oil displays acute and chronic toxicity effects if ingested and inhaled as well as it may cause eye irritation. On the other hand, it is normally considered as not dangerous for the skin as it shows low dermal toxicity. Subchronic or chronic topical exposure to refined white mineral oils in mice, rats and rabbits results in no histopathological changes in any internal organ or at the site of application (i.e. skin) but given to its widespread use in many topical products, mineral oil has been associated with few instances of allergic reactions. According to the Regulation EC 1223/2009 and respective amendments, there are no restrictions on the use of this ingredient in cosmetic products. The margin of safety calculated for this ingredient is 14610 (based on dermal studies performed in animal species), which is a value greater than 300 (which is the reference value considered as minimum to assume the ingredients' use as safe when short term animal studies are considered). Hence, there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

Caprylic/capric triglyceride is included in the chemical group of medium-chain triglycerides, which are used in a variety of pharmaceutical formulations including oral, parenteral and topical products, and which are generally regarded as essentially non-toxic and non-irritant materials. It is not expected that caprylic/capric triglyceride cause irritation to the skin or to the eyes neither reactions of hypersensitivity. Medium chain triglycerides showed little skin penetration in mice and guinea pigs, however, some of these triglycerides can enhance the skin penetration of other chemicals, so CIR Expert Panel recommends that care should be exercised in using these triglycerides in cosmetic products. According to the Regulation EC 1223/2009 and respective amendments there are no restrictions on its use in cosmetic products. The CIR expert panel evaluated the scientific data and concluded that caprylic/capric triglyceride is safe for use as cosmetic ingredient at concentrations up to 84%. The concentration of this ingredient in the cosmetic product – 8% - is according to the CIR Expert Panel recommendation. The margin of safety calculated for this ingredient is 1015 (based on intravenous studies performed in animal species), which is a value greater than 300 (which is the reference value considered as minimum to assume the ingredients' use as safe when animal studies of unknown duration are considered). Hence, there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

Glycerin is used in pharmaceutical oral, topical, ophthalmic and parenteral formulations, besides being also used as a food additive. The consumption of large amounts of glycerin may cause vomiting, nausea, diarrhea, headache, and hyperglycemia. Moreover, it may cause irritation of nose, throat and airways but does not cause skin irritation. It is to point out that glycerin is more toxic when administered intravenously, intraperitoneally or subcutaneously. Considering the extensive, widespread dermal exposure to glycerol in preparations repeatedly applied to the skin, the absence of case reports of humans showing skin reactions is consistent with glycerol having a very low skin sensitization potential. According to Regulation EC 1223/2009 and respective amendments there are no restrictions on its use in cosmetic products. The margin of safety calculated for this ingredient is 129 (based on oral studies performed in animal species), which is a value lower than 300 (which is the reference value considered as minimum to assume the ingredients' use as safe when short term animal studies are considered). Nevertheless, glycerin does not cause skin irritation and it is

considered to have a very low skin sensitization potential hence it can be assumed that there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

Glyceryl stearate SE is generally regarded as a non-toxic and non-irritant material. However, it may display acute toxicity effects by oral, inhalation and dermal administration routes as well as chronic dermal toxicity effects (skin irritation). It is non-irritating to the skinan it is a non-sensitizer agent. Moreover, at concentrations up to 100%, it is mildly irritating or non-irritating to the eyes (rabbit). According to the Regulation EC 1223/2009 and respective amendments, there are no restrictions on the use of this ingredient in cosmetic products. CIR considers this compound safe as used up to 25%. The concentration of this ingredient in the cosmetic product – 8% - is according to the CIR Expert Panel recommendation. As NOAEL for this ingredient is unknown, it is not possible to determine its margin of safety under normal conditions of use. Based on its toxicological profile - is non-irritating to the skin and it is a non-sensitizer agent there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and food products and is generally regarded as safe, also regarded as nontoxic and nonirritant at the levels employed as a pharmaceutical excipient. Xanthan gum is a nonirritating agent to the skin and it does not cause eye irritation, unless its statutory or recommended exposure limits are exceeded. In addition, xanthan gum is not a skin sensitizer. Exposure to airborne concentrations above statutory or recommended exposure limits may cause irritation of the nose, throat and lungs. According to the Regulation EC 1223/2009 and respective amendments there are no restrictions on its use in cosmetic products. The margin of safety calculated for this ingredient is 126 (based on oral studies performed in humans), which is a value greater than 10 (which is the reference value considered as minimum to assume the ingredients' use as safe when long term human studies are considered). Hence, there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final productChaves Thermal Water (Chaves Aqua) is has been widely used since the Roman times for the treatment of musculoskeletal, digestive and respiratory tract ailments therefore no toxicological risk is expected. Moreover, no skin reactions have been reported from its use. According to Regulation EC no. 1223/2009 and respective amendments there are no restrictions on the use of Chaves Thermal Water (Chaves Aqua) in cosmetic products.

Ceteareth-20 (one of polyoxyethylene alkyl ethers) is a nonionic surfactant widely used in topical pharmaceutical formulations and cosmetics and it is classified as not expected to be potentially toxic or harmful. In addition, it is not expected that this compound acts like a sensitizer. Nevertheless, ceteareth-20 is a skin and eye irritant agent. According to the Regulation EC 1223/2009 and respective amendments, there are no restrictions on the use of this ingredient in cosmetic products. CIR (Cosmetic Ingredient Review) considers this ingredient safe in the present practices of use and concentration in cosmetics, when formulated to avoid irritation. CIR refers that Ceteareth-20 is used at 0.02% to 11% in leave-on poducts and 0.008% to 10% in rinse-off products. The concentration of this ingredient in this leave-on cosmetic product – 1% - is according to the CIR Expert Panel recommendation. As NOAEL for this ingredient is unknown, it is not possible to determine its margin of safety under normal conditions of use. Based on its low systemic exposure value (0.1232 mg/kg/day), there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

1051936 NIVAL is a perfume that the exact composition is not known. The main allergens are Hexyl Cinnamal, Alpha-isomethyl ionone and Benzyl Salicylate. This ingredient is a skin and eye irritant and sensitization may occur when in contact with the skin. Benzyl salicylate (present allergen) via oral gavage showed mortality levels observed at 2500 and 5000 mg/kg. Hexyl cinnamal (the major present allergen) has a low skin-sensitizing potency. According to the Regulation EC 1223/2009 and respective amendments, there are no restrictions on the use of this ingredient in cosmetic products. As NOAEL for this ingredient is unknown, it is not possible to determine its margin of safety under normal conditions of use. This product contains allergens that according to the Annex III of the Regulation EC 1223/2009 are substances which cosmetic products must not contain except subject to some restrictions. This Annex III of the Regulation EC no. 1223/2009 states that these substances must be labeled in the final product if their concentration in the cosmetic product exceeds 0.01% in rinse-off products and 0.001% on leave-on products. In this leave-on product the allergens which must be labeled are: Alpha-Isomethyl Ionone, Benzyl Alcohol, Benzyl Salicylate, Butylphenyl Methylpropional, Citronellol, Coumarin, Eugenol, Geraniol, Hexyl Cinnamal, Hydroxycitronellal and Linalool. The presence of these allergens in the final cosmetic product can cause sensitization reactions in individuals with more sensitive skin. However, the margins of safety of these allergens were calculated. The margins of safety calculated for the allergens Alpha-Isomethyl Ionone, Benzyl Alcohol, Benzyl Salicylate, Butylphenyl Methylpropional, Coumarin, Eugenol, Geraniol, Hexyl Cinnamal, Hydroxycitronellal allergens are 828253, 50730519, 47972, 259491, 247466, 12175325, 128839415, 1528028 and 5312096, respectively (based on oral studies performed in animal species), which are values greater than 100 (which is the reference value considered as minimum to assume the ingredients' use as safe when long term animal studies are considered). Considering the allergens Citronellol and Linalool, the margins of safety calculated are 186167 and 6764, respectively (based on oral studies performed in humans), which are values greater than 10 (which is the reference value considered as minimum to assume the ingredients' use as safe when long term human studies are considered). Hence, there are no significant systemic risks to human health associated to the presence of these substances, under normal conditions of use of the final product.

Ethylparaben and Methylparaben are widely used in cosmetics, food products, and oral and topical pharmaceutical formulations. In general, parabens are practically non-irritating and non-sensitizing in the population with normal skin and they do not exhibit significant levels of photo-contact sensitization or photo-toxicity. Moreover, chronic oral studies indicate that parabens are practically non-toxic. On the other hand, parabens are often incorporated in creams, lotions and ointments that may be used in the region of the eyes, and occasionally cause redness and swelling of eyelids. Ethylparaben and Methylparaben are listed in Regulation EC 1223/2009 annex V (list of preservatives which cosmetic products may contain). According to this Regulation and respective amendments, the use of these parabens in cosmetic products is restricted to a maximum concentration of 0.4% (as acid) for single ester, and 0.8% (as acid) when a mixture of esters is used. CIR (Cosmetic Ingredient Review) considers that this compound is safe when applied in the above-mentioned concentrations. The concentration of the individual parabens (0.15% for ethylparaben and 0.15% for methylparaben) and the sum of concentrations of all parabens present in the cosmetic product – 0.30% - is according to the Regulation EC 1223/2009 and also according to CIR Expert Panel recommendation. The margins of safety calculated for ethylparaben and methylparaben are 293 and 293 respectively (based on subcutaneous studies performed in animal species), which are values lower than, but close to 300 (which is the reference value considered as minimum to assume the ingredients' use as safe when short term animal studies are considered). Moreover, in general, parabens are practically non-irritating and non-sensitizing in the population with normal skin and they do not exhibit significant levels of photo-contact sensitization or photo-toxicity. Hence, it can be considered that there are no significant systemic risks to human health associated to the use of these substances, under normal conditions of use of the final product.

Phenoxyethanol is an antimicrobial preservative used in cosmetics and topical pharmaceutical formulations, including vaccines. It has also been used at approximately 2% in superficial wounds, burns and minor skin infections as a disinfectant. Phenoxyethanol is practically non-toxic when oral administered (animal data), but it is able to cause respiratory tract irritation if inhaled, and moderate eye irritation. Moreover, Phenoxyethanol at 10% in mineral oil is not considered a primary nor a cumulative irritant, but the pure material is a moderate irritant to the skin. It is not a sensitizer or a photo-toxic agent, although mild skin irritation or contact urticaria due to phenoxyethanol have been reported. This substance is listed in the Regulation EC 1223/2009 as a preservative that can be used in cosmetic productsts up to a maximum concentration of 1%. CIR also considers that this ingredient is safe as used up to 1%. The concentration of this ingredient in the cosmetic product – 0.9% - is according to the Regulation EC 1223/2009 and also according to CIR Expert Panel recommendation. The margin of safety calculated for this ingredient is 93 (based on oral studies performed in animal species), which is a value lower than, but close to 100 (which is the reference value considered as minimum to assume the ingredients' use as safe when long term animal studies are considered). Moreover, considering the toxicological profile of this ingredient, Phenoxyethanol at 10% in mineral oil is not considered a primary or a cumulative irritant, and it is not a sensitizer or a photo-toxic agent. Hence, it can be considered that there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

Hydrochloric acid, in a concentrated solution, is corrosive and can cause severe damage if ingested. It can cause burns in gastrointestinal tract. The inhalation of vapors causes irritation of the airways. In case of contact with skin it can cause burns. Severe effects such as burns and irreversible damage of optic nerve can be expected from exposure to the eyes. When used diluted, at low concentration, hydrochloric acid is not usually associated with any adverse effects. According to the Regulation EC 1223/2009 and respective amendments, there are no restrictions on the use of this ingredient in cosmetic products. The margin of safety calculated for this ingredient is 104 (based on inhalation studies performed in animal species), which is a value greater than 100 (which is the reference value considered as minimum to assume the ingredients' use as safe when long term animal studies are considered). Hence, there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

Cetearyl alcohol is a long-chain aliphatic alcohol that is, at most, only slightly toxic when administered orally at doses of 5 g/kg and greater. It may cause irritation of nose, throat and respiratory airways. It may cause mild skin irritation with redness, burning, and swelling of skin to no irritation at all. The Food and Drug Administration (FDA) includes synthetic fatty alcohols including cetyl alcohol and stearyl alcohol on its list of food additives allowed for direct addition to food as multipurpose food additives. Although, there are some reported cases of allergic contact dermatitis derived from the use of this ingredient, there is no evidence of a potential sensitizing effect on the skin. Concerning ocular irritation, this ingredient demonstrated to be non to slightly eye irritating in rabbits. Regarding to its chronic toxicity effects, it can be mentioned that prolonged or repeated breathing of this compound may result in chronic bronchitis. According to the Regulation EC 1223/2009 and respective amendments there are no restrictions on its use in cosmetic products. Cosmetic Ingredient Review (CIR) considers that cetearyl alcohol is safe as used up to 25%. The concentration of this ingredient in the cosmetic product – 2% - is according to the CIR Expert Panel recommendation. As NOAEL for this ingredient is unknown, it is not possible to determine its margin of safety under normal conditions of use. Based on its low systemic exposure value (0.2464 mg/kg/day), there are no significant systemic risks to human health associated to the use of this substance, under normal conditions of use of the final product.

Phenonip ME is a mixture containing Phenoxyethanol, Methylparaben and Ethylparaben. Inhalation of vapours causes irritation of the respiratory system and mucous membranes, headache, nausea, dizziness, vomiting. Sensitization effects are not known. According to Regulation EC No. 1223/2009 and respective amendments there are no restrictions on the use of this mixture in cosmetic products. The regulatory restrictions of the substances present in this mixture are presented in: section 8.1. and their toxicological profiles and margins of safety are presented above.

Acido Clorhídrico 37% grado técnico is a mixture of Hydrochloric acid and Aqua. This mixture can cause irritation to the respiratory tract. This mixture is very corrosive to the skin. When in contact with eyes, the mixture can cause burns, blindness and irreversible lesions to the ocular nerve. If ingested, this mixture can cause burns in digestive tract. It can cause intestinal and esophageal perforation. According to Regulation EC No. 1223/2009 and respective amendments there are no restrictions on the use of this mixture in cosmetic products. The regulatory restrictions of the substances present in this mixture are presented in: section 8.1. and their toxicological profiles and margins of safety are presented above.

Considering the type of formulation, the composition, and the fact that no interactions between the substances are expected, it is unlikely that physico-chemical degradation occurs, putting in risk human health. At the time of this report, a long term stability study is under course, as well as the experimental determination of PAO.

Considering the microbiological stability as well as the results of the challenge test performed in a similar formula of DERMOCOSMÉTICA TERMAL AQUAE CREME HIDRATANTE CORPORAL, it can be concluded that this cosmetic product contains adequate preservatives so, it is not expected that its microbial contamination (which can be threat to human health) occurs.

Considering the packaging material used in the cosmetic product it is not expected that any risk to human health can be triggered due to the packaging selected. At the time of this report, a long term stability study is under course, where the product-packaging compatibility will alsobe evaluated.

There are no mandatory warnings to be included in the labelling of this cosmetic product.

The Safety Assessment of the cosmetic product " **DERMOCOSMÉTICA TERMAL AQUAE CREME HIDRATANTE CORPORAL"** was performed according to Regulation (EC) 1223/2009 and respective amendments. It was concluded that this cosmetic product is safe for human health under normal or reasonably foreseeable conditions of use taking into account its presentation, labeling, instructions for use and disposal and warnings, as long as:

- It passes the 30-month stability/product-packaging material compatibility study under course.

4. Assessor's credentials and approval of part B

Name of the Safety Assessor	Marta Alexandra de Oliveira Ferreira	
Address	INOVAPOTEK. Pharmaceutical Research and Development Lda UPTEC. Parque de Ciência e Tecnologia da Universidade do Porto, Rua Alfredo Allen n.º455/461 4200-135, Porto Portugal	
Qualifications of the safety assessor	Master in Pharmaceutical Sciences	
Approval of Part B	**Signature**	
	Date	30-10-2015

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inovapotek
PHARMACEUTICAL RESEARCH AND DEVELOPMENT

CURRICULUM VITAE

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CV Summary

Is currently the General Manager and Technical Director of inovapotek, a spin-off company of Oporto University proving R&D, testing and consulting services to the cosmetics and pharmaceutical industry. Holds a master's degree in Pharmaceutical Sciences and a master's degree in Pharmaceutical Technology and has now more than 10 years of experience in cosmetics product development, testing and regulatory affairs.

Professional experience

Founder, General Manager and Technical Director, *Inovapotek, Pharmaceutical Research and Development Lda. (since October 2008)*

Activities:

- Coordination of all Technical Department activities such as:
    - Safety assessment according with EU regulation
    - Safety and tolerance testing
    - Efficacy testing
    - Formulation development
    - Stability studies
    - New methods development and validation
    - Study plans design
- Coordination of Marketing/Sales Department
- Human resources management
- Coordination of Financial & Administrative Department

Consultant, *Fluidinova, Engenharia de Fluidos, SA (2008)*

Activities: definition of a R&D project in the cosmetic area, including definition of activities and tasks, planning and resources.

R&D manager of the project "Development of cosmetic products with S. Pedro do Sul Spring water", *Termalistur – Termas de São Pedro do Sul EM, in partnership with the Faculty of Pharmacy of Oporto University (2005-2008)*

Activities: Development of a new range of cosmetic products, including formulation, stability, safety and efficacy studies of the products. Responsible for the implementation of a new microbiological laboratory for the quality control of the spring water.

Invited Teacher of the Master of Pharmaceutical Technology , *Faculty of Pharmacy of Oporto University (2006 e 2007)*

Researcher at the Medicines Technologic Centre, *Pharmacies National Association (2005)*
Activities: Development of several monographs of semi-solid products for the Portuguese National formulary.

Pharmacist (Health assistant), *Hospital São João de Deus S.A., Vila Nova de Famalicão (2005)*

Pharmacist, *Farmácia Marques, Braga (2004 a 2005)*

Researcher at the Pharmaceutical Technology Department, *Faculty of Pharmacy of Oporto University (2002 a 2003)*
Activities: Planning and implementation of a R&D project for the development of a pediatric syrup.

Researcher at the Organic Chemistry, Phytochemistry and Pharmacology Studies Centre, Organic Chemistry Department, *Faculty of Pharmacy of Oporto University (2000 a 2002)*
Activities: Collaboration of a research project that aimed the development and selection of PLA-PEG nanocapsules for the incorporation and xanthonic compounds.

Education and Training

Good Laboratory Practices Principles Training, Eng.ª Helena Loureiro (2014)

I Course Good Clinical Practices, Lisbon Faculty of Medicine (2012)

Integrated Audits of Quality, Environment and Health and Safety, Process Advice (2010)

Master in Pharmaceutical Sciences, *Faculty of Pharmacy of Oporto University* (2009)

Master in Pharmaceutical Technology (classification: very good), *Faculty of Pharmacy of Oporto University* (2008)

Post-graduation in Pharmacotechnics (classification: 16/20), *Faculty of Pharmacy of Oporto University* (2007)

Advanced Program in Entrepreneurship, Business Creation and Business Development, National Association of Young Entrepreneurs, Porto (2005)

Primary Compounding Course, Professional Compounding Centres of America, Houston (2005)

Degree in Pharmaceutical Sciences (classification: 16/20), *Faculty of Pharmacy of Oporto University* (1998-2004)

Scientific curriculum

Thesis

1. Ferreira M.O. Efficacy testing of cosmetic products in human volunteers using objective instrumental methods. *Faculty of Pharmacy of Oporto University*, Porto, Portugal, 2009.
2. Ferreira M.O. Cutaneous effect of S. Pedro do Sul Spring water. *Faculty of Pharmacy of Oporto University*, Porto, Portugal, 2008.
3. Ferreira M.O. Bio-identical hormone replacement therapy. *Faculty of Pharmacy of Oporto University*, Porto, Portugal, 2007.

Papers

1. Ferreira M.O., Bahía M.F., Costa P. Stability of ranitidine hydrochloride in different aqueous solutions. EJHP 4/2004; 10: 61-63.
2. Ferreira M.O., Bahía M.F., Costa P. Effect of São Pedro do Sul thermal water on skin irritation. International Journal of Cosmetic Science, 2010, 32, 205–210.
3. Ferreira M.O., Amaral M.H., Costa P., Bahía M.F. Effects of São Pedro do Sul thermal water on skin hydration, pH, sebum and surface. (submitted to publication)
4. Neto A. P., Ferreira, M., Costa, P., Bahia, M., Skin Improvement of the methods for skin mechanical properties evaluation through correlation between different techniques and factor analysis. Skin Research and Technology, 2013; 0: 1-12.
5. Piccirillo C., Rocha C., Tobaldi D. M., Pullar R. C., Labrincha J. A., Ferreira M. O., Castro P. M. L., Pintado M. M. E.. A hydroxyapatite–Fe2O3 based material of natural origin as an active sunscreen filter. J. Mater. Chem. B, 2014, 2, 5999–6009
6. Rodrigues, F.; Pereira, C.; Pimentel, F.; Alves, R.; Ferreira, M.; Sarmento, B.; Amaral, M. Helena; Oliveira, M. Beatriz P.P. Are Coffee Silverskin extracts safe for topical use? An in vitro and in vivo approach. Industrial Crops and Products, 2014 (article in press)
7. Chitosan oral care strips - In vitro antimicrobial activities, clinical efficacy and consumer. Pintado M. M. E., Madureira A.R., Cardelle-Cobas A., Neto A.P., Ferreira M.O., Costa E., Tavaria F. (submitted to publication)
8. Figueiredo R. P., Costa P. C. and Ferreira M. O. Non-Invasive Skin Imaging Techniques. Skin Research and Technology (article in press)

Presentations in poster

1. Ferreira M.O., Almeida I.F., Bahía M.F., Costa P. Study of the effect of several thermal waters in skin surface hydration. Skin and Formulation, 2nd Symposium, Versailles (France), 9-10th October, 2006.
2. Ferreira M.O., Mota A.F., Oliveira A.Z., Ximenes C.S., Ribeiro A.M., Almeida I.F., Bahía M.F., Costa P. Mechanical characterization of an oleogel/hydrogel mixture. Skin and Formulation, 2nd Symposium, Versailles (France), 9-10th October, 2006.
3. L. Carvalho, A. J. Chambe, K. Krambeck, A. F. Lemos, S. Oliveira, M.O. Ferreira, P.C. Costa. Evaluation of the cutaneous hydration induced by O/W creams with different glycerin concentrations. 9th Annual Meeting of Skin Fórum, London (United Kingdom), 25-26th June, 2008.
4. Isabel F. Almeida, M.O. Ferreira, Paulo C. Costa, M. Fernanda Bahia. In vitro evaluation of the antioxidant activity of a semisolid formulation incorporating a plant extract. 9th Annual Meeting of Skin Fórum, London (United Kingdom), 25-26th June, 2008.

5. Ferreira M.O., Amaral M.H., Costa P., Bahía M.F., Assessment of age-related differences in skin surface, hydration, sebum and pH. Building Cosmetics: Research, Technology & Culture, 25th IFSCC Congress, Barcelona (Spain), 6-9th October, 2008.
6. Ferreira M.O., Amaral M.H., Costa P., Bahía M.F., Study of the inter-relations between skin surface parameters, hydration, sebum and pH. Building Cosmetics: Research, Technology & Culture, 25th IFSCC Congress, Barcelona (Spain), 6-9th October, 2008.
7. Ferreira M.O., Amaral M.H., Pereira T., Costa P., Bahía M.F., Evaluation of the skin compatibility of new cosmetic products. 2nd National Congress of Dermatocosmetic Sciences (1st congress of the Portuguese society of Cosmetic Sciences), Lisbon (Portugal), 27th March, 2009.
8. Neto P., Ferreira M., Evaluation of a new active complex in decreasing *vellus* hairs ratio, 21st EADV Congress, Prague, 2012.
9. Neto P., Ferreira M., Evaluation of a new active complex for increasing hair thickness in alopecia, 21st EADV Congress, Prague, 2012.
10. Neto P., Ferreira M., Efficacy evaluation of a new active complex for hair loss, 21st EADV Congress, Prague, 2012.

Oral presentations

1. Ferreira M.O. Cosmetic products development, Panel "Quality, Efficacy and Acceptability of Cosmetic Products", Dermatology and Cosmetology – health to promote well-being Congress, Porto (Portugal), 18-19th April, 2007.
2. Ferreira M.O., Costa P., Bahía M.F. Water and skin: the S. Pedro do Sul thermal water cutaneous effects, Panel "Dermatological and Allergic Studies", 36th Congress of the International Society of Medical Hydrology & Climatology, Porto (Portugal), 25-28th June, 2008.
3. Ferreira M.O. Development of the 1st Cosmetic Products with a Portuguese Thermal Water, Aquameeting – Health and Well-being International Seminar, Porto (Portugal), 19-21th September, 2008.
4. Ferreira M.O. Dermocosmetic Products with a Portuguese Thermal Water. 2nd National Congress of Dermatocosmetic Sciences (1st congress of the Portuguese society of Cosmetic Sciences), Lisbon (Portugal), 27th March, 2009.
5. Ferreira M.O. Cosmetic Products Development: quality, efficacy and safety aspects. Dermatocosmetic Workshop, Health School of the Bragança Polytechnic Institute, Bragança (Portugal), 5th June, 2009.
6. Ferreira M.O. How to prepare for importing to Europe. European Cosmetics Regulation Seminar (Ecore), Tel aviv, 3rd-5th February 2013
7. Ferreira M.O. Cosmetics Testing – compliance with the new regulation. European Cosmetics Regulation Seminar (Ecore), Cosmoprof Bologne, 10th March 2013
8. Ferreira M.O. Systemic Exposure of the Human Body to Cosmetic Ingredients and the Influence on Product. Safety European Cosmetics Regulation Workshop, Istanbul, 2nd October 2013
9. Ferreira M.O. Formulation principles & R&D exercises. Safety European Cosmetics Regulation Workshop, Istambul, 3rd October 2013
10. Ferreira M.O. Safety Assessment. Israeli Cosmetics Conference. Tel aviv, 12nd November 2013
11. Ferreira M.O. PIF = Product Information File. Israeli Cosmetics Conference. Tel aviv, 12nd November 2013
12. Ferreira M.O. Formulation principles & R&D exercises. European Cosmetics Regulation Workshop, Athens, 7th May 2014
13. Ferreira M.O. Safety Assessment (Opinion 1501/12) MoS Calculation - Practical Aspects on How to Make the MoS Calculations. European Cosmetics Regulation Workshop, Athens, 7th May 2014

14. Ferreira M.O. Safety Assessment for Different Types of Products & Examples. European Cosmetics Regulation Workshop, Athens, 7th May 2014
15. Ferreira M.O. PIF = Product Information File. European Cosmetics Regulation Seminar (Ecore), Tel aviv, 16th June 2014

Awards

1. Winner of the Portuguese Galenic Formulary Award (2004).
2. Winner of the "Best Communication" Award at the *II Congresso Nacional de Ciências Dermatocosméticas* (2009).

Presence in seminaries and scientific congresses

1. Skin and Formulation, 2nd Symposium, Versailles (France), 9-10th October, 2006.
2. Dermatology and Cosmetology – health to promote well-being Congress, Porto (Portugal), 18-19th April, 2007.
3. 36th Congress of the International Society of Medical Hydrology & Climatology, Porto (Portugal), 25-28th June, 2008.
4. 2008 Cosmetic Science Conference (CSC), In-cosmetics, Amsterdam (Netherlands), 2008.
5. Aquameeting – Health and Well-being International Seminar, Porto (Portugal), 19-21th September, 2008.
6. 2nd National Congress of Dermatocosmetic Sciences (1st congress of the Portuguese society of Cosmetic Sciences), Lisbon (Portugal), 27th March, 2009.
7. 2009 Cosmetic Science Conference (CSC), In-cosmetics, Munich (Germany), 22-23rd April, 2009.
8. SME's go Health International Information and Training Workshop, Istanbul (Turkey), 27th April, 2009.
9. 7th Framework Programme – Opportunities to SME's, 1st European Week of SME's 2009, Porto (Portugal), 7th May, 2009.
10. 3rd National Congress of Dermatocosmetic Sciences (2nd congress of the Portuguese society of Cosmetic Sciences), Lisbon (Portugal), 18th March, 2011.
11. 20th European Academy of Dermatology and Venereology Congress, Lisbon (Portugal), 20-24th October 2011
12. Day of the imaging technologies for the skin, 4th edition, DIIP Association, Tours (France), 27th September 2012.
13. European Cosmetics Regulation Seminar (Ecore), Tel aviv, 3rd-5th February 2013
14. European Cosmetics Regulation Seminar (Ecore), Cosmoprof Bologne, 10th March 2013
15. European Cosmetics Regulation Workshop, Istanbul, 30th September 2013 - 4th October 2013
16. Israeli Cosmetics Conference. Tel aviv, 12nd November 2013
17. European Cosmetics Regulation Workshop, Athens, 5th-9th May 2014
18. Cosmetics Europe Conference: Cosmetics at the Crossroads of Science and Regulation, 10-11th June 2014
19. European Cosmetics Regulation Seminar (Ecore), Tel aviv, 16th June 2014
20. III Cosmetology Innovation Workshop, Faculty of Pharmacy of Oporto University, 22nd May 2014

Personal skills

Language skills

English: excellent knowledge (860 points at *TOEIC*).
Spanish: good knowledge.
French: medium knowledge.

Informatics skills

Microsoft Word, Microsoft Excel, Microsoft Power Point, SPSS, EndNote

Additional information

Member of the following societies:
International Society for Biophysics and Imaging of the Skin (ISBS)
European Responsible Person Association (ERPA)
Portuguese Society of Cosmetic Sciences (SPCC)
OF

CERTIFICATE

Master's Degree

ISABEL GLÓRIA PEREIRA GUIMARÃES, Head of the Administration Office of the Faculty of Pharmacy of the University of Porto
Hereby certifies that

Marta Alexandra de Oliveira Ferreira
holder of Identity Card number 11658756, of portuguese nationality, completed at this University, on the 08th of September 2008, the MSc in Pharmaceutical Technology - Scientific Area in Pharmacotecnics, with the final grade of very good.
This degree was registered under number 11004863M050604002.
This Document is authenticated with the embossed seal of this Faculty.
Academic Services of the Faculty, 23rd of August 2010.

Isabel Guimarães

Emit. SRUNO
Emol. € 15,00
Cont. 16.

CERTIFICATE

Master's Degree

ISABEL GLÓRIA PEREIRA GUIMARÃES, Head of the Administration Office of the Faculty of Pharmacy of the University of Porto
Hereby certifies that

Marta Alexandra de Oliveira Ferreira

holder of Identity Card number 11658756, of portuguese nationality, completed at this University, on the 04th of September 2008, the MSc in Pharmaceutical Sciences, with the final grade of Sixteen (out of 20), corresponding to grade A on the European grading scale
This degree was registered under number 11009494M080601284.
This Document is authenticated with the embossed seal of this Faculty.
Academic Services of the Faculty, 23rd of August 2010.

ADMINISTRATIVE RESPONSIBLE

Isabel Guimarães

Emit. BRUNO
Emol. € 15,00
Conf. IG

inovapotek
PHARMACEUTICAL RESEARCH AND DEVELOPMENT

Estudo da Proposta n.º P135B13

TEXTOS ROTULAGEM DOS PRODUTOS:

CREME DE ROSTO

CREME DE MÃOS

CREME DE CORPO

Promotor:

Município de Chaves

Outubro 2015

UPTEC, Parque de Ciências e Tecnologia da Universidade do Porto ·Rua Alfredo Allen, n.º 455/461 · 4200-135 Porto · Portugal · tel.: +351 220 301 531 · fax: +351 220 301 532 · geral@inovapotek.com · www.inovapotek.com

CIDADE DE CHAVES
COOPERACIÓN TRANSFRONTERIZA ESPAÑA – PORTUGAL COOPERAÇÃO TRANSFRONTEIRIÇA
União Europeia
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EURO-REGIÓN termal y del agua
CHAVES TERMAS&SPA

De acordo com o Regulamento 1223/2009, a Rotulagem dos produtos cosméticos deve conter as seguintes informações:

- O nome ou a firma e o endereço da pessoa responsável;
- O conteúdo nominal no momento do acondicionamento, indicado em peso ou em volume;
- Data de durabilidade mínima: a própria data ou a indicação do sítio onde figura na embalagem é precedida da expressão: «A utilizar de preferência antes do final de…»;
- Período durante o qual o produto cosmético é seguro após a abertura e pode ser utilizado sem causar danos ao consumidor (PAO) – com a indicação do PAO no seu interior;

- As precauções especiais de utilização, pelo menos as indicadas nos anexos III a VI
- O número de lote de fabrico ou a referência que permita identificar o produto cosmético;
- A função do produto cosmético, salvo se esta decorrer claramente da respetiva apresentação;
- Uma lista de ingredientes.

Rotulagem do produto Cosmético	Creme Hidratante Rosto

DERMOCOSMÉTICA TERMAL AQUAE CREME HIDRATANTE ROSTO

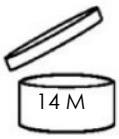
Gestão de Equipamentos do Município de Chaves, EM-SA
Largo Tito Flávio Vespasiano, s/n - 5400-534 Chaves, PORTUGAL
geral.termas@chaves.pt

50 mL ℮

(tamanho de letra com altura mínima de 2mm para "50 mL"; tamanho de letra com altura mínima de 3 mm para símbolo ℮)

Ingredients: Chaves Thermal Water (Chaves Aqua), Caprylic/Capric Triglyceride, Glyceryl stearate SE, Paraffinum Liquidum, Glycerin, Cetearyl alcohol, Ceteareth-20, Phenoxyethanol, Xanthan Gum, Aqua, Hydrochloric acid, Ethylparaben, Methylparaben, Parfum, Alpha-Isomethyl Ionone, Benzyl Alcohol, Benzyl Salicylate, Butylphenyl Methylpropional, Citronellol, Coumarin, Eugenol, Geraniol, Hexyl Cinnamal, Hydroxycitronellal, Linalool

"A utilizar de preferência antes do final de: ver embalagem"



Rotulagem do produto Cosmético	Creme Hidratante Corporal

DERMOCOSMÉTICA TERMAL AQUAE CREME HIDRATANTE CORPORAL

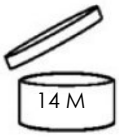
Gestão de Equipamentos do Município de Chaves, EM-SA
Largo Tito Flávio Vespasiano, s/n - 5400-534 Chaves, PORTUGAL
geral.termas@chaves.pt

200 mL ℮

(tamanho de letra com altura mínima de 3 mm para "200 mL"; tamanho de letra com altura mínima de 3 mm para símbolo ℮)

Ingredients: Chaves Thermal Water (Chaves Aqua), Caprylic/Capric Triglyceride, Glyceryl stearate SE, Paraffinum Liquidum, Glycerin, Cetearyl alcohol, Ceteareth-20, Phenoxyethanol, Xanthan Gum, Aqua, Hydrochloric acid, Ethylparaben, Methylparaben, Parfum, Alpha-Isomethyl Ionone, Benzyl Alcohol, Benzyl Salicylate, Butylphenyl Methylpropional, Citronellol, Coumarin, Eugenol, Geraniol, Hexyl Cinnamal, Hydroxycitronellal, Linalool

"A utilizar de preferência antes do final de: ver embalagem"



Rotulagem do produto Cosmético	Creme de Mãos

DERMOCOSMÉTICA TERMAL AQUAE CREME DE MÃOS

Gestão de Equipamentos do Município de Chaves, EM-SA
Largo Tito Flávio Vespasiano, s/n - 5400-534 Chaves, PORTUGAL
geral.termas@chaves.pt

100 mL℮

(tamanho de letra com altura mínima de 3 mm para "100 mL"; tamanho de letra com altura mínima de 3 mm para símbolo ℮)

Ingredients: Chaves Thermal Water (Chaves Aqua), Glycerin, Aqua, Butyrospermum parkii Butter, Ceteareth-20, Stearic acid, Cetearyl alcohol, Cetyl Alcohol, Isopropyl Myristate, Octyldodecanol, Phenoxyethanol, Alcohol denat., Ethylparaben, Methylparaben, Carbomer, Parfum, Triethanolamine, Hexyl Cinnamal, Alpha-Isomethyl Ionone, Benzyl Salicylate, Butylphenyl Methylpropional, Geraniol, Linalool, Hydroxycitronellal, Coumarin, Citronellol, Benzyl Alcohol, Eugenol.

"A utilizar de preferência antes do final de: ver embalagem"

Além das informações obrigatórias (definidas no Regulamento 1223/2009), pode ser incluído um texto introdutório, de cariz comercial ou outros. De ressalvar que **estes textos não devem alegar propriedades ao produto cosmético que não estejam devidamente suportadas**.

Caso estes produtos venham a ser comercializados em Farmácias, será necessário reservar um espaço para colocação do código CNP.

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PHARMACEUTICAL RESEARCH AND DEVELOPMENT

Proposta n.º P135B13

COMPROVATIVOS DA NOTIFICAÇÃO NO COSMETIC PRODUCTS NOTIFICATION PORTAL (CPNP)

Promotor:

Município de Chaves

Outubro 2015

UPTEC, Parque de Ciências e Tecnologia da Universidade do Porto ·Rua Alfredo Allen, n.º 455/461 · 4200-135 Porto · Portugal · tel.: +351 220 301 531 · fax: +351 220 301 532 · geral@inovapotek.com · www.inovapotek.com

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CHAVES TERMAS&SPA

According to Art 13(2) of Regulation 1223/2009 concerning cosmetic products, the original labelling and, where reasonably legible, a photograph of the corresponding packaging shall be submitted at the latest when the cosmetic product is placed on the market.

General information

CPNP Reference: 2045130
Industry Reference: N/A
Version: 1
Date first notification: 29/10/2015 13:58:17
Last modification date: 29/10/2015 13:58:17

Product Name	Shades (if applicable)	Language
DERMOCOSMÉTICA TERMAL AQUAE CREME HIDRATANTE CORPORAL		Português

Product specifically intended for children under 3 years of age: No

Responsible person: Gestão de Equipamentos do Município de Chaves, EM-SA
Responsible person address: Largo Tito Flávio Vespasiano, s/n 5400-534 Chaves Portugal
Phone:
Fax:
Email: geral.termas@chaves.pt

Contact person: Filipa Leite
Contact person address: Largo Tito Flávio Vespasiano, s/n 5400-534 Chaves Portugal
Phone: 00351276332445
Additional phone 1:
Additional phone 2:
Fax: 00351276332447
Email: filipaleite.termas@chaves.pt

Product ready to go on the market or product already on the market No

Product imported in the Community: No
Member State of first placing on the market: Portugal

Product details

Category level (1>2>3): Skin products > Skin care products > Body care products
Physical form: Cream / paste
Notification type: Concentration ranges

	Substance	Value (%w/w)	
Ingredients of concern (specific information)			
	ETHANOL	Not applicable	
	ISOPROPANOL	Not applicable	
	vitamin A or its derivatives	Not applicable	
xanthine derivatives		Not applicable	
	essential oils, camphor, menthol or eucalyptol total level	Not applicable	
essential oils, camphor, menthol or eucalyptol names and quantities		Not applicable	
Complete composition			
Formulation name: Skin Care Cream, Lotion, Gel			
Range	**AQUA**	**> 50 - ≤ 75%**	
Range	**GLYCERYL STEARATE SE**	**> 5 - ≤ 10%**	
Range	**CAPRYLIC/CAPRIC TRIGLYCERIDE**	**> 5 - ≤ 10%**	
Range	**CETEARYL ALCOHOL**	**> 1 - ≤ 5%**	
Range	**GLYCERIN**	**> 1 - ≤ 5%**	
Range	**PARAFFINUM LIQUIDUM**	**> 1 - ≤ 5%**	
Range	**METHYLPARABEN**	**> 0.1 - ≤ 1%**	
Range	**ETHYLPARABEN**	**> 0.1 - ≤ 1%**	
Range	**HYDROCHLORIC ACID**	**> 0.1 - ≤ 1%**	
Range	**XANTHAN GUM**	**> 0.1 - ≤ 1%**	
Range	**PHENOXYETHANOL**	**> 0.1 - ≤ 1%**	

Range	**PARFUM**	**≤ 0.1%**	
CMR			
None			
Nanomaterials			
None			

Original packaging (photograph)

Name	Options
No document	

Original labelling (image)

Name	Options
No document	

Comments

According to Art 13(2) of Regulation 1223/2009 concerning cosmetic products, the original labelling and, where reasonably legible, a photograph of the corresponding packaging shall be submitted at the latest when the cosmetic product is placed on the market.

General information

CPNP Reference: 2045099
Industry Reference: N/A
Version: 1
Date first notification: 29/10/2015 13:57:11
Last modification date: 29/10/2015 13:57:11

Product Name	Shades (if applicable)	Language
DERMOCOSMÉTICA TERMAL AQUAE CREME DE MÃOS		Português

Product specifically intended for children under 3 years of age: No

Responsible person: Gestão de Equipamentos do Município de Chaves, EM-SA
Responsible person address: Largo Tito Flávio Vespasiano, s/n 5400-534 Chaves Portugal
Phone:
Fax:
Email: geral.termas@chaves.pt

Contact person: Filipa Leite
Contact person address: Largo Tito Flávio Vespasiano, s/n 5400-534 Chaves Portugal
Phone: 00351276332445
Additional phone 1:
Additional phone 2:
Fax: 00351276332447
Email: filipaleite.termas@chaves.pt

Product ready to go on the market or product already on the market No

Product imported in the Community: No
Member State of first placing on the market: Portugal

Product details

Category level (1>2>3): Skin products > Skin care products > Hand care products
Physical form: Cream / paste
Notification type: Concentration ranges

	Substance	Value (%w/w)	
Ingredients of concern (specific information)			
	ETHANOL	**0.35**	
	ISOPROPANOL	Not applicable	
	vitamin A or its derivatives	Not applicable	
xanthine derivatives		Not applicable	
	essential oils, camphor, menthol or eucalyptol total level	Not applicable	
essential oils, camphor, menthol or eucalyptol names and quantities		Not applicable	
Complete composition			
Formulation name: Skin Care Cream, Lotion, Gel			
Range	**AQUA**	**> 50 - ≤ 75%**	
Range	**GLYCERIN**	**> 5 - ≤ 10%**	
Range	**ISOPROPYL MYRISTATE**	**> 1 - ≤ 5%**	
Range	**CETYL ALCOHOL**	**> 1 - ≤ 5%**	
Range	**CETEARYL ALCOHOL**	**> 1 - ≤ 5%**	
Range	**STEARIC ACID**	**> 1 - ≤ 5%**	
Range	**CETEARETH-20**	**> 1 - ≤ 5%**	
Range	**BUTYROSPERMUM PARKII BUTTER**	**> 1 - ≤ 5%**	
Range	**CARBOMER**	**> 0.1 - ≤ 1%**	
Range	**METHYLPARABEN**	**> 0.1 - ≤ 1%**	
Range	**ETHYLPARABEN**	**> 0.1 - ≤ 1%**	
Range	**ALCOHOL DENAT.**	**> 0.1 - ≤ 1%**	

Range	**PHENOXYETHANOL**	**> 0.1 - ≤ 1%**	
Range	**OCTYLDODECANOL**	**> 0.1 - ≤ 1%**	
Range	**TRIETHANOLAMINE**	**≤ 0.1%**	
Range	**PARFUM**	**≤ 0.1%**	
CMR			
None			
Nanomaterials			
None			

Original packaging (photograph)

Name	Options
No document	

Original labelling (image)

Name	Options
No document	

Comments

According to Art 13(2) of Regulation 1223/2009 concerning cosmetic products, the original labelling and, where reasonably legible, a photograph of the corresponding packaging shall be submitted at the latest when the cosmetic product is placed on the market.

General information

CPNP Reference: 2044992
Industry Reference: N/A
Version: 1
Date first notification: 29/10/2015 13:54:41
Last modification date: 29/10/2015 13:54:41

Product Name	Shades (if applicable)	Language
DERMOCOSMÉTICA TERMAL AQUAE CREME HIDRATANTE ROSTO		Português

Product specifically intended for children under 3 years of age: No

Responsible person: Gestão de Equipamentos do Município de Chaves, EM-SA
Responsible person address: Largo Tito Flávio Vespasiano, s/n 5400-534 Chaves Portugal
Phone:
Fax:
Email: geral.termas@chaves.pt

Contact person: Filipa Leite
Contact person address: Largo Tito Flávio Vespasiano, s/n 5400-534 Chaves Portugal
Phone: 00351276332445
Additional phone 1:
Additional phone 2:
Fax: 00351276332447
Email: filipaleite.termas@chaves.pt

Product ready to go on the market or product already on the market No

Product imported in the Community: No
Member State of first placing on the market: Portugal

Product details

Category level (1>2>3): Skin products > Skin care products > Face care products other than face mask
Physical form: Cream / paste
Notification type: Concentration ranges

	Substance	Value (%w/w)	
Ingredients of concern (specific information)			
	ETHANOL	Not applicable	
	ISOPROPANOL	Not applicable	
	vitamin A or its derivatives	Not applicable	
xanthine derivatives		Not applicable	
	essential oils, camphor, menthol or eucalyptol total level	Not applicable	
essential oils, camphor, menthol or eucalyptol names and quantities		Not applicable	
Complete composition			
Formulation name: Skin Care Cream, Lotion, Gel			
Range	**AQUA**	**> 50 - ≤ 75%**	
Range	**CAPRYLIC/CAPRIC TRIGLYCERIDE**	**> 5 - ≤ 10%**	
Range	**GLYCERYL STEARATE SE**	**> 5 - ≤ 10%**	
Range	**PARAFFINUM LIQUIDUM**	**> 1 - ≤ 5%**	
Range	**GLYCERIN**	**> 1 - ≤ 5%**	
Range	**CETEARYL ALCOHOL**	**> 1 - ≤ 5%**	
Range	**PHENOXYETHANOL**	**> 0.1 - ≤ 1%**	
Range	**XANTHAN GUM**	**> 0.1 - ≤ 1%**	
Range	**HYDROCHLORIC ACID**	**> 0.1 - ≤ 1%**	
Range	**ETHYLPARABEN**	**> 0.1 - ≤ 1%**	
Range	**METHYLPARABEN**	**> 0.1 - ≤ 1%**	

Range	**PARFUM**	**≤ 0.1%**	
CMR			
None			
Nanomaterials			
None			

Original packaging (photograph)

Name	Options
No document	

Original labelling (image)

Name	Options
No document	

Comments