**Avis de l'Anses**
**Saisine n°« 2025-MPEX-0083 »**

Le directeur général

Maisons-Alfort, le 9 septembre 2025

# AVIS
# de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail

## relatif aux contributions de l'Agence en 2024 aux consultations publiques sur les avis préliminaires du comité pour la sécurité des consommateurs (CSSC) concernant l'évaluation des risques des substances cosmétiques

*L'Anses met en œuvre une expertise scientifique indépendante et pluraliste.*
*L'Anses contribue principalement à assurer la sécurité sanitaire dans les domaines de l'environnement, du travail et de l'alimentation et à évaluer les risques sanitaires qu'ils peuvent comporter.*
*Elle contribue également à assurer d'une part la protection de la santé et du bien-être des animaux et de la santé des végétaux et d'autre part à l'évaluation des propriétés nutritionnelles des aliments.*
*Elle fournit aux autorités compétentes toutes les informations sur ces risques ainsi que l'expertise et l'appui scientifique technique nécessaires à l'élaboration des dispositions législatives et réglementaires et à la mise en œuvre des mesures de gestion du risque (article L.1313-1 du code de la santé publique).*
*Ses avis sont publiés sur son site internet.*

## 1. CONTEXTE ET OBJET DE LA SAISINE

Les produits cosmétiques sont réglementés au niveau européen par le règlement (CE) n°1223/2009. Son article 3 stipule qu'un produit cosmétique mis à disposition sur le marché doit être sûr pour la santé humaine lorsqu'il est utilisé dans des conditions d'utilisation normales ou raisonnablement prévisibles. En appui à la mise en œuvre de cette exigence, une liste de substances interdites dans les cosmétiques figure à l'annexe II. Par ailleurs, des restrictions concernant certaines substances intégrées dans des cosmétiques et des listes positives pour certains usages font l'objet des annexes III à VI[1].

La logique du règlement est double : formaliser la responsabilité des opérateurs économiques en matière de sécurité, sous la surveillance des Etats membres et encadrer l'usage de certaines substances chimiques dont les dangers ou risques sont connus au regard de leur utilisation dans la composition de produits cosmétiques, grâce à des processus de maîtrise des risques animés par la Commission européenne.

[1] Annexe II : substances interdites ; Annexe III : substances faisant l'objet de restrictions ; Annexe IV : colorants autorisés ; Annexe V : agents conservateurs autorisés ; Annexe VI : filtres ultraviolets autorisés

L'évaluation de la sécurité est décrite dans l'article 10 du règlement. Ainsi, avant la mise sur le marché d'un produit cosmétique et afin de démontrer que le produit est conforme à l'article 3, la personne responsable veille, à ce que sa sécurité soit évaluée sur la base des informations appropriées et à ce qu'un rapport sur la sécurité du produit cosmétique soit établi conformément à l'annexe I de ce règlement. Ce rapport sur la sécurité est inclus dans le dossier d'information produit.

Par ailleurs, afin de mettre à jour les annexes II à VI du règlement, la Commission européenne[2] s'appuie notamment sur deux instances : le comité scientifique pour la sécurité des consommateurs (CSSC[3]) qui est un comité scientifique indépendant et le comité technique pour les produits cosmétiques (COMCOS[4]) réunissant les autorités des Etats membres.

Dans ce cadre, la Commission européenne mandate le CSSC pour émettre des avis sur la sécurité de certaines substances cosmétiques. Cette sollicitation peut découler notamment de préoccupations émergentes en matière de sécurité sur une substance particulière. Elle peut aussi faire suite à une demande de la part d'industriels de modifier les conditions d'utilisation d'une substance, telles que décrites dans les annexes. Ainsi, le CSSC produit un avis préliminaire qui est soumis à consultation publique sur le site internet de la Commission européenne[5] afin de donner l'opportunité à toutes les parties prenantes de présenter leurs commentaires et toutes informations pertinentes. A la suite de cette étape de consultation, le CSSC répond directement aux commentaires reçus et finalise son avis.

En tenant compte de l'avis du CSSC, la Commission peut ainsi modifier les annexes du règlement cosmétique. Pour cela, la Commission est assistée par le COMCOS, composé de représentants des autorités des Etats membres de l'Union européenne. Ainsi, il donne un avis sur les modifications nécessaires pour adapter aux progrès techniques les différentes annexes du règlement cosmétique et procède au vote concernant les règlements Omnibus (figure 1).

[2] Et notamment la DG GROW (Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs)
[3] SCCS en anglais : « scientific committee on consumer safety »
[4] Standing Committee on Cosmetic Products
[5] https://health.ec.europa.eu/scientific-committees/scientific-committee-consumer-safety-sccs/sccs-opinions_en

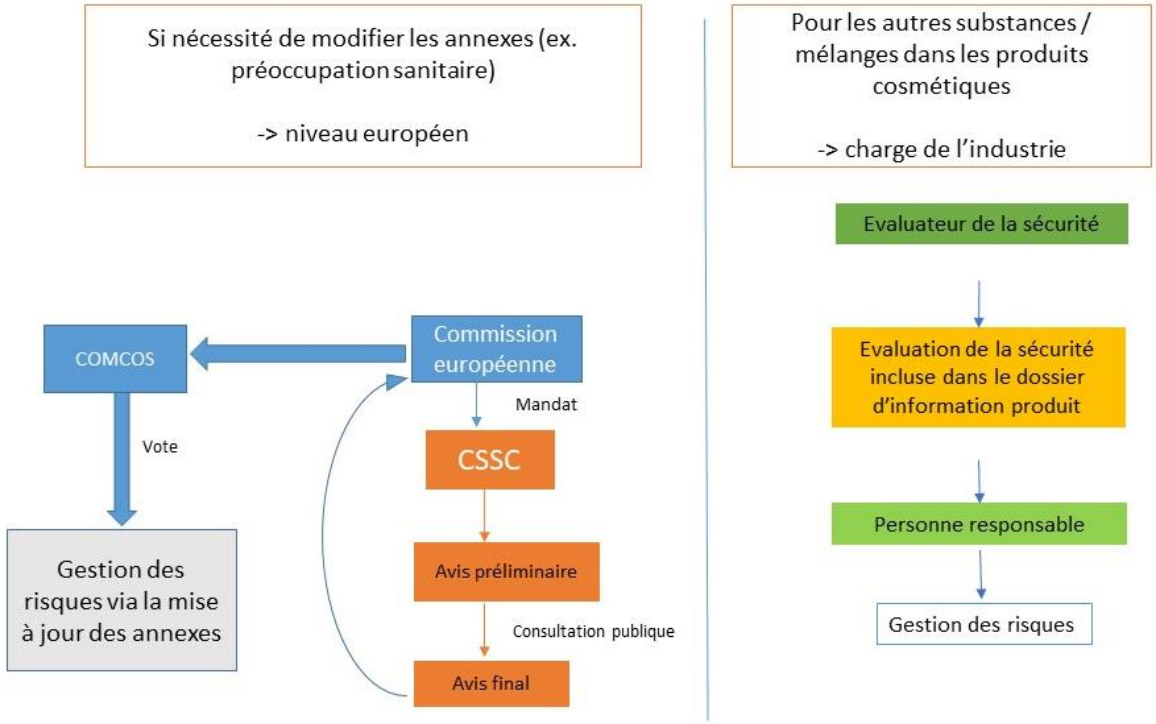


**Figure 1 : Evaluation de la sécurité des substances et produits cosmétiques**

Depuis le 1er janvier 2024, l'Anses est en charge des missions de vigilance et d'expertise en France relatives aux produits cosmétiques et de tatouage (article L1313-1du Code de la Santé Publique), ainsi que des substances que ces produits contiennent. Ces expertises incluent l'évaluation des dangers et des risques des substances cosmétiques. L'élaboration de commentaires sur les avis préliminaires du CSSC mises en consultation fait partie des missions qui ont été confiées à l'Anses.

**Le présent avis a pour objet de faire la synthèse des commentaires élaborés par l'Anses en 2024 sur les avis préliminaires du CSSC mis en consultation publique, en lien avec le règlement cosmétique.**

## 2. ORGANISATION DE L'EXPERTISE

### ■ Organisation générale

Les expertises ont été réalisées dans le respect de la norme NF X 50-110 « Qualité en expertise - Prescriptions générales de compétence pour une expertise (Mai 2003) ».

L'expertise concernant les substances et produits cosmétiques relève du domaine de compétences du Comité d'Experts Spécialisé (CES) « Substances chimiques visées par les règlements REACH et CLP » (CES REACH-CLP) et du CES « Evaluation des risques chimiques liés aux articles et produits de consommation » (CES CONSO).

Ne s'agissant pas de conduire une évaluation des risques, mais de soumettre des commentaires sur des évaluations scientifiques réalisées par le CSSC dans un délai contraint (généralement 2 mois), ceux-ci ont été produits en mobilisant l'expertise interne de la Direction de l'évaluation des risques de l'Anses.

Cet avis relatif aux commentaires sur les avis préliminaires du CSSC soumis à consultation publique en 2024 a été présenté pour information au CES REACH-CLP réuni le 8 juillet 2025.

L'Anses analyse les liens d'intérêts déclarés par les experts avant leur nomination et tout au long des travaux, afin d'éviter les risques de conflits d'intérêts au regard des points traités dans le cadre de l'expertise.

Les déclarations d'intérêts des experts sont publiées sur le site internet https://dpi.sante.gouv.fr.

## 3. ANALYSE ET CONCLUSIONS

Au cours de l'année 2024, l'Anses a commenté 9 avis préliminaires du CSSC parmi les 13 mises en consultation publique sur le site de la Commission européenne. En fonction des ressources disponibles, la priorité a été donnée aux substances classées en tant que cancérogène, mutagène et/ou toxique pour la reproduction ainsi qu'aux substances sous la forme de nanomatériau et substances présentant des préoccupations de perturbation endocrinienne. Les substances qui ont fait l'objet d'une consultation du CSSC en 2024 sont les suivantes :

**Tableau 1 : Substances pour lesquelles un avis du CSSC a été soumise à consultation publique en 2024**

| **Substances** | **Numéro CAS** | **Référence** | **Mandat du CSSC par la Commission européenne** |
|---|---|---|---|
| Salicylate d'hexyle | 6259-76-3 | SCCS/1658/23 | Evaluation de la sécurité suite à sa classification en tant que toxique pour la reproduction de catégorie 2 et sensibilisant cutané (article 15(1) du règlement cosmétique) |
| *Hydroxypropyl p-phenylenediamine et son sel dihydrochlorure (A165)*<br>*(non commentée par l'Anses)* | *73793-79-0*<br>*1928659-47-5* | *SCCS/1659/23* | *Réévaluation de la sécurité suite à la soumission de données de la part de l'industrie concernant la génotoxicité.* |
| *Benzophenone-4*<br>*(non commentée par l'Anses)* | *4065-45-6* | *SCCS/1660/23* | *Evaluation de la sécurité car la substance fait partie de la liste prioritaire[6] de la Commission européenne des perturbateurs endocriniens potentiels à évaluer dans le cadre du règlement cosmétique* |
| Dioxyde de titane | 13463-67-7<br>1317-70-0<br>1317-80-2 | SCCS/1661/23 | Réévaluation de la sécurité avec un focus sur la génotoxicité et sur l'exposition par inhalation et par voie orale |
| Aluminium | | SCCS/1662/23 | Réévaluation de la sécurité concernant la demande de mise à jour des concentrations de cette substance dans les produits cosmétiques suite à la soumission de données de la part de l'industrie concernant l'estimation de l'exposition |

6 https://single-market-economy.ec.europa.eu/sectors/cosmetics/cosmetic-products-specific-topics/endocrine-disruptors_en

| **Substances** | **Numéro CAS** | **Référence** | **Mandat du CSSC par la Commission européenne** |
|---|---|---|---|
| Huile de vétiver acétylée | 84082-84-8 | SCCS/1663/24 | Réévaluation de la sécurité de la substance dans les produits cosmétiques pulvérisables suite à la soumission de données de toxicité par inhalation de la part de l'industrie |
| Triphenyl phosphate | 115-86-6 | SCCS/1664/24 | Evaluation de la sécurité car la substance fait partie de la liste prioritaire[6] de la Commission européenne des perturbateurs endocriniens potentiels à évaluer dans le cadre du règlement cosmétique |
| Argent | 7440-22-4 | SCCS/1665/24 | Evaluation de la sécurité suite à sa classification en tant que toxique pour la reproduction de catégorie 2 (article 15(1) du règlement cosmétique) |
| *Citral*<br>*(non commentée par l'Anses)* | *5392-40-5* | *SCCS/1666/24* | *Réévaluation de la sécurité liée au potentiel sensibilisant de la substance* |
| Dioxyde de titane avec un nouveau revêtement de surface (nano) | | SCCS/1667/24 | Evaluation de la sécurité suite à la soumission de données de la part de l'industrie |
| Salicylate d'hexyle | 6259-76-3 | SCCS/1668/24 | Evaluation complémentaire à l'avis ci-dessus (SCCS/1658/23) afin de prendre en compte l'utilisation chez des enfants de moins de 3 ans (article 15(1) du règlement cosmétique) |
| Biphenyl-2-ol et Sodium 2-biphenylolate | 90-43-7 and 132-27-4 | SCCS/1669/24 | Réévaluation de la sécurité suite à sa classification en tant que substance cancérogène de catégorie 2 (article 15(1) du règlement cosmétique) |
| *HC Yellow No.16*<br>*(non commentée par l'Anses)* | *1184721-10-5* | *SCCS/1670/24* | *Evaluation de la sécurité suite à la soumission de données de la part de l'industrie concernant la pureté de la substance* |

Une synthèse des commentaires émis est présentée ci-dessous.

Concernant les avis SCCS/1658/23 et SCCS/1668/24 relatives au salicylate d'hexyle, l'Anses a formulé un certain nombre de préoccupations concernant, notamment, la nécessité d'approfondir l'évaluation :

- des propriétés de sensibilisation cutanée avant de conclure que ce risque est négligeable,
- du potentiel de perturbation endocrinienne en prenant en compte, dès qu'elles seront disponibles, les conclusions pour son métabolite, l'acide salicylique, dans le cadre de la réglementation sur les produits biocides.

Par ailleurs, l'Anses a noté que plusieurs études de toxicologie (étude de toxicité répétée, études de toxicité prénatale, mutagénicité *in vitro*) sont actuellement en cours de réalisation dans le cadre du règlement REACH sur le salicylate d'hexyle. Il a également été porté à la connaissance du CSSC l'existence d'un essai de dépistage de la toxicité pour la reproduction et le développement réalisé avec un analogue structural, l'éthyle hexyle de salicylate. Une mise à jour de l'évaluation de la sécurité pourrait être nécessaire en fonction des résultats.

De plus, l'Anses a questionné l'absence d'évaluation des risques pour les enfants de moins de 3 ans (SCCS/1658/23).

Concernant l'addendum qui a suivi et qui focalise sur l'évaluation de la sécurité chez les enfants de moins de 3 ans (SCCS/1668/24), l'Anses a soulevé des questions sur les choix de paramètres d'exposition retenus. L'Anses considère également que l'évaluation de la sécurité et les dispositions réglementaires en découlant doivent être alignées avec celles existant pour l'acide salicylique pour cette population.

Enfin, l'Anses a souligné la nécessité de conduire une évaluation de l'exposition agrégée sachant que de nombreux salicylates présents dans la composition de produits cosmétiques se dégradent en acide salicylique, celui-ci étant responsable de la toxicité systémique de ces substances.

Concernant l'avis SCCS/1661/23 relative au dioxyde de titane ($TiO_2$), l'Anses a soumis des commentaires sur la composition et les propriétés physico-chimiques des formes de $TiO_2$ couvertes par cet avis ainsi que sur l'analyse des tests de génotoxicité.

Dans l'ensemble, l'Anses converge sur le fait que des données additionnelles sont nécessaires pour conclure à la sécurité des formes de $TiO_2$ listées dans cet avis. Parmi les 84 formes (nanométriques et micrométriques) couvertes par cet avis, des données de génotoxicité sont disponibles seulement sur deux formes nanométriques sphéroïdes (rutile ou rutile contenant jusqu'à 5% d'anatase) avec un revêtement de surface (silice ou alumine et dimethicone). L'Anses considère que les études présentent des limites pour conclure de manière définitive sur ces formes spécifiquement. De plus, les données sont jugées insuffisantes pour démontrer qu'elles sont représentatives de l'ensemble des formes couvertes dans cet avis, d'autant plus en l'absence d'approche harmonisée pour le regroupement des nanomatériaux et en raison du nombre élevé de formes utilisées dans les produits cosmétiques.

Enfin, l'Anses a informé le CSSC des préoccupations actuellement soulevées dans la littérature concernant les effets de certaines formes de $TiO_2$ (anatase sous forme nanométrique) sur les fonctions de reproduction et sur le développement.

En plus des commentaires soumis, il est à noter que l'Anses a également publié une note d'appui scientifique et technique relative à l'analyse des données fournies dans le cadre de l'évaluation du $TiO_2$ dans les produits cosmétiques[7].

Concernant l'avis SCCS/1662/23 relative à l'aluminium, l'Anses a noté les résultats contradictoires rapportés dans les études de génotoxicité, et considère qu'elles ne permettent pas de conclure à une absence de génotoxicité.

L'Anses a également attiré l'attention sur le fait que d'autres composés de l'aluminium non identifiés par le CSSC peuvent exister dans les cosmétiques, en particulier sous la forme nanométrique selon la base de données française R-nano.

Concernant l'avis SCCS/1663/24 relative à l'huile de vétiver acétylée, l'Anses a soulevé des questions concernant les choix des paramètres d'exposition retenus.

Concernant l'avis SCCS/1664/24 relative au triphényl phosphate, l'Anses a porté à la connaissance du CSSC le fait qu'une étude sur la toxicité pour la reproduction de cette substance est en cours par le NTP[8]. Une mise à jour de l'évaluation de la sécurité pourrait être nécessaire en fonction des résultats.

[7] Anses. (2024). Note d'AST relatif à l'analyse des données fournies dans le cadre de l'évaluation du dioxyde de titane (TiO2) dans les produits cosmétiques. (saisine 2024-AST0114). Maisons-Alfort : Anses, 2024, 21 p. https://www.anses.fr/fr/system/files/REACH2024AST0114.pdf

[8] US National Toxicology Program

L'Anses fait également référence à son expertise relative à l'analyse des meilleures options de gestion des risques pour cette substance pour porter à la connaissance du CSSC des études non détaillées dans son avis[9].

Concernant l'avis SCCS/1665/24 relative à l'argent, la substance est à considérer selon l'Anses comme un nanomatériau sur la base des données analytiques ne permettant pas de conclure sur l'absence de particule constitutive identifiable et au regard de la définition d'un nanomatériau d'après le règlement sur les produits cosmétiques. Une évaluation spécifique de sa sécurité devrait donc être conduite, en considérant les spécificités liées à la taille nanométrique.

L'Anses a également soulevé des questions concernant les choix de la valeur d'absorption cutanée, les paramètres d'exposition retenus ainsi que sur les lectures croisées proposées avec différentes formes d'argent dont le zéolite d'argent et de zinc.

Concernant l'avis SCCS/1667/24 relative au dioxyde de titane avec un nouveau revêtement de surface (nano), l'Anses a formulé des demandes de clarifications sur certains paramètres physico-chimiques.

Concernant l'avis SCCS/1669/24 relative au biphenyl-2-ol et au sodium 2-biphenylolate, l'Anses a émis des questions concernant les choix de paramètres d'exposition retenus, particulièrement pour le calcul de l'exposition agrégée, et a soulevé le fait que la substance doit être considérée comme un sensibilisant cutané étant donné sa classification.

L'ensemble des commentaires soumis par l'Agence sont transcrits dans l'annexe de cet avis.

## 4. CONCLUSIONS ET RECOMMANDATIONS DE L'AGENCE

Depuis le 1er janvier 2024, l'Anses est en charge des missions de vigilance et d'expertise relatives aux produits cosmétiques et de tatouage, ainsi que des substances que ces produits contiennent.

Pour sa première année d'exercice, l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail a commenté 9 avis préliminaires du CSSC parmi les 13 mises en consultation publique sur le site de la Commission européenne.

Par ailleurs l'Agence a réalisé d'autres expertises concernant l'évaluation des dangers et des risques de substances et/ou produits cosmétiques. Il s'agit des expertises suivantes :

- Note d'appui scientifique et technique de l'Agence relatif à l'analyse des données fournies dans le cadre de l'évaluation du dioxyde de titane ($TiO_2$) dans les produits cosmétiques (saisine n°2024-AST-0114)
- Note d'appui scientifique et technique de l'Agence relatif à la mise à jour de la recommandation de la Commission européenne du 22 septembre 2006 relative aux produits de protection solaire et aux allégations des fabricants quant à leur efficacité (saisine n°2024-AST-0113)

Les résultats de ces expertises sont publiés par l'Agence sur son site internet.

Pr. Benoit Vallet

[9] Anses. Analysis of the most appropriate risk management option (RMOA). Triphenyl phosphate (TPP). July 2019.

## MOTS-CLÉS

cosmétique, CSSC, évaluation des risques, dioxyde de titane, salicylate de méthyle, salicylate d'hexyle, aluminium, huile de vétiver acétylée, triphenyl phosphate, argent, biphenyl-2-ol, sodium 2-biphenylolate

## CITATION SUGGÉRÉE

Avis relatif aux commentaires soumis en 2024 par l'Agence sur les avis préliminaires du comité pour la sécurité des consommateurs (CSSC) concernant l'évaluation des risques des substances cosmétiques. (saisine 2025-MPEX-0083). Maisons-Alfort : Anses, 33 p.

## ANNEXE 1

### Présentation des intervenants

**PRÉAMBULE** : les experts membres de comités d'experts spécialisés, de groupes de travail ou désignés rapporteurs sont tous nommés à titre personnel, *intuitu personae*, et ne représentent pas leur organisme d'appartenance.

## COMITÉ D'EXPERTS SPÉCIALISÉ

- CES « Substances chimiques visées par les règlements REACH et CLP » *(cinquième mandature, du 1er septembre 2024 au 31 août 2028)*

### Président

M. Christophe MINIER – Professeur des Universités – Université Le Havre - Normandie.

### Vice-présidents

M. Fabrizio PARISELLI – Ingénieur de recherche toxicologue – CNRS.

Mme Sylvie BALTORA-ROSSET – Professeur des Universités (Université Picardie Jules Verne) – Compétences : chimie analytique et évaluation des risques.

### Membres

Mme Isabelle BILLAULT – Maître de conférences (Université Paris-Saclay) – Compétences : chimie organique, chimie analytique, propriétés physico-chimiques des substances.

M. Fabien BRETTE – Chargé de recherche (Inserm, Université de Montpellier, CNRS) – Compétences : physiologie cardiovasculaire, modèles *in vitro* et *in vivo*, écotoxicologie, environnement.

M. Christophe CALVAYRAC – Maître de conférences (Université de Perpignan Via Domitia) – Compétences : chimie analytique, devenir environnemental, dégradation biotique et abiotique, microbiologie, écologie microbienne.

M. Sébastien ELIS – Directeur de recherche (INRAE, Centre Val de Loire, Nouzilly) – Compétences : biologie de la reproduction (ovaires, ovocytes, métabolisme lipidique, bisphénols, reproduction femelle, PFAS).

M. Benjamin EVEN – Maître de conférences (Université Paris Est - Créteil UPEC) – Compétences : vieillissement, toxicologie, signalisation cellulaire et moléculaire.

M. Pascal FROMENT – Directeur de recherche (INRAE, Centre Val de Loire, Nouzilly) – Compétences : biologie de la reproduction (gonades, fonction testiculaire, perturbateurs endocriniens, modèle aviaire, rongeur, humain).

Mme Aurore GELY-PERNOT – Maître de conférences (EHESP-IRSET, Rennes) – Compétences : biologie de la reproduction, pesticides, toxicologie, santé environnement, perturbateurs endocriniens.

Mme Laure GEOFFROY – Ecotoxicologue (INERIS) – Compétences : environnement, écotoxicologie, nanomatériaux, perturbateurs endocriniens.

Mme Aurélie GOUTTE – Maître de conférences (Ecole Pratique des Hautes Etudes - UMR METIS - EPHE - Université de la Sorbonne Paris 5) – Compétences : pesticides, résidus pharmaceutiques, phtalates, perturbations endocriniennes, poissons, transferts des substances ressources.

Mme Catherine GROSDEMANGE-BILLIARD – Professeur de chimie (Université de Strasbourg) – Compétences : chimie organique et analytique, analyse de méthode, antimicrobiens, nanomatériaux.

M. Ludovic LE HEGARAT – Chef d'unité adjoint Toxicologie des contaminants (Laboratoire de Fougères – Anses) – Compétences : génotoxicité, toxicologie, valeurs toxicologiques de référence, hépatotoxicité, métabolisme.

M. Nicolas LOISEAU – Directeur de recherche (INRAE) – Compétences : chimie, toxicologie, hépatotoxicologie, QSAR, pharmacologie.

M. Jean-François MASFARAUD - Maître de conférences (Université de Lorraine, CNRS) – Compétences : écotoxicologie/toxicologie, étude de risques, contaminants, appréciation dangers.

M. Christophe MINIER – Professeur des Universités (Université Le Havre – Normandie) – Compétences : écotoxicologie, contexte réglementaire, endocrinologie, perturbateurs endocriniens.

M. Thierry ORSIERE – Ingénieur de recherche HDR (Université Aix Marseille) – Compétences : toxicologie génétique.

M. Fabrizio PARISELLI – Ingénieur de recherche toxicologue – CNRS - Compétences : toxicologie, réglementation, santé et sécurité au travail, évaluation des risques.

Mme Cécile QUANTIN – Professeure d'université (Université Paris Sud) – Compétences : contamination des sols, traçage isotopique, métaux, HAP, géochimie environnementale

Mme Sophie ROBERT – Expert assistance conseil en risques chimiques et toxicologiques en santé au travail (INRS, Paris) – Compétences : réglementation produits chimiques et biocides, prévention risques chimiques professionnels, sécurité des travailleurs, études de filière.

Sylvaine RONGA-PEZERET – Médecin toxicologue, évaluateur de risques sanitaires (EDF - Service des Etudes Médicales) – Compétences : médecine, toxicologie, évaluation de risques.

Mme Sylvie BALTORA-ROSSET – Professeur des Universités (Université Picardie Jules Verne) – Compétences : chimie analytique et évaluation des risques.

M. Bernard SALLES – Professeur émérite de l'Université de Toulouse - Compétences : toxicologie, environnement et santé, cancérogenèse, NAMs

Mme Pascale TALAMOND - Ingénieure (IRD, ISE-M, Université de Montpellier II) – Compétences : chimie de la biologie, chimie de l'environnement, caractérisation chimique, biomarqueurs des activités anthropiques.

Mme Paule VASSEUR – Professeur de toxicologie émérite de l'Université de Lorraine, chercheur toxicologue écotoxicologue - Compétences : toxicologie, santé publique, santé environnement, évaluation des risques sanitaires.

Mme Catherine VIGUIE – Directrice de recherche, vétérinaire (INRAE) - Compétences : endocrinologie, perturbateurs endocriniens, toxicologie, pharmacologie.

## PARTICIPATION ANSES

### Coordination scientifique

Mme Sandrine CHARLES – Cheffe de projets scientifiques - Unité REACH CLP PE - Direction de l'évaluation des risques

### Contribution scientifique

Mme Sandrine CHARLES – Cheffe de projets scientifiques - Unité REACH CLP PE - Direction de l'évaluation des risques

Mme Pauline GUILLOU – Cheffe de projets scientifiques – Unité d'Evaluation des Valeurs de référence et des Risques des Substances Chimiques - Direction de l'évaluation des risques

Mme Léa LAPLANTE – Chargée de projets scientifiques - Unité REACH CLP PE - Direction de l'évaluation des risques

Mme Alice MATEUS – Chargée de projets scientifiques - Unité REACH CLP PE - Direction de l'évaluation des risques

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### Secrétariat administratif

Mme Agnès BRION

## ANNEXE 2 : COMMENTAIRES SOUMIS PAR L'AGENCE

**ANSES comments on the SCCS preliminary opinion on hexyl salicylate (SCCS/1658/23)**

### 2. Mandate from the European Commission

Table 1: the unit of maximum concentration (expressed in %w/w) should be indicated.

### 3.3.2. Skin sensitisation

Anses acknowledges that human data are negative. However, some reasons may explained the absence of reactions, as described in the RAC opinion. Anyway, the substance is currently classified as Skin Sens. 1 according to CLP Regulation, based on animal data. More argumentation is thus needed before concluding that the risk is negligible (for example with performing a quantitative risk assessment using EC3 value from the LLNA).

### 3.2.4. Calculation of SED /LED – inhalation route

According to the SCCS Notes of Guidance, exposure data are available in the open literature. When no specific values were given in the SCCS Notes of guidance for the amount of the products, the results from other studies can be used. For example, Ficheux & Roudot (2017) provide exposure data for several cosmetic products formulations.

Another study (Loretz et al. (2006); not cited in the SCCS Notes of Guidance) was used to estimate the systemic exposure dose after inhalation exposure to hexyl salicylate in hair spray formulation. This choice to select one study against another should be more justified in the SCCS opinion. In particular, this exposure study was performed in US and the relevance for European population would be discussed. Moreover, the SCCS retains the P95 values from this study to estimate the amount of product per day. Even if more conservative, Anses notes that the P90 is generally chosen.

Moreover, the study by Hall et al. (2007) was used for deodorant /antiperspirant spray formulation leading to an amount by application of 6.1 g/d (3050 mg/application; 2 applications per day). Anses notes that, according to this publication, the value refers to arms use only; for product used over torso and under arms, the P90 is 6.54 g/d (as also cited in the SCCS Notes of Guidance page 27). Could you please justify the choice made in the SCCS opinion?

*Reference: Hall et al. 2007. European consumer exposure to cosmetic products, a framework for conducting population exposure assessments. Food and Chemical Toxicology 45 (2007) 2097–2108*

An exhaustive review of the literature on this point is encouraged as these parameters are key for the risk assessment performed. If literature exists that lead to more stringent parameters, they should be cited and the reason why discarded explained. Overall more justifications of the choices made in the exposure parameters and detailed calculations (within an annex for example), in particular when calculations were remade by the SCCS, would have been appreciated for a better understanding.

### 3.2.4.3. Exposure of children < 3 years to hexyl salicylate in cosmetic products

According to SCCS, specific exposure calculations for children are needed. No calculation of the MoS is provided in the SCCS opinion. It is thus not clear if SCCS considers hexyl salicylate is safe for this population.

### 3.2.3. Other studies on toxicokinetics

- Oral bioavailability

Anses notes that in addition to Davison et al. (1961) studies, another study performed with methyl salicylate (Yamagata et al., 1976) can be used, as supportive information, in the SCCS opinion. This study is summarised in the CLH report on methyl salicylate.

References:


- Yamagata T, Inoue H, Kodama R et al. 1976. Metabolic fate of methyl salicylate. I. Absorption, distribution and excretion in hairless mice. Oyo Yakuri 12:371-383.Yano T, Nakagawa A, Tsuji M, Noda K. 1986. Skin permeability of various non-steroidal anti-inflammatory drugs in man. Life Sci.;39(12):1043-50.
- https://echa.europa.eu/documents/10162/d619c80c-d1f2-f3a6-0005-0fa599cce911
- https://echa.europa.eu/documents/10162/c4cbf667-aff6-d148-fc50-f41e61a27942


### 3.3.4. Repeated dose toxicity

In the context of Reach Regulation, Anses notes that a decision on testing proposals (TPE) is ongoing for hexyl salicylate. The deadline for submission is 23 February 2026.

A. Information required from the registrants subject to Annex IX of Reach:
- Subchronic toxicity study (90-day)(Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) by oral route, in rats with an additional reproductive toxicity cohort of females included to cover the endpoints of a reproduction/developmental screening test (according to OECD TG 421)

Update of safety evaluation may be needed when this study will be available, depending on the results obtained.

Reference


- https://echa.europa.eu/documents/10162/7dd23fc0-a3e3-910b-55f3-4c17bc72030c


### 3.3.5. Reproductive toxicity

In the SCCS opinion, it is refered to analogous substances, such as cyclohexyl salicylate. However, no rationale is provided to justify (structural and toxicological) similarity with hexyl salicylate.

In addition, within CLP process, France, as dossier submitter of the proposed classification as Repr. 2 for hexyl salicylate, identified a reproduction /developmental toxicity screening test (according to OECD TG 421) with another analogous substance, ethyl hexyl salicylate (EHS). This study was considered by Anses as EHS is a relevant substance for read across with hexyl salicylate. Moreover, the effects reported are similar to those found with other salicylates (as methyl salicylate or salicylic acid). The study summary is available on ECHA Dissemination website. Based on the observation of increased post-implantation loss, reduction in gestation index and lower litter size, the LOAEL for developmental toxicity is 80 mg/kg bw/d and the NOAEL is 25 mg/kg bw/d. The LOAEL for maternal toxicity is 250 mg/kg bw/d (NOAEL being 80 mg/kg bw/d). Thus, this study shows developmental toxicity of EHS, and the effects reported are similar to those found with other salicylates (as methyl salicylate, sodium salicylate or salicylic acid).

In the context of Reach Regulation, Anses notes that a decision on testing proposals (TPE) is ongoing for hexyl salicylate. The deadline for submission is 23 February 2026.

A. Information required from the registrants subject to Annex IX of Reach:
- Prenatal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) by oral route, in one species (rat or rabbit)

B. Information required from the registrants subject to Annex X of Reach:
- Prenatal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) by oral route, in a second species (rat/rabbit)

Update of safety evaluation may be needed when these studies will be available, depending on the results obtained.

References

- https://echa.europa.eu/fr/registry-of-clh-intentions-until-outcome/-/dislist/details/0b0236e18471782f
- https://echa.europa.eu/fr/registration-dossier/-/registered-dossier/14203/7/9/3
- https://echa.europa.eu/documents/10162/7dd23fc0-a3e3-910b-55f3-4c17bc72030c

### 3.3.6. ED

ED assessment according to ECHA/EFSA Guidance for the identification of endocrine disruptors in the context of Regulations (EC) No 1107/2009 is still ongoing by NL for salicylic acid.

At the time being, Anses considers that more data is needed to confirm effects and concerns seen in studies performed with other salicylates. In particular, endocrine activity (such as effects on thyroid hormones, testosterone and cortisol) is reported with aspirin but it is not clear to what extent these results can be extrapolated to salicylic acid. Moreover, a more in-depth assessment of the possible different modes of action and interactions (EAS, T possibly via ENV testing or COX), should be carried out.

### 3.3.6. Mutagenicity / genotoxicity

Anses notes that a decision on compliance check (CCH) is ongoing for hexyl salicylate in the context of Reach Regulation. The deadline for submission is 22 April 2025.

A. Information required from all the registrants subject to Annex VIII of Reach

- *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490).

Update of evaluation of mutagenicity may be needed when this study will be available, depending on the results obtained.

Regarding clastogenic potential, *in vitro* and *in vivo* data with methyl salicylate are available and also point to negative results.

References:

- https://echa.europa.eu/documents/10162/dac8e79c-da62-4995-0cde-4982e7d56b6b
- Food and Drug Administration (FDA). Center for Drug Evaluation and Research. 2006. Pharmacology / Toxicology review and evaluation. FS-67 Patch (10% Methyl salicylate & 3% l-menthol Topical patch). NDA number 22-029

### 3.4. Safety evaluation

At the time being, there is no repeated-dose toxicity study with hexyl salicylate. Anses agrees with the approach followed using the POD (NOAEL = 75 mg/kg bw/day) from data with salicylic acid as metabolite of hexyl salicylate. Anses notes that consistent but slightly lower NOAEL can be identified from data with structural analogues, such as methyl salicylate and EHS, for example:

- Methyl salicylate:
  - NOAEL = 50 mg/kg bw/day (LOAEL = 250 mg/kg bw/d) from repeated dose toxicity study (Webb and Hansen, 1963)
  - NOAEL between 20 and 60 mg/kg bw/day from developmental toxicity studies (FDA, 2006; NTP, 1984)
- Ethyl hexyl salicylate
  - NOAEL = 25 mg/kg bw/d (LOAEL = 80 mg/kg bw/d) from an OECD 421 study (Unamed, 2012 – disseminated study summary).

Finally, a repeated-dose toxicity study is expected to be performed within Reach Regulation. Update of safety evaluation may be needed depending on the result of this study.

References:

- https://echa.europa.eu/documents/10162/6fa86360-6573-cbbe-19d9-a36e30ca197b
- https://echa.europa.eu/fr/registration-dossier/-/registered-dossier/14203/7/9/3

## ANSES comments on the addendum to the SCCS preliminary opinion on hexyl salicylate (SCCS/1668/24)

3.2.2. Dermal / percutaneous absorption

**Regarding dermal absorption,** Anses considers that cautious should be made in the choice of the dermal absorption value due to the uncertainties linked to the duration of the exposure in the study (8 hours instead of 24 hours as required in the OECD TG 428) and the fact that children's skin can be more permeable than adult's skin (Yun et al. 2022).

As a more conservative approach, Anses considers that "the potentially absorbed dose" obtained in group B (5.20% instead of 3.04%) should be *a minima* retained. Indeed, as mentioned in the OECD guidance notes on dermal absorption studies (OECD, 2022), test substance in the lower layers of the stratum corneum should be assumed to form a reservoir. This may become systemically available, unless it can be demonstrated that:

- absorption is complete and
- this test substance will remain in the stratum corneum and
- exfoliation can be assumed (OECD, 2022).

As a consequence, this would lead to a dermal absorption of 15.6% instead of 13.4%, after taking into account the correction factor of 3 for duration extrapolation in the study.

Reference:

- OECD guidance notes on dermal absorption studies. ENV/JM/MONO(2011)36/REV1. 20 September 2022.
- Yun YE, Calderon-Nieva D, Hamadeh A, Edginton AN. Development and Evaluation of an In Silico Dermal Absorption Model Relevant for Children. Pharmaceutics. 2022 Jan 12;14(1):172. doi: 10.3390/pharmaceutics14010172. PMID: 35057066; PMCID: PMC8780349.

**Regarding metabolism of hexyl salicylate**, additional information (mainly as QSAR estimation) can be retrieved in the additional information report elaborated by Anses under C&L process.

Reference:

https://echa.europa.eu/documents/10162/0767b838-6a37-406a-b8c4-b0d524ef581e

3.2.4. Calculation of SED / LED

According to table A7.2 of the SCCS Notes of Guidance, children are not supposed to be exposed to:

- Lipstick and fragrance products
- Hair conditioner under age of 1 year

However, we acknowledge that taking into account these products lead to a worst case aggregated exposure. If hair conditioner and fragrance products are considered by the SCCS as appropriate for children for this case, an estimation of exposure by inhalation should be provided unless it can be demonstrated that these products are not sprayed.

In table 4, the exposure data for children were deduced from the daily exposure data for adults taking into consideration the body surface area of adults and children. However, Anses notes that specific data for this category of population are available for certain product types (e.g Gomez-Berrada et al. 2017; Garcia-Hidalgo et al. 2017; Ficheux and Roudot, 2017) as found in table A.7.1 of the SCCS Notes of Guidance. **Extrapolation from exposure data in adults should only remain a default approach if specific data is not available for a particular product type** and/or if the value obtained is more conservative. However, this does not seems always the case here.

For example, for shower gel, the following values are proposed by the applicant:

- 0.05 g/day (after applying the retention factor of 0.01) or 5.43 mg/kg bw/day in infants (0.5-1 year)
- 0.06 g/day (after applying the retention factor of 0.01) or 5.11 mg/kg bw/day in toddlers (1 - 3 years)

Higher values are consistently reported by Gomez-Berrada et al. 2017 (P95 = 10.5 g/day in children aged 0-23 months old, which would correspond to a daily exposure of 0.105 g/d after applying a retention factor of 0.01), Ficheux et al. 2016 (P95 = 9.37 mg/kg bw/d for children aged 0-3 years) or Garcia-Hidalgo et al. 2017 (P95 = 9 g/application for female toddlers and 15.1 g/application for male toddlers before applying a retention factor).

This comment can also apply to other product types, and in particular shampoo, fragrance products and body lotion.

In this context, could you please provide argumentation to justify the sentence "*A 2017 study in Swiss children by Garcia-Hidalgo et al. shows that for toddlers 0-5 years old, the derived data for use amounts covers approximately the P95. The approach is therefore accepted*." on page 20 of the opinion. Indeed, according to table S61 of this publication, the P95 are higher than the extrapolated values from adults. As indicated above, for shower gel, as an example, the P95 equals to 9 g/application for female toddlers, which is equivalent to 0.09 g/day if we consider a frequency of 1/d and a retention factor of 0.01.

Finally, Anses notes that the SCCS has recalculated the oral exposure for toothpaste based on exposure studies rather than extrapolation from adults as made by the applicant. To be consistent, the same approach should be followed for other product types when specific exposure data are available in publications.

Concerning SCCS comment on toothpaste: on page 20 line 33: please correct 2.4 mg/day into 2.4 g/day in the sentence: "*the SCCS uses for babies (0-3 years old) the P95 from Gomez-Berrada et al., 2018, for children 2-6 years (1.18 g/application) to derive a daily amount of 2.4 mg/day (Frequency: 2 times per day)".*

References:

- Ficheux AS, Dornic N, Bernard A, Chevillotte G, Roudot AC. Probabilistic assessment of exposure to cosmetic products by French children aged 0-3 years. Food Chem Toxicol. 2016 Aug;94:85-92. doi: 10.1016/j.fct.2016.05.020. Epub 2016 May 30. PMID: 27255804.
- Garcia-Hidalgo E, von Goetz N, Siegrist M, Hungerbühler K. Use-patterns of personal care and household cleaning products in Switzerland. Food Chem Toxicol. 2017 Jan;99:24-39. doi: 10.1016/j.fct.2016.10.030. Epub 2016 Nov 3. PMID: 27818321.
- Gomez-Berrada MP, Ficheux AS, Guillou S, Berge C, de Javel D, Roudot AC, Ferret PJ. Consumption and exposure assessment to cosmetic products for children under 2 years old. Food Chem Toxicol. 2017 Jul;105:151-160. doi: 10.1016/j.fct.2017.04.011. Epub 2017 Apr 12. PMID: 28412405.

3.3.6. Endocrine disrupting effects

Based on concerns seen in studies performed with other salicylates, Anses considers that ED properties cannot be excluded for hexyl salicylate. In addition, the SCCS have concluded in its opinion on salicylic acid that "More specific studies using salicylic acid need to be performed to conclude on the ED properties of salicylic acid."

Moreover, ED assessment of salicylic acid is currently ongoing within Biocidal Regulation. ED assessment was discussed at the Biocidal WG Meeting in June 2024. Minutes would be made publicly available soon. Thus, conclusion made in this framework should be taken into account.

https://echa.europa.eu/documents/10162/0/WG-II-2024_Revised_Draft_Agenda+%283%29.pdf/7100ae34-745b-df1c-e646-19d9bda38223?t=1717661553915

3.4. Safety evaluation

The safety evaluation for hexyl salicylate is based on a POD obtained from a study with salicylic acid, "*given that hexyl salicylate itself is not regarded as the main toxicant, but rather salicylic acid as the chief hydrolysis product via all routes of exposure*".

In the SCCS opinion on salicylic acid (SCCS/1646/22), it is noted that "*The Cosmetic Regulation does not allow the use of salicylic acid in products for children under 3 years of age. As the concerns for this opinion is on ED, which may lead to some specific effects in vulnerable populations such as children, specific exposure calculations for children (above 3 years old), by age categories are needed for a specific evaluation for children. In the absence of exposure data of Salicylic acid in cosmetic products for children, some safety concerns are noted for the younger age groups*".

Similar concerns are raised for hexyl salicylate as salicylic acid is the main metabolite and considered to be responsible of the systemic toxicity of hexyl salicylate. Moreover, the SCCS comments that the report on children's use of cosmetics has not been made available to SCCS and that no children specific use amount have been taken into account (page 20).

Taking into these elements, Anses considers that the conclusion of **the safety evaluation for children should be consistent with the SCCS opinion on salicylic acid and dispositions set accordingly under Cosmetic Regulation**.

Finally, various salicylic esters (including methyl salicylate, hexyl salicylate etc) are present in many cosmetic products. Concerns are raised concerning the aggregated exposure of consumers to salicylic acid formed from these esters (in addition to salicylic acid also used as a cosmetic ingredient) when consumers are exposed to different cosmetics. This is in line with the call for data to assess the aggregate exposure to salicylic acid from various salicylic esters used in cosmetic products in the framework of the Cosmetic Product Regulation (EC) 1223/2009[10].

10 https://single-market-economy.ec.europa.eu/consultations/call-data-ingredients-used-cosmetic-products-1_en

## ANSES comments on the SCCS scientific advice on titanium dioxide (SCCS/1661/23)

### 3.1. Chemical and physical specifications

#### 3.1.4 Purity, composition and substance codes

It is noted that "*it is not possible to know whether aluminium is present as Al2O3 or Al(OH)3 or similarly if the analysed elemental silicon is related to silica, silicones or silanes. Only an approximation can be made based on the manufacturing process*." (on page 14 line 34 - 6)

For Anses, it is possible to identify the nature of impurities even at trace levels. Applicants should argue why it is challenging to distinguish impurities and specify if they used a combination of analytical techniques.

Table 3.1.4.A1: Pigmentary grades – categories by composition

It would be useful to add a column specifying the crystallinity of the grades considered.

Table 3.1.9.2: Particle size and distribution

According to TEM results for constituent particles sizes, % of nano is higher than 50 for some pigmentary grades of $TiO_2$, considering at least one TEM data. Specifically, according to table 3.1.9.1.A2 in Annex L, several grades (RM26, RM27, RM67, RM70a, b, c) were reported with more than 50% of particles by number < 100 nm (determined by TEM). However, these raw materials were reported as pigmentary grades in paragraph 3.1.1.5.
Since TEM gives better resolution than SEM and allow to distinguish the primary particle boundaries, Anses considers as a conservative approach, that these grades (RM26, RM27, RM67, RM70a, b, c) should be considered as nanomaterials, even if other data provided (from SEM and/or TEM) gives a particle size distribution with less than 50% of particle <100 nm.

Table 3.1.9.3: Aerodynamic diameter

Anses questions the very low percentage (close to 0) of particles with an aerodynamic diameter below 10 µm, despite the spheroidal shape of pigmentary samples and certain nanograde samples (RM09, RM11, RM55, RM56, RM57, RM58, RM59, RM60, RM61, RM62, RM64, RM65, RM74a, RM74b, RM74c, RM74d, RM74e, RM78, RM81, and RM82). These results imply that none of these grades fulfil criteria for classification as Carc. 2 by inhalation.

The aerodynamic diameter is defined as the physical diameter of a sphere with a density equal to 1, moving through the air at the same velocity as the particle in question (such as titanium). This parameter determines the behavior of the particle suspended in the air. It is a function of the geometric diameter, shape factor, and the density of the aerosolized particle.

In general, for spheroid particles, the aerodynamic diameter is often close to the physical diameter. Regarding aerodynamic diameter results provided, Anses believes that, if nanoscale titanium samples with a spheroid shape contain less than 1% of particles with an aerodynamic diameter <10 µm, it is primarily due to the particle aerosolization system generating aggregated/agglomerated particles.

As this parameter is a key criteria for classification as Carc. 2 by inhalation, more information is needed regarding the measurement of aerodynamic diameter. Therefore, measurement results' must be accompanied by (i) the characteristics of the dustiness test and (ii) the number-based particle size distribution of aerosols generated during the dustiness test. Moreover, (iii) the aerosolization of the samples during the measurement of the aerodynamic diameter should be representative of the exposure resulting from titanium dioxide used in cosmetics.

Reference:
https://echa.europa.eu/fr/information-on-chemicals/cl-inventory-database/-/discli/details/100661

3.1.11 Dispersibility
It is noted that « *among the 40 nano titanium grades, 3 nano grades have been tested in toxicity studies: RM09, RM11 and RM75*".

While genotoxicity results are provided with RM09 and RM11, it is not clear to what type of studies the SCCS refers to for RM75.

Moreover, the rationale behind the choice of these particular nano grades as representatives of the 40 ones declared with cosmetic uses should be made clearer in the SCCS opinion together with the fact that this rationale is not convincing enough to read-across to the remaining 37 grades.

**3.4.1. 1. Mutagenicity / genotoxicity *in vitro***

Gene mutation assay with RM09

It is noted that a short-term treatment is considered inadequate for nanomaterials as cellular uptake of the test item needs to be demonstrated. However, Anses considers that it would have been relevant to perform a short exposure duration in addition to the 24h treatment (Charles & Jomini et al., 2018).

- Reference

Charles & Jomini et al., 2018. Assessment of the *in vitro* genotoxicity of TiO2 nanoparticles in a regulatory context. Nanotoxicology. Volume 12 – issue 4. https://www.tandfonline.com/doi/full/10.1080/17435390.2018.1451567

Extract: "*Short exposure duration of few hours can allow detecting genotoxicity when the compound is easily absorbed by the cell or when DNA damage is due to oxidative stress. In contrast, longer exposure duration (>=24 h) may be necessary to adequately detect NPs genotoxicity in proliferating cells considering that NPs may need more time than other chemicals to penetrate cells and/or nuclei (Karlsson 2010). […] In contrast, tests with long-exposure times may be less sensitive, as they allow the possibility of DNA repair mechanisms to occur."*

Moreover, it is stated that "*the SCCS is of the opinion that cellular uptake of RM09 was convincingly demonstrated, however, at RM09 concentrations higher than those recommended by the OECD TG 490 (paragraph 29). According to the information on precipitation provided by the Applicant, the highest acceptable concentration tested should be 6.3 µg/mL (Exp I) or 12.5 µg/mL (Exp IA), and these concentrations were not tested for cellular uptake, i.e. the lowest concentration tested by the Applicant for uptake was 25 µg/mL."*

In addition, statement provided in Annex R for RM09 Gene Mutation Assay: "*most of the observed V79 cells showed agglomerates of RM09 nanoparticles. Only occasionally separated particles or single small agglomerates can be observed*" cannot be confirmed. Agglomerated particles present inside the cell is due, among other things, to sample preparation through chemical fixation and dehydration. Anses believes that to confirm or refute this statement, images from cryo-TEM need to be provided.

In these conditions (no short-term treatment and no data on cellular uptake at tested doses in the genotoxicity study), it is difficult to conclude firmly that the study is negative.

Gene mutation assay with RM11:

It is noted that the mutation frequency was sporadically statistically significantly increased in the 24-hour experiment without metabolic activation. Even if the results are reported as consistent with historical control and not dose related, they should have been considered as "equivocal" rather than "clearly negative", according to OECD guideline 476 ("evaluation and interpretation of results). In this case, further investigation (as repeat test using same conditions) could have been useful to reach firm conclusion.

The following statement provided in Annex R for RM11 Gene Mutation Assay "*Nevertheless, many cells show no obvious internalization of RM11 nanoparticles and many of the RM11 nanoparticle*

*agglomerates can be observed outside the cells. The majority of the RM11 nanoparticles (inside and outside the cells) are present in agglomerated form. Only occasionally separated particles or single smaller agglomerates can be seen*" based on low resolution TEM micrographs, cannot be accurate. In fact, the low resolution TEM micrographs provided do not clearly distinguish the location of small isolated particles inside or outside the cell. Therefore, Anses believes that high resolution (corresponding to a resolution greater than or equal to the size of the smallest particles in the sample) images need to be provided.

Moreover, the SCCS concludes that cellular uptake was convincingly demonstrated at all concentrations, although applicant stated that obvious internalization of RM11 nanoparticles was not shown in many cells. Anses asks SCCS to provide more argumentations allowing its conclusion.

Finally, it is noted that "*according to the information on precipitation provided by the Applicant, the highest acceptable concentration tested should be 6.3 µg/mL (4 or 24 h of exposure), and these concentrations were not tested for cellular uptake, i.e. the lowest concentration tested by the Applicant for uptake was 25 µg/mL*". In these conditions, how can it be possible to conclude firmly that the study is negative?

This comment on the lack of demonstration of cellular uptake at concentrations tested in genotoxicity also applies to the micronucleus assay with RM11.

Micronucleus assay with RM09

Anses has the same comments concerning treatment duration and cellular uptake as for the gene mutation assay with RM09.

The SCCS notes that positive control cell cultures treated with griseofulvin showed mean micronucleus frequency which is below the minimal value of the historical control data. This result may raise some uncertainties on the sensibility of the test to detect mutagens of low potency (and thus on the negative conclusion of this test).

### 3.4.1.2. Mutagenicity / genotoxicity in vivo

Creutzenberg study (2022):

Anses notes that this preliminary study was not performed in accordance with criteria/parameters set in the ECHA decision (within Reach Substance Evaluation process), in particular concerning the number of animals, the number of concentrations, the observation times and the Comet assay protocol. New data performed according to requirements of the Reach Substance Evaluation is expected in the next years.

### 3.4.1.3.2 Published literature search carried out by the SCCS

According to table on page 67: rutile coated (or rutile with up to 2% anatase) nano grades were considered as inclusion criteria. However, it is noted that nano grades used in cosmetics can contain up to 5% anatase. Please clarify.

An additional publication has been identified in the literature:

- Cao et al. Genotoxicity Evaluation of Titanium Dioxide Nanoparticles In Vivo and In Vitro: A Meta-Analysis. Toxics. 2023 Oct 27;11(11):882. doi: 10.3390/toxics11110882. https://pubmed.ncbi.nlm.nih.gov/37999534/

Please consider if this publication is relevant for SCCS opinion.

## 4. Conclusion

Anses agrees with the SCCS that more experimental data is needed to conclude on safety of $TiO_2$ used in cosmetic products.

Anses recognizes the effort made to provide data on specific nanoforms regarding their genotoxicity. However, based on the above-mentioned limits, we are of the opinion that no firm conclusion can neither be made for RM09 nor RM11. In addition, there is no convincing rationale for considering them as representative of all cosmetic grades.

Regarding question 5 "does the SCCS have any further scientific concerns regarding the use of Titanium dioxide in cosmetic products?", Anses notes that, in addition to genotoxic concerns, several alerts related to reproductive toxicity (male and female reproduction and development) have been found in the scientific literature with nano grades of $TiO_2$. Most of these studies are performed by oral route with anatase crystallinity and sizes ranging from 6 to 21 nm. No data are available with coated $TiO_2$ nor with rutile crystallinity.

**Annexes 1, 2, 3:**
Some information are lacking for some studies in particular in column "exposure conditions" (e.g. biological medium, FBS serum and statistics "other genotoxicity endpoints – H2AX" (Vignard et al., 2023)), "information on the characteristics of the test substance" and "results" (e.g. see Ferrante et al. 2013). Please check and complete.

## Anses comment on the SCCS preliminary opinion on aluminium (SCCS/1662/23)

### 3.2.4. 1 Concentrations in cosmetics

It would have been useful to have more complete information on the use survey (e.g. number of products considered for each product type, number of Al-ingredient identified across the product types, min, max and mean for the percentage of aluminium concentration in each product type).

### 3.3. Toxicological evaluation

Mutagenicity/Genotoxicity:

Anses considers that *in vitro* genotoxicity data are inconsistent and positive results have been reported *in vivo* studies with aluminium soluble salts. As these studies have shortcomings, no firm conclusion can be done. In order to clarify the *in vivo* genotoxic potential and mode of action, ECHA had requested in 2017 a combined *in vivo* mammalian erythrocyte micronucleus test and an *in vivo* mammalian Comet assay with additional specific investigation on oxidative DNA damage in rats by oral route, using aluminium sulphate.

https://echa.europa.eu/documents/10162/5c324f33-c319-4ec0-5647-946f037788c8

This information is present in the SCCS opinion. However, please note that the board of appeal of ECHA annuled the decision to request this new study.

https://echa.europa.eu/documents/10162/4133890c-5e3f-f63c-d9af-2db6962d698c

**Other comment:**

This SCCS opinion concerns the safety of aluminium compounds as declared in table 1 of the previous SCCS opinion set in 2014 (SCCS/1525/14). However, Anses would like to bring to the SCCS attention that other aluminium compounds (not listed in the SCCS opinion), and in particular nanomaterials, may be used on cosmetic products.

As an example, the following nano aluminium compounds are declared in R-nano database in France for cosmetic uses (R-nano is the French register that collects data on substances at nanoscale through an annual declaration; see public report on the declarations 2021):

- Aluminium oxide as opacifying agent
- Sodium Magnesium Aluminium Silicate (SMAS) for exfoliating and viscosity properties

https://www.anses.fr/en/content/nanomaterials-assessment-r-nano-national-reporting-scheme

Anses considers that the current SCCS opinion do not cover these forms of aluminium.

If cosmetic uses are confirmed for these nanoforms of aluminium, specific safety evaluation should be performed taken into account the SCCS guidance on nanomaterials.

**Anses comments on the SCCS preliminary opinion on the inhalation toxicity of the fragrance ingredient Acetylated Vetiver Oil – AVO in sprayable cosmetic products [Submission IV] (SCCS/1663/24)**

### 3.4.2. Parameters

- References

It seems that most of the Ref. numbers cited in the text do not correspond to the reference list at the end of the SCCS opinion. There are also errors in some of the references themselves (e.g. ECHA Guidance reference year). Please check.

- Fine fragrance spray

In the SCCS opinion, it is noted: *Regarding the **daily amount use (g/d)** for fine fragrance spray, this is taken from AVO Opinion SCCS/1599/18, that is 0.28 g/day reported as the weight loss after use (Ref. 44).*

The amount of 280 mg/application refers to the arithmetic mean for the use amounts from Ficheux et al. (2017). Instead, Anses considers that the P95 of 618 mg/application should be used in the calculation. This is consistent with the SCCS approach taken in its opinion on Hexyl Salicylate (SCCS/1658/23).

Regarding the number of application per day, the 12$^{th}$ Revision of the SCCS Notes of guidance proposes a frequency of application for fragrances products of 1 application/day (Table 4). However, Ficheux et al. (2017) provides P95 data on the frequency of application, which is between 2 and 3 applications per day. In order to be conservative, consideration of these frequencies of application can be made. In addition, it can be questionable to apply one part of Ficheux et al. data for this type of products, and another source for another parameter. In this case, this should be explained in the opinion.

- Hairspray

In the SCCS opinion, it is noted: *Regarding the daily amount of product use for hairspray, (Ref. 43) reported 6.8 g/d for hairspray (aerosol) (Ref. 41) and 3.6 g/d for hairspray (pump spray) (Ref. 47).*

The source of the daily amounts of product cannot be adequately checked since it seems that there are mistakes in the reference numbers. However, it seems that the value of 6.8 g/d comes from Bremmer et al. (2006). This is a P75 value, which is not a conservative approach.

Instead, the daily amounts of product can be taken from Loretz et al. (2006). For example, according to the SCCS opinion on hexyl salicylate, the SCCS has used:

- 9890 mg/day (P95) for propellant spray
- 15620 mg/day (P95) for pump spray

Anses considers that these values are appropriate and should be taken into account in the calculations. If this is not the case, it should be explained why the proposed values are preferred.

Reference:

Loretz L, Api AM, Barraj L, Burdick J, Davis de A, Dressler W, Gilberti E, Jarrett G, Mann S, Laurie Pan YH, Re T, Renskers K, Scrafford C, Vater S. Exposure data for personal care products: hairspray, spray perfume, liquid foundation, shampoo, body wash, and solid antiperspirant. Food Chem Toxicol. 2006 Dec;44(12):2008-18. doi: 50 10.1016/j.fct.2006.06.029. Epub 2006 Jul 18. PMID: 16920244.

- Duration of inhalation exposure

1 minute has been selected as default parameter in the first box. According to the SCCS notes of guidance, a duration of 2 minutes is recommended for the near field. Anses considers that this duration

should be used on the calculations. If this is not the case, it should be explained why the proposed values is preferred.

### 3.4.3. Two box model

- Exposure estimate

For better reading, could you please provide a summary table with the parameters retained / modified by the SCCS?

### 3.5 Safety evaluation

For aggregated SED, the SCCS considers the values used in SCCS/1559/2018 for dermally applied products. As the parameters used are not clearly described and in order to ensure the accuracy of the aggregated SED, could you please confirm that no update of the SCCS/1559/2018 is needed in the SED calculation for these products, in the light of the revision of the SCCS Notes of Guidance or any other exposure data.

## ANSES comments on the SCCS preliminary opinion on Triphenyl phosphate (SCCS/1664/24)

**General comment:**

There is a switch between CAS and EC numbers. Please correct.

References to "Anses/ECHA 2023" are made in this SCCS opinion. This refers to the French Substance evaluation that focused on ED properties on the environment. Even if the SCCS mandate does not address environmental aspects and because there are already references to "Anses/ECHA 2023" in the document, please note that the substance has been proposed by France as a SVHC substance regarding its ED properties for the environment. This information can be added in this SCCS opinion as a complementary information to "Anses/ECHA 2023" reference.

### 3.3.2 Calculation of SED/LED

(Yin et al. 2024) recently published a study assessing the systemic exposure of nail cosmetics trough the nail plate. This study could be useful for assessing the safety of Triphenyl phosphate.

Reference:

Yin, Xuejun J., Nicola J. Hewitt, Steffen Erler, Paul Bryson, Brunhilde Blömeke, Anthony A. Gaspari, et Carsten Goebel. 2024. « Safety Assessment for Nail Cosmetics: Framework for the Estimation of Systemic Exposure through the Nail Plate ». *Regulatory Toxicology and Pharmacology* 148 (mars):105588. doi:10.1016/j.yrtph.2024.105588.

### 3.4.4.1. Repeated dose (21 – 28 days) oral / dermal / inhalation toxicity.

- Oral (page 16/17): 28-day study in Wistar rats (study 2).

The NOAEL established for this study was 23 mg/kg bw/day for male based on effects on body weights and 701 mg/kg bw/day for female rats.

This indicates that no adverse effect is reported for females up to the highest tested dose. However, significant increase in absolute and relative liver weights associated with hepatocyte hypertrophy is noted for females at the top dose. It is not clear why these effects are not used for the establishment of the NOAEL.

Please provide more details (% of liver weight increase; incidence of hypertrophy) if you consider that this effect is not relevant for setting the NOAEL in females. However, it should be highlighted that liver toxicity is also reported in the OECD TG 408 study and used as critical effect for the NOAEL in this study. If liver toxicity is retained, the NOAEL for females should be 161 mg/kg bw/day instead of 701 mg/kg bw/day.

### 3.4.5 Reproductive toxicity

According to the substance evaluation conclusion (Anses, 2023): "*a 'one-generation reproductive toxicity study' is currently being undertaken under the auspices of the US NTP".*

Update of safety evaluation (including NOAEL establishment) will be needed when this study will be available.

Reference:

- Anses. 2023. Substance evaluation conclusion as required by Reach Article 48 and evaluation report for triphenyl phosphate (EC No. 204-112-2; CAS No. 115-86-6).

https://echa.europa.eu/documents/10162/916779d9-ec10-07fa-f178-9562bdd7dedc

#### 3.4.6.1. Mutagenicity /genotoxicity *in vitro*

- Gene mutation - Table 4: Summary of gene mutation tests reported on TPP

For the first study, the reference would be "Study report. 2011, cited in ECHA, 2021" instead of ECHA AMES.

For the OECD 476 study, the reference would be: Study report. 1978, cited in ECHA, 2021

- *In vitro* chromosomal damage

For # Study 1, the reference would be: Study report. 2008 cited in ECHA, 2021

### 3.4.9. Human data

Two studies, not based on urine metabolites, are summarised in Anses report (2019):

*TPP concentrations in breast milk were analysed in a study on a human cohort conducted in Sweden between 1997 and 2007. Median concentration across all subjects was 8.5 ng/g of lipids (minimum and maximum values: 3.2 and 11 ng/g, respectively) (Sundkvist, Olofsson, and Haglund 2010).*

*Meeker and Stapleton, (2010), reported a relationship between decreased sperm counts and altered levels of thyroxine and prolactin on the one hand, and the high level of 2 organophosphate flame retardants (OPFRs) (Tris(1,3- dichloroisopropyl)phosphate (TDCPP) and TPP) in the dust of the homes of the men concerned, on the other hand (Meeker and Stapleton 2010). The authors analysed TDCPP and TPP in the dust of the houses of 50 men recruited through a U.S. infertility clinic, and assessed the relationships between the levels of these two OPFRs and reproductive and thyroid hormone levels, as well as semen quality parameters. TDCPP and TPP were detected in 96% and 98% of samples, respectively, with widely varying concentrations ranging from 0.17 and 1800 mg/g (mean value = 7.4 mg/g) for the TPP. In models adjusted for age and body mass index, each interquartile range of TPP increase in house dust samples was associated with a 19% (95% Confidence Interval (CI), -30% to -5%) decrease in sperm concentration and a 10% (95%, 2-19%) increase in prolactin levels. No causal formal link between concentration of TPP in dust and effects on fertility or thyroid function can be found in this transversal study.*

Consideration of including these studies in the SCCS opinion should be made.

References:

- Sundkvist, Anneli Marklund, Ulrika Olofsson, and Peter Haglund. 2010. "Organophosphorus Flame Retardants and Plasticizers in Marine and Fresh Water Biota and in Human Milk" 12 (4): 943–51. doi:10.1039/B921910B.
- Meeker, John D., and Heather M. Stapleton. 2010. "House Dust Concentrations of Organophosphate Flame Retardants in Relation to Hormone Levels and Semen Quality Parameters." Environmental Health Perspectives 118 (3): 318–23. doi:10.1289/ehp.0901332.

**Anses comments on the SCCS preliminary opinion on the safety of silver used in cosmetic products (SCCS/1665/24)**

## General comment:

The SCCS opinion only covers silver under the form of MicroSilver BG as characterization is provided exclusively for this form. This should be made clearer in the title of the document because, as currently expressed, this suggests that all forms of silver have been assessed which is not the case.

Moreover, in the abstract, it should be clearly stated that forms of silver other than MicroSilver BG have not been assessed in this document.

## 2. Mandate from the European Commission

Could you please add a summary table of the maximum concentrations of micro-sized particulate silver in cosmetic products as reported by the applicant?

It is noted that the dossier received by the Commission services refers to silver as a conditioning agent. Anses is questioning this claimed function, and not as colorant, for eye shadow. Could you please confirm?

## 3.1.2 Physical form

Measurement of external dimensions

The physicochemical analysis of the particle size distribution presented by the applicants is not sufficient to ensure that particle size distribution of MicroSilver BG™ is not at the nanometric scale. This can be explained by two arguments:

- According to the information provided by the applicants, the D50 = 106 nm in TEM and 116 nm in SEM are very close to 100nm.
- The TEM images provided do not help imaging identifiable constituent particles and assess their physical boundaries.

In order to perform a quick analysis of the images used to calculate the size distribution of particles, Anses used image analysis software (ImageJ) to screen the particles shown in applicants TEM micrograph (the 3rd TEM image in Figure 2 of the opinion). The image is presented in figure 1 below:

19 particles that could be distinguished in the image were selected. A quick screening of the dimensions (length or width) of these particles shows nanometric dimensions (see figure 2 below).

On the other hand, the selected regions 21, 22, 23, 24 show that the particles are not identifiable, due either to the dispersion protocol or to the TEM acquisition protocol that does not allow characterizing the aggregated samples. Indeed, the magnification of the TEM images provided does not allow to see clearly the particles and the contrast should be enhanced (i.e, by using STEM technique).

Even though applicants consider that the particles do not present clear boundaries, Anses believes that the physicochemical **analyses presented are not robust enough to exclude the nanometric scale of silver**, in particular:

- Images displayed in figure 2 of the opinion, do not provide a good contrast and enough magnification to allow for the analysis of the constituent particles of the sample and the distinction of boundaries.
- The dispersion protocol must be adapted to better disperse the particles. Similarly, the concentration of the sample must be reduced to limit aggregation/agglomeration.
- Scanning electron microscopy is not suitable for calculating the size distribution of particles by number for MicroSilver BG™. Since this technique provides access to surface information (in secondary electron imaging mode), it is not suited for analyzing aggregated samples.

- Moreover, images in TEM must be obtained at higher resolution. The HR STEM technique (high resolution scanning transmission electron microscopy) is recommended because it provides better contrast and allows for clearer distinction of the boundaries.
- If images in TEM are insufficient to confirm or refute the presence of particle boundaries, 3D electron tomography images must be provided. 3D tomography allows for the demonstration of whether the particles are fused or if they have clear boundaries, which might not be apparent in the TEM micrographs due to the acquisition protocol.
- Reproductibility of the physicochemical characterization data must be proven.
- Figure 7 is not readable.

If physicochemical analyses do not confirm the micrometric form of MicroSilver BG™, the risk assessment must be nanospecific.

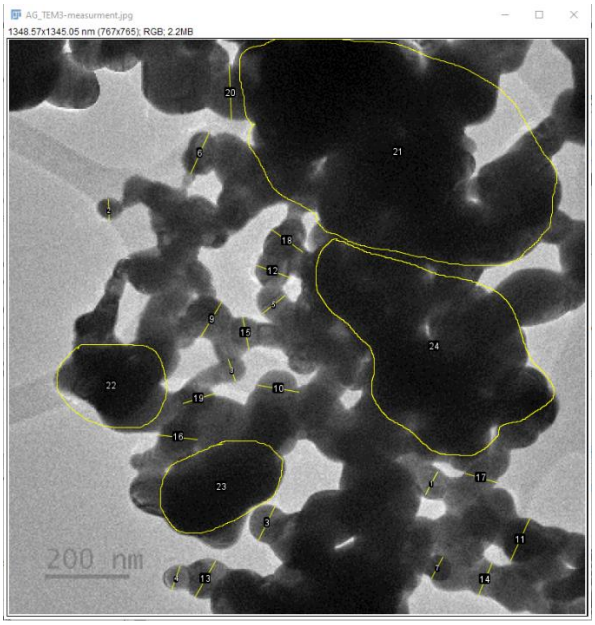


**Figure 2 Anses assessment of the TEM micrograph presented by the applicants: screening of particles in TEM micrographs shows particle selection for measurements. Particle 1 to 19 are approximately measured (see measurements in the table below). Their dimensions are in the nanometer scale. The selected regions 21, 22, 23, 24 show undistinguishable electron dense cluster of particles. This is due to aggregation and has an impact on the D50 measurement, which appears to be greater than 100nm in the results presented by the applicants.**

Results

File Edit Font Results

| | Label | Area | Mean | Min | Max | Angle | Length |
|---|---|---|---|---|---|---|---|
| 1 | AG_TEM3.PNG:0589-0561 | 108.199 | 213.788 | 170.221 | 255 | -118.072 | 59.780 |
| 2 | AG_TEM3.PNG:0227-0134 | 86.559 | 81.368 | 56.778 | 170 | -87.879 | 47.505 |
| 3 | AG_TEM3.PNG:0642-0343 | 157.661 | 92.840 | 68.560 | 187 | -116.053 | 88.070 |
| 4 | AG_TEM3.PNG:0715-0223 | 105.108 | 104.776 | 85.000 | 146.727 | -109.537 | 57.835 |
| 5 | AG_TEM3.PNG:0352-0352 | 120.565 | 101.807 | 83.759 | 170.000 | -141.340 | 67.549 |
| 6 | AG_TEM3.PNG:0152-0254 | 185.484 | 81.023 | 51.000 | 136.000 | -113.962 | 103.900 |
| 7 | AG_TEM3.PNG:0701-0569 | 102.016 | 55.555 | 36.672 | 97.000 | -118.179 | 55.850 |
| 8 | AG_TEM3.PNG:0439-0297 | 92.742 | 100.588 | 75.621 | 153.000 | -72.181 | 51.711 |
| 9 | AG_TEM3.PNG:0372-0270 | 163.844 | 78.628 | 51.000 | 153.000 | -120.964 | 92.270 |
| 10 | AG_TEM3.PNG:0464-0359 | 170.027 | 87.442 | 68.000 | 126.000 | 170.362 | 94.521 |
| 11 | AG_TEM3.PNG:0664-0679 | 188.575 | 46.716 | 18.250 | 146.000 | -114.444 | 106.224 |
| 12 | AG_TEM3.PNG:0308-0351 | 148.387 | 93.201 | 61.261 | 171.000 | -19.983 | 82.319 |
| 13 | AG_TEM3.PNG:0716-0262 | 173.118 | 84.321 | 51.361 | 162.000 | 60.642 | 96.831 |
| 14 | AG_TEM3.PNG:0717-0632 | 148.387 | 103.777 | 85.000 | 189.000 | -112.714 | 81.961 |
| 15 | AG_TEM3.PNG:0390-0315 | 136.022 | 107.057 | 85.000 | 161.000 | -79.216 | 75.174 |
| 16 | AG_TEM3.PNG:0528-0226 | 160.753 | 51.759 | 34.000 | 153.000 | -6.710 | 90.289 |
| 17 | AG_TEM3.PNG:0582-0627 | 136.022 | 86.084 | 61.333 | 146.000 | -16.314 | 75.112 |
| 18 | AG_TEM3.PNG:0268-0370 | 154.570 | 67.533 | 51.167 | 119.000 | -35.942 | 86.868 |
| 19 | AG_TEM3.PNG:0477-0253 | 139.113 | 76.336 | 50.227 | 189.000 | 17.199 | 77.302 |

**Figure 3 : length in nm of some distinguishable particles (particles 1 to 19) displayed in TEM micrographs above. Measurement shows that particles have length/width belonging to the nanometer range. Dense aggregates and indistinguishable cluster of particles (selected regions 21, 22, 23, 24) are not displayed in the measurement.**

### 3.1.9. Homogeneity and stability: release of silver ions

Anses is questioning the biopersistent property of silver because it is not soluble in water (and maybe in sweat) and tends to remain almost on the skin. In this context, using toxicological data on silver ions may not be fully relevant. Particulate effect should also be considered.

Additional data such as dissolution kinetics studies (in sweat simulant fluid, for example) would have been essential to conclude on the relevance of using data on silver ion.

Moreover, it is noted that "*in conformity with ECHA, the SCCS will base its toxicological evaluation on the exposure to silver ions (expressed as silver ion equivalents)".* Could you please specify the source of the reference to ECHA?

### 3.2.1. Dermal / percutaneous absorption

a. *In vitro* studies

*In vitro* dermal absorption using MicroSilver BG

According to OECD TG 428: " *Under normal conditions of human exposure to chemicals, finite doses are usually encountered. Therefore, an application that mimics human exposure, normally 1-5 mg/cm² of skin for a solid and up to 10 µl/cm² for liquids, should be used".* This is also in line with the recommendations from the SCCS Notes of guidance.

In this study, the test substance formulation was applied topically in a nominal quantity of 20 mg/cm², corresponding to 0.3 and 0.1 mg silver/cm² for formulation A and B, respectively. It should be explained why the tested doses are considered more relevant than those recommended in the OECD guideline.

The substance is of low solubility in water. Is the solubility of the test formulation in the receptor fluid checked? This information is important to validate the reliability of the study.

Anses considers that skin sample (excluding tape strips 1 and 2) should also be taken into account in the absorbed amount. In addition, as the recovery is rather low, consideration should be made to add the missing amount in the calculation as a conservative approach (see also EFSA guidance, 2017).

Finally, it is noted that the SCCS retains the dermal absorption value from the formulation containing 0.5% of MicroSilver BG in hydrophilic cream. By comparison, the categories of products supported by the applicant include creams but also body lotion, shampoo, deodorant, eye shadow, after shave, lip balm, toothpaste and mouthwash. The composition of these products can be very different from hydrophilic cream and can influence dermal absorption of MicroSilver BG. Moreover, the concentrations claimed by the applicant in this document range from 0.05 to 0.3%. Overall, Anses questions the relevance of the dermal absorption value issued from this study for products with formulations other than cream and containing MicroSilver BG at a concentration far below 0.5%. If SCCS considers this value still applicable to the declared products and concentrations, this should be explained in the document.

Reference:

EFSA. 2017. Guidance on dermal absorption. Doi: 10.2903/j.efsa.2017.4873

### 3.3.2 Calculation of SED/LED

The estimated daily amount applied ($q_x$) used to determine Systemic Exposure Doses are taken from tables 3A and 3B of the SCCS NoG (SCCS/1647/22). However, these tables also provide the associated relative daily exposure values (Eproduct), which have not been used in this assessment. In particular, in the SCCS opinion of silver, the body weight used to determine the SED is a default value (60 kg). In contrast the Eproduct from the SCCS NoG is calculated using the body weight of the persons involved in the study. Anses considers that it would have been more relevant to use the body weight of the persons involved in the study.

For shampoo, in the SCCS NoG, the Eproduct is 1.51 mg/kg/d (after having taken into account the body weight and the retention factor). In contrast, in the table 6 of this document, the Eproduct is set at 0.18 mg/kg/d. Please check or provide more information on the calculation.

For foot cream, the RIVM has adopted a value of 1.2 g per application of the product, with a frequency of 730 times a year, i.e. 2 times a day. In this opinion, the SCCS considers that foot cream is only applied once a day. Moreover, this value is extrapolated from exposure data using hand cream. Recent data from Ficheux et al. (2017) provided a value of 8.49 g/application of foot cream (value derived from the P95) which could be used for a more conservative scenario. Can you explain this choice of frequency and quantity in the opinion?

ANSES does not obtain the same SED values for the products concerned by oral exposure when using the parameters cited in the opinion. Moreover, the oral absorption value used in the calculations is not specified in this section. Please check or specify how the calculations were carried out.

It seems that there is a mistake in Ref. number cited for children's toothpaste. The reference number would be 3 and not 4.

## 3.4. Toxicological evaluation

The toxicological profile describes data on various forms of silver. In particular, the safety evaluation proposed by the SCCS is based on a NOAEL derived from silver zinc zeolite in rats. It should be specified in the SCCS opinion how the read-across from these various substances sources (and in particular silver zinc zeolite) is applicable to MicroSilver BG.

Relevant factors should be considered, including the extent to which silver ions are released, the similarity in bioavailability, physical, chemical and toxicological properties. In the absence of such data for MicroSilver BG, uncertainties remain on the relevance to use data on other forms of silver and thus in the present safety assessment.

Moreover, SCCS does not consider toxicological studies from nano silver particles. Anses has doubt that MicroSilver BG is not a nanoparticles considering the D50 close to 100 nm and the low quality of the images provided for particle size distribution. Complementary data are thus deemed necessary to firmly conclude that the substance is not a nanomaterial (see comments above on section 3.1.2). In the absence of such data, the guidance on the safety assessment of nanomaterial in cosmetics should be followed as a conservative approach.

### 3.5 Safety Evaluation

As indicated in section 3.3.2, SED values need to be checked and possibly reviewed for the final calculation of Safety Margins.

Taken into account our comments raised on exposure calculation, toxicological assessment and the characterization as a potential nanomaterial of the substance, it is not difficult to conclude firmly on acceptable uses based on the present assessment.

Same remark as in section 3.3.2 for the reference number.

## Anses comments on the SCCS preliminary opinion regarding new coating for Titanium Dioxide (nano form) (SCCS/1667/24)

### 3.1.1.5 Structural formula

Anses comment:

The chemical formula of the dimethicone coating is (C2H6OSi)n.

Therefore, the chemical structure shown on page 9 must be corrected, as it corresponds to dimethicone with the chemical formula C8H24O2Si3.

### 3.1.1.6 Empirical formula

Anses comment:

The chemical formula of dimethicone should be replaced by (C2H6OSi)n.

### 3.1.4 Purity, composition and substance codes

The following description was provided by the applicant

**Table 1.** Typical composition of Eclipse 70

| Components | % w/w | CAS No. | EINECS No. |
|---|---|---|---|
| **Ultrafine titanium dioxide** | **70** | - | - |
| Titanium dioxide | (80-90) | 13463-67-7 | 236-675-5 |
| Aluminium hydroxide | (10-20) | 21645-51-2 | 244-492-7 |
| **Sodium myristoyl sarcosinate** | **14** | 30364-51-3 | 250-151-3 |
| **Dimethicone** | **10** | 63148-62-9 | Not regulated |
| **Aluminium hydroxide** | **6** | 21645-51-2 | 244-492-7 |

**Ref.:** 0. TM_Eclipse 70 DOSSIER_06Aug23.pdf

Anses comment:

According to the information provided in Table 1, the components of ultrafine titanium dioxide are titanium dioxide and aluminum hydroxide. The proportions are 80-90% titanium dioxide and 10-20% aluminum hydroxide. This is not consistent with the description of the chemical structure provided in paragraph 3.1.1.5 Structural Formula.

Anses asks for clarification on whether the core contains aluminum hydroxide. If it does, the purity of titanium dioxide should be reassessed along with its physicochemical properties.

### 3.1.5 Impurities

Typical impurities of Eclipse 70 are provided by the applicant in Table 2.

Anses comment:

Anses reminds that the presence of traces of CMR substances must complies with Article 17 of the CPR. No information is provided to confirm that the traces of heavy metals are technically unavoidable.

Regarding the safety aspects of these impurities, the applicant refers to "generally accepted limits" without providing details on these values.

Anses considers that the applicant should clarify the "generally accepted limits" and confirm that the traces of prohibited substances are technically unavoidable.

### 3.1.6 Solubility

Anses comment:

The applicant stated that uncoated titanium dioxide is insoluble in water and organic solvent but no information is provided for the UV filter Eclipse 70 as a whole. Anses is wondering if the coating impacts the solubility of the UV filter in the water and organic solvents. This information should be provided by the applicant.

### 3.1.8 Additional physical and chemical specifications

Anses comment:

Anses notes that the aspect ratio is close to 3, which raises safety concerns and justifies further investigation. An aspect ratio greater than 3 indicates a fibrous material. This observation is supported by the needle shape morphology as cited in the **3.1.2 Physical form paragraph** based on the morphological observation by scanning electron microscopy (SEM).

The needle shape, the nanoscale, and the insolubility of the Eclipse add a further degree of concern over the safety of an NM as mentioned[11] by the SCCS guidance on nanomaterials. Anses considers that further investigation is needed, such as:

- information on dustiness[12] of dry powder materials should be provided.

- the number-based distribution of the aspect ratio should be also given. Moreover, number-based aspect ratio distribution should include the use of an EM method. Proportion of particles with aspect ratio > 3 should be provided.

- data on biopersistance should be provided.

### 3.1.10.2 Primary article size distribution

The SCCS notes that the particle size distribution is not completely monomodal as shown in Figure 7 on particle size distribution of Eclipse 70 measured by SEM.

Anses comment:

If the distribution is not monomodal, it may be due to the presence of aluminum in the core. This should be confirmed by the applicant.

Anses agrees with the SCCS that "*the actual median size of core TiO2 nanoparticle is most likely below 21 nm. That renders Eclipse 70 outside the particle size range covered in the SCCS Opinion 38 (SCCS/1516/13 - Revision of 22 April 2014)*"

Anses comment:

Regarding the response of the applicants "*While the coating represents a significant proportion by weight, the overall thickness of the coating layer is only a few nanometers*", Anses observes that in order to prove the very thin coating (few nm) compared to the core (20-30 nm), applicant must provide a high-

[11] According to the SCCS guidance on nanomaterials:
« Each of the following attributes should add a further degree of concern over the safety of an NM. For example, where:

- The NM has constituent particles that have sizes in the lower range of the nanoscale.
- The NM is insoluble, or only partially soluble.
- The chemical nature of the NM suggests the potential for a toxicological hazard.
- The NM has certain physical/morphological features (e.g. needle shape, rigid long fibres) that point to the potential for harmful effects"

[12] Table 1: Important parameters and methods for identification and characterisation of nanomaterials intended for use in cosmetic products that should be provided

resolution image of titanium with EDX that allow to measure the thickness of the core versus the coating materials.

Moreover, Anses notes that the physicochemical characterizations of nanomaterials presented in the SCCS opinions of 2013 (SCCS/1516/13), particularly the size measurements, are no longer valid. They were obtained using CPS Disc Centrifuge, LUMisizer Centrifuge, and DLS (dynamic light scattering) techniques, which do not provide access to the primary constituent particles but rather to the agglomerates/aggregates. According to Annex K of the SCCS opinion of 2023 (SCCS/1655/23), 32/40 grades of nanoscale $TiO_2$ have median primary particle sizes below 30 nm (the lowest median size being 9 nm) based on electron microscopy analysis.

This explains the differences in average size observed with Eclipse 70. It is worth noting that the primary particle sizes described in 2023 are consistent with values close to 20 nm.

**Anses comments on the SCCS preliminary opinion on the safety of Biphenyl-2-ol and Sodium 2-biphenolate used in cosmetic products (SCCS/1669/24)**

### 3.4.2 Skin sensitization

Anses acknowledges that animal data are negative. However, few human skin sensitization studies show positive results and led to an opinion from the RAC to classify OPP as a skin sensitiser category 1B, according to CLP regulation. More argumentation is thus needed before concluding that the risk of skin sensitisation to OPP or SOPP in cosmetics is not a concern.

### 3.4.5.2 Developmental Toxicity

A NOAEL of 25 mg/kg bw/d is chosen as the PoD from a developmental toxicity study (Zablotny et al 1991c). Anses agrees with this choice which is conservative, but notes that the NOAEL set in this study is different in more recent assessments, notably in the CLH report and in the RAC opinion.

References:

European Commission. November 2021. Proposal for Harmonised Classification and Labelling (CLH Report) according to Regulation (EC) N°1272/2008.

Committee for Risk Assessment. December 2022. Opinion proposing harmonized classification and labelling at EU level of biphenyl-2-ol; 2-phenylphenol; 2-hydroxybiphenyl.

### 3.3.2 Calculation of SED/LED

It is regrettable that "leave-on" and "rinse-off" product categories are presented as a whole for SED calculation in table 4 rather than specific product categories. The lack of details on the product categories considered does not permit to know whether an oral (in case of oral care products) and/or inhalation (in case of sprayable products) exposure assessment should be carried out.

The values used for exposure calculations should be clarified. The quantities of rinse-off and leave-on products used per day refer to table 5 of the SCCS Notes of Guidance 12$^{th}$ revision (SCCS/1647/22). However, the exposure value (E product) of 17.4 g/d used for leave-on products in the SCCS opinion of OPP and SOPP do not refer only to leave-on products but to the aggregate exposure to all product categories according to the SCCS Notes of Guidance. This thus also includes rinse-off products, make-up products and oral care products. As a consequence, rinse-off products are considered two times for OPP/SOPP. Moreover, can you specify whether make-up products and oral care products are claimed for OPP and SOPP? If yes, oral exposure must be assessed for oral care products, separately.

Please note that the E product corresponding to the quantity of 17.4 g/d is 269 mg/kg bw/d (in agreement with the SCCS Notes of Guidance) and not 290 mg/kg bw/d as indicated in table 4.

According to the SCCS Notes of Guidance, the retention factor to be applied for rinse-off products is 0.01. In contrast, this retention factor is not taken into account in the calculation of the SED value. This should therefore be corrected in table 4.

### 3.5 Safety evaluation

The exposure assessment should be reviewed for both OPP/SOPP in light of the comments made above, as this directly impacts the calculation of the MoS.

Moreover, references to the SCCS NoG 12$^{th}$ revision should be made in this section instead of the 8$^{th}$ revision.