DRAFT Media/talking points regarding sunscreen ingredient safety

Contents

The media responses and talking points listed below are drafts needing EL2, AS, and FAS approval. Their accuracy can change with new developments or information, and may also need clearance from relevant business areas

DRAFT media responses:

Why has the TGA been slow to act following the US FDA or European SCCS banning of certain sunscreen active ingredients based on reports they are unsafe?

Response 1:

- The TGA remains committed to safeguarding public health by ensuring that sunscreen ingredients used in Australia meet the highest safety standards. The benefits of sunscreen in preventing sunburn and skin cancers are well established and sun protection should remain a priority. There is currently no definitive evidence to suggest that sunscreens contribute to cancer risk.
- While some international regulatory bodies like the US FDA and European SCCS have expressed concerns over certain ingredients in sunscreens, the TGA does not automatically align with these viewpoints, acknowledging that regulatory conclusions can vary due to different frameworks. We base our regulatory decisions on a careful analysis of the latest scientific evidence, tailored to Australia's distinct environmental conditions and health requirements.
- Given that Australia has the highest incidence of skin cancer in the world, sunscreens designed primarily for UV protection are regulated as therapeutic goods with more stringent compliance standards, unlike some sunscreens overseas that may be regulated as cosmetics.
- The European Union prohibits using data from animal testing to substantiate the safety of sunscreens that are regulated as cosmetics, however the TGA does not have such a prohibition for therapeutic products. This allows for use of a broader scope of scientific evidence, including information derived from animal studies. Such differences mean the TGA may come to a different conclusion about the safety of an ingredient based on scientific evidence.
- It should be noted that the US FDA's proposal on the GRASE (Generally Recognised As Safe and Effective) status of certain sunscreen ingredients is based on a lack of sufficient data. It is not a final determination of their safety.
- We are closely monitoring international developments, and are also conducting our own comprehensive literature review of a number of common active ingredients used in Australian sunscreens, and considering all available scientific information. We have developed a novel Australian sunscreen exposure model which underwent public consultation in August 2024, and will be used to finalise these safety assessments.
- Once our review is complete, we will implement any necessary regulatory measures, share our findings, and engage in public consultation where appropriate.

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Response 2:

- The TGA does not automatically adopt international regulatory actions. We undertake a thorough investigation of the current scientific evidence before deciding on any action.
- While some international bodies such as the European SCCS and the US FDA have raised concerns about certain sunscreen ingredients, we consider the unique Australian context before deciding on how to address Australia's specific public health challenges.
- The US FDA is reviewing the GRASE (Generally Recognized As Safe and Effective) status of some sunscreen ingredients because of insufficient data. It is important to remember that

they have only made a proposed order; they have not announced a final decision to ban these ingredients or concluded that they are unsafe for use in sunscreens. They are calling for additional data to understand what levels of skin absorption can be considered safe before they can make a final determination. We have been actively monitoring developments from the FDA while they gather further data.

- The US FDA's findings were based on exploratory studies for some sunscreen active ingredients that found they could be absorbed through the skin at 0.5 ng/mL. However, it is important to note that if an ingredient is absorbed through the skin, it does not necessarily mean it is unsafe, and the US FDA has called for further data and testing from industry before they finalise their GRASE status.
- We are aware of the FDA's (and/or SCCS's) review and are conducting our own proactive review of active ingredients (including X) used in Australian therapeutic sunscreens. This review includes a comprehensive literature search and assessment to evaluate the potential risks associated with these ingredients. Our review is informed by recent international scientific reviews and regulatory action, in the context of how therapeutic sunscreens are used in Australia which may differ to how they are used in other countries.
- We have also developed a novel Australian sunscreen exposure model to finalise these safety assessments based on the most current scientific evidence. This model is intended to reflect the unique Australian context, including that we have the highest incidence of skin cancer compared to any other country in the world, higher UV radiation levels, a sunny climate, and outdoor lifestyle. This necessitates a tailored approach to sunscreen regulation with stricter standards in Australia than some jurisdictions where sunscreens are deemed cosmetics and skin cancer is less prevalent.
- We conducted targeted consultation on this model in April 2024 and public consultation between July and August 2024. The model was supported by the majority of respondents, and when finalised will inform our review of sunscreen active ingredients which is anticipated to be completed in 2024.
- We will take necessary regulatory actions based on the outcomes, including publishing our findings, and conducting public consultation on any proposals if required.

Response 3:

- International reviews of sunscreen ingredients are an important consideration, but they do not automatically dictate the safety or appropriateness of these ingredients for use in therapeutic sunscreens in Australia. The Therapeutic Goods Administration (TGA) conducts its own thorough investigations, grounded in the most current scientific evidence, before deciding on any regulatory action.
- We are actively finalising our own review of a number of sunscreen active ingredients, (including X), used in therapeutic sunscreens. This review encompasses a comprehensive literature search and assessment to evaluate the potential risks associated with these ingredients. Furthermore, we have developed a novel Australian sunscreen exposure model designed to finalise these safety assessments. This model is tailored to the unique Australian context, which includes the highest incidence of skin cancer globally, higher UV radiation levels, and a culture that enjoys Australia's sunny outdoor climate. These factors necessitate a tailored approach and stricter standards compared to other countries where skin cancer is less prevalent.
- As our review and consultation process continues, we maintain that sunscreen sponsors (product owners) have a legal responsibility to ensure the safety of their products. We will take action if products are found to contain unacceptable ingredients or impurities or fail to meet other regulatory requirements. We are committed to upholding the regulatory standards for sunscreens to protect the health and safety of Australians that use these products.

Response 4:

- We are aware of international research and are proactively reviewing the safety of several common sunscreen active ingredients used in Australia. Our approach is comprehensive and

informed by the unique Australian context, including that we have the highest incidence of skin cancer compared to any other country in the world necessitating a rigorous and tailored review process.

- There is clear and overwhelming evidence of the benefits of sunscreen in the prevention of sunburn and skin cancers. There is currently no conclusive evidence that sunscreens contribute to cancer.
- Our review process is thorough and ongoing. We have developed an appropriate sunscreen exposure model that reflects actual usage by Australians. The outcomes of our safety reviews will be concluded once the model is finalised and our outcomes are published.
- Sunscreen sponsors are legally obligated to ensure the safety of their products. The TGA will take necessary actions for therapeutic sunscreens should any products fail to meet regulatory standards.

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Response 5

- The TGA is committed to safeguarding public health and takes the safety of sunscreen ingredients, (including X), very seriously.
- We are finalising a comprehensive safety review of common sunscreen active ingredients used in Australia and have established a Sunscreen Taskforce to prioritise and advance this work.
- A novel Australian sunscreen exposure model has been developed by the Taskforce to finalise these, and future safety assessments based on the most current scientific evidence and unique Australian context. A public consultation on adopting this model was published in July, enhancing our ability to assess the safety of sunscreen ingredients based on Australian use, rather than reliance on international assessments.
- Regulatory standards and classifications for sunscreens differ internationally. In Australia, sunscreens are regulated as therapeutic goods as we have the highest incidence of skin cancer globally, a sunny climate with high UV radiation levels, and an outdoor culture, necessitating stricter standards than some jurisdictions where they are deemed cosmetics. It is also the legal responsibility of sponsors of therapeutic sunscreens to ensure the safety of their products, including adherence to manufacturing standards and ongoing pharmacovigilance responsibilities.

Response 6

- The US FDA has evaluated safety data available to them and concluded that the risks associated with use of aminobenzoic acid (PABA) and trolamine salicylate as active ingredients in sunscreens outweigh their benefits. They have classified these ingredients as not GRASE for use in sunscreens due to safety concerns.
- The TGA removed PABA from the Permissible Ingredients Determination in November 2022. At the time of the removal, there were no listed medicines that contained PABA.
- Regarding trolamine salicylate in listed therapeutic sunscreens, the TGA took proactive measures to alert sponsors intending to list new medicines containing trolamine salicylate in the Australian Register of Therapeutic Goods (ARTG) until an updated safety review could be conducted. At the time these measures were taken, there were no listed medicines that contained trolamine salicylate in the Australian market.

AICIS has published a safety review of homosalate, is the TGA aware of this and do you have any comments?

Key messages:

1. TGA is aware and working with AICIS
2. TGA supports ongoing review and this is part of our standard process.

3. We are undertaking our own review. A public consultation will occur if regulatory changes are recommended.

Background:

- Australia has the highest incidence of skin cancer in the world, and it is a decision of government that primary sunscreens (those that are primarily intended for UV protection) are regulated as therapeutic goods by the TGA. These therapeutic sunscreens must have an "AUST L" number on the front of the label.
- Most secondary sunscreens (those that are not primarily intended for UV protection, such as make-up and anti-wrinkle products with an SPF rating) are excluded from therapeutic goods legislation and regulated as cosmetics in Australia. The Australian Industrial Chemicals Introduction Scheme (AICIS) is the regulatory authority that evaluates the safety of ingredients used in cosmetic sunscreens, and the Australian Competition and Consumer Commission (ACCC) oversees product issues such as safety and misleading claims.

Response 1

- The TGA has been working closely with AICIS and are aware of the review for homosalate used in industrial chemicals, which includes cosmetics sunscreens. The ingredients in these products are regulated by AICIS.
- The TGA is also conducting our own comprehensive safety review of homosalate for use in therapeutic sunscreens (such as those that are primarily intended for UV protection). We are considering all available scientific information, including the AICIS assessment.
- We have also developed a novel Australian sunscreen exposure model specifically tailored for how therapeutic sunscreens are used in Australia. Our model underwent public consultation in August 2024, and once finalised, it will be used to complete our safety assessment.
- We anticipate our findings will be available by the end of this year. As per the TGA's normal process, there will be a thorough public consultation process to consider any regulatory changes.

Response 2

- The Therapeutic Goods Administration (TGA) has been working with AICIS and are aware of their review of homosalate in industrial chemicals. This review includes use in cosmetic sunscreens that are not regulated by the TGA.
- Sunscreens that are primarily intended for UV protection are regulated as therapeutic goods by the TGA due to Australia's high incidence of skin cancer.
- As part of the standard post-market monitoring framework, the TGA also undertakes safety reviews of ingredients used in therapeutic goods when new information warrants investigation.
- The TGA is actively conducting a comprehensive review of homosalate used in Australian therapeutic sunscreens. This review includes a thorough examination of the latest scientific literature on homosalate. As per the TGA's normal process, we will publish our recommendations and there will be a public consultation process if any regulatory changes are recommended.
- It is important to note that compliant therapeutic sunscreens on the Australian market are subject to rigorous safety, quality, and efficacy standards.
- To improve how we do our risk assessments and ensure they are appropriate for the Australian context, we developed an Australian sunscreen exposure model based on how Australians use sunscreen today. Our model underwent public consultation in August 2024. Once our model is finalised, it will be used to complete our review of homosalate. You can read more about our consultation here.

Are sunscreens still safe for use this summer?

Key messages

1. Therapeutic sunscreens are strictly regulated and need to meet rigours safety, quality and efficacy standards. Sponsors have responsibility to ensure safety of the product (AUST L not pre-market assessed).
2. UV protection should be a priority as skin cancer is significant public health concern, including use of sunscreen if needed.
3. The TGA does not provide advice on specific products – best to consult a doctor for personalised advice.

Background:

- Australia has the highest incidence of skin cancer in the world, and it is a decision of government that primary sunscreens (those that are primarily intended for UV protection) are regulated as therapeutic goods by the TGA. These therapeutic sunscreens must have an “AUST L” number on the front of the label.
- Most secondary sunscreens (those that are not primarily intended for UV protection, such as make-up and anti-wrinkle products with an SPF rating) are excluded from therapeutic goods legislation and regulated as cosmetics in Australia. The Australian Industrial Chemicals Introduction Scheme (AICIS) is the regulatory authority that evaluates the safety of ingredients used in cosmetic sunscreens, and the Australian Competition and Consumer Commission (ACCC) oversees product issues such as safety and misleading claims.

Response 1

- It is important to take measures to limit UV radiation exposure, as this is the main cause of skin cancer which can be prevented. Given the widely recognised public health importance of sunscreens, Australians should continue to use sunscreens along with other sun protective behaviours when the UV index is 3 or more. The 5 slip, slop, slap, seek, slide protective measures include seeking shade, wearing a hat, wearing protective clothing and eyewear and using sunscreen.
- Sunscreens that are primarily intended for UV protection are regulated as therapeutic goods. These sunscreens are an important tool to assist in preventing skin cancer and are subject to rigorous safety, quality and efficacy standards. Part of the TGA’s role is to undertake post-market monitoring of all therapeutic goods in Australia.
- Sponsors (product owners) have additional compliance requirements such as ensuring their product is safe. This is not limited to the ingredients they use, but also how they are presented for sale, ongoing pharmacovigilance responsibilities requiring monitoring of emerging safety information relating to their products, and being required to manufacture products under the principles of Good Manufacturing Practice.
- The TGA does not provide advice on which product would be appropriate for use on individuals, but if you have specific concerns regarding the use of sunscreens we advise consulting with your doctor for tailored advice.

Response 2

- Compliant therapeutic sunscreens on the Australian market meet the TGA's rigorous safety, quality, and efficacy standards. Our risk-based regulatory framework is designed to be proportionate to the low levels of adverse event reports, while also considering Australia's unique context, including that we have the highest incidence of skin cancer in the world.

- While some international reports have highlighted that certain sunscreen active ingredients may be absorbed into the skin, it's important to understand that absorption does not inherently mean harm.
- The US FDA's review of these ingredients is based on preliminary studies, and they have called for additional data to conclusively determine safety. We are actively monitoring these developments and will consider any new evidence as it becomes available. Research into the clinical significance of these findings is ongoing. The FDA does not conclude that chemical sunscreens are unsafe for use, and sun protection should remain a priority.
- We are actively finalising our own review of a number of sunscreen active ingredients, (including X), used in therapeutic sunscreens. This review encompasses a comprehensive literature search and assessment to evaluate the potential risks associated with these ingredients. As our review and consultation process continues, we maintain that sunscreen sponsors (product owners) have a legal responsibility to ensure the safety of their products. We will take action if products are found to contain unacceptable ingredients or impurities or fail to meet other regulatory requirements.
- **Background**: In Australia, sunscreens that are primarily for UV protection are regulated as therapeutic goods due to the high incidence of skin cancer, necessitating stringent safety, quality, and efficacy standards. This contrasts with many overseas jurisdictions where sunscreens are regulated as cosmetics and may not meet the same regulatory standards.

Should consumers continue using sunscreen?

- Exposure of unprotected skin to UV radiation is well-documented to cause skin cancer and sun protection should be a priority.
- While the TGA conducts its review of certain sunscreen active ingredients, consumers should continue using sunscreen when required for sun protection. There is no conclusive evidence linking sunscreens to cancer, and they play a critical role in preventing sunburn and skin cancers, especially considering Australia has the highest rates of skin cancer in the world.
- If going outside when the UV index is predicted to reach 3 or more, sunscreen is recommended on exposed skin as part of a comprehensive sun protection strategy, which includes seeking shade, wearing protective clothing, hats, and sunglasses. Similar recommendations are endorsed by the Australasian College of Dermatologists and many other organisations in Australia. If sunscreen is used, the TGA encourages the use of a broad-spectrum sunscreen with an SPF of at least 30, along with other sun protective measures. Pregnant women and those with concerns about using sunscreens on infants or children should consult with their doctor for advice before using any products or medicines.
- This approach ensures that the benefits of sunscreen use, which are substantial, are balanced against any theoretical risks.

Commented [S22] Awaiting tox review to be finalised

What is the TGA doing about benzophenone?

- The TGA is actively addressing the concerns surrounding benzophenone in sunscreens. Our current assessment is that octocrylene, an approved ingredient in Australia at a maximum concentration of 10%, does not present an unacceptable safety risk when used as directed. Benzophenone has been detected only in trace amounts in octocrylene-containing products, and there is currently insufficient information to conclude that compliant sunscreens with octocrylene are unsafe. The TGA has conducted tests on products containing octocrylene and will act if unacceptable levels are found.
- There is no internationally agreed safety or quality limit for benzophenone in medicines or sunscreens. In the absence of a standard, manufacturers must establish appropriate quality control specifications and stability protocols to monitor relevant impurities, and ensure the safety of each batch of product throughout its shelf life.
- Furthermore, we have developed a novel Australian sunscreen exposure model, which, once finalised, will inform our review of benzophenone. Targeted consultation on this model was

conducted in April 2024, and public consultation took place between July and August 2024. The final exposure model and the review of benzophenone are anticipated to be completed in 2024.
- We will take necessary regulatory actions based on the outcomes, including publishing the findings and conducting public consultation on any proposals if necessary.

What is the TGA is doing to protect consumers from these harmful ingredients/ to ensure sunscreens are safe?

- The TGA has a comprehensive post-market monitoring system, that is designed to monitor and review sunscreens to ensure they meet regulatory requirements. Or framework allows us to identify potential problems early on and take steps to mitigate risk to help ensure that Australians have access to safe and effective sunscreens. This system includes:
    - **Post-market reviews** to assess continued compliance with regulatory requirements.
    - **Laboratory testing** to verify the quality (and therefore the safety and efficacy) of sunscreen ingredients.
    - **Monitoring of advertising** to ensure truthful and compliant product promotion.
    - **Reviewing adverse events** to promptly address any safety concerns.
    - **Staying aware of emerging safety data** to inform our regulatory decisions.
- When products are found to be non-compliant or contain unacceptable levels of impurities, the TGA takes decisive action depending on the nature of the breach. Our measures range from providing education and guidance to sponsors, to enforcing product cancellations from the Australian Register of Therapeutic Goods (ARTG), or pursuing prosecution when necessary. More information can be found on our website (https://www.tga.gov.au/how-we-regulate/compliance-and-enforcement-hub/compliance-management).
- We are currently engaged in an extensive review of the latest scientific literature regarding the safety of common active ingredients in sunscreens approved for use in Australia. This review is expected to be completed in 2024, and we will take appropriate regulatory action depending on the findings.
- We encourage everyone to report any concerns about sunscreens to the TGA. Your reports enable us to better respond to safety concerns and uphold the stringent sunscreen standards that protect all Australians.

What happens if a sunscreen is found to be in violation of the law?

- When a sunscreen is determined to be non-compliant with the law, we take a risk-based approach to determine the appropriate action. Sunscreens listed on the Australian Register of Therapeutic Goods (ARTG) are subject to compliance reviews to ensure they meet all regulatory requirements for labelling, advertising, efficacy, safety, and quality. If a sunscreen fails to comply, our actions are based on the risk to consumers, the potential for rectification by the sponsor, and the sponsor's compliance history. The TGA regularly publishes compliance review outcomes, that can be found here (https://www.tga.gov.au/resources/resource/guidance/listed-medicine-compliance-reviews). Possible actions include instructing the sponsor to update labels, cancelling the product from the ARTG, or recalling the product from the market, particularly if public safety is at risk. This process safeguards public health and ensuring that sunscreens meet the highest regulatory standards.

Sunscreen ingredients have been found in, and can harm the marine environment, why is the TGA not promoting marine-friendly products?

- Environmental matters do not fall under therapeutic goods legislation. It is beyond our legal powers to promote marine-friendly products.
- Questions about environmental policy and impact of chemicals should be directed to the Department of Climate Change, Energy, the Environment and Water.

Draft talking points:

Who's responsibility is it to ensure the safety of sunscreen products? Is it the sponsor or the TGA?

- It is primarily the responsibility of the product sponsor – they make a legal declaration when listing their product on the ARTG and are responsible to ensure that their product is safe for its intended use.
- The TGA operates under a comprehensive regulatory framework, post market monitoring and testing scheme, that ensures sponsors comply with their regulatory obligations.
- All sunscreens regulated by the TGA are listed via the "low-risk" medicines pathway.
- Sponsors use ingredients permitted by the TGA to formulate their products (manufactured under GMP) without the need for premarket assessment. In doing so they have to ensure that their product will be safe and they hold evidence that it works.
- In terms of the ingredients permitted for use in the listed medicines framework, they were permitted based on legislation and the scientific data available at the time of their approval. However, as we know, new scientific methods and data may come to light that may require reconsideration of the conditions for those historical approvals.
- TGA regularly monitors scientific and international developments and conducts its own updated ingredient reviews, that can lead to setting new restrictions if necessary.
- What I can tell you is that the TGA is conducting its own safety review of a number of common sunscreen active ingredients used in listed therapeutic sunscreens and looking at the latest scientific data. We are aiming to have our findings available before the end of the year.

The US FDA has banned numerous chemical sunscreen ingredients that are not GRASE because they are not safe, why has the TGA not banned them?

- Other than 2 ingredients (PABA and Trolamine salicylate), the US FDA has not banned those ingredients.
- To be clear, the US FDA have stated that they have not concluded that the active ingredients proposed as non-GRASE are unsafe for use in sunscreens or that chemical sunscreens are unsafe or ineffective. They have requested additional information to evaluate their GRASE status in light of changed conditions, including substantially increased sunscreen usage and evolving information about potential risks since they were originally evaluated
- The US FDA's proposed rule was initiated following findings from experimental studies that tested sunscreen formulations applied to 75% of volunteers' bodies, 4 times a day, for 4 consecutive days, which is a very large quantity of sunscreen. The studies reported that the active ingredients could be absorbed through the skin above 0.5 ng/mL.

- At this threshold, under the US FDA's framework, they require further safety data and testing before they can say it is GRASE.
- It is important to note that if an ingredient is absorbed through the skin, it does not necessarily mean it is unsafe, and the US FDA has called for further data and testing from industry before they finalise their GRASE status.
- They've also stated that if there is a lack of progress on generating this data, or sufficient evidence becomes available to answer the outstanding questions about whether these ingredients are GRASE, then they will move forward with finalising their proposal. As they have yet to do so, it could be likely that data is being generated to support the safety of these ingredients.
- The TGA is not waiting for US FDA to finalise their proposal, and we have started our own safety review to look at the most up to date scientific data. We are aiming to finalise our review by the end of the year and will share our findings.
- If there are any risk management measures required, we will consult on those as is standard process.
- Sun protection should be a priority. What's important to keep in mind is that the risk of skin cancer is real and UV radiation exposure from the sun is an established carcinogen.

The TGA has reviewed some sunscreen ingredients, are you planning to review all other sunscreen ingredients?

- A number of common ingredients have already assessed and we are continuing to monitor if there are any further developments or concerns.
- Ingredients for use in sunscreens have been approved based on the legislation and safety data available at the time of their approval. Many sunscreen active ingredients were also considered by previous medicines evaluation committees to ensure their safety.
- The TGA is a risk-based regulator, and we will, and regularly do, review other ingredients if safety signals come to our attention.
- The current mandatory data requirements to substantiate the safety of a sunscreen ingredient (as described in the Australian Regulatory Guidelines for Sunscreens) are comprehensive.
- The requirements consider whether an ingredient has the potential to absorb through the skin, and applicants must provide evidence to support their safety before a new ingredient can be approved. This ensures that any ingredients used in therapeutic sunscreens are safe for consumers.

Can you explain how some sunscreens are regulated by the TGA and others are not? What does that mean if the TGA deems an ingredient as safe or not?

- It's important to understand that all sunscreens (therapeutic or cosmetic) are required to comply with the Australia/New Zealand Sunscreen Standard for SPF and broad-spectrum testing. This ensures a consistent standard for their performance across different sunscreens.
- Australia has the highest incidence of skin cancer in the world, and it is a decision of government that primary sunscreens (those that are primarily intended for UV protection) are regulated as therapeutic goods by the TGA, with higher regulatory standards, than other countries where skin cancer is less prevalent.
- Most secondary sunscreens (those that are not primarily intended for UV protection, such as make-up and anti-wrinkle products with an SPF raiting) are excluded from therapeutic goods legislation and regulated as cosmetics in Australia. The Australian Industrial Chemicals

Introduction Scheme (AICIS) is the regulator that evaluates the safety of ingredients used in cosmetic sunscreens and the Australian Competition and Consumer Commission (ACCC) oversees product issues such as safety and misleading claims.
- Where there are ingredients that are used in both therapeutic, and cosmetic sunscreens, the TGA works closely with our regulatory partners to share information and ensure products are appropriately regulated under the correct legal framework.

Background:

Australian regulation of sunscreen

- See Business Improvement and Support Section Media standard words
- International reviews or regulatory actions regarding sunscreens may not be relevant in Australia. Importantly, our regulatory standards and classifications for sunscreens differ to other countries. For example, sunscreens are regulated as cosmetics in Europe and other parts of the world. However, sunscreens that are primarily for preventing UV damage and skin cancer are regulated as therapeutic goods in Australia by the TGA, and can make claims relating to skin cancer and are required to comply with Australian therapeutic goods laws.
- Furthermore, sponsors (product owners) have additional compliance requirements such as ensuring their product is safe. This is not limited to the ingredients they use, but also how they are presented for sale, ongoing pharmacovigilance responsibilities, and being required to be manufactured under the principles of Good Manufacturing Practice. We also actively monitor therapeutic sunscreens in the market through a range of ways such as laboratory testing and compliance reviews, and we take appropriate regulatory actions if needed.

Ingredients under TGA review

- We are currently reviewing the scientific literature to ascertain the safety of seven active ingredients used in sunscreens marketed in Australia:
    - Avobenzone
    - Ethylhexyl triazone (EHT)
    - Homosalate
    - Octocrylene
    - Octinoxate
    - Oxybenzone
    - PSBA (phenylbenzimidazole sulfonic acid)
- Our review includes a comprehensive literature search and assessment to evaluate the potential risks associated with these ingredients, informed by recent international scientific reviews and regulatory action. The review is expected to be completed in 2024. The TGA will take necessary regulatory actions based on the review's outcomes, including publishing our findings, and conducting public consultation on any proposals if required.
- Sponsors of sunscreens can continue using ingredients that are in the Therapeutic Goods (Permissible Ingredients) Determination for listed medicines, noting that it is also the legal responsibility of each sponsor to ensure that their listed medicine is safe for the purposes for which it is to be used.

Past TGA activities

- We have completed a survey of aerosol sunscreens for benzene contamination, consulted on establishing a safe daily exposure limit for benzophenone (an impurity found in octocrylene containing sunscreens), and most recently we have developed a novel Australian sunscreen exposure model for assessing the safety of sunscreen ingredients.

- Benzene is not permitted as an ingredient for use in sunscreens regulated as listed medicines in Australia. The health consequences of benzene exposure depend on how much, the length of exposure and the route of exposure, as well as the age and health conditions of the person. The levels of benzene must be below 2 parts per million (ppm) and the TGA Laboratories have tested a range of products supplied in Australia for compliance. You can read more here.
- The decision to amend the requirement for octocrylene in the Therapeutic Goods (Permissible Ingredients) Determination to address the safe levels of benzophenone was deferred pending further consultation on developing an appropriate sunscreen exposure model that could be used to set a regulatory cut-off. The sunscreen exposure amount used in the public consultation paper in August 2023 (140 mL/day) was an overestimate of the daily sunscreen usage by Australians and meant the calculations for the maximum benzophenone limit were overly conservative. New data received as part of the consultation also demonstrating much less benzophenone is likely absorbed through the skin than initially proposed, so there is no imminent safety concern with compliant listed sunscreens that contain octocrylene in the Australian market.

US FDA GRASE (generally recognised as safe and effective) ingredients:

- The US FDA's review of publicly available evidence has found sufficient safety data on both zinc oxide and titanium dioxide to support a proposal that these ingredients are GRASE in sunscreens (with a concentration up to 25%).

US FDA non-GRASE ingredients where further data required:

- The US FDA has *proposed* certain sunscreen active ingredients (inoxate, dioxybenzone, ensulizole, homosalate, meradimate, octinoxate, octisalate, octocrylene, padimate O, sulisobenzone, oxybenzone, and avobenzone) are non-GRASE, because they do not have sufficient publicly available information to support positive GRASE determinations. The US FDA have requested more information from industry and other interested parties for additional safety data, and are reviewing these ingredients to determine if they are GRASE before they can establish a final order.
- It should be noted, the US FDA have emphasised that they have not concluded that the active ingredients proposed as non-GRASE are unsafe for use in sunscreens. They have requested additional information to evaluate their GRASE status in light of changed conditions, including substantially increased sunscreen usage and evolving information about potential risks since they were originally evaluated (p 5 of proposed rule).
- The US FDA has yet to publish their findings or final order. They plan to re-evaluate the progress of studies periodically. If the US FDA later decides that the studies are not progressing or otherwise are not productive, or sufficient evidence becomes available to answer the outstanding questions about whether these ingredients are GRASE, they would expect to move forward with a final order.
- The US FDA's findings were based on exploratory studies for some sunscreen active ingredients that found they could be absorbed through the skin. However, it is important to note that if an ingredient is absorbed through the skin, it does not necessarily mean it is unsafe, and the US FDA has called for further data and testing to show repeated use of those ingredients are safe.
- The US FDA requires that ingredients absorbed into the blood at 0.5 ng/mL or more, or have potential safety concerns, need to further data to understand if they increase the risk of adverse effects such as cancer or birth defects. This, and other safety data is used to inform the overall benefit-risk evaluation of ingredient.
- See FDA Q and A on deemed final order and proposed order and FDA proposed rule

US FDA status of PABA and trolamine salicylate:

- The US FDA evaluated safety data available to them and concluded that the risks associated with use of aminobenzoic acid (PABA) and trolamine salicylate as active ingredients in sunscreens outweigh their benefits. They have stated the risks for trolamine salicylate

include the potential for serious bleeding and salicylate toxicity (vomiting, hyperventilation, metabolic disturbances, coma and death) when used in sunscreens. For PABA, they noted the risks include significant rates of allergic and photoallergic skin reactions, as well as cross-sensitization with structurally similar compounds that may lead to allergies to commonly used medications. Accordingly, they proposed these ingredients are not GRASE for use in sunscreens.

SCCS framework and regulatory actions for sunscreen ingredients

- The Scientific Committee on Consumer Safety (SCCS) is an advisory body of the European Commission that provides independent scientific advice on the health and safety risks of non-food consumer products. The SCCS conducts risk assessments and issues opinions on various substances, including those used in cosmetics and sunscreens. These opinions are based on scientific data and are intended to inform regulatory decisions within the European Union (EU). The opinions of the SCCS present the views of the independent scientists who are members of the committee. They do not necessarily reflect the views of the European Commission.
- Regulation (EC) No 1223/2009 harmonises the safety of cosmetics within the European Member States. Article 3 of the Cosmetics Regulation specifies that a cosmetic product made available on the European market shall be safe for human health when used under normal or reasonably foreseeable conditions of use. The safety-in-use of cosmetic products has been established in Europe by controlling the substances, their chemical structures, toxicity profiles, and exposure patterns. (p 145 sccs_o_250.pdf (europa.eu)). Article 18 states 'To ensure their safety, cosmetic products placed on the market should be produced according to good manufacturing practice' and it appears there is an ISO GMP guideline for cosmetics.
- It's important to note that while the SCCS provides opinions, the European Commission takes these into account but makes its own decisions regarding the regulation of products and whether they will be included in the relevant cosmetic annexes (e.g. Annex II List of prohibited substances).
- The SCCS uses various models and data, including European usage patterns, to calculate the sunscreen exposure, and the Margin of Safety (MoS). However, these models may not account for the specific conditions and practices of other regions, such as Australia, which has a unique sun exposure environment and different sunscreen application habits.
- Annexes to Regulation (EC) No 1223/2009 relevant to sunscreens are:

    - Annex II List of prohibited substances
    - Annex III List of restricted substances
    - Annex VI List of allowed UV filters

  The safety of the Annex substances is evaluated by the SCCS; while the safety of cosmetic products with all their ingredients is evaluated by the industry placing them on the EU market.

- There are certain bans in Europe, such as use of animal studies for ingredients developed for cosmetics (p 5 Memorandum on alternative Test Methods in Human Health Safety Assessment of Cosmetic Ingredients in the European Union, 8 Decem (europa.eu); Article 18 of the EC No 1223/2009 also refers), meaning some safety data may not be able to be relied on for the purposes of establishing the safety of those ingredients as these would fall under an Article 18 ban (p 150, sccs_o_250.pdf (europa.eu)). Article 18 permits exceptional circumstances where a derogation can be granted from the ban only where:

  (a) the ingredient is in wide use and cannot be replaced by another ingredient capable of performing a similar function;

(b) the specific human health problem is substantiated and the need to conduct animal tests is justified and is supported by a detailed research protocol proposed as the basis for the evaluation.

Australia does not have a ban on use of animal data for therapeutic goods (including listed sunscreens).

- Article 3 of the Regulation (EC) No 1223/2009, provides that a cosmetic product made available on the market must be safe for human health when used under normal or reasonably foreseeable conditions of use.
- Current UV filters permitted in the EU and their requirements/transitions are available at REGULATION (EC) No 1223/2009 (Annex VI): https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02009R1223-20240424
    - Homosalate:
        - From 1 January 2025 cosmetic products containing homosalate and not complying with the conditions (maximum 7.34% in face products - not permitted in propellent spray products) shall not be placed on the Union market. From 1 July 2025 cosmetic products containing that substance and not complying with the conditions shall not be made available on the Union market.
    - Oxybenzone and Octocrylene:

Reference number	Substance identification				Conditions			Wordings of conditions of use and warnings
	Chemical name/INN	Name of Common Ingredients Glossary	CAS number	EC number	Product type, body parts	Maximum concentration in ready use preparation	Other	
a	b	c	d	e	f	g	h	i
4	2-Hydroxy-4-methoxy-benzophenone Oxybenzone (*1)	Benzophenone-3	131-57-7	205-031-5	a)Face products, hand products, and lip products, excluding propellant and pump spray products b)Body products, including propellant and pump spray products c)Other products	a)6 % b)2,2 % c)0,5 %	For a) and b) Not more than 0,5 % to protect product formulation a)If used at 0,5 % to protect product formulation, the levels used as UV filter must not exceed 5,5 %. b)If used at 0,5 % to protect product formulation, the levels used as UV filter must not exceed 1,7 %.	For a) and b): Contains Benzophenone-3 (*2)
10	2-Cyano-3,3-diphenyl acrylic acid, 2- ethylhexyl ester Octocrylene (*1) (*2)	Octocrylene	6197-30-4	228-250-8	a)Propellant spray products b)Other products	a)9 % b)10 %		

(*1) However, cosmetic products containing that substance and complying with the restrictions set out in Regulation (EC) No 1223/2009 as applicable on 27 July 2022 may be placed on the Union market until 28 January 2023 and be made available on the Union market until 28 July 2023.

(*2) Not required if concentration is 0,5 % or less and when it is used only for product protection purposes.

(*2) Benzophenone as an impurity and/or degradation product of Octocrylene shall be kept at trace level."

- 4-Methylbenzylidene camphor (The EC issued the new regulation on 3 April 2024):
  - From 1 May 2025 products containing 4-MBC shall not be placed on the Union market. From 1 May 2026 cosmetic products containing 4-MBC shall not be made available on the Union market.

From: s22
To: s22
Subject: RE: Safety Review of Active Sunscreen Ingredients [SEC=OFFICIAL]
Date: Thursday, 13 March 2025 4:22:59 PM
Attachments: image001.png
image002.png
image003.png
image004.png
image006.png

Hi s22

George has now cleared both documents (by TRIM workflow).

Kind regards
s22

s22
Scientific Evaluation Branch
Medicines Regulation Division | Health Products Regulation Group
Australian Government, Department of Health and Aged Care
T: s22 | E: s22 @health.gov.au

Location: Fairbairn ACT
PO Box 100, Canberra ACT 2601, Australia

The Department of Health acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to elders both past and present.

From: s22 @health.gov.au>
Sent: Tuesday, 11 March 2025 5:04 PM
To: s22 @health.gov.au>; s22
s22 @health.gov.au>; s22 @health.gov.au>
Subject: RE: Safety Review of Active Sunscreen Ingredients [SEC=OFFICIAL]

Hi s22 ,

Many thanks for getting the 2x safety reviews ready for the next steps.

As we are nearing the final stages in compiling the various documents prior to the publication of the documents, Avi has reminded us that approval of the safety reviews should come from George, given the reviews are under Tox's ownership. Grateful if you can obtain George's approval (by TRIM workflow) for both documents (D24-3026768, D24-3266384) before **COB 13 March 2025**, while Avi takes carriage of the approval of web publication of all related documents (i.e. Media release, Sunscreen Ingredients landing page).

Thanks,
s22

From: s22 @health.gov.au>
Sent: Wednesday, 26 February 2025 10:01 AM
To: s22 @health.gov.au>; s22
s22 @health.gov.au>
Cc: s22 @health.gov.au>
Subject: RE: Safety Review of Active Sunscreen Ingredients [SEC=OFFICIAL]

Hi s22

I have made the changes that you pointed out below to all the relevant tables under Under '*Further consideration for homosalate*', '*Further consideration for Oxybenzone*'.

Cheers
s22

s22
Scientific Evaluation Branch
Medicines Regulation Division | Health Products Regulation Group
Australian Government, Department of Health and Aged Care
T: s22 | E: s22 @health.gov.au

Location: Fairbairn ACT
PO Box 100, Canberra ACT 2601, Australia

The Department of Health acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to elders both past and present.

From: @health.gov.au>
Sent: Monday, 24 February 2025 1:03 PM
To: s22 @health.gov.au>
Cc: s22 @health.gov.au>; s22
s22 @health.gov.au>
Subject: RE: Safety Review of Active Sunscreen Ingredients [SEC=OFFICIAL]

Hi s22

Just noticed some errors in the Safety Review of the Seven Active Sunscreen Ingredients: D24-3026768.

Under '*Further consideration for homosalate*', '*Further consideration for Oxybenzone*':

- The tables reflect Adult 'head' twice. The second occurrences should be Adult 'face' instead. I have shown the tracked change for one of the tables below:

Further consideration for homosalate

If the use of a sunscreen product containing homosalate is applied to specific parts of the body e.g. face, the MoS may increase. However, as shown in the two tables below for application of a homosalate-containing sunscreen product twice a day for 240 days per year and 365 days per year, respectively, the various estimates are still less than satisfactory, i.e. a MoS less than 100.

Annual use considered for 240 days/years based upon Scenario 1 of the ASEM.

Scenario *	Skin Surface Area (cm^2)	Body weight (kg)	Reapplications (no. per day)	Annual use (days/year)	SED (mg/kg bw/d)	MoS
Adult Head only	1350	107	2	240	0.18	38
Adult Hands only	1200	107	2	240	0.16	43
Adult Head + Hands	2550	107	2	240	0.33	20
Adult ~~Head~~ Face only	675	107	2	240	0.09	76
Adult ~~Head~~ Face + Hands	1875	107	2	240	0.24	27

*95th percentile for SSA body parts and total body weight (average of male and female adult values combined).

Please let me know if you would like to amend those or would you prefer that CMES make those edits.

Thanks
s22

From: s22 @health.gov.au>
Sent: Friday, 21 February 2025 11:38 AM
To: s22 @health.gov.au>
Cc: s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>
Subject: Safety Review of Active Sunscreen Ingredients [SEC=OFFICIAL]

Hi s22 ,

As agreed previously, we have finalised the following 2 reports for CMES:

- Safety Review of the Seven Active Sunscreen Ingredients: D24-3026768
- Benzophenone safety review: D24-3266384

The final conclusion has been approved by Prof Robyn Langham.

Thanks,

s22

s22 [redacted]

[redacted]

Scientific Evaluation Branch

Medicines Regulation Division | Health Products Regulation Group

Australian Government Department of Health and Aged Care
T: s22 [redacted] | E: s22 [redacted] @health.gov.au
Therapeutic Goods Administration
27 Scherger Drive, Fairbairn, ACT 2609
PO Box 100, Woden ACT 2606, Australia

The Department of Health acknowledges the Traditional Custodians of Australia and their continued connection to land, sea and community. We pay our respects to all Elders past and present.

From: s22
To: s22
Cc: s22
Subject: Updated Safety Review of the Seven Active Sunscreen Ingredients [SEC=OFFICIAL]
Date: Friday, 30 May 2025 9:57:38 AM
Attachments: image001.png
image002.png
image004.png

Hi s22

The Safety Review of the Seven Active Sunscreen Ingredients (D25-2148966) has now been updated following discussions with the executive, Tox, CMES and the scheduling secretariate in early May.

The updates to the document include additional exposure calculations and options to be considered for scheduling for the sunscreen ingredients homosalate and oxybenzone.

Specifically, we have:

- Clarified on pg 10 to highlight that Australians use higher amounts of sunscreen compared to other regions and therefore have used a tailored approach to assess the MoS of sunscreen ingredients;
- included additional calculations (for toddler scenarios) in the Homosalate (pg 48-52) and Oxybenzone (pg 59-61) safety assessment sections and updated the Recommendations for both of those to reflect the additional OPTIONS for Scheduling to consider.

Thank you to s22 for their work on this document. This report has been cleared by s22 (A/g branch head for SEB).

Kind regards
s22

s22
Scientific Evaluation Branch
Medicines Regulation Division | Health Products Regulation Group
Australian Government, Department of Health, Disability and Ageing
T: s22 | E: s22 @health.gov.au

Traditional Owners of Country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Safety Review of Seven Active Sunscreen Ingredients

Butyl methoxydibenzoylmethane (avobenzone), ethylhexyl triazone, homosalate, octocrylene, octyl methoxycinnamate (octinoxate), oxybenzone and phenylbenzimidazole sulfonic acid (PBSA)

May 2025

Copyright

Contents

Glossary

Abbreviation	Explanation
ABS	Australian Bureau of Statistics
AICIS	Australian Industrial Chemicals Introduction Scheme
ARGS	Australian Regulatory Guidelines for Sunscreens
ARGS	Australian regulatory guidelines for sunscreens
ARNS	Application Requirements for New Substances in listed medicines
ARPANSA	Australian Radiation Protection and Nuclear Safety Agency
ARTG	Australian Register of Therapeutic Goods
ASEM	Australian Sunscreen Exposure Model
BoM	Bureau of Meteorology
MoS	Margin of Safety
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
PoD	Point of Departure
SCCNFP	Scientific Committee on Cosmetic and Non-Food Products intended for Consumers
SCCS	Scientific Committee on Consumer Safety
SED	Systemic Exposure Dose
SPF	Sun Protection Factor
SSA	Skin Surface Area
Sunscreen Standard	Australian/New Zealand Standard Sunscreen products - Evaluation and classification AS/NZS 2604:2021 Amd 1:2022
TGA	Therapeutic Goods Administration
Therapeutic sunscreen	Primary and some secondary sunscreens regulated under the *Therapeutic Goods Act 1989*
UF	Uncertainty Factor
UV	Ultraviolet

Executive summary

The TGA conducted a safety review of 7 active ingredients in therapeutic sunscreens:

- butyl methoxydibenzoylmethane (also known as ‘avobenzone’)
- ethylhexyl triazone
- homosalate
- octocrylene
- octyl methoxycinnamate (also known as ‘octinoxate’)
- oxybenzone
- phenylbenzimidazole sulfonic acid

This safety review was dependent on the national and international safety assessment reports and peer reviewed publications investigating the safety and toxicokinetics of the ingredients, where available. These ingredients were selected for priority review considering the status of the availability of nonclinical safety data to TGA and their reported use in higher number of sunscreen products marketed in Australia in addition to the safety signals reported overseas.

Based on available scientific data, the following active ingredients were considered to be low risk and appropriate for use in therapeutic sunscreens:

- butyl methoxydibenzoylmethane
- ethylhexyl triazone
- octocrylene
- octyl methoxycinnamate
- phenylbenzimidazole sulfonic acid.

However, based on the data considered in this safety review, the TGA recommends regulatory controls for homosalate and oxybenzone to restrict their permitted concentrations and use in therapeutic sunscreens.

The two main issues considered in this safety review were the evidence for the ability of these ingredients to penetrate the skin to reach viable cells systemically and the potential toxicity exerted by them.

Based on the data available for these ingredients, a Margin of Safety (MoS) was determined for each of the ingredients using the Australian Sunscreen Exposure Model (ASEM) which underwent public consultation in 2024. A MoS of 100 or more is considered to be satisfactory for controlling for the risks to human health and safety from long-term use of an ingredient by the Australian population. The MoS was calculated based on the current maximum permitted concentrations in therapeutic sunscreens (which are regulated as listed medicines).

However, it is important to note that the concentrations of these actives in products can be less than the maximum permitted amounts; and that some products contain a combination of the active ingredients.

The ASEM has been used to calculate the highest estimated average daily sunscreen exposure modelled to account for use of therapeutic sunscreens applied long-term to the face and body by children and adults. The MoS for butyl methoxydibenzoylmethane, ethylhexyl triazone, octocrylene, octyl methoxycinnamate and phenylbenzimidazole sulfonic acid were above 100. These ingredients are unlikely to cause any significant systemic toxicity and are therefore considered low risk when used in therapeutic sunscreens.

In the case of homosalate and oxybenzone, the MoS using the highest estimated sunscreen exposure for application of a general sunscreen to the body, at the maximum permitted concentration, was less than 100. Hence, the ASEM was utilised to estimate alternative exposures based on specific parts of the body e.g. head, face and/or hands. In this case, the MoS was more than 100 and considered low-risk for long-term use when limited to the face and hands at concentrations between 11.4% and 2.7% homosalate, and 9.8% to 10 % for oxybenzone, depending on the type of product and the directions for use (e.g. limited to face-only use).

The limitations of this review are:

a) The toxicological endpoints, (NOAELs), were collected from published international safety assessment reports and scientific literature. As full data sets, including all raw study data, were not available for independent corroboration of the findings from these reports and literature, this review was dependent on the veracity of the details provided in those reports and literature.
b) Additional studies would be required to fully evaluate the pharmacokinetics of the active ingredients.
c) The available information on butyl methoxydibenzoylmethane, homosalate, octocrylene, octyl methoxycinnamate and oxybenzone indicate potential endocrine effects, however, the data are not adequate to derive a conclusion as to their causality in humans. Further data on the endocrine modifying potential of these chemicals are warranted.
d) Consumer products other than sunscreens that contain the same active ingredients were not considered in this review.
e) The exposure to metabolites of these ingredients or impurities present in these ingredients has not been considered in this review.

Introduction

The *Therapeutic Goods (Permissible Ingredients) Determination (No. 1) 2025* currently lists 30 sunscreen active ingredients approved for use in Australia. The safety of these ingredients has been addressed by various means, including the assessment of toxicological data, utilisation of overseas regulatory reports, and consideration by committees such as the then Medicines Evaluation Committee.

The TGA has been monitoring the emerging scientific literature of the safety of sunscreens and working cooperatively with international agencies to monitor these issues to ensure that appropriate action is undertaken if any unacceptable risks are identified.

The TGA seeks to promote high standards of therapeutic product vigilance for the protection of the health and safety of Australians. It does this by monitoring the continuing safety, quality and efficacy of therapeutic goods in the market through therapeutic product vigilance activities. The TGA's strong pharmacovigilance program also involves the assessment of adverse events that are reported to the TGA by consumers, health professionals, the pharmaceutical industry, international medicines regulators or by the medical and scientific experts. Information on the TGA's approach to managing compliance risk is available via the TGA website: www.tga.gov.au/about/compliance.htm https://www.tga.gov.au/hubs/compliance-and-enforcement/compliance-management

Post-market monitoring of listed medicines also includes environmental scanning such as collection and review of scientific and medical literature, media reports and regulatory news to identify safety issues that require further investigation.

US FDA's proposed rule relating to sunscreen active ingredients

In 2019, the US FDA published a guidance for industry concerning safety and effectiveness data necessary to determine that a sunscreen active ingredient is generally recognized as safe and effective (GRASE) under the Sunscreen Innovation Act which introduced a new requirement to conduct Maximal Usage Trials (MUsT) in order to study human absorption correlating to real-world use (FDA, 2019a). The FDA published two studies in 2019 and 2020 looking at the dermal absorption of the most common active ingredients in sunscreens (Matta *et al.,* 2020; 2019). Both studies demonstrated that the studied sunscreen active ingredients were absorbed in appreciable quantities (i.e. detected at >0.5 ng/mL in plasma) and that active ingredients can remain in plasma for an extended time after the last application.

This was followed by the publication of an FDA proposed rule in 2019 elaborating the requirement for testing and labelling of sunscreens by manufacturers (FDA, 2019b). The rule divided the 16 active ingredients approved in USA into three categories:

- Category I (GRASE) includes ZnO and TiO_2;
- Category II (not GRASE) includes trolamine salicylate and para-aminobenzoic acid (PABA) (neither of which is used in products currently marketed in Australia); and
- Category III (additional data needed) includes the remaining 12 organic filters (cinoxate, dioxybenzone, ensulizole, homosalate, meradimate, octinoxate, octisalate, octocrylene, padimate O, sulisobenzone, oxybenzone, avobenzone; (FDA, 2019b)). Ensulizole, homosalate, octinoxate, octisalate, octocrylene, oxybenzone, avobenzone are used in Australian products, as of 12February 2025.

The FDA proposed rule also dictated that if an adequately conducted MUsT demonstrates a steady-state blood level of an ingredient under 0.5 ng/mL, and an adequately conducted toxicological study does not raise any other safety concerns, then studies on systemic carcinogenicity and developmental and reproductive toxicity may not be required. The 0.5 ng/mL limit was selected because it represents approximately the highest plasma concentration under which the risk of carcinogenicity of any unknown compound would be below 1/100,000 following a single dose (FDA, 2019c).

TGA's safety review

Given the greater use and importance of sunscreens in Australia; and the current interest by the US FDA in the ongoing safety of sunscreen active ingredients, the TGA conducted a safety review to better understand the safety profile of these ingredients. Following consideration of the highest reported use of the sunscreen products in Australia containing these active ingredients, a targeted safety assessment of was undertaken for 7 ingredients: butyl methoxydibenzoylmethane, ethylhexyl triazone, homosalate, octocrylene, octyl methoxycinnamate, oxybenzone and phenylbenzimidazole sulfonic acid. This document reviews whether these ingredients are low-risk and appropriate for use in therapeutic sunscreens.

A literature review was conducted for the scientific information available for the 7 active ingredients butyl methoxydibenzoylmethane, ethylhexyl triazone, homosalate, octyl methoxycinnamate, octocrylene, oxybenzone and phenylbenzimidazole sulfonic acid for use in sunscreens. These ingredients have been widely used in sunscreen products in Australia. The safety review is intended to provide an overview of the publicly available safety information for these ingredients, calculate the MoS as per the Australian Sunscreen Exposure Model (ASEM) using the maximum concentration of the ingredients approved in Australia, and provide information needed to assess the suitability of these ingredients for use in therapeutic sunscreens.

Given the TGA makes use of assessments from comparable overseas bodies (COBs), where possible, in evaluations for complementary medicines and ingredients for use in listed medicine (e.g. sunscreens) and the list for COBs includes the SCCS to support the safety of sunscreen ingredients,[1] the safety assessment of the selected ingredients was based on information provided in the newest opinions from the SCCS where available, and information identified from a literature search in PubMed and an open search for information on specific endpoints from published reports from the internet. Review articles and documents focusing on the individual toxicological endpoints were featured in the hazard assessment where no recent SCCS opinions were available. REACH registration dossiers for individual ingredients published by ECHA and risk assessment by national regulatory agencies (i.e. AICIS) were also considered if available. Exposure to metabolites of these ingredients or impurities present in these ingredients has not been considered for safety assessment in this review.

Within 2020-21, the European Commission published opinions (preliminary and/or final) on the safety of oxybenzone, homosalate (2021 and later updated in December 2021) and octocrylene. Based on the available information, the SCCS conducted risk assessments of each of these ingredients and determined a Margin of Safety (MoS) as per SCCS guidelines. The SCCS found that the levels of oxybenzone and homosalate used in the European market were not safe and proposed limits later put into effect by the European Union (EU). For oxybenzone, the new EU requirements are 6% in face, hand and lip products, excluding aerosols, 2.2% in body products including aerosols, and 0.5% in other products. Cosmetic products containing oxybenzone complying with the previous restrictions set out in Regulation (EC) No 1223/2009 as applicable on 27 July 2022, may be placed on the Union market until 28 January 2023 and be made available on the Union market until 28 July 2023. For homosalate, the new EU requirements and transition periods are: from 1 January 2025 cosmetic products containing homosalate and not complying with the conditions (maximum 7.34% in face products - not permitted in propellent spray products) shall not be placed on the Union market. From 1 July 2025 cosmetic products containing homosalate and not complying with the conditions shall not be made available on the Union market. For octocrylene, the new EU requirements and transition periods are that octocrylene can only be present at a maximum concentration of 9% in propellant spray products, and 10% in other products. Cosmetic products containing octocrylene complying with the previous restrictions set out in Regulation (EC) No 1223/2009 as applicable on 27 July 2022, may be placed on the Union market until 28 January 2023 and be made available on the Union market until 28 July 2023.

[1] Comparable overseas bodies (COBs) for complementary medicines | Therapeutic Goods Administration (TGA)

The TGA safety review follows a similar approach of risk assessment based on a MoS determination as per the SCCS guidelines while recognising limited available data (2008-2023). To accurately evaluate the long-term risk of exposure to these active ingredients from sunscreen, further randomized controlled trials may need to be conducted. However, this is subject to ethical considerations.

It was noted that some of the Category III (additional data needed) organic filters have been widely used in sunscreen products in Australia. One of them was octisalate (octyl salicylate also known as ethylhexyl salicylate). Based on the available information, the Cosmetic Ingredient Review Expert Panel (Cosmetic Ingredient Review Expert Panel, 2019) reached the conclusion that octisalate is safe as used in cosmetics in the European use settings and concentration (at 0.003% to 5% concentration as of 2018 data) described in the safety assessment when formulated to be non-irritating and non-sensitizing, which may be based on a quantitative risk assessment (QRA). As such, the literature review was not conducted for octisalate (octyl salicylate).

To ensure the safety review was based on current sun protection practices and recommendations in Australia, the TGA developed the ASEM. This model estimates how much sunscreen Australians use, rather than relying on international models such as from the European Scientific Committee on Consumer Safety (SCCS) that may not reflect Australia's unique environment and practices. The model was subject to targeted and public consultation in 2024 before it was finalised and used in this review. The model incorporates evidence-based data on sunscreen application frequency and quantity, highlighting that Australians apply sunscreen more often and in larger amounts than populations in other countries.

What are these ingredients?

Chemical properties

The chemical and physical properties and the molecular structures of these seven ingredients are provided in the following tables (Yap et al. 2017; Gilbert et al. 2013).

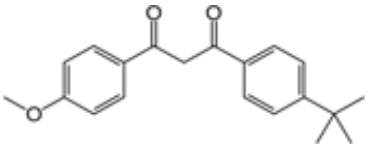
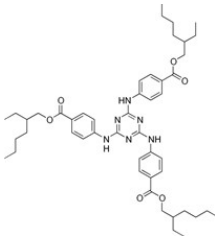
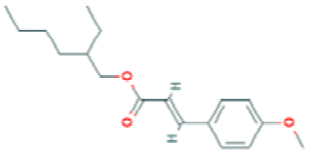
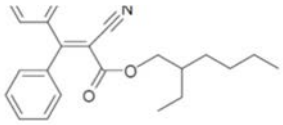
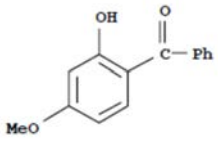
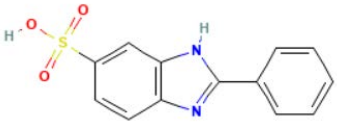
Chemical and Physical Properties of the active ingredients under review

Active ingredient (*absorption spectrum*)	CAS no.	Chemical name	Molecular formula	Physical properties				Other names
				Water solubility	MW g/mol	Density	Log P_{ow}	
Butyl methoxydibenzoylmethane (avobenzone, BMDM or BMDBM) *UVA* λ_{max} *355 nm*	70356-09-1	1,3-Propanedione, 1-[4-(1,1-dimethylethyl)phenyl]-3-(4-methoxyphenyl)-	$C_{20}H_{22}O_3$	0.01 mg/L	310.4	1.1±0.1 g/cm^3	4.5-6.1	Butyl methoxydibenzoylmethane, Eusolex® 020, Parsol® 1789, 4-tert-butyl-4'methoxydibenzoyl methane, BMDBM
Ethylhexyl triazone *UVB* λ_{max} *314 nm*	88122-99-0	2,4,6-Trianilino-(p-carbo-2'-ethylhexyl-l'-oxy)-1,3,5- triazine	$C_{48}H_{66}N_6O_6$	0.005 mg/L at 20°C	823.1	1.1±0.1 g/cm^3	15.5	Uvinul T150, (octyl triazone)

Active ingredient (*absorption spectrum*)	CAS no.	Chemical name	Molecular formula	Physical properties				Other names
				Water solubility	MW g/mol	Density	Log P_{ow}	
Homosalate *UVB* *λ_{max} 306 nm*	118-56-9	3,3,5-trimethylcyclohexyl) 2-hydroxybenzoate	$C_{16}H_{22}O_3$	0.4 mg/L at 25°C	262.3	1.045 g/cm^3	4.7	Benzoic Acid, 2-Hydroxy-, 3,3,5-Trimethylcyclohexyl Ester Cyclohexanol, 3,3,5-trimethyl-, salicylate. Homomethyl salicylate Salicylic acid, 3,3,5-trimethylcyclohexyl ester Caswell No. 482B, Neo Heliopan® HMS, CCRIS 4885, Filtersol "A''
Octyl methoxycinnamate (OMC or EHMC) *UVB* *λ_{max} 310nm*	5466-77-3	2-Ethylhexyl 4-methoxycinnamate	$C_{18}H_{26}O_3$	0.1 g/100 mL at 27°C	290.4	1.01 to 1.02 g/cm^3	5.9	EHMC or octyl-methoxycinnamate (OMC)
Octocrylene (OC) *UVB* *λ_{max} 303 nm*	6197-30-4	2-Propenoic acid, 2-cyano-3,3-diphenyl-, 2-ethylhexyl ester	$C_{24}H_{27}NO_2$	40 µg/L at 20 °C	361.5	1.051 g/mL	6.1	2-Cyano-3,3-diphenyl acrylic acid, 2-ethylhexyl ester, 2-Ethylhexyl-2-cyano-3,3 diphenylacrylate, K.SORB 1139, Octocrylene USP, Parsol 340, Sunkem OTC, Sunobel®23 OCT, Uvinul 3039, 24 UVINUL N 539 T
Oxybenzone (BP-3) *UVB* *λ_{max} 286 nm & λ_{max} 324 nm*	131-57-7	2-benzoyl-5-methoxyphenol; 4-Methoxy-2-hydroxybenzophenone	$C_{14}H_{12}O_3$	0.0037 g/L at 20°C	228.3	1.32 g/mL	>3.7	Benzophenone-3
Phenylbenz-imidazole sulfonic acid *UVB* *λ_{max} 302 nm*	27503-81-7	2-Phenylbenzimidazole-5-sulfonic acid	$C_{13}H_{10}N_2O_3S$	> 30%	274.3	1.5 g/cm^3	-1.1 at pH 5	Ensulizole, Benzimidazole, 2-phenyl, 5-sulfonic acid

*the active ingredients are referred to throughout the report as either their AAN, INN or the abbreviated names. UV absorption range: UVA: 320-400 nm; UVB: 290-340 nm.

Molecular structure of the active ingredients under review

Active ingredient	Structure
Butyl methoxydibenzoylmethane	
Ethylhexyl triazone	
Homosalate	
Octyl methoxycinnamate	
Octocrylene	
Oxybenzone	
Phenylbenzimidazole sulfonic acid	

Current restrictions in Australia and internationally

The following ingredients are currently approved in Australia for use as active ingredients in therapeutic sunscreens for dermal application (see the table below), not to be used in topical products for eyes, with appropriate safety warnings mandated on the label. It is noted that the regulation of sunscreens differs internationally, for example the USA regulate these as OTC drugs while they are regulated as cosmetics in the EU.

Active ingredient	Maximum % approved				
	Australia	EU	USA	Canada[2]	Japan[3]
Butyl methoxydibenzoylmethane	5	5	3	3	10
Ethylhexyl triazone †	5	5	Not approved	Not approved	5
Homosalate	15	7.34 (restricted to face product)	15	15	10 (restricted in all types of cosmetics)
Octyl methoxycinnamate	10	10	7.5	7.5	10
Octocrylene**	10	9 (propellant spray products); 10 (other products)	10	10	10 (restricted in all types of cosmetics)
Oxybenzone∆	10	6 (for face /hand/lipstick products, excluding propellent and pump spray products); 2.2 (for body products)	6	6	5 (cosmetics not used for mucosa and not to be washed away)
Phenylbenzimidazole sulfonic acid γ	4	8	4 (referred to as Ensulizole)	4	3 (cosmetics not used for mucosa and to be/not to be washed away)

**Octocrylene is approved as a UV filter in cosmetic formulation at ≤10% (as acid) in both Europe (Annex VI/10) and USA. The specific migration limit (SML) of octocrylene from food contact materials is 0.05 mg/kg (FDA 2018); European Parliament and the Council (2009); Restriction in EU - Benzophenone as an impurity and/or degradation product of Octocrylene shall be kept at trace level.
†EU: Annex VI, Regulation (EC) No. 1223/2009; γ EU: cosmetics directive in annex VII, part 1 list of permitted UV filters under entry 6;
∆ Annex VI/4, oxybenzone is also allowed at concentrations of up to 0.5 % to protect product formulations in all other cosmetic products (Annex VI/4).

[2] http://webprod.hc-sc.gc.ca/nhpid-bdipsn/atReg.do?atid=sunscreen-ecransolaire&lang=eng

[3](https://www.mhlw.go.jp/english/dl/cosmetics.pdf

How is safety evaluated for sunscreen ingredient?

Margin of Safety (MoS)

As per the *SCCNFP's notes of guidance for the testing of cosmetic ingredients and their safety evaluation, 9th-11th revision* (SCCS, 2016, 2018 and 2021a), the risk assessment of active ingredients in sunscreens can be conducted by calculating the MoS using uncertainty factors. MoS can be extrapolated from animals to humans to predict the potential risk in human. Usually, a MoS > 100 would indicate that the ingredient is safe under the proposed use conditions. The MoS is the ratio between a NOAEL and a Systemic Exposure Dose (SED).

$$MoS = \frac{NOAEL\ (mg/kg\ bw/day)}{SED\ (mg/kg\ bw/day)}$$

The SED of a cosmetic substance is the amount expected to enter the blood stream (and therefore be systemically available) per kg body weight and per day. It is expressed in mg/kg body weight (bw)/day. The NOAEL of a substance is the amount that has been demonstrated to not cause an adverse effect after being administered to test animals or human subjects. Similarly, it is expressed in mg/kg body weight (bw)/day.

The TGA has drawn upon the same risk assessment method developed by the SCCS for cosmetic ingredients to calculate the SED and MoS. However, the Australian Sunscreen Exposure Model (ASEM) utilises a different estimated average daily sunscreen exposure (external exposure) for therapeutic sunscreens than is used by the SCCS to calculate the SED and MoS for cosmetics including sunscreens.

The ASEM is a model that calculates the estimated average daily sunscreen exposure using a formula, and the input into that formula is based on Australian expected sunscreen use scenarios.

ASEM Formula

The ASEM formula calculates and therefore estimates how much sunscreen is used by Australians daily. It is based on data for skin surface area, age, and body weight for the Australian population. The formula calculates the daily sunscreen exposure by considering how many times it is applied a day, number of days of the year it is applied, and the skin surface area of each body part it is applied to.

$$ASEM\ (method\ 1) = \frac{Appl\ Rate\ x\ SSA\ x\ AF\ x\ Duration}{BWt\ x\ AT}$$

$$ASEM\ (method\ 2) = \frac{SSA\ x\ AF\ x\ Duration}{BWt\ x\ AT}$$

Parameter	Description	Explanation
ASEM	Estimated average daily sunscreen exposure (mg/kg bw/d) or (cm^2/kg bw/day)	The ASEM formula provides the amount of sunscreen applied to the skin per day relative to body weight (kg). The amount is expressed in units of either mass (mg) or surface area (cm2), depending on how the data for dermal absorption of an ingredient is reported.

Parameter	Description	Explanation
Appl Rate	Application rate of product mg/cm^2	For a sunscreen product to reach the labelled sun protection factor (SPF), it must be applied in quantities similar to those used in SPF testing. This application rate of 2 mg/cm2 is specified in the Sunscreen Standard. **NOTE:** Appl rate is not required for Method 2 calculations because it is accounted for as part of the dermal absorption study protocol.
SSA	Surface area of skin sunscreen applied to (cm^2) per application	The skin surface area exposed to sunscreen (per application) is predicted based on the practices outlined in the various ASEM scenarios for different population groups and activities, e.g. an individual working outdoors may be wearing a hat, shorts. half-sleeved shirt and footwear, and therefore the exposed skin where sunscreen is applied would include the face, neck, hands, forearms, and lower legs. The scenarios account for parts of Australia with warmer climates where less clothing may be worn year-round. The 95th percentile value has been chosen to capture the vast majority of the population.
Bwt	Body weight linked to SSA (kg)	The 95th percentile value has been chosen to capture the vast majority of the population.
AF	Application Frequency (applications/day)	Application frequency is expressed as the number of sunscreen applications per day. This can range from 2 – 3 applications per day for the different exposure scenarios outlined in ASEM Scenarios.
Duration	Annual Use (days)	Duration is expressed as the number of days in a year sunscreen application/exposure is expected to occur. The ASEM scenarios for the use of sunscreens in Australia provides information on the duration anticipated by different population groups.
AT	Averaging time (365 days)	An average daily dose based on exposure over a 1-year period (i.e. 365) is being calculated.

All the variables in the ASEM formula (SSA, BW, Age, AF and Duration) can change based on how the sunscreen is used and who it is used by. The respective input values for these variables are described in the various ASEM Scenarios provided in the Australian Sunscreens Exposure Model.[4]

[4] Australian Government, Department of Health and Aged Care, Therapeutic Goods Administration (2024). Australian Sunscreen Exposure Model. Consultation on an exposure model for assessing the safety of sunscreen ingredients in Australia. Version 1.0, July 2024.

Calculation for the highest estimated average daily sunscreen exposure

For general therapeutic sunscreens meant to be used by the whole population, a highest estimated average daily sunscreen exposure amount was calculated based on the highest use scenarios in the most vulnerable population (toddlers aged 1-2 years). This has been calculated to account for the highest realistic exposure across the year.

More details on how the highest estimated average daily sunscreen exposure values were derived can be found in the recent ASEM consultation paper. The exposure values are reproduced below depending on how dermal absorption data for the ingredient is reported.

How dermal absorption data is reported	ASEM highest estimated average daily
Method 1 (%)	$\frac{Appl\ Rate\ x\ SSA\ x\ AF\ x\ Duration}{BWt\ x\ AT}$ = 673 mg/kg bw/day
Method 2 (µg/cm^2)	$\frac{SSA\ x\ AF\ x\ Duration}{BWt\ x\ AT}$ = 336 cm^2/kg bw/day

In circumstances where ingredients are not considered low risk for use in general therapeutic sunscreens, exposure estimation has been conducted based on specific use restricted to a subset of the population, using the ASEM. The specific circumstances and the approaches considered have been discussed further below in the respective safety assessment sections.

Calculation of SED and MoS – ASEM Method 1

$$ASEM\ (method\ 1) = \frac{Appl\ Rate\ x\ SSA\ x\ AF\ x\ Duration}{BWt\ x\ AT}$$

$$SED = ASEM_{(method\ 1)} \times DA_p \times C$$

$$MoS = \frac{NOAEL}{SED}$$

ASEM	ASEM Method 1 – highest estimated sunscreen exposure (673 mg/kg bw/day)
Appl Rate	Application rate of product (2 mg/cm^2) (A/NZ Standard)
SSA	Skin Surface Area that had sunscreen applied to (cm^2)
AF	Application Frequency of daily application (1-4/day)
Duration	Annual Use (days)
BWt	Body weight linked to SSA (kg)
AT	Averaging Time. Average daily dose over a 1-year period (365 days)
DAp	Dermal Absorption of the active ingredient reported as a percentage (%)

C	Concentration of the active ingredient in the finished sunscreen product (%)
MoS	Margin of Safety
NOAEL	No Observed Adverse Effect Level (mg/kg bw/day)
SED	Systemic Exposure Dose (mg/kg bw/day)

Calculation of SED and MoS – ASEM Method 2

$$ASEM\ (method\ 2) = \frac{SSA\ x\ AF\ x\ Duration}{BWt\ x\ AT}$$

$$SED = ASEM_{(method\ 2)} \times DA_p \times C$$

$$MoS = \frac{NOAEL}{SED}$$

ASEM	ASEM Method 2 – highest estimated sunscreen exposure (336 cm^2/kg bw/day)
Appl Rate	Application rate of product (2 mg/cm^2) (A/NZ Standard)
SSA	Skin Surface Area that had sunscreen applied to (cm^2)
AF	Application Frequency of daily application (1-4/day)
Duration	Annual Use (days)
BWt	Body weight linked to SSA (kg)
AT	Averaging Time. Average daily dose over a 1-year period (365 days)
DAp	Dermal Absorption of the active ingredient reported as µg/cm^2
C	Concentration of the active ingredient in the finished sunscreen product (%)
MoS	Margin of Safety
NOAEL	No Observed Adverse Effect Level (mg/kg bw/day)
SED	Systemic Exposure Dose (mg/kg bw/day)

Literature review of the selected ingredients

Method of data search

The literature review was conducted using keywords such as the chemical name, Australian Approved Name (AAN) or the International Nomenclature Cosmetic Ingredient (INCI) names, and "sunscreen" as the search items. Publications during a 15-year period were searched (between 2008 and March 2023). See Attachment 1: Literature review search strategy for details.

In summary, the following data sources have been used for the literature search:

- Assessments from national regulatory agencies (e.g., AICIS, previously known as NICNAS) where available.
- Opinions from the Scientific Committee on Consumer Safety (SCCS, previously known as SCCNFP/SCCP/SCC) where available.[5]
- Information identified through literature search in PubMed and on the internet where a newer SCCS is not available.
- The publicly available registration dossiers for the ingredients submitted by industry under the EU REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) Regulation and available on the website of the European Chemicals Agency (ECHA). This information includes unpublished study summaries submitted by industry, in response to the standard data requirements of the REACH Regulation. Data from key studies in the registration dossiers have been considered for assessment in this review.

Information on the health hazards is available for all the selected ingredients considered, although the amount of information available varies considerably and does not cover all toxicological endpoints for all ingredients. Endocrine activity modulation properties of ingredients may give rise to a concern for human health. The evaluation of endocrine activity modulation properties was described collectively. Of note, all articles dealing with environmental matters relating to the ingredients were excluded as they do not fall under Australian therapeutic goods legislation.

Pharmacokinetics

The main safety concerns for these active ingredients arise from the knowledge gap around the toxicokinetic and pharmacokinetics data. Cutaneous permeation is a critical parameter in the kinetics of these active ingredients. Although most organic UV filters are lipophilic, *in vitro* cell permeation studies were also conducted with some of these ingredients to demonstrate systemic absorption by intact skin. Dermal absorption data from either relevant SCCS opinion, ECHA dossiers, AICIS assessments or published literature were reviewed in this document. Limited permeation data were noted for some active ingredients. In the absence of dermal toxicity data, oral toxicity data were considered when considering systemic toxicity in the worst-case scenario. Where appropriate, the dermal absorption value from the most recent SCCS opinions for the relevant active ingredients, were noted. Note that dermal absorption values apply to intact skin and may not be applicable for abraded skin or areas of sensitive skin e.g. lips.

Butyl methoxydibenzoylmethane

The molecular weight of butyl methoxydibenzoylmethane is in the range (MW < 500 D) where skin penetration can occur, but the log P_{ow} is slightly above the range favouring penetration (log P_{ow} in

[5] https://ec.europa.eu/health/ph_risk/committees/04_sccp/sccp_opinions_en.htm

range -1 to +4). Butyl methoxydibenzoylmethane has a low water solubility. Based on these physico-chemical data, only low dermal penetration is expected.

The toxicokinetic data for butyl methoxydibenzoylmethane were assessed in ECHA 2021 (ECHA 2021a). The executive summary of the assessed data is given below (for details see ECHA 2021a).

- In a 21 day dermal rabbit toxicity study (Keller 1980), there was an absence of a biological response (no adverse effects were observed in rats up to the high dose of 360 mg/kg bw/day, both in groups with intact skin or with abraded skin), and there was no indication of systemic bioavailability following dermal exposure.
- *In vitro* studies with isolated pig skin using ^{14}C-labelled BMBDM (butyl methoxydibenzoylmethane) at a concentration of 2% or 7.5 % in cream formulations exposed for 6 hours, showed that majority of the topically applied BMDBM remained on the skin surface (95%), 1.0-1.7% were found on the stratum corneum, 0.9-3.4% absorbed in the skin and only a minimum (≤ 0.5%) was found to pass the skin. Briefly, the results indicate a low penetration rate of butyl methoxydibenzoylmethane when applied on pig skin (up to 1.5 % of applied radioactivity 6 h post application). Dermal penetration in pig skin was not influenced by UV light (ECHA 2021a).
- In an *in vitro* study (DSM 1982) with ^{14}C-labelled BMDBM (butyl methoxydibenzoylmethane) using isolated human abdominal cadaver skin, up to 2.7 % of the applied radioactivity was observed in the epidermis, 7.3 % in the dermis 18 hr post dose but no activity was found in the collection fluid at any time and lower skin corium contained only 0.34 % after the longest exposure period (ECHA 2021a).
- A human *in vivo* study also indicated a very low level of systemic penetration of BMDBM (butyl methoxydibenzoylmethane) or its metabolites. In the study, a preliminary study (occluded) was followed by the main study where human volunteers were exposed to a 10% solution of ^{14}C-labelled BMBDM in carbitol for 8 hours.[6] The amounts of BMDBM found in the urine were 0.08 and 0.016 % for the occluded and non-occluded experiment, respectively. No radioactivity was found in the blood or faeces in any subject. Therefore, these data confirm only a very low level of systemic penetration of BMDBM or its metabolites (ECHA 2021a).

A recent study demonstrated that there was very poor skin permeation of butyl methoxydibenzoylmethane after single or repeated applications of sunscreens (Montenegro *et al.* 2018). However, recent randomised clinical trials indicate that butyl methoxydibenzoylmethane was systemically absorbed in humans (see Clinical Trials).

In the absence of further kinetic data for butyl methoxydibenzoylmethane and based on the data from the *in vitro* study using isolated human abdominal cadaver skin ((ECHA 2021a), **a 7.3% dermal absorption** of butyl methoxydibenzoylmethane was assumed.

Ethylhexyl triazone

No specific pharmacokinetic data are available for ethylhexyl triazone. The ingredient is expected to have low oral and dermal bioavailability based on its physiochemical properties (Molecular weight > 500 Dalton and Log P_{ow} > 4; Table 2.1)

Ethylhexyl triazone did not penetrate the receptor fluid in an *in vitro* study by Monti *et al.* (2008) when applied to the reconstructed human skin model and the rat skin. However, BASF (1995) reported *in vitro* permeation of ethylhexyl triazone in the sunscreen formulation, but no value was provided.

In an *in vitro* diffusion study (6-h exposure of the *ex-vivo* porcine-ear skin to the sunscreen, water-oil emulsion containing 10% oxybenzone and 5% ethylhexyl triazone, doses of 1 mg/cm^2 and 2 mg/cm^2), 23.2 ± 4.1 mg/cm^2 and 18.3 ± 2.5 µg/cm^2 of oxybenzone and ethylhexyl triazone, respectively were found in the stratum corneum, whereas 1.5 ± 0.3 mg/cm^2 of oxybenzone was found in the receptor fluid (Hojerová *et al.* 2017). Ethylhexyl triazone was not determined in the receptor fluid. The study authors concluded, that approximately 0.54 mg/cm^2 of ethylhexyl triazone (i.e., ~1.08% of the amount

[6] The dose was applied to a small square of gauze (10 cm^2) taped to the skin.

of ingredient applied) permeated the excised human epidermis into the receptor fluid. Approximately 1.3 and 1.8 × higher content of oxybenzone and ethylhexyl triazone were found in the viable epidermis and dermis, respectively, and 2.3- and 1.5-times higher content in the receptor fluid, respectively, when the study was conducted on shaved skin. Insignificant percutaneous absorption of ethylhexyl triazone across the shaved skin was noted. The total recovery in the whole study (intact and/or shaved skin) was 87.5- 90.4% consistent with the recovery (85- 115%) allowed by the ECHA (2016). The SED after the sunscreen application at 1 mg/cm^2 for 6 h on the: (i) face; and (ii) whole-body skin, was (i) 136 and 30; (ii) 4200 and 933 mg/kg bw/day for oxybenzone and ethylhexyl triazone, respectively. Reapplication caused approximately 1.4 -fold increase in the SED values indicating partial saturation after the first application.

Preferential ethylhexyl triazone distribution into stratum corneum was also noted by Sauce *et al*. (2020) in tape strip samples obtained from human volunteers (*n* = 12) treated with 100 µg/mL of the compound emulsified in cosmetic oil/water formulation (5% w/w) and applied at 2.0 mg/2.25 cm^2 for 2 h. However, only first 10 µm of the upper layers was collected (thickness of stratum corneum is ~30 µm) and given that the total recovery observed in this section was 56.34 %, the authors concluded that the remaining 44.66% of the dose penetrated deeper strata.

An *in vivo* study investigating the penetration of ethylhexyl triazone in human stratum corneum demonstrated that 21.9% (± 4.9) of the applied ethylhexyl triazone dose diffused into the stratum corneum. However, the skin penetration reduced significantly (by 45.7%) when ethylhexyl triazone was applied in microencapsulated form (Scalia *et al.* 2019).

In the absence of an appropriate dermal absorption value for ethylhexyl triazone, a **dermal absorption of 10%** was assumed based upon physicochemical parameters.

Homosalate

Studies in animals and human skin showed that homosalate could penetrate the skin in a variable manner. *In vitro* experiments indicated that about 1.1% of the applied dose was absorbed by human skin (range: 0.9-2.0%) (CTFA 2005).

Maximum plasma concentrations of homosalate after topical application varied between 13.9 and 23.1 ng/ml and $t_{½}$ between 46.9 and 78.4 h in clinical trials (see Clinical Trials). Homosalate was also detected in human milk samples after topical application in samples from different cohorts (2004, 2005, 2006) (Schlumpf *et al.* 2010). 15.1% of mothers reported use of homosalate exclusively in sunscreens with no additional use of other cosmetics. Homosalate was detected in 5.56% of total milk samples. However, homosalate could not be detected in human breast tissue samples (Barr 2018).

The *in vitro* metabolism of homosalate was investigated in rat and human liver microsomes. Homosalate (10 mM) incubated with human or rat liver microsomes (1 mg/ml protein) was hydrolysed into salicylic acid and 3,3, 5-trimethylcyclohexanol. In addition, conjugation and hydroxylation of intact homosalate was detected *in vitro*.

Commercial products often contain mixtures of cis- and trans-homosalate isomers (*cis*-HMS and *trans*-HMS respectively). Ebert *et al.* (2022) reported 87.2 - 91.9% of *cis*-HMS and 8.1-12.8% of *trans*-HMS in total homosalate content in 10 examined sunscreen products. However, following oral administration, homosalate isomers displayed diastereoselective metabolism, which was skewed towards *trans*-HMS e.g., metabolite levels derived from *trans*-HMS (6.4 %), including carboxylic acid and alkyl-hydroxylated compounds, were 142-fold higher compared to *cis*-HMS (0.045 %) while its bioavailability was 10-times higher. Although it is currently unknown whether homosalate applied dermally also undergoes divergent isomer metabolism, preliminary data of Ebert *et al.* agree with the findings from the oral study.

The SCCS selected a new skin penetration study using human skin from which **a dermal absorption of 5.3%** (mean + 1SD: 3.86±1.43) was derived (SCCS 2021b).[7]

Octocrylene

Octocrylene is expected to be absorbed in the GI tract by micellar solubilisation based on its physicochemical properties (ECHA 2020d). The inhalational uptake of octocrylene is likely to be low due to the very low vapour pressure (4 x10^{-7} Pa at 20°C) (ECHA 2020d).

Octocrylene has been found to induce xenobiotic-metabolising enzymes based on mechanistic studies, oral repeated dose toxicity and reproductive/developmental toxicity studies (SCCS 2021d; ECHA 2020d). An *in vitro* study on the hydrolysis-stability in rat liver S9 fraction indicated that octocrylene was metabolized in liver S9 fraction only (ECHA 2020d).

Human octocrylene metabolism and the pathways were described by Bury *et al.,* (2019). Six metabolites of octocrylene were detected in human urine after both oral and dermal exposure simulating a regular-use scenario with whole body application to octocrylene. 2-cyano-3,3-diphenylacrylic acid (CDAA) was identified as the major urinary metabolite (~45% of the octocrylene dose) followed by 2-ethyl-5-hydroxyhexyl 2-cyano-3,3-diphenyl acrylate (5OH–OC) and 2-(carboxymethyl) butyl 2-cyano-3,3-diphenyl acrylate (dinor OC carboxylic acid, DOCCA). Faecal excretion was observed. *In vitro* study with human and rat liver microsomes in the presence of NADPH and glutathione (GSH) suggested that the ester bond of octocrylene can be hydrolysed to form 3,3-diphenyl cyanoacrylate (DPCA) and 2-ethylhexanol based on the chemical structure of octocrylene (Guesmi *et al.* 2020).

Dermal exposure resulted in much lower concentrations of metabolites with considerably delayed elimination despite much higher octocrylene (> 25-fold) applied dermally (dermal dose 217 mg *vs* oral dose ~5 mg). This suggests a slower uptake of octocrylene through the skin.

Toxicokinetic data in urine after oral and dermal exposure to octocrylene (adapted from Bury *et al* 2019)*

Ingredient			CDAA	5OH-OC	DOCCA
Oral (*n*=3)	Concentration (µg/g creatinine)		2450 (1150-4410)	1.85 (1.62-2.11)	10.6 (9.94-11.1)
	t_{max} (hours)		4.2 (2.7-5.0)	3.2 (1.4-4.4)	3.6 (1.4-5.0)
	$t_{½}$ (hours)	1st phase	5.7 (3.8-7.1)	1.3 (1.1-1.5)	3.0 (2.1-3.6)
		2nd phase	16 (14-20)	6.4 (5.7-7.5)	16 (10-21)
Dermal (*n*=1)	Concentration (µg/g creatinine)		71.4	0.14	1.15

*Median (range) values are reported.

Following dermal application of octocrylene (8-10%) in *in vitro* studies, poor skin penetration (< 5%) of octocrylene was observed with mostly remaining in the stratum corneum (Freitas *et al.* 2015; Potard *et al.* 2000; Hayden *et al.* 2005). The dermal absorption (%) was not determined in these studies. Similar findings were observed in a study with a formulation (8% octocrylene) applied on freshly dermatomized human skin (344 ± 61 µm) in static diffusion cells at a dose of 3 mg/cm^2 for a 16-hour period. 0.1%, 0.005% and 4.3% of the applied dose were found in epidermis, dermis and in the stratum corneum, respectively (ECHA 2020d). No octocrylene was detectable in the receptor fluid.

[7] The June 2021 SCCS opinion for homosalate uses a different dermal absorption value for the SED calculation than an earlier SCCS opinion. The systemic exposure dose for homosalate used as a UV filter in cosmetic products is calculated using a dermal absorption value of 5.3% derived from an *in vitro* dermal penetration study using viable human skin (Finlayson 2021, as cited in SCCS 2020) and a standard sunscreen formulation containing 10% homosalate.

After 24 hours of dosing, octocrylene bioavailability (epidermis, dermis and receptor fluid) was estimated ~ 0.1% of the applied dose (ECHA 2020d; SCCS 2021d). In another study, a cream formulation (8% octocrylene) was applied for 16 hours (3 mg formulation/cm^2) on freshly dermatomed pig (700 ± 50 µm) and human (350 ± 50 µm) skin in static diffusion cells (ECHA 2020d). In the study with pig skin, no octocrylene was detectable in the receptor fluid whereas 2.8% and 0.3% of the applied dose were found in pig epidermis and dermis, respectively, and 14% were detected in the stratum corneum. In the study with human epidermis and dermis, only 0.125% of the applied dose were found, whereas 5.4% was determined for human stratum corneum. Based on these data, the amount bioavailable (epidermis, dermis and receptor fluid) represents approximately 0.2% and 3% of the applied dose in the human and pig skin, respectively (ECHA 2020d). The SCCS (2021d) also referred to the octocrylene Chemical Safety Report (2010) which indicated a low dermal absorption rate (≤ 0.25%).

A recent *in vitro* study (Fabian and Landsiedel 2020, as cited in SCCS 2021d) with a formulation (10% octocrylene) applied at a dose of 3 mg formulation/cm^2 on dermatomized human skin preparations (*n* =12 skin samples from six females) for 24 hours was evaluated by SCCS (2021d). At 24 hours post-dose, the amount considered as absorbed (epidermis, dermis and receptor fluid) was estimated to be a maximum of 0.45±0.52 µg/cm^2 (~ 0.15% of the applied dose) consistent with previous findings. The **dermal absorption of 0.97 µg/cm^2** (Fabian and Landsiedel 2020, as cited in SCCS 2021d) was considered a worst-case scenario for octocrylene and was used in the calculation of SED and MoS by the SCCS (2021d).

Octyl methoxycinnamate

Octyl methoxycinnamate absorption studies (oral and dermal) in rats and mice indicate octyl methoxycinnamate can be absorbed dermally and orally (Fennell *et al.* 2018). Octyl methoxycinnamate was rapidly cleared from rat hepatocytes (half-life ≤3.16 min) compared to human hepatocytes (half-life ≤48 min). [^{14}C]-octyl methoxycinnamate was extensively absorbed and excreted primarily in urine by 72 h after oral administration (65-80%) and a lesser extent (3-8%) in faeces and as CO_2 (1-4%).

Five metabolites were found in rat urine after oral exposure to octyl methoxycinnamate (200 mg/kg bw and 1000 mg/kg bw) (Huang *et al.* 2019). The major metabolites of octyl methoxycinnamate were 4-methoxycinnamic acid (4-MCA) and 4′-methoxyacetophenone (4′-MAP). The concentration of two metabolites was found to be much higher than octyl methoxycinnamate, highlighting that measuring octyl methoxycinnamate alone could not comprehensively evaluate the human exposure to octyl methoxycinnamate.

Dermal penetration was observed to be dependent on the vehicles, when using the tape-stripping technique. Significantly greater amounts were absorbed when the chemical was applied in emulsions than when microencapsulated (HSDB). Octyl methoxycinnamate was able to penetrate the skin, and derivatives were formed when it was applied with oleaginous cream as a vehicle on excised rat skin. In contrast, octyl methoxycinnamate penetration was not observed following the administration of octyl methoxycinnamate as entrapped into solid lipid microspheres (SLM) (Yener *et al.* 2003).

Studies with porcine skin showed that about 9% of the applied dose of octyl methoxycinnamate penetrates the skin with a flux of 27 µg/cm^2·h (Touitou and Godin 2008). An accumulation of ~9% of octyl methoxycinnamate in epidermis and ~2-3% in dermis were observed following application of 2 mg/cm^2 and 0.5 mg/cm^2 of octyl methoxycinnamate, respectively for 6 h exposure (Schneider *et al.* 2005). Octyl methoxycinnamate accumulation is expected to increase over time as the accumulation in dermis was found to be ~12-15% of the dose applied and 2-4% of the dose was found to cross the dermis and enter into the circulation after 24 hours.

An *in vitro* absorption study with sunscreen (O/W , oil in water emulsion and W/O, water in oil emulsion) containing octyl methoxycinnamate or EHMC (10%) on full-thickness pig-ear skin, mimicking human in-use conditions revealed the skin distribution of octyl methoxycinnamate from the sunscreen dose of 0.5 mg/cm^2 after 6-h exposure to the epidermis of frozen-stored skin was 4.8± 0.7 µg/cm^2, dermis 1.2 ± 0.1 µg/cm^2 and undetectable in receptor fluid, whereas 3.4 ± 0.6 µg/cm^2,

2.1 ± 0.4 µg/cm^2 and 0.9 ± 0.1 µg/cm^2 of octyl methoxycinnamate was distributed to epidermis, dermis and receptor fluid after following 18-h permeation, respectively (Klimova *et al.* 2015). Almost two-fold higher absorption was noted when water in oil emulsion containing 10% octyl methoxycinnamate was applied on pig skin in the same study (Klimova *et al.* 2015).

In this study, the authors "*tried to mimic the real-life habits of consumers when applying sunscreen as closely as possible".* In this way the time of exposition was reduced to 6 hours (in contrast of classic studies using long skin exposure), and a smaller dose of sunscreen was used (0.5 mg/cm^2) (Klimova *et al.* 2015). Considering that some chemical substances, instead of passing entirely through the skin, can remain partly in the skin and released later in time, the dermal absorption was evaluated at the end of the exposure period and then following washing and an 18-h permeation.

The dermal absorption was obtained by the sum of the filter absorbed in the dermis and the receptor fluid (RF) (which was considered systematically available), corrected by the fresh/frozen – stored skin permeability coefficient. It is noted that pig-ear skin has been recognized by the international authorities and scientists as a practical alternative and relevant model for predicting permeability of cosmetic ingredients in humans (Klimova *et al.* 2015).

Human *in vitro* and *in vivo* studies showed that the permeation of octyl methoxycinnamate in human skin was dependent on both the lipid lipophilicity and structure of the lipid used in the microemulsion and the type of surfactant used (Montenegro *et al*. 2011; TGA 2020).

The systemic absorption of octyl methoxycinnamate in humans was demonstrated by Janjua *et al* (2008). Maximum plasma concentration of octyl methoxycinnamate was reached at ~ 3 h (10 ng/ml for females and 20 ng/ml for males) following daily whole-body topical application of 2 mg/cm^2 of cream formulation with 10% octyl methoxycinnamate. Octyl methoxycinnamate was also detected in urine (5 and 8 ng/mL in females and males, respectively). Similar findings were reported following a 4-day exposure to this ingredient, which were detectable in the human plasma just 2 h following application (Janjua *et al.* 2004).

Another human study reported in SCC (2000) with a cream formulation containing 10% octyl methoxycinnamate suggested that an insignificant amount of octyl methoxycinnamate was absorbed under the conditions of the experiment (SCC 2000). Applications were made to the interscapular area and there was no evidence of any rise in plasma levels after 24 h. In addition, the urine concentration of octyl methoxycinnamate did not change during the experiment (collected until 96 h).

Based on all dermal absorption studies described above, no clear relationship between applied dose and dermal absorption could be established for octyl methoxycinnamate. Therefore, a **dermal absorption of 1.77 µg/cm^2** was considered a worst-case scenario (Klimova *et al.* 2015).

Oxybenzone

Oxybenzone is expected to be rapidly absorbed after oral, intravenous or topical skin administration based upon studies in rats and piglets as per European Safety assessment reports (SCCS 2021e). Oxybenzone was well absorbed following a single gavage administration of [^{14}C]-oxybenzone (3.01 to 2570 mg/kg) in male rats, with the administered dose excreted primarily *via* urine (63.9% to 72.9%) and faeces (19.3% to 41.7%) by 72 hours post-administration. The radioactivity remaining in tissues 72 hours after administration was low (~0.1%) in all dose groups. Oxybenzone is widely distributed in rats. Jung *et al.* (2022) assessed that bioavailability in rats following topical application as 6.9%.

Oxybenzone is metabolised in rats to 2-OH BP and BP-1, with a trace of 2, 3, 4-triOH BP. The major metabolite of oxybenzone, 2,4-diOH BP (BP-1) was present in most tissues including the liver, kidney, testes, intestine, spleen and skin six hours post-dose. Liver was the major distribution site of oxybenzone and BP-1 (SCCS 2021e). BP-1 is also the major metabolite in humans. Oxybenzone metabolites were detected in piglet plasma 2 hours post dose after dermal administration of oxybenzone (SCCS 2021e). Systemic absorption of oxybenzone has been demonstrated in recent clinical studies (Section 2.1). Oxybenzone binds to human serum albumin with Ka= 1.32 x 10^5 L/mol.

Elimination of oxybenzone is predominately *via* the urine (39-57%) and faeces (24-42%) in rats and mice, with differences observed between the species or the route of administration (oral or dermal).

Following topical application studies in piglets, the elimination half-lives of oxybenzone ranged from 7.14 and 8.04 h (SCCS 2021e), while in rats it was 18.3 h (Jung *et al.* 2022).

A number of *in vitro* and *in vivo* dermal absorption studies have been evaluated by the SCCP 2008 and SCCS 2021e. Following application of 6% oxybenzone, the **dermal absorption of oxybenzone was determined to be 9.9%.** The dermal absorption value of 9.9% was calculated by the SCCP using an *in vitro* study using pig ear skin and applying a safety factor of 2 standard deviations to account for limitations in the data set (3.1% + 2 SD [2 x 3.4%] = 9.9%) (SCCS 2021e). This *in vitro* study was chosen for oxybenzone in the absence of adequate information from *in vivo* studies.

Phenylbenzimidazole sulfonic acid

Absorption and plasma kinetics of phenylbenzimidazole sulfonic acid were examined in pregnant rats (SCCP 2006b). [^{14}C]-phenylbenzimidazole sulfonic acid sodium salt was administered to pregnant rats on day 18 of gestation (1 mg/kg bw IV or 1000 mg/kg bw PO, single dose). The pharmacokinetic parameters were: T_{max} 5 min (IV) and 15 min (oral), with a $t_{½}$ of 0.4 h (IV) and 24 h (oral). The amount of absorption from the gastrointestinal tract was estimated to be 3 – 4%.

Dermal penetration was examined in male volunteers (SCCP 2006b). Although the penetration rate of phenylbenzimidazole sulfonic acid was not established, cumulative penetration of 0.159% (range 0.107-0.259%) of the applied dose (8% formulation of phenylbenzimidazole sulfonic acid), was derived from total excretion. Total recovery of radioactivity was 78.8%. There was no indication of accumulation in any of the organs investigated. Trace amounts of radioactivity are found in brain and fetuses after IV administration but not following oral administration. This indicates that both blood/brain- and placental barriers were not passed. No data on metabolism were available.

Excretory pathways were examined in male rats (SCCP 2006b). Elimination of phenylbenzimidazole sulfonic acid sodium salt was virtually completed by 72 hours. Elimination occurs *via* urine and faeces in male rats. In pregnant rats, elimination predominantly occurred *via* the faeces following oral administration and *via* both the urine and faeces following IV administration. Maximum **absorption through the skin of 0.259% (0.416 µg/cm^2) determined** in the *in vivo* study in humans following application of an 8% formulation of phenylbenzimidazole sulfonic acid was used by the SCCP to determine the margin of safety for phenylbenzimidazole sulfonic acid (SCCP 2006b).

Clinical trials

In a recent randomised clinical trial, healthy volunteers (*n*=24; 6/ group) were treated with four sunscreen products, four times per day for 4 days, in indoor conditions, at a rate of 2 mg/cm^2 on 75% of body surface area. The sunscreen products were spray 1 (3% butyl methoxydibenzoylmethane/ 6% oxybenzone/2.35 % octocrylene/ 0% ecamsule[8]), spray 2 (3% butyl methoxydibenzoylmethane/5% oxybenzone/ 10% octocrylene/ 0% ecamsule), lotion (3% butyl methoxydibenzoylmethane/ 4% oxybenzone/ 6% octocrylene/ 0% ecamsule); and cream (2% butyl methoxydibenzoylmethane/ 0% oxybenzone/ 10% octocrylene/ 2% ecamsule). The overall maximum plasma concentrations (C_{max}) of butyl methoxydibenzoylmethane, oxybenzone and octocrylene ranged from 4 to 4.3 ng/mL, 169.3 to 209.6 ng/mL and 2.9 to 7.8 ng/mL, respectively. The AUC increased from day 1 to day 4 and terminal half-life ($t_{½}$) was relatively long (33-55 h, 27-31 h and 42–84 h, respectively), suggesting a possible accumulation of the ingredients (Matta *et al.* 2019). The systemic exposure of butyl methoxydibenzoylmethane and oxybenzone in human plasma was re-quantified by Pilli *et al.* (2021) using novel UHPLC-MS/MS method and in general, the C_{max} values were comparable to the results obtained previously.

[8] Ecamsule (CAS 92761-26-7) is commonly used as an active ingredient in sunscreen. However, currently it is not used in any sunscreen product marketed in Australia.

Similar findings were observed in a follow up study with six active ingredients (butyl methoxydibenzoylmethane, oxybenzone, octocrylene, homosalate, octisalate[9], and octyl methoxycinnamate) (Matta *et al.* 2020). Four groups (*n*=12) of healthy adults received 2 mg/cm^2 (75% of body surface area) on day 1 and 4 times on day 2 to day 4 at 2-hour intervals and blood samples were collected over 21 days from each participant.

The C_{max} of all these ingredients exceeded the US FDA threshold (> 0.5 ng/mL) after a single application and remained above the threshold until day 7 for butyl methoxydibenzoylmethane (95%; *n* = 42/44), octisalate (75%; *n* = 24/32), and octyl methoxycinnamate (90%; *n* = 18/20); day 10 for octocrylene (67%; *n* = 22/33); and day 21 for homosalate (55%; *n* = 17/31) and oxybenzone (96%; *n* = 22/23). The overall exposure throughout the study (Days 1-21) is summarised in the following table taken from Matta *et al.* (2020).

	Geometric mean maximum plasma concentration, ng/mL (coefficient of variation, %)			
	Lotion	Aerosol spray	Nonaresol spray	Pump spray
Butyl methoxydibenzoylmethane	7.1 (73.9)	3.5 (70.9)	3.5 (73.0)	3.3 (47.8)
Oxybenzone	258.1 (53.0)	180.1 (57.3)	NA	NA
Octocrylene	7.8 (87.1)	6.6 (78.1)	6.6 (103.9)	NA
Homosalate	NA	23.1 (68.0)	17.9 (61.7)	13.9 (70.2)
Octisalate	NA	5.1 (81.6)	5.9 (77.4)	4.6 (97.6)
Octyl methoxycinnamate	NA	NA	7.9 (86.5)	5.2 (68.2)

Another study investigating systemic absorption of butyl methoxydibenzoylmethane and octocrylene using real-life exposure scenario demonstrated similar systemic absorption of the ingredients (Hiller *et al.* 2018). Following dermal exposure, butyl methoxydibenzoylmethane, octocrylene and CDAA (major urinary metabolite of octocrylene) reached concentrations up to 11.3 µg/L, 25 µg/L and 1352 µg/L, respectively, in plasma (**Error! Reference source not found.**). When kinetic models were fitted for octocrylene and CDAA in plasma and CDAA in urine, concentration peaks reached between 10 and 16 h after first application and elimination half-life ($t_{½}$) were 36-48 hours. Octocrylene and CDAA showed slower elimination.

Toxicokinetic data in humans following dermal exposure to octocrylene and butyl methoxydibenzoylmethane

Study details		*n*=20; commercial sunscreen lotion containing octocrylene was applied three times (2 mg/cm^2 initially, then 1 mg/cm^2 after 2 h and 4 h) to 75–80% BSA)		
Ingredient		Octocrylene	Butyl methoxydibenzoylmethane	CDAA
Concentration	(%)	10.85	2.34	NA
C_{max} plasma (µg/L)	Mean (max)	11.7 (25)	4(11.3)	570 (1352)
C_{max} in urine (µg/g creatinine)	Median (max)	9.6 (< LOD–91.4)	3.4 (< LOD–25.2)	2072 (5207)
T_{max} plasma (hours), day 1	Median (95% CI)	10 (6.9-13.4)	ND	14.5 (13.2-15.9)
T_{max} urine (hours), day 1		ND	ND	15.9 (15.2-16.7)
$t_{½}$ plasma (hours)		43.9 (19.0-68.7)	ND	36.1 (31.0-41.2)

[9] Octisalate or octyl salicylate is an active ingredient used in sunscreen. This has been evaluated by TGA as an excipient to be used in prescription medicines.

Study details		*n*=20; commercial sunscreen lotion containing octocrylene was applied three times (2 mg/cm² initially, then 1 mg/cm² after 2 h and 4 h) to 75–80% BSA)		
Ingredient		Octocrylene	Butyl methoxydibenzoylmethane	CDAA
$t_{½}$ urine (hours)		ND	ND	37.7 (35.1-40.4)

*81% of samples < LOD' c: concentration; C_{max}: max plasma concentration; ND: not determinable; T_{max}: time to maximum concentration; $t_{½}$: half-life; CDAA: 2-cyano-3,3-diphenylacrylic acid

Toxicity

The information on the safety of butyl methoxydibenzoylmethane, ethylhexyl triazone, homosalate, octyl methoxycinnamate, octocrylene, oxybenzone and phenylbenzimidazole sulfonic acid using various toxicological endpoints, has been summarised in the following sections. It is important to note that the original toxicological study reports were not available for independent verification and therefore this report is reliant on the accuracy of various published safety assessment reviews (reviews by SCCS/SCC/SCCP, NICNAS, ECHA etc. see bibliography).

Acute toxicity

Butyl methoxydibenzoylmethane, ethylhexyl triazone, homosalate, oxybenzone, octocrylene, phenylbenzimidazole sulfonic acid and octyl methoxycinnamate displayed low acute oral toxicity. Low acute dermal toxicity was observed for homosalate, oxybenzone, octocrylene, phenylbenzimidazole sulfonic acid and octyl methoxycinnamate. Information for acute inhalational toxicity is only available for octyl methoxycinnamate (shown below).

Summary of acute toxicity studies for sunscreen ingredients

Butyl methoxydibenzoylmethane (ECHA (2021a; DEPA 2015)	Ethylhexyl triazone (ECHA 2021b; DEPA 2015)	Homosalate (SCCS 2021b,c; ECHA 2021c)	Octyl methoxycinnamate (ECHA 2021e)	Octocrylene (SCCS 2021d; ECHA 2021d)	Oxybenzone (SCCP 2006a; 2021c)	Phenylbenzimidazole sulfonic acid (SCCP 2006b)
Oral >16000 mg/kg bw (rats) Dermal, inconclusive*	Oral > 5000 mg/kg bw (rats)	Oral > 5000 mg/kg (rats) Dermal > 5000 mg/kg bw (rabbits)	Oral >8 g/kg (mice) >20 mL/kg (20.0 mg/kg) (rats) Dermal >126.5 mg/kg (rats) Inhalation LC50 >0.511 mg/L (rats)	Oral > 5000 mg/kg bw (rats) Dermal > 2000 mg/kg bw (rats)	Oral > 6000 mg/kg bw (rats) Dermal > 16000 mg/kg bw (rabbits)	Oral >5000 mg/kg bw (mice) >1600 mg/kg bw (rats) Dermal >3000 mg/kg bw (rats) IP 1000 – 1500 mg/kg bw (rats)

The values are LD_{50} determined in relevant studies extracted from the safety assessment reviews; *Acute dermal toxicity was tested up to a dose of 1000 mg/kg bw in rats showing no deaths. Slight erythema was observed in treated animals and in the vehicle control, assuming that the vehicle, carbitol, has a slight irritant effect to skin. Concerning acute dermal toxicity, the test item was only tested up to a maximum dose of 1000 mg/kg bw, whereas the regulatory cut-off level for classification according to Regulation (EC) No 1272/2008 (CLP) is 2000 mg/kg bw.

Local tolerance

Skin irritation and eye irritation studies were generally conducted as per the OECD TG 404 and 405 guidelines, respectively. All ingredients examined were found to be non-irritants to the skin and eye in *in vivo* studies in animals (see below).

Summary of skin and eye irritation studies for sunscreen ingredients

Study	Butyl methoxydibenzoylmethane (ECHA (2021a; DEPA 2015)	Ethylhexyl triazone (ECHA (2021b; DEPA 2015	Homosalate (SCCS 2021b,c; ECHA 2021c)	Octyl methoxycinnamate (ECHA 2021e)	Octocrylene (SCCS 2021d; ECHA 2021d)	Oxybenzone (SCCP 2006a; 2021c)	Phenylbenzimidazole sulfonic acid (SCCP 2006b)
Skin	Non-irritant (at 10% in rabbits)	Non-irritant, undiluted (rabbits)	Non-irritant (mice, Guinea pigs)	Non-irritant, undiluted (rabbits, guinea pigs)	Non-irritant (rabbits)	Non-irritant (rabbits)	Non-irritant (rabbits)
Eye	Non-irritant (at 5-20% in rabbits)	Non-irritant, undiluted (rabbits)	Non-irritant (at 10%)	Non-irritant, undiluted (rabbits)	Non-irritant (rabbits)	Non-irritant (rabbits)	Non-irritant (rabbits)

Sensitisation

With the exception of octocrylene, all the ingredients were not found to be skin sensitisers in *in vivo* studies in animals (see below).

Summary of skin sensitisation studies for sunscreen ingredients

Butyl methoxydibenzoylmethane (ECHA 2021a; DEPA 2015)	Ethylhexyl triazone (ECHA (2021b; DEPA 2015	Homosalate (SCCS 2021b,c; ECHA 2021c)	Octyl methoxycinnamate (ECHA 2021e)	Octocrylene (SCCS 2021d; ECHA 2021d)	Oxybenzone (SCCP 2006a; 2021c)	Phenylbenzimidazole sulfonic acid (SCCP 2006b)
Not sensitising (at 6% and 20% in GPMT)	Not sensitising (GPMT)	Not sensitizing (GPMT and mice) Not sensitising (at 15%, HRIPT)	Not sensitising (GPMT)	Not sensitizing (GPMT) Moderate sensitising in a LLNA (not properly conducted)	Not sensitizing (GPMT) Not sensitising (LLNA)	Not sensitising (GPMT)

GPMT: Guinea Pig Maximization Test; LLNA: Local Lymph Node Assay; HRIPT: Human repeated insult patch test

Repeat dose toxicity

A summary of repeat-dose toxicity studies for each sunscreen ingredient is shown in the table below:

Repeat-dose toxicity studies for sunscreen ingredients

Active ingredient	Study details$^{\Delta}$	Major findings
Butyl methoxydibenzoylmethane	Rats (*n*=12/sex/dose), doses: 0, 200, 450, and 1000 mg /kg bw/day (diet), 13 weeks	No treatment-related mortality. No effect on the body weight and food consumption. ↓ RBC in ♀ rats at 1000 mg/kg bw/day.

Active ingredient	Study details[Δ]	Major findings
(ECHA 2021a; DEPA 2015)		No findings in eyes. No treatment-related necropsy findings. Treatment-related ↑ liver weights at 1000 mg/kg bw/day in ♂ and at 200, 450, and 1000 mg/kg bw/day in ♀ compared to control. All effects were fully reversed after a treatment-free period of 4 weeks. Hypertrophic hepatic parenchyma cells in ♀ at 1000 mg/kg bw/day. **NOAEL: 450 mg/kg bw/day** *Applying route to route extrapolation, by assuming that penetration of butyl methoxydibenzoylmethane through skin is equal to penetration through the intestinal wall, the same effect levels as for oral route shall apply for the dermal route of exposure (ECHA 2021)*
	Rabbits (*n*=10/sex/group), 1.5, 5 and 18 % w/v solutions in carbitol (vehicle) (30, 100 and 360 mg/kg bw/day) (dermal once daily), exposure: 6 hours/day, 28 days	No treatment-related mortality. ↑ dose dependent severe dermal reactions ≥ 30 mg/kg/day, more persistent at 100 mg/kg bw/day. ↑ Incidence of epidermal thickening in both vehicle control and treatment groups compared to the untreated control group. NOAEL: 360 mg/kg bw/day (based on systemic effects). LOAEL: 30 mg/kg/bw/day (dermal)
Octocrylene (ECHA 2021d; SCCS 2021d)	Rats (Wistar), *n* = 10/sex/dose 0, 58, 175, 340 and 1085 mg/kg bw/day (diet), 13 weeks Study BASF 50S0227/92059	No treatment-related mortality. No treatment-related clinical signs. Body weight gain: ↓ at HD in both sexes along with decreased food consumption Haematology: RBC affected (↓MCV, ↓MCH, ↓MCHC) at HD in both sexes Organ weights (bodyweight-relative): ↑ absolute and relative weight of liver at 340 and 1085 mg/kg bw/day Histopathology: hypertrophy of periacinar and centriacinar hepatocytes at 340 and 1085 mg/kg bw/day; Slight or moderate hypertrophy of the thyroid, follicular epithelium and associated pale staining colloid at 340 and 1085 mg/kg bw/day NOAEL: 175 mg/kg bw/day
	Rabbits (NZW), *n* = 5/sex/dose 0, 130, 264, 534 mg/kg bw/day (dermal) 5 days/week; 13 weeks (Odio *et al.,* 1994)	Slight to moderate skin irritation (erythema and desquamation) at all doses at the site of application correlated to ↓ bodyweight gain at 264 and 534 m/kg bw/day. No evidence for haematological or macroscopic and histopathological abnormalities No effects were reported on testicular and epididymal morphology as well as on sperm count and motility NOAEL: 534 mg/kg bw/day (systemic toxicity) NOAEL: 130 mg/kg bw/day (dermal)
	A follow up mechanistic study was conducted in rats to investigate mechanisms related to potential thyroid effects of octocrylene observed in the 13-week oral repeat dose study in rats Rats (Wistar), *n* = 5/sex/dose 72, 215, 720 mg/kg bw/day PO (Subset A) 63, 188, 630 mg/kg bw/day PO (Subset B) 28 days (Subset A) 14 days (Subset B)	No treatment-related mortality No treatment-related clinical signs. Body weight gain: ↓ at HD in both subsets Serum chemistry: ↑ TSH at 630 mg/kg bw/day in ♀ in subset B; ↑ TSH at 720 mg/kg bw/day in both sexes in subset A Organ weights (bodyweight-relative): ↑ absolute and relative weight of liver at high doses in both sexes in both subsets Histopathology: minimal follicular cell hypertrophy/hyperplasia of the thyroid gland at high doses in both sexes in both subsets NOAEL: 188-215 mg/kg/day

Active ingredient	Study details[Δ]	Major findings
Octyl methoxycinnamate (ECHA 2021e)	Rats (not specified), *n*=5/sex/dose, at 300, 900 and 2700 mg/kg bw/day (gavage), 3 weeks	↓ body weight, ↓ relative and absolute weight of the thymus at HD, ↓absolute weight of the left kidney (♂) and ↓ absolute weight of the heart (♀) at HD. NOAEL: 900 mg/kg bw/day.
	Rats (SPF), *n*=12/ sex/dose, at 200, 450 and 1000 mg/kg/day (oral), 13 weeks with recovery period of 5 weeks	↑ Kidney weights at HD, reversed during the recovery period (5 weeks). ↓ glycogen in the liver and ↑ iron in the Kupfer cells at HD, ↑ GLDH in ♀ at HD. Some of the effects were reversed during the recovery period; however, then reversed effects were not listed in the AICIS report. NOAEL: 450 mg/kg/day based on the minor and reversible changes at 1000 mg/kg bw/day
	Rats (SD), *n*=10/sex/dose, 55.5, 277 and 555 mg/kg/day, 5 days/ week, 13 weeks (dermal)	Mortality: none treatment-related ↑ (non-significant) serum alanine phosphatase (SAP) levels and ↑ relative liver weight at HD. Liver effects were not observable upon microscopic examination. NOAEL: 555 mg/kg bw/day based on no significant adverse effects at the highest treated dose
	Rats (SD), *n*=15/sex/dose; 0, 500, 1500 or 5000 mg/kg/day applied occlusively on the abraded skin, 6 days/ week, 28 days (dermal)	No systemic effects, body weight changes, ocular defects, haematology effects or changes in blood chemistry parameters were observed. Dose dependent low-grade epidermal proliferation at all doses (more prominent in ♂). The chemical was considered as a low-grade irritant under the conditions of this study (OECD TG 410) NOAEL: 5000 mg/kg bw/day
	Rabbits (NZW), *n* = 10/sex/dose, 500, 1500 or 5000 mg/kg bw/day applied occlusively on the abraded skin, 6 hours/day, 21 days (dermal)	Mortality: 3 at HD Lethargy, hunched posture, hair loss, soiled coats, emaciation, increased respiration, swelling of the conjunctivae, and reproductive effects (retardation of testicular growth) at HD. Haematological changes including ↑ neutrophils and urea nitrogen, and ↓ lymphocytes and alkaline phosphatase activity at HD. Dermal irritation effects (erythema, oedema, desquamation, cracking and atonia) were observed at all doses but were more severe at the HD. Histopathology of the skin sites showed an epidermal proliferative response with low grade inflammatory reaction (dose dependent). NOAEL: 1500 mg/kg bw/day
Ethyl hexyl triazone (ECHA 2021b; DEPA 2015)	Rats (Wistar), *n*=10/sex/group, 0, 1000, 4000, and 16000 mg/kg bw/day;7 days/week, 90 days (oral)	Slight variations in the haematological and clinical chemistry parameters corresponded to the range of biological variation in the species. ↑ Liver-weight without histological correlates among treated female animals could not be interpreted as being treatment-related. **NOAEL: 1000 mg/kg bw/day** (nominal) was mentioned.
	Rats, *n* = 10/sex/group, 0, 1000, 4000, and 16000 mg/kg bw/day (diet); 7 days/week, 90 days	Clinical signs: none treatment-related in the haematological and clinical chemistry parameters No treatment-related effects on organs NOAEL: ≤ 1275 mg/kg bw/day (nominal)
Oxybenzone (SCCP 2006a; 2021c)	Mice (B6C3F1; *n* = 5/sex/group), 0, 3125, 6250, 12500, 25000, 50000 ppm (equivalent to 1021, 2041, 4430, 8648, 20796 mg/kg bw/day), 14 days (diet)	Mortality: none Bodyweight gain: ↓ in ♂at HD. Organ weight: ↑ liver weights (♂ & ♀) from LD, associated histopathology observed at 2041 mg/kg bw/day; ↓ kidney weight in ♂ from 8648 mg/kg bw/day. NOAEL: 992 (♂)/1050 (♀) mg/kg/day

Active ingredient	Study details[Δ]	Major findings
	Mice (B6C3F1; *n* = 10/sex), doses: 0, 0, 3125, 6250, 12500, 25000, 50000 ppm (equivalent to 554, 1246, 2860, 6780, 16238 mg/kg bw/day), 90 days (diet)	Mortality: none Bodyweight: ↓ BW gain in ♂ & ♀ from 6780 mg/kg bw/day Organ weights: ↑ liver weight from 1246 mg/kg bw/day with histopathology from 6780 mg/kg bw/day. Renal histopathology at HD in ♂. Reproductive parameters: ↓ sperm density and ↑ abnormal sperm in ♂ and ↑ oestrus cycle length in ♀ at HD NOAEL: 2860 mg/kg/day (equivalent to 1068 and 1425 mg/kg/day in ♂ and ♀, respectively)
	Rats (F344/N; *n* = 5/sex/group), Doses: 0, 3125, 6250, 12500, 25000, 50000 ppm (equivalent to 303, 576, 1132, 2238, 3868 mg/kg bw/day), 14 days (diet)	Mortality: none Bodyweight gain: ↓ in ♂at HD. Organ weight: ↑ liver (♂ & ♀) and kidney (♂) weights from LD, associated histopathology observed at 576 mg/kg bw/day in liver and at HD in kidney. NOAEL: 303 mg/kg/day (equivalent to 295 and 311 mg/kg/day in ♂ and ♀, respectively)
	Rats (F344/N; *n* = 10/sex/group), Doses: 0, 3125, 6250, 12500, 25000, 50000 ppm (equivalent to 0, 204, 411, 828, 1702, 3458 mg/kg bw/day), 90 days (diet)	Mortality: none. Clinical signs: coloured urine from LD. Bodyweights: ↓ BW gain in ♂ & ♀ from 1702 mg/kg bw/day. Clinical pathology: serum protein levels from 411 mg/kg bw/day, ↑ platelet counts from 1702 mg/kg bw/day Organ weights: ↑ liver weight from LD; ↑ kidney weight in ♀ from 1702 mg/kg bw/day with dilation of renal tubules, inflammation with fibrosis in renal interstitium at HD. Reproductive parameters: ↓ sperm motility in ♂ and ↑ oestrus cycle length in ♀ at HD. NOAEL: 411 mg/kg bw/day (equivalent to 429 and 393 in ♂ and ♀, respectively)
	Mice (B6C3F1; *n* = 5/sex/group), Doses: 0, 0.5, 1.0, 2.0, 4.0, 8.0 mg/mouse in acetone or lotion* (equivalent to 24.8, 48.4, 100, 196, 388 mg/kg bw/day), 14 days (dermal)	Mortality: none Organ weights: ↑ liver weight from 196 mg/kg bw/day. NOAEL: 388 (♀) mg/kg bw/day (equivalent to 384 and 432 mg/kg/day in ♂ and ♀, respectively)
	Mice (B6C3F1; *n* = 10/sex/group), Doses: 0, 22.8, 45.5, 91, 183, 364 mg/kg bw/day in acetone or lotion*, 90 days (dermal, 5 days/week)	Mortality: none. Organ weights: ↑ kidney weight in ♂ at all doses Reproductive parameters: ↓ epididymal sperm density in ♂ at all doses. NOAEL: 364mg/kg bw/day in ♂ and ♀
	Rats (F344/N; *n* = 5/sex/group), doses: 0, 1.25, 2.5, 5, 10, 20 mg/rat in acetone or lotion* (equivalent to 7, 13.6, 27.7, 54.9 and 110 mg/kg bw/day), 14 days (dermal) (5 days/week for 2 weeks)	Mortality: none Organ weights: ↑ liver weight in ♀ from 27.7 mg/kg bw/day, ↑ kidney weight in ♀ at HD NOAEL: 100 (♂)/140 (♀) mg/kg bw/day
	Rats (SD; *n* = 6♂/group), 0, 100 mg/kg bw/day, 28 days (twice daily) (dermal)	No treatment-related effects (limited evaluation). NOAEL: 100 (♂) mg/kg bw/day
	Rats (F344/N; *n*-10/sex/group), doses: 0, 12.5, 25, 50, 100, 200 mg/rat in acetone or lotion* (equivalent to 12.5, 25, 50, 100, 200 mg/kg bw/day), 90 days (dermal)(5 days/week)	Mortality: none. Clinical pathology: ↓ reticulocyte counts from LD, ↑ platelet counts from 50 mg/kg bw/day, ↑ whole blood cell count produced by lymphocytosis at HD. NOAEL: 200 mg/kg bw/day
Phenylbenzimidazole sulfonic acid (SCCP 2006b)	Rats (Wistar; *n* = 5/sex/group) Doses: 0, 100, 330 and 1000 mg/kg bw, 13 weeks (oral)	No treatment-related effects. NOAEL: 1000 mg/kg bw/day
Homosalate	Rats, n=5/sex/dose, 0, 100, 300, 1000 mg/kg bw/day, 2 weeks (gavage)	Mortality: none Clinical signs: none treatment related

Active ingredient	Study details[Δ]	Major findings
(SCCS 2021b,c; ECHA 2021c)		Body weight gain: ↓ at HD in ♂ along with decreased food consumption Haematology: none treatment related Serum chemistry: ↑ Triglycerides in both sexes at HD ↑APTT in ♂ at MD NOAEL: > 300 mg/kg bw/day ♂ NOAEL: >1000 mg/kg bw/day ♀
	Repeat dose/ reproduction/ developments study Rats (Wistar), *n* =10/sex, 0, 60, 120, 300, 750 mg/kg bw/day (gavage), 7 weeks duration (ECHA 2020)	*Mortality:* 2 ♀ at 750 mg/kg bw/day *Clinical signs:* none treatment-related *Body weight gain:* ↓ at 750 mg/kg bw/day in ♂ and ♀ *Haematology:* none treatment-related *Serum chemistry:* ↑ Albumin and ↓ Globulin in ♂ at 300 mg/kg bw/day *Urinalysis:* not conducted *Organ weights (bodyweight-relative):* ↑ absolute and relative weight of liver in both sexes at 300 and 750 mg/kg bw/day, ↑ kidney in ♀ at 300 mg/kg bw/day. ↓ thymus in both sexes at 750 mg/kg bw/day. ↓ prostate and seminal vesicles at HD 750 mg/kg bw/day. *Gross pathology:* no treatment-related findings *Histopathology:* ↑ Minimal/moderate intra-epithelial hyaline droplets in the kidneys ♂ from 60 mg/kg bw/day (associated with ↑ in foci of basophilic tubules, single cell death and/or the presence of granular casts). * Minimal/mild hypertrophy of hepatocytes (1/5 ♂) at 120 mg/kg bw/day, and almost every ♂ and ♀ from 300 mg/kg bw/day. Hypertrophy of the follicular epithelium of thyroid gland in ♂ at 750 mg/kg bw/day and in ♀ from 300 mg/kg bw/day. ↓ Cortical lymphocytes in males from 300 mg/kg bw/day and in ♀ at 750 mg/kg bw/day *NOAEL:* ** mg/kg bw/day *The REACH registrants considered this as manifestations of hyaline droplet nephropathy without giving further evidence. **Based on this study, the REACH registrants derived a NOAEL of 300 mg/kg/day for general toxicity based on mortality in HD females. However, at this dose effects on kidneys, liver, thyroid and thymus occurred. In males, effects were noted **from the lowest dose of 60 mg/kg bw/d**, therefore the SCCS considers this dose as LOAEL.

[Δ] GLP compliance was not specified in the reviews

Genotoxicity

A summary of genotoxicity studies for each sunscreen ingredient is shown in the table below. With the exception of homosalate, all sunscreen ingredients were negative in *in vitro* and *in vivo* tests. Homosalate was negative in the Ames test and the gene mutation test in Chinese hamster cells *in vitro.* However, homosalate induced DNA damage the Comet assay in isolate human peripheral lymphocytes and in the micronucleus assay *in vivo*.

Table 3-7. Summary of genotoxicity studies with sunscreen ingredients

Butyl methoxydibenzoylmethane (ECHA (2021a; DEPA 2015)	Ethylhexyl triazone (ECHA (2021b; DEPA 2015	Homosalate (SCCS 2021b,c; ECHA 2021c)	Octyl methoxycinnamate (ECHA 2021e)	Octocrylene (SCCS 2021d; ECHA 2021d)	Oxybenzone (SCCP 2006a; 2021c)	Phenylbenzimidazole sulfonic acid (SCCP 2006b)
In vitro	*In vitro*	*In vitro*	*In vitro*	*In vitro*	*In vitro*	*In vitro*

Butyl methoxydibenzoylmethane (ECHA (2021a; DEPA 2015)	Ethylhexyl triazone (ECHA (2021b; DEPA 2015	Homosalate (SCCS 2021b,c; ECHA 2021c)	Octyl methoxycinnamate (ECHA 2021e)	Octocrylene (SCCS 2021d; ECHA 2021d)	Oxybenzone (SCCP 2006a; 2021c)	Phenylbenzimidazole sulfonic acid (SCCP 2006b)
Negative AMES test and gene mutation study V79 Chinese hamster cells In vivo Negative Bone marrow poly-chromatic erythrocytes (mice)	Negative AMES test, Chinese hamster lung fibroblasts for chromosome aberration, Chinese hamster ovary (CHO) cells, in vivo chromosome aberration test	Negative AMES test and gene mutation study in V79 Chinese hamster cells Findings from the SCGE comet assay in isolated human peripheral lymphocytes and micronucleus assay in MCF-7 cells suggest that homosalate induced DNA damage in a dose dependent manner and it is clastogenic when the cells were incubated at cytotoxic concentrations (Yazar et al. 2018; 2019)	Negative AMES test, mammalian cell transformation assay (BALB/c-3T3 clone A31-11 cells), micronucleus test (mice), Unscheduled DNA synthesis assay (rat primary hepatocytes), Chromosomal aberrations (human peripheral blood lymphocytes) In vivo Negative Chromosomal aberrations in micronucleus assay in bone marrow polychromatic erythrocytes, Cell gene mutation assay (V79, ± S9) showed a very slight increase in mutant colonies (up to 20 mg/mL)	Negative AMES test, gene mutation test, cytogenicity test in mammalian cells, chromosome aberrations tests In vivo Negative Cytogenicity test in mice (ECHA 2020, SCCS 2021b,c)	Negative AMES test (weak positive: TA97 (30% hamster +S9), 10% hamster or 10% and 30% rat S9), Chinese hamster lung fibroblasts for chromosome aberration ±S9, CHO cells –S9; Sister-chromatid exchanges and chromosomal aberrations + S9 In vivo Negative micronucleus test (mice), chromosome aberration test (rats), Drosophila (SMART)†	Negative AMES test and chromosome aberration test in human peripheral blood lymphocytes In vivo No data

† In a recently published study (Majhi *et al.* 2020), benzophone-3 (1 and 5 µM) increased DNA damage similar to that of E2 treatment in a ERα-dependent manner. Benzophone-3 exposure caused R-loop formation in a normal epithelial cell line when ERα was introduced. R-loops and DNA damage were also detected in mammary epithelial cells of mice treated with benzophone-3.

Carcinogenicity

No carcinogenicity data were available for butyl methoxydibenzoylmethane, octyl methoxycinnamate, octocrylene, ethylhexyl triazone, homosalate or phenylbenzimidazole sulfonic acid. Oxybenzone was carcinogenic in mice (bone marrow, spleen, kidney and liver), with equivocal evidence of carcinogenicity observed in rats (brain, spinal cord, thyroid and uterus). Findings are provided in the following table.

Table 3-8. Summary of carcinogenicity studies with sunscreen ingredients

Active ingredient	Study details	Major findings
Butyl methoxydibenzoylmethane	–	No data
Ethyl hexyl triazone	–	No data
Homosalate	–	No data
Octyl methoxycinnamate	–	No data
Octocrylene	–	No data
Oxybenzone (SCCP 2006a; 2021c)	Mice (B6C3F1/N; *n*=50/sex/group), 0, 1000, 3000, 10000 ppm (equivalent to 113/109, 339/320, 1207/1278 mg/kg bw/day in ♂/♀) Rats (SD; *n*=10/sex/group), 0, 1000, 3000, 10000 ppm (equivalent to 58/60, 168/180, 585/632 mg/kg bw/day in ♂/♀) Two years (beginning on GD6 in ♀)	Mice: ↑ lesions in the bone marrow, spleen, and kidney of both sexes and in the liver in ♂ Rats: ↑ incidence of brain and spinal cord malignant meningiomas at 3000 ppm in ♂ and thyroid C-cell adenomas at 3000 ppm) and uterine stromal polyps at 3000 ppm in ♀ without any dose-response relationship. These findings are considered equivocal evidence of carcinogenicity.
Phenylbenzimidazole sulfonic acid	–	No data

Reproductive and developmental studies

A summary of reproductive and developmental toxicity studies for each sunscreen ingredient is shown in the table below.

Table 3-9. Summary of reproductive and developmental toxicity studies with sunscreen ingredients

Active ingredient	Study details	Major findings
Butyl methoxydibenzoylmethane (ECHA 2021a; DEPA 2015)	Rats at 0, 250, 500 and 1000 mg/kg bw/day (oral gavage), GD 7 -16.	No treatment-related skeletal malformations were observed. One pup with two fused sternal elements was seen at LD. A slight increase of incised neural arches and sternebrae was seen at 500 mg/kg/day. The soft tissue examination displayed one fetus of the 500 mg/kg dose group with unilateral missing ovarium and uterus. No effects were considered treatment related in the absence of dose dependence. In the rearing group, all measured parameters were well comparable to concurrent control group values. Maternal and developmental NOAEL: 1000 mg/kg bw/day.

Active ingredient	Study details	Major findings
	Rabbits, single dose of 500 mg/kg bw/day GD 7-19 (oral, daily)	No treatment-related effects or teratogenicity.
Octyl methoxycinnamate (ECHA 2021e)	Rats (Wistar); *n* = 25/sex/dose. 0, 150, 450 or 1000 mg/kg bw/day (oral), The parental (F0) generation was exposed throughout premating period (73 days), mating (21 days), gestation (21 days), and up to weaning of the F1 offspring (21 days). The duration of exposure for the F1 generation was similar to F0.	No adverse effects were observed on oestrous cycles, sperm and follicle parameters, mating, fertility, morphology and motility, gestation and parturition. ↓ food consumption and body weight, ↑ liver weight and hepatic cytoplasmic eosinophilia related to hepatic enzyme induction, and ↑ ulceration of the glandular stomach mucosa at HD. In the offspring, ↓ lactation weight gain and organ weights, and slightly delayed sexual maturation (vaginal opening and preputial separation) at HD. **NOAEL: 450 mg/kg bw/day** for fertility and reproduction parameters, and for systemic parental and developmental toxicity (Schneider *et al.* 2005, REACH).
	Pregnant rabbits (*n*=20/dose), 80, 200 or 500 mg/kg bw/day on GD 7–20.	Reproductive parameters were not affected. Except for a slight reduction of maternal and foetal weight at HD, no abnormality was found. The fetuses did not show any skeletal or visceral abnormalities. ↓ body weight at HD, but within the range of other doses and the controls. NOAELs: 500 mg/kg bw/day (Maternal and developmental).
	Rats (albino, ♀), single dose of 1000 mg/kg bw/day on GD 7–16 (oral gavage)	No maternal, embryotoxic or teratogenic effects were observed. No other information was provided.
	NTP-DART-06 (2022b) Modified one-generation study Rats (SD); *n*=26/dose; exposure through feed and/or lactation 1000, 3000, 6000 ppm (equivalent to 70 to 87, 207-418, 419-842 mg/kg/day) F_0 dams: GD6 - LD 28 F_1 offspring were exposed in utero and during lactation through postnatal day (PND) 28 and evaluated for signs of toxicity. After weaning, F_1 offspring were allocated into prenatal, reproductive performance or subchronic exposure cohorts. Exposure to test article continued in feed until necropsy on PND96, 120 or 150. F_2 offspring were exposed in utero, during lactation and postweaning until necropsy on GD21 or PND28.	Octyl methoxycinnamate did not induce overt F_0 or F_1 maternal toxicity or affected mating or pregnancy indices. Reproductive performance (fertility and fecundity), numbers of live fetuses and pups ware not affected. Octyl methoxycinnamate exposure was not associated with any effects on fetal weight or the incidences of external, visceral, or skeletal malformations. Equivocal evidence of developmental toxicity was observed: ↓ Mean pup body weight (F1) at HD ↑ Vaginal opening (F_1) from MD ↑ Balanopreputial separation (F_1) at HD NOAEL: 6000 ppm for parental systemic toxicity, fertility and reproduction performance NOAEL: 1000 ppm for developmental toxicity
Octocrylene (SCCS 2021d; ECHA 2021d)	Extended one generation reproductive toxicity study (EOGRTS), GLP Rat (Wistar); Dose: (diets) 55, 153, 534 mg/kg bw/day ♂ 58, 163, 550 mg/kg bw/day ♀ *n*= 27 or 28 /sex /dose F1: Cohort 1A: 19/sex/ dose	↓ number of implantation sites and consequently a lower number of pups at HD ↓ bodyweight of pups at HD No effects on male fertility and male and female reproductive parameters such as oestrus cycle, epididymal and testicular sperm parameters at all doses. No effects on sexual and neurodevelopmental parameters in pups.

Active ingredient	Study details	Major findings
	Cohort 1B: 25/sex/dose Cohort 2A: 10/sex/ dose Cohort 2B: 10/sex/dose ♂: 10-week premating period, during mating up to the day of sacrifice (~ 13 weeks) ♀: P: 10-week premating period, termination on LD 21 F1: from weaning up to sacrifice (~ 10 weeks in Cohort 1A, ~ 13 weeks (♂) and approx. 18 weeks (♀) in Cohort 1B; ~ 8 weeks in cohort 2A) F2: until weaning (indirectly) (ECHA 2021d; SCCS 2021d)	Based on effects on parental and pup body weights, a lower number of implantation sites and lower number of pups delivered. **NOAEL: 153/163 mg/kg bw/day for males/females** for parental systemic toxicity, fertility/reproduction performance, and general and sexual development
	Pregnant rats (Wistar); *n* = 25/ ♀/dose, Dose: 0, 100, 400, 1000 mg/kg bw/day PO GD6–GD15; termination on GD21	F0: Transient salivation at HD. ↑ relative liver weight at MD and HD F1: No treatment related effects. NOAEL: ≥ 1000 mg/kg bw/day (teratogenicity)
	Mice (CD-1); *n*= 12 ♀/dose, Dose: 0, 100, 300, 1000 mg/kg bw/day (oral gavage); GD8–GD12; termination on LD3 Odio *et al*. (1994)	No treatment related adverse effects. NOEL: 1000 mg/kg bw/day (mice)
	Rabbit (NZW); *n* = 17 ♀/dose Dose: 0, 65, 267 mg/kg bw/day, (Dermal, open, clipped area on the back), dosing GD6–GD18; termination on GD21 Odio *et al*. (1994)	No treatment related adverse effects. NOEL (percutaneous): 267 mg/kg bw/day (rabbits)
Ethylhexyl triazone (ECHA 2021b; DEPA 2015	Rats (wistar), Prenatal Developmental Toxicity study (*n*=25/dose). Dosing the dams 7 days/week for an unspecified period (0, 100, 400 and 1000 mg/kg bw/day).	No treatment-related effects reported. Maternal NOAEL = 1000 mg/kg bw/day; Developmental NOAEL = 1000 mg/kg bw/day
Homosalate (SCCS 2021b,c; ECHA 2021c)	The evaluation of potential toxicity of homosalate on fertility and development was performed in a combined repeat dose toxicity study with the reproduction/developmental toxicity-screening test (described above in repeat-dose toxicity section). The study findings were considered as inconclusive and unreliable due to a technical error that maintained the animals under a constant light. In the context of a compliance check process under REACH, the ECHA adopted a decision in 2018 requesting a sub-chronic toxicity study, a prenatal developmental toxicity study, an extended one-generation reproductive toxicity study, and the identification of degradation products (ECHA 2018, ECHA decision CCH-D-2114386909-26-01/F). An appeal was filed against this decision; however, the Board of Appeal dismissed the appeal and decided that the information must be provided by 25 February 2024.	
Oxybenzone (SCCP 2006a; 2021c)	Mice (CD-1), RACB (Reproductive Assessment by Continuous Breeding): 1850, 3950, 9050 mg/kg bw/day (14 days; *n*=20/sex); 1000, 2100, 4700, 10200, 15700 mg/kg bw/day (14 weeks; *n*=8/sex)	No effect on fertility at doses up to 8600/9500 mg/kg bw/day in♂/♀ mice (highest dose). Effects on reproductive performance included a slightly lower number of live pups at birth. Impaired body weight/body weight gain in pups was also observed. All effects were observed at dose levels resulting maternal toxicity including decreased bodyweight and premature death at doses of 1850 mg/kg bw/day. The NOAEL for systemic, reproductive and developmental toxicity was 1800/1900 mg/kg bw/day in males/females.

Active ingredient	Study details	Major findings
	Rats (F344/N; *n*=10/sex) and mice (B6C3F1; *n*=10/sex): 0, 3125, 12500, 50000 ppm (equivalent to 204, 828, 3458 mg/kg bw/day in rats and 554, 2860, 16238 mg/kg bw/day in mice);13 weeks (dietary)	↓ Epididymal sperm counts, and decreased absolute cauda, epididymal and testis weight as a consequence of the reduced body weight in male rats and ↑ in the length of the oestrous cycle in female rats. ↓ in the epididymal sperm count and ↑ the incidence of abnormal sperm was observed in male mice, and there was an ↑ in the length of the oestrous cycle in female mice (as seen in rats). Oestrous cyclicity was not affected in either rats or mice. NOAEL for reproductive parameters was established at 828 mg/kg bw/day in rats and 2860 mg/kg bw/day in mice (SCCP 2006a).
	Rats (SD; n=not reported) doses up to 200 mg/kg bw/day and mice (B6C3F1; *n*= x ♂);0, 20, 100, 400 mg/kg bw/day; 13 weeks (dermal)	No effects on selective reproduction parameters and a NOAEL was established at 200 mg/kg bw/day, the highest dose tested in rats. In mice, there were no effects on reproductive organ weight, cauda epididymal sperm concentration, sperm parameters, testicular spermatid concentration or testicular histology. NOAEL: 400 mg/kg bw/day, the highest dose tested.
	Prenatal developmental toxicity study in rats (Wistar; *n*=25 ♀), at doses of 0, 40, 200, 1000 mg/kg bw/day PO	Slight ↑ rates of fetuses/litter with skeletal variations (incomplete ossification of different skull bones and cervical arch, supernumerary 14th ribs) and therefore ↑ rates of total variations were observed at 1000 mg/kg bw/day. These effects were associated with maternal toxicity (clinical signs, reduced bodyweight and food consumption). The NOAEL was established at 200 mg/kg bw/day.
	Reproductive toxicity study in rats (SD) at doses of 3000, 10000 and 30000 ppm (equivalent to 242, 725 and 3689 mg/kg bw/day) in the diet from GD 5-15.	The maternal NOAEL was established at 3000 ppm (206-478 mg/kg bw/day) based on reduced bodyweight gain during GD 6-9 and lactation day 4-21. The developmental NOEL was established at 3000 ppm (206-478 mg/kg bw/day) based on impaired postnatal bodyweight performance at 10000 ppm (660-1609 mg/kg bw/day) (SCCS 2021e).
	Nakamura *et al.* (2015) Reproductive toxicity study in rats (SD; *n*=7-8 mated ♀); Doses: 0, 1000, 3000, 10,000, 25,000, or 50,000 ppm, equivalent to 67.9, 207.1, 670.8, 1798.3, and 3448.2 mg/kg bw/day, respectively. Treatment from GD6-PND23. The effects of maternal exposure during gestation and lactation on development and reproductive organs of offspring of mated female rats was examined.	Exposure to <10,000 ppm oxybenzone was not associated with adverse effects on the reproductive system in rats. At higher doses, a decrease in the normalised anogenital distance in male pups at PND 23, impairment of spermatocyte development in testes of male offspring, delayed follicular development in females was observed at doses of ≥207 mg/kg bw/day. The **NOAEL was established at 67.9 mg/kg bw/day.**
	Han *et al.* (2022) Reproductive toxicity study in mice (ICR; *n*=13-15 mated ♀) Doses: 0, 0.1, 10, 1000 mg/kg/day PO Treatment from GD1-GD13	No adverse effect on maternal body weight and the relative weights of the liver, brain and the uterus. Slight ↑ rate of fetal loss at HD; ↑ placental thrombosis and necrosis from LD (severity not assessed)
	NTP-DART-05 (2022a) Modified one-generation study Rats (SD; mated ♀; *n*= 25/dose) Doses: 0, 3000,10000, 30000 ppm; exposure through feed and/or lactation	There was equivocal evidence of reproductive toxicity of oxybenzone based on ↓ F_2 litter size at HD. There was some evidence of developmental toxicity from MD based on ↓ F_1 and F_2 mean body weights; this effect on body weight contributed to the apparent oxybenzone -related ↓ in male reproductive organ weights from MD.

Active ingredient	Study details	Major findings
	(equivalent of 205 to 426, 697 to 1621, and 2,644 to 5944 mg/kg/day respectively) F_0 GD6 - LD28 F_1 GD6 - LD28; after weaning, F_1 offspring were allocated into cohorts for prenatal, reproductive performance, or additional assessments (e.g., subchronic or biological sampling cohorts) and exposure to test article in feed continued until necropsy on PND96, PND120 or PND150 F_2 offspring were exposed in utero, during lactation and postweaning until necropsy on GD21 or PND28.	The relationship of the ↑ occurrence of diaphragmatic and hepatodiaphragmatic hernias in F_1 adults and F_2 pups from MD is unclear. Exposure to oxybenzone was associated with ↑ nonneoplastic kidney lesions in the F_0, F_1, and F_2 generations at HD Exposure to oxybenzone was not associated with signals consistent with alterations in estrogenic, androgenic, or antiandrogenic action. NOAEL: 3000 ppm
Phenylbenzimidazole sulfonic acid (SCCP 2006b)	A prenatal developmental study (rats, *n*=25♀/group), treatment GD 6-15, doses: 0 and 1000 mg/kg bw/day (gavage)	No treatment-related findings were noted in the study. The NOAEL for maternal and fetal toxicity was 1000 mg/kg bw/day.

Active ingredients in human milk

In a cohort study between 2004 and 2006, 54 human milk samples were analysed, and UV filters were detectable in 46 samples and levels were positively correlated with the reported usage of UV filter products (Schlumpf et al., 2010). Concentrations of octyl methoxycinnamate or ethylhexyl methoxy cinnamate (EHMC), octocrylene (OC), 4-methylbenzylidene camphor (4-MBC), homosalate (HMS) and oxybenzone (BP-3) ranged 2.10–134.95 ng/g lipid, with octyl methoxycinnamate/EHMC and octocrylene being most prevalent (42 and 36 positive samples, respectively) and an average of 7 positive samples for the other three (Schlumpf et al., 2010). In another study, levels of oxybenzone in maternal urinary samples taken in gestational weeks 6–30 were positively correlated with the overall weight and head circumference of the baby (Philippat et al. 2012). The significance of these limited postnatal and prenatal exposure findings to human mothers are unclear.

Endocrine activity modulation

In the light of the recent regulations in Europe, several studies have been conducted to investigate the endocrine disruption potential of most of these ingredients. Since the FDA released its draft proposal (FDA, 2019b), several studies published in 2020 support previous findings that oxybenzone can act as an endocrine disruptor and may increase the risk of breast cancer and endometriosis (Kariagina 2020, Santamaria 2020).

A systemic review on oxybenzone and octyl methoxycinnamate suggest that current evidence is not sufficient to support the causal relationship between the elevated systemic level of oxybenzone and octyl methoxycinnamate and adverse health outcomes (Suh 2020). There are either contradictory findings among different studies or insufficient number of studies to corroborate the observed association. To accurately evaluate the long-term risk of exposure to oxybenzone and octyl methoxycinnamate from sunscreen, a well-designed longitudinal randomized controlled trial needs to be conducted which is not feasible from ethical point of view.

Most current SCCS opinions have evaluated the most current data on endocrine disruption potential for these ingredients.

For ethylhexyl triazone, the only information on reproductive toxicity or endocrine disrupting potential was from a short SCCS opinion (Hojerová *et al.* 2017). Therefore, further information would be required for the endocrine disruption potential of ethylhexyl triazone. The available data (evaluated in

SCCS opinions) on butyl methoxydibenzoylmethane, homosalate, octocrylene, octyl methoxycinnamate and oxybenzone indicate potential endocrine effects, however, they are not adequate to regard them as an endocrine disrupting ingredient, or to derive a toxicological point of departure based on endocrine disrupting properties for use in human health risk assessments.

Chemicals with endocrine activity modulation are exogenous chemicals that can alter hormone action, thereby potentially increasing the risk of adverse health outcomes, including cancer, reproductive impairment, cognitive deficits and obesity. In 2013, publicly available data on endocrine disruptive properties of 23 ingredients including the ingredients reviewed in this document were collected and evaluated by the Danish Centre on Endocrine Disruptors (Axelstad *et al.* 2013). The overall conclusion of the evaluation was that there were not enough data to conclude whether the ingredients have endocrine disruptive properties or not.

> *"In conclusion, very little is known on the endocrine disrupting potential of these 23 UV-filters. For 14 of the 23 assessed UV-filters[10] no in vivo studies in rodents, assessing endpoint that are sensitive to endocrine disruption, have been performed, and it was therefore not possible to conclude anything on their endocrine disrupting potential, with regard to human health…*
>
> *Two of these (octocrylene and butyl methoxydibenzoylmethane) showed no adverse effects in the used test systems. Seven of the UV-filters (placed in groups C & D) were tested in the Uterotrophic assay, and regardless of their estrogenic potential in vitro, none of them caused increased uterine weights, indicating lack of estrogenic potential in vivo. The three compounds in-group E[11] were also investigated for androgen receptor (AR) agonism/antagonism in vitro, and the results differed somewhat depending on which type of study had been performed. However, since no in vivo studies investigating the anti androgenic effects of the compounds were present, it is difficult to conclude anything on their endocrine disrupting potential with regard to the possible androgenic/antiandrogenic mode of action. Information on human health endocrine disrupting potential of last two UV-filters (octocrylene and titanium dioxide) was also scarce. Since no adverse effects on testicular and epididymal morphology or on sperm quality were seen in a 90-day study of octocrylene, this UV filter did not seem to be a potent anti-androgen. Read across assessment showed possible resemblance of the chemical structures of some of the presently evaluated UV-filters to known or suspected endocrine disrupting UV-filters, however more knowledge on the endocrine disrupting potential of the presently evaluated UV-filters could be obtained by doing QSAR analyses. Unfortunately no published reports of such analysis were present in the open literature."*

An extensive review in 2016 also discussed the potential endocrine disruption of typical UV filters including benzophenones (i.e. oxybenzone), camphor derivatives and cinnamate derivatives (i.e., octocrylene, octyl methoxycinnamate etc.) (Wang *et al.* 2016). The review (Wang *et al.* 2016) concluded:

> *"These UV filters are generally involved in the disruption of the hypothalamic–pituitary–gonadal system. As revealed by in vivo and in vitro assays, exposure to these chemicals induced various endocrine disrupting effects such as estrogenic disrupting effects, androgenic disrupting effects as well as the disrupting effects towards TR, PR. The underlying mechanism of endocrine disruption was summarized … The minor structural changes of these kinds of UV filters have influence on the potency of their endocrine disrupting effects."*

The Table 2 (summarising the Endocrine Activity Modulation effects of the commonly used UV filters) from the Wang review is provided in Attachment 2: List of endocrine activity modulation effects of commonly used UV filters.

In a recent *in vitro* study, Rehfeld *et al.* (2018) found that the homosalate, oxybenzone, butyl methoxydibenzoylmethane, octyl methoxycinnamate and octocrylene induced Ca^{2+} influx in human sperm cells whereas ethylhexyl triazone did not. It concluded:

[10] Ethylhexyl triazone was included in these 14 ingredients

[11] Homosalate and butyl methoxydibenzoylmethane were included

> "*In conclusion, chemical UV filters that mimic the effect of progesterone on Ca^{2+} signaling in human sperm cells can similarly mimic the effect of progesterone on acrosome reaction and sperm penetration. Human exposure to these chemical UV filters may impair fertility by interfering with sperm function, e.g. through induction of premature acrosome reaction. Further studies are needed to confirm the results in vivo".*

Lee *et al.* (2022) screened octyl methoxycinnamate, octocrylene, butyl methoxydibenzoylmethane and homosalate among 35 other chemicals used in consumer products, for their ability to modulate estrogen receptor (ER) or androgen receptor (AR) *in vitro.* Octyl methoxycinnamate was a weak agonist of ER, while octocrylene acted both as a very weak agonist or a weak antagonist of ER, but both were negative for AR. Butyl methoxydibenzoylmethane and homosalate did not activate either ER or AR.

In the light of increased safety concerns regarding the Endocrine Activity Modulation potential of the active ingredients in sunscreens, in 2018, the ECHA and the European Food Safety Authority (EFSA) published "Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009 (Andersson *et al.* 2018). The Biocidal Products Regulation (EU No 528/2012; BPR) restricts approvals of the active substances considered to have endocrine disruption properties, unless the risk from exposure to the active substance is shown to be negligible or unless there is evidence that the active substance is essential to prevent or control a serious danger to human health, animal health, or the environment.

A recent Consensus Statement discussed ten key characteristics (KCs) of Endocrine Activity Modulation based on hormone actions and Endocrine Activity Modulation effects, the logic behind the identification of these KCs and the assays that could be used to assess several of these KCs (la Merrill *et al.* 2020).

A systematic review assessed 29 studies that addressed the impact of oxybenzone on human health (Suh 2020). The review suggests increased systemic level of oxybenzone had no adverse effect on male and female fertility, female reproductive hormone level, adiposity, fetal growth, child's neurodevelopment and sexual maturation (Suh 2020). However, the association of oxybenzone level on thyroid hormone, testosterone level, kidney function and pubertal timing has been reported warranting further investigations to validate a true association. The health effects of an increased octyl methoxycinnamate level have been less extensively studied presumably. The current evidence shows that topical application of octyl methoxycinnamate does not have biologically significant effect on thyroid and reproductive hormone levels (Suh 2020). However, the topical application of octyl methoxycinnamate results in systemic absorption greater than 0.5 ng/mL, a threshold established by the FDA for waiving toxicology assessment, and therefore further drug safety assessment on octyl methoxycinnamate is crucial.

The review concluded that:

> *"To evaluate the long-term risk of exposure to BP-3 or OMC from sunscreens, a well-designed longitudinal randomized controlled trial is of high priority."*

The latest SCCS opinions on these ingredients considered available information on the endocrine activity of these active ingredients and suggested inadequate evidence is available for relevant safety determination.

The key conclusions from the evidence above are given below for each individual ingredient.

Butyl methoxydibenzoylmethane

The Danish Centre on Endocrine Disruptors (Axelstad *et al.* 2013) evaluated publicly available data on endocrine disruptive properties of substances and based on the assessment it concluded that there were not enough data to conclude whether butyl methoxydibenzoylmethane has endocrine disruptive properties or not.

Homosalate

According to Danish QSAR database, homosalate was predicted to activate the E2R (Leadscope and SciQSAR)[12] and to act as an antagonist of androgen receptor (AR)(CASE Ultra and Leadscope).[12]

The SCCS (2021b) conclusion was based on a Risk Management Options Analysis (RMOA) 2016 by ANSES[13]. As per the RMOA, *the available data from non-testing methods and in vitro assay and the inadequate in vivo studies provide indications for an ED potential of homosalate, whereas the rest of the studies were of limited relevance and do not indicate the potential for ED concern. Despite the poor quality of the in vivo studies, findings that could be linked to an endocrine disruption were identified, in particular fluctuations of hormones, sperm changes and effects on the thyroid*. These effects raised some concerns regarding ED properties of homosalate.

Therefore, the SCCS (2021b) concluded:

> "*It needs to be noted that the SCCS has regarded the currently available evidence for endocrine disrupting properties of homosalate as inconclusive, and at best equivocal. This applies to all of the available data derived from in silico modelling, in vitro tests and in vivo studies, when considered individually or taken together. The SCCS considers that, whilst there are indications from some studies to suggest that homosalate may have endocrine effects, the evidence is not conclusive enough at present to enable deriving a specific endocrine-related toxicological point of departure for use in safety assessment."*

Octocrylene

The endocrine activity modulation potential of octocrylene was extensively discussed in SCCS (2021d). The SCCS opinion concluded that:

> *"The SCCS considers that, whilst there are indications from some in vivo studies to suggest that Octocrylene may have endocrine effects, the evidence is not conclusive enough at present to enable deriving a specific endocrine-related toxicological point of departure for use in safety assessment".*

Oxybenzone

The endocrine activity modulation potential of oxybenzone was extensively discussed in SCCS (2021e). The SCCS (2021e) evaluated the potential endocrine mode of action for oxybenzone (BP-3) *in vitro* and *in vivo* and endocrine-related adverse effects in humans and animals.

The SCCS concluded:

> "*The currently available evidence for endocrine disrupting properties of BP-3 is not conclusive, and is at best equivocal. This applies to the data derived from in silico modelling, in vitro tests and in vivo studies, when considered individually or taken together. There are either contradictory results from different studies, or the reported data do not show dose-response relationship, and/or the effect are seen only at relatively very high doses that can only be considered far beyond the human exposure range. In view of this, the SCCS considers that whilst there are indications from some studies to suggest that BP-3 may have endocrine effects, it is not conclusive enough at present to enable deriving a new endocrine-related toxicological point of departure for use in safety assessment."*

[12] QSAR software for modelling and predicting toxicity of chemicals. CASE Ultra has both methodologies (statistics based and expert rule based) built in for a complete ICH M7 compliant assessment. Leadscope Model Applier (Leadscope, Inc.) is a chemoinformatic platform that provides QSAR models for the prediction of potential toxicity and adverse human clinical effects of pharmaceuticals, cosmetics, food ingredients and other chemicals.
[13] French Agency for Food, Environmental and Occupational Health & Safety (ANSES) – See Eurometaux (2016).

Octyl methoxycinnamate

Most of the available data suggest that octyl methoxycinnamate has an estrogenic activity, androgenic and anti-thyroid activity in rats and humans [NICNAS (currently known as AICIS), 2017; Lorigo *et al.* 2018].

Regarding the octyl methoxycinnamate mechanism of action, several studies showed that the effects exerted by Estradiol (E2) and octyl methoxycinnamate were not always totally shared and it is possible that octyl methoxycinnamate could act by a mechanism different from the classic E2R (α y β). There are few data regarding the anti-androgenic activity of octyl methoxycinnamate, and the studies suggest that octyl methoxycinnamate is not able to bind to androgen receptors. Studies in rats showed that octyl methoxycinnamate could disturb the homeostasis of the thyroid hormones by mechanisms different from the classical ones of hormone-dependent regulation and feedback.

More studies in rodents and very few in humans, suggest that an increase exposure to octyl methoxycinnamate could be related to infertility or changes in GnRH and disturbance of reproductive hormone levels. A public call by the European Commission for data on the endocrine activity modulation potential of ingredients used in cosmetics, including octyl methoxycinnamate, was undertaken from 15 February to 15 November 2021 (EU 2021).

A recent review summarises the endocrine effects of these ingredients recognising limited data availability (Fivenson 2020). This was a retrospective literature review that involved many different types of studies across a variety of species. Comparison between reports is limited by variations in methodology and criteria for toxicity.

Other studies

The photo-allergic potential of butyl methoxydibenzoylmethane has been extensively reviewed in several publications (Nash and Tanner 2014). However, given the mechanistic understanding and known photo-degradation of butyl methoxydibenzoylmethane, the findings were inconsistent. For example, the *in vitro* skin phototoxicity of cosmetic formulations containing butyl methoxydibenzoylmethane, other UV filters and vitamin A palmitate was assessed by two *in vitro* techniques [3T3 Neutral Red Uptake Phototoxicity Test (3T3-NRU-PT) and Human 3-D Skin Model *In Vitro* Phototoxicity Test (H3D-PT)](Gaspar *et al.* 2013).The phototoxicity potential was ‘positive’ for butyl methoxydibenzoylmethane alone and in combination with other UV filters (3T3-NRU-PT). However, when tested on a human skin model, the ‘positive’ results were no longer observed. It has been suggested by several studies and reviews that the photoallergic potential of butyl methoxydibenzoylmethane may be the result of the photoproducts formed following exposure to UV. These data suggest that photo-degradation of butyl methoxydibenzoylmethane forms classes of photoproducts (arylglyoxals and benzils) which have strong potential for sensitization (Karlsson *et al.* 2009).

A survey in Canada (2001-2010) indicated that the most common photoallergens were oxybenzone, octyl dimethyl para-amino- benzoic acid and butyl methoxydibenzoylmethane whereas the most common contact allergens were octyl dimethyl para-aminobenzoic acid, oxybenzone and sandalwood (Yap 2017).

The SCCS (SCCS 2000) stated that octyl methoxycinnamate did not have phototoxic potential based on one study of 10 subjects exposed to patches of octyl methoxycinnamate for 24 hours and then exposed to a sub-erythematous dose of UV irradiation. No further details were supplied in the SCCS report. Recent *in vitro* (3T3 viable monolayer fibroblast cultures) and *in vivo* studies indicated that octyl methoxycinnamate was not phototoxicity (Gomes *et al.* 2015).

A human repeated insult patch test (HRIPT) was carried out at a concentration of 2% octyl methoxycinnamate in 53 subjects. There was no sensitisation. Similar studies using different formulations (7.5 % octyl methoxycinnamate in petrolatum or 10 % octyl methoxycinnamate in dimethylphthalate) also did not show any adverse reaction after 24 and 48 h. In a study in 32 healthy volunteers, daily whole–body topical application of 2 mg/cm^2 of cream formulation without (week 1)

and with (week 2) the sunscreen (octyl methoxycinnamate 10%) for one week was performed. Hormone changes (testosterone, oestradiol and inhibin B levels) were observed following treatment but were not considered to be biologically significant. Following 1–2 hours of application, the chemical was detected in the parent form both in plasma and in urine (more than 86 % of the applied dose).

Oxybenzone was not phototoxic in the 3T3-NRU-PT test and was not phototoxic in *S. cerevisiae* or *E. coli in vitro*. Oxybenzone was not phototoxic in guinea pigs *in vivo* at a concentration of 10% (oxybenzone applied to shaven and depilated skin for 30 minutes followed by irradiation (UV-A) for 60 minutes). Oxybenzone did not cause photosensitisation in rabbits *in vivo* (study details not available). Oxybenzone was not photomutagenic in the photo Ames test or an *in vitro* chromosome aberration assay in CHO cells.

Oxybenzone was tested for photobinding to human serum albumin and histidine photo-oxidation potential in a mechanistic *in vitro* test for the discrimination of the photo-allergic and photo-irritants where oxybenzone revealed no phototoxic potential (SCCP 2006a). However, in a recent study, oxybenzone was shown to cause photoallergenic reactions being second most frequent photo contact allergen among the UV filters (European photo patch test task force) (Subiabre-Ferrer *et al.* 2019).

Ethylhexyl triazone (10%) did not cause photosensitisation in guinea pigs. Separate tests with *Saccharomyces cerevisiae* and CHO cells exposed to the ethylhexyl triazone and UVA and UVB irradiation did not show any potential photomutagenic effects of ethylhexyl triazone.

Phototoxicity, photosensitisation and photomutagenicity of phenylbenzimidazole sulfonic acid was examined in the SCCP opinion on phenylbenzimidazole sulfonic acid and its salts (SCCP 2006b). Phenylbenzimidazole sulfonic acid was not a photo-irritant in mice or guinea pigs *in vivo*, or in 3T3 cells *in vitro* (Photo irritation factor of 1.4). In addition, phenylbenzimidazole sulfonic acid was not photomutagenic in the photo Ames test, a yeast gene conversion assay or an *in vitro* chromosome aberration assay in CHO cells. A few cases of photoallergic contact dermatitis reactions have been reported in the literature following use of products containing phenylbenzimidazole sulfonic acid, however no skin reactions have been observed in dedicated patch tests studies in human volunteers at concentrations up to 10%, with or without irradiation (SCCP 2006b).

The incidence of positive reactions (0.08%) was reported in a recent patch study among patients administered with octocrylene at 10% in petrolatum (n = 2577) (Uter *et al.* 2017). Similar findings were reported in an EU multicentre photopatch test study where contact allergy was reported in only 0.7% of the 1031 patients patch tested with 10% octocrylene in petrolatum for suspected photoallergic contact dermatitis (Klimova *et al.* 2015).

Contact allergy to octocrylene appears to be more frequent and severe in children (EMCPPTSA 2012; Gilaberte and Carrascosa 2014) whereas photoallergic contact dermatitis to octocrylene was found to be much more frequent in adults (NICNAS 2017). Photocontact allergy to octocrylene was reported in 4% of the 1031 adult patients that were patch-tested for suspected photoallergic contact dermatitis (EMCPPTSA 2012). The occurrence of photoallergic contact dermatitis to octocrylene was found to be related to a previous photoallergy to topical ketoprofen (Loh and Cohen 2016). Patients with photoallergic contact dermatitis caused by sunscreens and positive photopatch tests to octocrylene have been mainly reported in France, Belgium, Italy and Spain, countries in which topical ketoprofen is used regularly in consumer products (de Groot and Roberts 2014). This was confirmed in a recent study conducted in Italy where concomitant photocontact allergy to ketoprofen was reported in 61.5% of 156 patients (Romita *et al.* 2018). A very recent review has evaluated these findings extensively (Berardesca *et al.* 2019).

Several hypotheses were proposed to illustrate the mechanism for the co-reactivity of octocrylene namely: (i) the role of the benzophenone moiety of ketoprofen (although the benzophenone moiety is not part of the octocrylene structure, aminolysis and hydrolysis of octocrylene in the skin may result in the formation of benzophenone which then can lead to cross-reactivity); (ii) hyper-photo susceptibility to ingredients that are nonrelevant allergens; and (iii) co-reactivity – i.e. concomitant sensitization or prior or subsequent *de novo* photosensitisation – may be involved in place of cross-reaction.

The presence of sensitizing impurities in some commercial batches of octocrylene were also suspected to be allergens contributing to photocontact allergy (Aerts *et al.* 2016).

Neurotoxic effects of active ingredients in sunscreens were reviewed extensively (Ruszkiewcz *et al.* 2017). The table listing the effects from the treatment of octyl methoxycinnamate, oxybenzone and octocrylene is shown below. However, this is not reviewed in this discussion elaborately as similar mechanisms apply on endocrine activity modulation potential of these ingredients (Ruszkiewcz *et al.* 2017).

Obesogenic potential of butyl methoxydibenzoylmethane was demonstrated *in vitro* by Shin et al. (2020) and Ahn et al. (2019). In normal human epidermal keratinocytes, butyl methoxydibenzoylmethane (10 µM) increased expression of genes associated with lipid metabolism, including peroxisome proliferator-activated receptor γ (PPARγ) and promoted adipogenesis in human bone marrow mesenchymal stem cells (EC_{50} = 14.1 µM). Nevertheless, butyl methoxydibenzoylmethane did not bind PPARγ and the butyl methoxydibenzoylmethane-induced adipogenesis-promoting activity was not affected by PPARγ antagonists (Ahn *et al.* 2019). Even though potential obesogenic effect in human subject cannot be unequivocally excluded, it is unlikely given that mean C_{max} (12.89 nM or 4 µg/L; see **Clinical Trials**) of butyl methoxydibenzoylmethane following a dermal application was ~1000 lower than concentrations promoting adipogenesis *in vitro*.

Similarly, obesogenic potential of octocrylene was postulated by Ko *et al.* (2022), but in contrast to butyl methoxydibenzoylmethane, octocrylene directly bound PPARγ, although with a relatively low affinity (Ki = 37.8 µM). *In vitro* octocrylene induced (EC_{50}= 29.6 µM) adiponectin secretion by human bone marrow mesenchymal stem. However, like butyl methoxydibenzoylmethane, the obesogenic impact of octocrylene applied dermally is not expected, as mean plasma C_{max} of (32 nM or 11.7 µg/L; (see Clinical Trials) was 925 lower than the EC_{50} of adiponectin secretion *in vitro*.

The immunomodulatory effect of butyl methoxydibenzoylmethane was reported *in vitro*. At 50 µM the compound increased IL-8 secretion by monocyte-like THP-1 cells as well as by THP-1 derived macrophages (Weiss *et al.* 2023). However, the immunomodulatory effect of butyl methoxydibenzoylmethane in sunscreen applications is not predicted considering low systemic exposures (C_{max} = 12.89 nM) and relatively low impact *in vitro* (fold changes of affected factors were generally < 2) at concentrations exceeding C_{max} ~4000 times.

Table Error! No text of specified style in document.**-10 Summaries of other studies**

Compound	Exposure model	Experimental design	Effect
Octyl methyoxycinnamate or octinoxate	Wistar rats	Oral (gavage) administration during gestation and lactation	Decreased motor activity in female offspring, increased spatial learning in male offspring.
	Sprague-Dawley rats, female	Oral (gavage) administration for 5 days; 10–1000 mg/kg/day	Non-estrogenic interference within the rodent HPT axis; no changes in pre-proTRH mRNA in mediobasal-hypothalamus.
	Wistar rats	In vitro incubation of hypothalamus isolated from adult rats; 60 min; 0.263 µM	Decreased hypothalamic release of GnRH. Increased GABA release and decreased Glu production in males. Decreased Asp and Glu production in females.
	Wistar rats	in vitro incubation of hypothalamus isolated from immature rats; 60 min; 0.263µM	Decreased hypothalamic release of LHRH. Increased GABA release in males, decreased Asp and Glu levels in females.
	SH-SY5Y neuroblastoma cell line	72 h; 10^{-8}–10^{-4}M	Decreased cell viability and increased caspase-3 activity.
	Rainbow trout (Cahova *et al.* 2023)	Administered with food; 6 weeks; 6.9 – 395 µg/kg/day	Increased plasma thyroxine levels at 395/kg/day

			(~325 ng/mL) *c.f.* controls (~200 ng/mL)
	Wistar rats (Lorigo and Cairrao 2022)	*In vitro*; isolated rat aortas 0.001–50 µmol/L	Increased vasorelaxant effect by endothelium-dependent mechanisms
	Human umbilical arteries (Lorigo *et al.* 2021, 2022)	*In vitro,* 24h incubation; 1 -50 µmol/L	Decreased vasorelaxation response by interference with NO/sGC/cGMP/PKG pathway Increased reactivity to the contractile agents – serotonin, histamine and KCl In silico analysis suggests that octyl methoxycinnamate might compete with T3 for the binding centre of THRα.
Benzophenone-3 or oxybenzone	Zebrafish	Waterborne; 14 days for adult, 120 h for embryos; 10–600 µg/L	Anti-androgenic activity: decreased expression of *esr1*, *ar* and *cyp19b* expression in the brain of males.
	Zebrafish (Babich *et al.* 2020)	Embryonic oxygen consumption rate; 0.004 – 4 mg/L	Negligible effect on mitochondrial respiration
	Zebrafish (Xu *et al.* 2021)	Waterborne; 0.056 - 38 µg/L 42 days post fertilization	Decreased female to male ratio from 2.3 µg/L Increased expression of estrogen receptors *esr2a* and *vtg2 i*n the brain and hepatic *vtg2* at HD
	Zebrafish (Bai *et al.* 2023)	Waterborne; 6 h post fertilisation to adulthood(~5months); 10 µg/mL (0.04 µM)	Reduced social aggression, learning and memory in ♀; cognition deficits in ♀ correlated with neurotoxicity and increased brain cell apoptosis. Reduced social preference in ♂ and ♀.
	Sprague-Dawley rats	Dermal application; 30 days; 5 mg/kg/day	No changes in behavioural tests (locomotor and motor co-ordination).
	Rat primary cortical astrocytes and neurones	1–7 days; 1–10 µg/mL	Decreased cell viability of neurons but not of astrocytes.
	Kumming (KM) mice (Zhang *et al.* 2021)	*In vitro*; Sertoli cells; 24 h; 5-150 µM	Impaired cell viability and disturbed cell morphology from 100 µM and increased Bcl-2 levels. Reduced expression of Rictor (component of mTORC2 complex) from 50 µM
	SH-SY5Y neuroblastoma cell line	72 h; 10^{-8}–10^{-4}M	Decreased cell viability and increased caspase-3 activity.
Octocrylene	Zebrafish	Waterborne; 14 days; 22–383 µg/L	Impaired expression of genes related with development and metabolism in the brain.
	Zebrafish (Meng *et al.* 2021)	96 h incubation; hatching rates of zebrafish (50-250uM) 96 h incubation; larvae death and zebra fish liver cell line (ZFL) – concentration range not reported.	Impaired hatching from 200 µM and increased larvae death (LC_{50} = 251.8 µM) Increased cytotoxicity (96 h LC_{50} = 5.5 µM) and expression of *cyp1a, cyp3a65,* estrogen receptors (*erα, erβ1, gper, vtg1*) and sex determination genes (*brca2, drtm1, cyp19a sox9a)* in ZFL at 10% LC_{50}
	ICR mice (Chang *et al.* 2022)	*In vitro;* oocytes incubated until maturation; 8-50 nM	Disturbed meiotic maturation and reduced oocyte quality from

			40 nM, likely due to impaired mitochondrial function.
	Human bone marrow mesenchymal stem cells (Ko *et al.* 2022)	*In vitro*; 72h; concentration range was not reported	Octocrylene directly binds to PPARγ with K_i = 37.8 µM and acts as a partial agonist Increased adipogenesis and secretion of adiponectin (EC_{50} = 29.6 µM).

Abbreviations: ar: androgen receptor; Asp: aspartate; cyp19b: cytochrome P450 aromatase b; esr1: estrogen receptor; GABA: gamma amino butyric acid; Glu: glutamate; GnRH: gonadotrophin-releasing hormone; HPT: hypothalamo-pituitary-thyroid; pre-proTRH: pre-pro-thyrotrophin-releasing hormone.

Safety assessment of the selected ingredients

Butyl methoxydibenzoylmethane (Avobenzone) safety assessment

Currently butyl methoxydibenzoylmethane (avobenzone) is approved in Australia for use as an active ingredient in sunscreens at 5% for dermal application, not to be used in topical products for eyes and with appropriate safety warnings in the labelling. This assessment is based on the international safety assessment reports (ECHA, 2021a; DEPA, 2015) and available peer reviewed publications investigating the safety and toxicokinetics of butyl methoxydibenzoylmethane.

The ECHA dossier suggested low percutaneous absorption of butyl methoxydibenzoylmethane. Potential systemic availability of butyl methoxydibenzoylmethane or metabolites at a high oral dosage was suggested from the oral toxicity studies in rats with up to 3 months exposure. Low systemic exposure from dermal contact was also noted in the ECHA dossier and insignificant inhalation exposure was assumed due to the low vapour pressure. In a study with pigskin (2% and 7.5% butyl methoxydibenzoylmethane containing formulations), about 95 % of butyl methoxydibenzoylmethane remained on the skin surface, 1-2 % were in the stratum corneum, 1 - 3.4 % in the skin and only ≤0.5 % was found to pass the skin (ECHA 2021A). In an *in vitro* dermal absorption study with human skin (2% butyl methoxydibenzoylmethane in water-oil cream) dermal absorption increased with exposure time from 0.3% to 7.3% (the latter value has been used in the MoS calculation, see below) after 18 hours (DSM, 1982). In a recent study (Montenegro *et al.* 2018) to investigate the effects of the vehicle and repeated applications of sunscreens on skin permeation, the skin permeation was demonstrated to be very poor after single or repeated applications leading to a MoS above the accepted safety limit (>100).

Nonetheless, recent randomised clinical trials indicate that butyl methoxydibenzoylmethane could be systemically absorbed (Matta *et al.,* 2020; 2019). The systemic exposure of butyl methoxydibenzoylmethane in all product types (spray, lotion, aerosol spray) exceeded 0.5 ng/mL on single application and remained above the threshold until 23 hours after application, and up to 7 days in more than 50% of participants. The long terminal half-life typically exceeded 48 hours and the ingredient remained detectable through to day 21, suggesting absorption through the skin is the rate-limiting step. However, further studies are required to determine other kinetic parameters e.g. elimination rate constants.

The available information reported for butyl methoxydibenzoylmethane indicate it has low acute toxicity (rats) and it is not an irritant to skin (very slight irritation at 10%) and eye (≤ 20%) in rabbits. No treatment-related effects were seen in guinea pig studies investigating irritation, sensitization, phototoxicity, and photoallergenicity potential. The ingredient was not found to be genotoxic, mutagenic, photo mutagenic or teratogenic in animals. Clinical data have shown the ingredient to be a rare allergen and/or photoallergen.

Dose related local dermal effects like erythema and oedema were seen in a 28-day dermal, repeat dose study in rabbits with no systemic effects. In this study, the putative systemic NOAEL was

determined to be 360 mg/kg/day bw (18% butyl methoxydibenzoylmethane) whereas the LOAEL (dermal) was 30 mg/kg/day bw (1.5% butyl methoxydibenzoylmethane) based on topical local effects. As no systemic effects were observed, it is likely that the animals did not receive a sufficient dose and therefore these NOAELs were not used in the calculation of the MoS (shown below). A NOAEL (oral) for maternal, developmental and embryotoxicity of 1,000 mg/kg bw/day was determined in rats.

Based on a 13-week oral repeated dose toxicity study in rats, the **NOAEL of butyl methoxydibenzoylmethane was considered to be 450 mg/kg bw/day** and used for the MoS calculation given the longer duration of the study and a better reflection of systemic toxicity.

Exposure estimate and Margin of Safety for Avobenzone

Butyl methoxydibenzoylmethane – standard parameters for the estimation of the systemic exposure dose

Parameter	Value
NOAEL	450 mg/kg bw/day
Dermal absorption (DAp)	7.3%
Highest concentration permitted to be used in Australian sunscreen products (C)	5%

Estimated butyl methoxydibenzoylmethane SED and MoS using the Australian Sunscreen Exposure Model (ASEM)

ASEM method 1 (%) MoS calculation

$$SED = ASEM_{(\text{method 1})} \times DA_p \times C$$

$$= 673\ mg/kg\ bw/day\ \times 7.3\ \% \times 5\% = 2.456\ mg/kg\ bw/day$$

$$MoS = \frac{NOAEL\ (mg/kg\ bw/day)}{SED\ (mg/kg\ bw/day)} = \frac{450\ mg/kg\ bw/d}{2.456\ mg/kg\ bw/d} = \mathbf{183}$$

DA_p: Dermal Absorption, C: Concentration

Recommendation

A MoS greater than 100 was calculated using the ASEM. As a result, butyl methoxydibenzoylmethane is deemed to present a low risk to human health and safety when used at the highest maximum permitted concentration of 5% in therapeutic sunscreens. No changes are recommended to the current permitted use.

Ethylhexyl triazone safety assessment

The assessment is primarily based on the REACH dossier (ECHA, 2021b) and published peer reviewed articles.

The ECHA registration dossier indicated the dermal uptake of ethylhexyl triazone was negligible or low (maximum uptake of 1.3%). Recent *in vitro* experiments with a static skin diffusion cell design under real life conditions indicated that 18.3 ± 2.5 µg/cm^2 of ethylhexyl triazone was found in the stratum corneum, whereas no ethylhexyl triazone was determined in the receptor fluid following the application of a sunscreen with 5% ethylhexyl triazone on the intact human skin at the dose of 1mg/cm^2 for 6 h (Hojerová *et al.* 2017). The study authors concluded, that approximately 0.54 mg/cm^2 of ethylhexyl triazone (i.e., ~1.08% of the amount of ingredient applied) permeated the excised human epidermis into the receptor fluid. Higher ethylhexyl triazone absorption was noted on shaved skin. Preferential distribution of ethylhexyl triazone into upper layers of stratum corneum was also noted by Sauce *et al.* (2020).

Undiluted ethylhexyl triazone is not expected to be a skin or eye irritant. There are no data for respiratory irritation. It was not found to be sensitising in guinea pigs. The NOAELs were determined 1000 mg/kg/day and ≤ 1275 mg/kg/day in two 90-day oral repeat dose studies in rats, respectively. Ethylhexyl triazone was not found to be genotoxic in *in vivo* and *in vitro* studies. No carcinogenicity data were available, and no adverse effects were reported in a pre-natal developmental study (**maternal and developmental NOAEL 1000 mg/kg/day bw**).

Because a dermal repeated-dose toxicity study for ethylhexyl triazone was unavailable from the literature, and concordant with the guidance provided in SCCS (2016), the NOAEL value (1000 mg/kg bw/day) from oral repeated dose toxicity studies in rats was used in the MoS determination.

Public exposure to ethylhexyl triazone is expected to be widespread and frequent through a daily use of listed medicines containing the ingredient at concentrations up to 5% (approved on TGA permitted list).[14] In the absence of an appropriate dermal absorption value for ethylhexyl triazone, a 10% dermal absorption was assumed for SED calculation considering the

Exposure estimate and Margin of Safety for Ethylhexyl triazone

Ethylhexyl triazone – standard parameters for the estimation of the systemic exposure dose

Parameter	Value
NOAEL	1000 mg/kg bw/day
Dermal absorption (DAp)	10%
Highest concentration permitted to be used in Australian sunscreen products (C)	5%

Estimated ethylhexyl triazone SED and MoS using the Australian Sunscreen Exposure Model (ASEM)

[14] Therapeutic Goods (Permissible Ingredients) Determination (No. 2) 2021

ASEM method 1 (%) MoS calculation

$$SED = ASEM_{(\text{method1})} \times DA_p \times C$$

$$= 673\ mg/kg\ bw/day\ \times 10\ \% \times 5\% = 3.365\ mg/kg\ bw/day$$

$$MoS = \frac{NOAEL\ (mg/kg\ bw/day)}{SED\ (mg/kg\ bw/day)} = \frac{1000\ mg/kg\ bw/d}{3.365\ mg/kg\ bw/d} = \mathbf{297}$$

DA_p: Dermal Absorption, C: Concentration

Recommendation

A MoS greater than 100 was calculated using the ASEM. As a result, ethylhexyl triazone is deemed to present a low risk to human health and safety when used at the highest maximum permitted concentration of 5% in therapeutic sunscreens. No changes are recommended to the current permitted use.

Homosalate safety assessment

This assessment is based on the published literature, ECHA dossier and SCCS opinions (ECHA, 2021c; SCCS, 2021b, c). The SCCS first published their opinion on homosalate in 2007 (SCCS, 2007), and recently extended their preliminary opinion (SCCS, 2021b) based on new information of homosalate in late 2021 (SCCS, 2021c).

Animal studies and studies with human skin showed that homosalate could penetrate the skin. Evidence from *in vitro* experiments indicates that about 1.1% of the applied dose was absorbed in human skin (range: 0.9-2.0%) (CTFA, 2005). The maximal absorption value observed in the donor with highest absorption values (5.3 %) was taken for MoS calculation.[15]

Maximum plasma concentrations of homosalate after topical application varied between 13.9 and 23.1 ng/ml and $t_{½}$ between 46.9 and 78.4 h in clinical trials.

Homosalate was found to be systemically absorbed in recent randomised clinical trials (Matta *et al.,* 2020, 2021). The systemic exposure of homosalate in sunscreens (spray) exceeded 0.5 ng/mL on single application and repeated applications (in > 50% of participants up to 21 days). The continued presence of homosalate at skin up to 21 days and long terminal half-life (> 48 hours) suggest skin absorption of homosalate (Matta *et al.,* 2020). Intravenous studies would be required to determine elimination rate constants. Homosalate was also detected in human milk samples after topical application in human volunteers (Schlumpf *et al.* 2010). Given homosalate systemic exposure was noted in clinical trials, the clinical relevance of the presence of homosalate in human milk after topical application raises safety concerns around the use of products containing homosalate warranting further investigation.

In vitro, homosalate was hydrolysed into salicylic acid and 3,3,5-trimethylcyclohexanol associated with conjugation and hydroxylation of intact homosalate.

Based on publicly available safety information from animal studies, homosalate was found to be of low acute oral and dermal toxicity, not a skin or eye irritant (at 10%) and with no sensitising potential. Undiluted homosalate was also found to be a non-irritant in a human epidermis skin test with no sensitising potential at 15% in a human repeat patch test.

A general toxicity NOAEL of 300 mg/kg bw/day was established in a combined repeat dose and reproductive/developmental screening study in rats based on mortality in female rats at the highest

[15] A 5.3% dermal absorption value was used in the final SCCS opinion on homosalate (SCCS, 2021c)

dose. However, treatment-related effects were observed in kidneys, liver, thyroid and thymus in male rats at 60 mg/kg bw/day. Therefore, the SCCS concluded that this dose should be considered LOAEL. The SCCS also states that technical errors might have contributed to the effects observed, influencing the reliability of the study. A NOAEL of > 300 mg/kg bw/day in males and >1000 mg/kg bw/day in females was established in a two-week study in rats. Both these studies indicate that the treatment-related effects were more adverse in males. The human relevance of this species-specific effect is uncertain.

While two studies indicated that there was a genotoxic potential for homosalate, the studies were found inadequate due to methodological errors (Yazar *et al.* 2018; 2019). No carcinogenicity data were available. A combined repeated dose and reproductive/developmental screening study in rats by gavage up to 750 mg/kg bw/day has been reported (SCCS, 2021b; ECHA, 2018). The SCCS noted that the occurrence of constant lighting (illumination) during the conduct of the study significantly affected the reliability of this study, especially for developmental/reproductive effects. In addition, the low number of pregnancies per group questions the validity of the data on the development of offspring in this study.

Homosalate was found to adversely affect the survival, proliferation, and invasiveness of human trophoblast cells *in vitro* which are highly associated with the development of human placenta during early pregnancy (Yang *et al.* 2018). The relevance of these findings in this cell line to human pregnancies is also uncertain.

Therefore, further studies (e.g. a sub-chronic toxicity study, a prenatal developmental toxicity study, an extended one-generation reproductive toxicity study, and the identification of degradation products) would be required to fully allay concerns related to homosalate exposure and reproductive and developmental concerns.

The SED for homosalate when used as a UV filter in cosmetic products, was calculated using a dermal absorption value of 5.3% derived from an *in vitro* dermal penetration study using viable human skin and a standard sunscreen formulation containing 10% homosalate.

The SCCS (2021b) report noted the following when calculating the margin of safety:

> *"As point of departure for risk assessment, a LOAEL of 60 mg/kg bw/day was used, based on a combined repeated dose toxicity study with the Reproduction/Developmental Toxicity Screening Test (OECD Guideline 422) … Since the point of departure was based on a LOAEL, an additional uncertainty factor of 3 was added to account for LOAEL-NOAEL extrapolation. Furthermore, due to lack of information on oral bioavailability, 50% of the administered dose was used as the default oral absorption value, resulting in* ***an adjusted NOAEL of 10 mg/kg bw/day.****"*

The SCCS (2021b) also noted that:

> *"On the basis of safety assessment of homosalate, and considering the concerns related to potential endocrine disrupting properties, the SCCS has concluded that homosalate is not safe when used as a UV-filter in cosmetic products at concentrations of up to 10%."*
>
> *"In the SCCS's opinion, the use of homosalate as a UV filter in cosmetic products is safe for the consumer up to a maximum concentration of 0.5% homosalate in the final product."*
>
> *"It needs to be noted that the SCCS has regarded the currently available evidence for endocrine disrupting properties of homosalate as inconclusive, and at best equivocal. This applies to all of the available data derived from in silico modelling, in vitro tests and in vivo studies, when considered individually or taken together. The SCCS considers that, whilst there are indications from some studies to suggest that homosalate may have endocrine effects, the evidence is not conclusive enough at present to enable deriving a specific endocrine-related* toxicological point of departure for use in safety assessment."

The SCCS (2021c) report subsequently noted that:

> *"On the basis of safety assessment, and considering the concerns related to potential endocrine disrupting properties of Homosalate, the SCCS is of the opinion that Homosalate is safe as a UV-filter at concentrations up to 7.34% in face cream and pump spray."*

The SCCS (2021c) also noted that:

> *"The available data on Homosalate provide some indications for potential endocrine effects. However, the current level of evidence is not sufficient to regard it as an endocrine disrupting substance, or to derive a toxicological point of departure based on endocrine disrupting properties for use in human health risk assessment."*

Exposure estimate and Margin of Safety for Homosalate

Homosalate – standard parameters for the estimation of the systemic exposure dose

Parameter	Value
NOAEL (adjusted for LOAEL & bioavailability)	10 mg/kg bw/day
Dermal absorption (DAp)	5.3%
Highest concentration permitted to be used in Australian sunscreen products (C)	15%

Estimated homosalate SED and MoS using the Australian Sunscreen Exposure Model (ASEM)

ASEM method 1 (%) MoS calculation

$$SED = ASEM_{(\text{method 1})} \times DA_p \times C$$

$$= 673\ mg/kg\ bw/day\ \times 5.3\ \% \times 15\ \% = 5.35\ mg/kg\ bw/day$$

$$MoS = \frac{NOAEL\ (mg/kg\ bw/day)}{SED\ (mg/kg\ bw/day)} = \frac{10.0\ mg/kg\ bw/d}{5.35\ mg/kg\ bw/d} = \mathbf{1.9}$$

DA_p: Dermal Absorption, C: Concentration

See ASEM Method 1 for parameters.

Therefore, for a general sunscreen product, the acceptable concentration of Homosalate would be 0.28%, based on the MoS calculation below.

Homosalate concentration for an acceptable SED and MoS using the ASEM method 1 (%)

$$SED = ASEM_{(\text{method 1})} \times DA_p \times C$$

$$= 673\ mg/kg\ bw/day\ \times 5.3\ \% \times 0.28\ \% = 0.1\ mg/kg\ bw/day$$

$$MoS = \frac{NOAEL\ (mg/kg\ bw/day)}{SED\ (mg/kg\ bw/day)} = \frac{10.0\ mg/kg\ bw/d}{0.1\ mg/kg\ bw/d} = \mathbf{100}$$

DA_p: Dermal Absorption, C: Concentration

Further consideration for homosalate

If the use of a sunscreen product containing homosalate is applied to specific parts of the body e.g. face, the MoS may increase. However, as shown in the two tables below for application of a homosalate-containing sunscreen product, either by the whole family or adults only, twice a day for 240 days per year and 365 days per year, respectively, the various estimates are still less than satisfactory, i.e. a MoS less than 100.

The whole family calculation works with the assumption that if the specific application scenario is acceptable for toddlers (1-2 y.o), it is acceptable for the whole family.

Annual use considered for 240 days/years based upon Scenario 1 of the ASEM.

Scenario*	Skin Surface Area (cm^2)	Body weight (kg)	Reapplications (no. per day)	Annual use (days/year)	SED (mg/kg bw/d)	MoS
Face only (Toddlers)	500	13	2	240	0.8	12
Face + Hands (Toddlers)	900	13	2	240	1.45	7
Adult Face only	675	107	2	240	0.13	76
Adult Face + Hands	1875	107	2	240	0.37	27

*95th percentile for SSA body parts and total body weight (For Adult: average of male and female adult values combined).

Annual use considered for 365 days/years if sunscreen product containing homosalate is used every day.

Scenario*	Skin Surface Area (cm^2)	Body weight (kg)	Reapplications (no. per day)	Annual use (days/year)	SED (mg/kg bw/d)	MoS
Face only (Toddlers)	500	13	2	365	1.22	8
Face + Hands (Toddlers)	900	13	2	365	2.2	5
Adult Face only	675	107	2	365	0.2	50
Adult Face + Hands	1875	107	2	365	0.56	18

*95th percentile for SSA body parts and total body weight (For Adult: average of male and female adult values combined).

For these homosalate-containing sunscreen products to reach a satisfactory MoS (≥100) based on specific part of the body and for use by whole family vs adult only, the concentration of homosalate would need to be reduced as shown in the table below for different periods of use (240 & 365 days/year).

The concentration of homosalate that is low-risk in sunscreen products, if applied to specific areas of the body.

Scenario*	Concentration (%) 240 d/yr	Concentration (%) 365 d/yr
Toddler Face only	1.87	1.23
Toddler Face + Hands	1.04	0.68
Adult Face only	11.4	7.5
Adult Face + Hands	4.1	2.7

*95th percentile for SSA body parts and total body weight (For Adult: average of male and female adult values combined).

Recommendation

A MoS less than 100 was calculated using the ASEM. As a result, homosalate is not deemed to present a low risk to human health and safety when used at the highest maximum permitted concentration of 15% in therapeutic sunscreens.

To mitigate the risk from chronic exposure to homosalate in therapeutic sunscreens, it is recommended that homosalate is listed in the Poisons Standard. To manage the potential risks associated with homosalate it is recommended that the entry restrict the use of homosalate in therapeutic sunscreens, giving consideration to the following:

OPTION 1

- Homosalate can be deemed low-risk and appropriate for use in general therapeutic sunscreens for daily use at a concentration up to 0.28%.

OPTION 2

- Specific use sunscreens are likely to be used differently by consumers, such as daily application year-round, compared with the use pattern for general sunscreens which are applied to larger parts of the body. Calculations for 240 days/year (based on ASEM scenario 1 for indoor workers) and 365 days/year exposure assumptions have been provided above.

- Homosalate can be deemed low-risk and appropriate for use in specific therapeutic sunscreens for daily use when:

– Used by adults only;

– Limited to face-only or face and hand application, not to the whole body; and

– At a reduced maximum concentration (between 2.7% and 11.4% of the product), depending on the types of products that are currently marketed and their directions for use.

OR

- Homosalate can be deemed low-risk and appropriate for use in general therapeutic sunscreens for daily use by the whole family when:

– Limited to face-only or face and hand application, not to the whole body; and

– At a reduced maximum concentration (between 0.68% and 1.87% of the product), depending on the types of products that are currently marketed and their directions for use.

Homosalate can be a common ingredient in other products such as cosmetic sunscreens. Consideration should be given to potential exposure of homosalate from other sources. Use of specific warning statements or directions for use, and/or product packaging limitations to ensure appropriate use.

It is important to note that therapeutic sunscreens listed on the ARTG contain different concentrations of homosalate, ranging from as low as 3% with claimed SPF rating of 50+.

Octocrylene safety assessment

This assessment is based on the safety data on octocrylene from the ECHA website (ECHA, 2020), as well as those reported in the SCCS opinions (SCCS, 2021a) and scientific articles from peer-reviewed journals. In a recently published SCCS opinion on the safety of octocrylene (SCCS, 2021a), the SCCS considered that octocrylene was safe at concentrations of up to 10% when used individually or together as a UV-filter in cosmetic products, i.e. in sunscreen cream/lotion, sunscreen pump spray, face cream, hand cream and lipstick (SCCS, 2021a). However, a lower concentration of octocrylene (9%) was considered safe in sunscreen propellant spray when the sunscreen propellent spray is used along with face cream, hand cream, and lipstick (containing 10% octocrylene).

Extensive studies were available investigating octocrylene pharmacokinetics, and these have been summarised in the preceding section.

Octocrylene is a lipophilic substance, and it is reported to be metabolised to a variety of metabolites where CDAA is the main metabolite. Information was lacking on whether the most significant toxic agent was octocrylene or its metabolites. Considering the relatively long half-life of both octocrylene and CDAA in plasma and the low elimination rate of CDAA in urine, an accumulation of octocrylene and CDAA in the human body following repeated dermal applications would be expected.

The higher maximum observed concentration of CDAA (1351.7 ng/mL) *vs* octocrylene (25.0 ng/mL) also suggested that measuring only unmetabolized octocrylene might underestimate total systemic absorption and thereby influencing the safety assessment of octocrylene. In addition, it was noted that higher absolute concentrations of octocrylene were observed from exposure to “real-life” conditions compared to “indoor maximal use conditions”, indicating peak plasma concentrations may be even higher in real-world usage conditions.

Systemic absorption of octocrylene was demonstrated in recent randomised clinical trials following dermal application. The plasma concentration of octocrylene from sunscreens exceeded 0.5 ng/mL on single application (until 23 hours after application) whereas the systemic exposure to octocrylene remained above the threshold of 0.5 ng/mL in plasma in more than 50% of participants for up to 10 days. The continued presence of octocrylene in skin at days 10 and its long terminal half-life suggested absorption through skin was the rate-limiting step. Intravenous studies with octocrylene would be required to determine elimination rate constants to the parent.

The SCCS determined that the SEDs for dermal exposures to octocrylene from sunscreen cream/lotion were 0.566 mg/kg bw/day (SCCS, 2021d). SEDs for inhalation exposures to sunscreen sprays were 0.176 and 0.002 mg/kg bw/day for propellant and pump spray, respectively (SCCS, 2021d).

As tabulated in the preceding section, octocrylene was found to be of low acute toxicity. Octocrylene was not an eye or skin irritant based on available data. It was found to not sensitising in a Guinea Pig Maximization Test (GPMT). Octocrylene was found to be a moderate skin sensitiser and a skin photosensitiser [local lymph nose assay (LLNA) with 1- 30% octocrylene, EC3: 7.7% and human patch studies with 10% octocrylene]. However, the LLNA study was not considered properly conducted. None the less, octocrylene was considered a skin sensitiser at 10%. The occurrence of photoallergy to octocrylene was suspected to be related to a previous photoallergy to topical ketoprofen. Photoallergic contact dermatitis to octocrylene has been found to be much more frequent in adults than in children whereas contact allergy cases to octocrylene have been reported more in children compared to adults. This is likely due to the immaturity of the skin epidermal barrier and the

prevalence of atopic dermatitis in young children as the study authors suggested (Gilaberte & Carrascosa, 2014).

No systemic effects were reported in rabbits after dermal exposure to octocrylene at 534 mg/kg bw/day. After oral exposure, effects on liver and thyroid were reported in a study in rats (males) at 340 and 1085 mg/ kg bw/day. These effects on liver and thyroid were investigated in an additional mechanistic study which showed that effects on thyroid were indirect and probably due to hepatic enzyme induction potential of octocrylene. Recently reported repeat dose toxicity studies with octocrylene (SCCS, 2021a; ECHA, 2020) do not alter the previously established NOAEL of 175 mg/kg bw/day, noted in a previous SCCS report for octocrylene.

Octocrylene is not expected to be genotoxic based on available genotoxicity data. No carcinogenicity data were available.

Benzophenone, an important impurity and degradant of octocrylene, is considered to be genotoxic, carcinogenic and shown to disrupt endocrine signalling. It has been found to accumulate in 16 commercially available products containing octocrylene subjected to 6 week accelerated stability aging protocol (Downs *et al*. 2022). The mean content of benzophenone increased from baseline by 14.5% to 199.4% and ranged from 5.0 to 461.4 ppm. Benzophenone is both a manufacturing impurity and a degradant of octocrylene.

Based on the effects on rat parental and pup body weights, a lower number of implantation sites and lower number of pups in the extended one generation reproductive toxicity study (EOGRTS), a NOAEL was established at 153/163 mg/kg/day for males and females, respectively, for parental systemic toxicity, fertility/reproduction performance, and general and sexual development. No neuro-developmental effects were observed at the highest dose level tested (534/550 mg/kg/day, male/female).

A monitoring study revealed that during the periods of pregnancy and lactation, > 78% of the women used some cosmetic product containing UV filters and UV filters were detected in 82.5% of human milk samples (Schlumpf *et al.* 2010, 2008). Octocrylene (OC) was one of the most frequently used UV filters and most frequently detected in milk samples (i.e. 30.18 ± 22.15 ng/g of lipids) (Schlumpf *et al.* 2010, 2008). Use of UV filters and concentration in human milk were significantly correlated. The results indicate transdermal passage of UV filters and potential placental transfer of octocrylene.

Public exposure to octocrylene would be expected to be widespread and frequent through a daily use of sunscreen products containing ingredient typically at concentrations up to 10 %**.**

Given that the dermal absorption value of 0.97 µg/cm^2 was available from experimental data for octocrylene, option 2 was used for systemic exposure dose (SED) calculation to estimate the MoS by the SCCS. The SED was determined to be 0.339 mg/kg bw/day for octocrylene in sunscreen (for a 60 kg bw person) in the SCCS opinion (SCCS 2021a) (**dermal absorption value of 0.97 µg/cm^2** from Fabian & Landsiedel, 2020; octocrylene concentration of 10%). The NOAEL of 153 mg/kg bw/day based on the EOGRTS is used for the calculation of MoS. Based on an oral bioavailability of 50% (Bury *et al.*, 2019), **an adjusted NOAEL of 76.5 mg/kg bw/day** was determined.

Exposure estimate and Margin of Safety for Octocrylene

Octocrylene – standard parameters for the estimation of the systemic exposure dose

Parameter	Value
NOAEL (adjusted for oral bioavailability)	76.5 mg/kg bw/day
Dermal absorption (DAp)	0.97 µg/cm^2
Highest concentration permitted to be used in Australian sunscreen products (C)	10 %

Estimated octocrylene SED and MoS using the Australian Sunscreen Exposure Model (ASEM)

ASEM method 2 (µg/cm²) MoS calculation

$$SED = ASEM_{(\text{method 2})} \times DA_a$$

$$= 336\ cm^2/kg\ bw/day \times 0.97\ \mu g/cm^2$$

$$= 326\ \mu g/kg\ bw/day = 0.326\ mg/kg\ bw/day$$

$$MoS = \frac{NOAEL\ (mg/kg\ bw/day)}{SED\ (mg/kg\ bw/day)} = \frac{76.5\ mg/kg\ bw/d}{0.326\ mg/kg\ bw/d} = \mathbf{235}$$

DA_a: Dermal Absorption

Recommendation

A MoS greater than 100 was calculated using the ASEM. As a result, octocrylene is deemed to present a low risk to human health and safety when used at the highest maximum permitted concentration of 10% in therapeutic sunscreens. No changes are recommended to the current permitted use.

Octyl methoxycinnamate (Octinoxate) safety assessment

This assessment was based on the safety data from the ECHA website, the SCCS opinion (SCC, 2000), NICNAS Human Health Tier II Assessment Report, and scientific articles from peer-reviewed journals (NICNAS 2017, currently known as AICIS; ECHA 2021e).

Available *in vitro* and *in vivo* studies indicate octyl methoxycinnamate can poorly penetrate the skin. Systemic absorption of octyl methoxycinnamate was also demonstrated in recent randomised clinical trials (Matta *et al.,* 2020). However, elimination rate constant was not determined due to the absence of intravenous studies.

Octyl methoxycinnamate was found to be of low and moderate acute oral toxicity in mice and rats, respectively. Based on the limited data available, the chemical is not considered to be a skin irritant or an eye irritant. The chemical is not considered to be a skin sensitiser in humans. There is potential for photosensitivity following UV exposure, but the results are inconclusive.

No systemic effects were reported in a 13-week dermal repeat dose study in rats administered up to 534 mg/kg/day. The NOAEL was determined 450 mg/kg/day in a 13-week oral repeat dose study. Based on the available studies, the chemical was not considered to cause serious damage to health from repeated dermal exposure.

Octyl methoxycinnamate is not expected to have genotoxic potential, however, the lack of studies with isomers *cis* and *trans* was noted.

No carcinogenicity study was conducted as per ICH guidelines. The chemical has not been shown to be a tumour initiator in photocarcinogenesis studies in mice. No genotoxic potential was observed. Quantitative Structure-Activity Relationship (QSAR) modelling gave an alert for potential non-genotoxic carcinogenicity, but no details are available (OECD QSAR Toolbox ver.3.2).

The SCC and NICNAS report stated that *"based on the available data, the chemical is not considered to be reproductively or developmentally toxic at doses relevant to human exposure".* **A NOAEL of 450 mg/kg bw/day** was established for fertility and reproduction parameters, and for systemic parental and developmental toxicity (Schneider *et al.* 2005).

A study (Axelstad *et al.* 2011) to investigate the effect of octyl methoxycinnamate treatment (500-1000 mg/kg/day, oral) on the endocrinological and neurological development of rat offspring indicated decreased motor activity in female offspring and increased spatial learning in male offspring (transient effects on thyroid axis, and in oestrogen level were also observed). The effects were observed at a much higher doses compared to clinical doses (Axelstad *et al.* 2011).

The value of 1.77 µg/cm^2 following 6-h pig-ear skin exposure + 18-h free permeation after an application of oil-in-water emulsion sunscreen dose (0.5 mg/cm^2) containing 10% octyl methoxycinnamate was used in the SED calculation using as per the SCCS opinion (Klimova *et al.* 2015).

Exposure estimate and Margin of Safety for octyl methoxycinnamate

Octyl methoxycinnamate – standard parameters for the estimation of the systemic exposure dose

Parameter	Value
NOAEL	450 mg/kg bw/day
Dermal absorption (DAp)	1.77 µg/cm^2
Highest concentration permitted to be used in Australian sunscreen products (C)	10 %

Estimated octyl methoxycinnamate SED and MoS using the Australian Sunscreen Exposure Model (ASEM)

ASEM method 2 (µg/cm²) MoS calculation

$$SED = ASEM_{(\text{method 2})} \times DA_a$$

$$= 336\ cm^2/kg\ bw/day \times 1.77\ \mu g/cm^2$$

$$= 595\ \mu g/kg\ bw/day = 0.595\ mg/kg\ bw/day$$

$$MoS = \frac{NOAEL\ (mg/kg\ bw/day)}{SED\ (mg/kg\ bw/day)} = \frac{450\ mg/kg\ bw/d}{0.595\ mg/kg\ bw/d} = \mathbf{756}$$

DA_a: Dermal Absorption

Recommendation

A MoS greater than 100 was calculated using the ASEM. As a result, octyl methoxycinnamate is deemed to present a low risk to human health and safety when used at the highest maximum permitted concentration of 10% in therapeutic sunscreens. No changes are recommended to the current permitted use.

Oxybenzone safety assessment

This assessment was based on peer-reviewed publications and the SCCS opinion on benzophenone-3 (2021c; SCCP, 2006a; SCCP, 2008).

Oxybenzone was shown to be rapidly absorbed after oral, intravenous, or topical skin administration and widely distributed in animals, 2,4-diOH BP (BP-1) was the major metabolite of oxybenzone in rats and humans. Oxybenzone was primarily excreted though urine.

A number of *in vitro* and *in vivo* dermal absorption studies have been evaluated by the SCCS. A dermal absorption value of 9.9% was used to calculate the MoS for oxybenzone. This value was calculated from a dermal absorption value of 3.1% obtained following application of a 6% formulation of oxybenzone to pig ear skin in *vitro* and applying a safety factor of 2 standard deviations to account for limitations in the data set (3.1% + 2 SD [2 x 3.4%] = 9.9%) (SCCS 2021c).

Clinical trials indicated that oxybenzone could be systemically absorbed. The plasma concentration of oxybenzone in sunscreens (spray) exceeded 0.5 ng/mL on single application and remained above this threshold until 23 hours after application. The systemic exposure of oxybenzone remained above 0.5 ng/mL in more than 50% of participants for up to 21 days. The authors concluded that the continued presence of sunscreen active ingredients in skin at days 21 and the long terminal half-life (> 48 hours) suggest absorption through skin is the rate-limiting step; hence, intravenous studies are required to determine their elimination rate constants.

Oxybenzone was found to be of low acute oral and dermal toxicity and did not cause skin or eye irritation (rabbits) or skin sensitisation (guinea pigs and mice). However, oxybenzone was shown to cause photoallergenic reactions - being the second most frequent photo contact allergen among the UV filters (European photo patch test task force) (Subiabre-Ferrer *et al.* 2019).

Repeat-dose studies with oxybenzone were conducted in mice and rats following oral and dermal administration. After repeated oral administration of oxybenzone in rats and mice, decreased bodyweight gain and reduced food consumption were observed. Effects on the kidney (decreased weight and renal tubule histopathology) and the liver (increased weight and adaptive changes in histopathology) with associated changes in clinical chemistry parameters were also observed. There were no treatment-related findings following dermal administration except for increases in liver weight with no associated histopathology or clinical pathology. The NOAEL (oral) was established at 6250 ppm (429/393 mg/kg bw/day in males/females) in rats and 6250 ppm (1068/1425 mg/kg bw/day in males/females) in mice. The NOAEL for repeat-dose dermal toxicity was established at 200 mg/kg bw/day in rats and 364 mg/kg bw/day in mice.

In reproductive and developmental toxicity studies in rats, decreased normalised anogenital distance was observed in male pups of treated dams, at PND 23. Impairment of spermatocyte development in testes of male offspring and delayed follicular development in females was also observed indicating a potential endocrine disrupting effect. A **NOAEL for these effects was established at 67.9 mg/kg bw/day** (Nakamura *et al.,* 2015).

The findings from the genotoxicity studies with oxybenzone were found to be equivocal. Two-year carcinogenicity studies with oxybenzone were performed in mice and rats. An increased incidence of brain and spinal cord malignant meningiomas in males and thyroid C-cell adenomas and uterine stromal polyps in females were observed in rats, with no dose-response relationship. These findings in rats were also considered to be equivocal evidence of carcinogenicity. There was no direct evidence of carcinogenic activity in male or female mice other than lesions in bone marrow, spleen, kidney and liver.

The SCCS (2021c) determined a **dermal absorption of 9.9%** [mean (3.1%) + 2 SD (2*3.4%)] for the use of oxybenzone as a UV filter, at an oxybenzone concentration 6% for the calculation of SED and the MoS for sunscreen products.

Exposure estimate and Margin of Safety for Oxybenzone

Oxybenzone – standard parameters for the estimation of the systemic exposure dose

Parameter	Value
NOAEL	67.9 mg/kg bw/day
Dermal absorption (DAp)	9.9 %
Highest concentration permitted to be used in Australian sunscreen products (C)	10 %

Estimated oxybenzone SED and MoS using the Australian Sunscreen Exposure Model (ASEM)

ASEM method 1 (%) MoS calculation

$$SED = ASEM_{(\text{method 1})} \times DA_p \times C$$

$$= 673\ mg/kg\ bw/day\ \times 9.9\ \% \times 10\ \% = 6.66\ mg/kg\ bw/day$$

$$MoS = \frac{NOAEL\ (mg/kg\ bw/day)}{SED\ (mg/kg\ bw/day)} = \frac{67.9\ mg/kg\ bw/d}{6.66\ mg/kg\ bw/d} = \mathbf{10}$$

DA_p: Dermal Absorption, C: Concentration

Therefore, for a general sunscreen product, the acceptable concentration of Oxybenzone would be 1%, based on the MoS calculation below.

Oxybenzone concentration for an acceptable SED and MoS using the ASEM method 1 (%)

$$SED = ASEM_{(\text{method 1})} \times DA_p \times C$$

$$= 673\ mg/kg\ bw/day\ \times 9.9\ \% \times 1\ \% = 0.666\ mg/kg\ bw/day$$

$$MoS = \frac{NOAEL\ (mg/kg\ bw/day)}{SED\ (mg/kg\ bw/day)} = \frac{67.9\ mg/kg\ bw/d}{0.666\ mg/kg\ bw/d} = \mathbf{100}$$

DA_p: Dermal Absorption, C: Concentration

Further consideration for Oxybenzone

If the use of a sunscreen product containing oxybenzone is applied to specific parts of the body e.g. face, the MoS may increase. As shown in the two tables below for application of an oxybenzone-containing sunscreen product twice a day for 240 days per year and 365 days per year, respectively, the various estimates are satisfactory for adults, i.e. a MoS is greater than 100, except for twice daily application for 365 days a year to adult head and hands (MoS of 72), and adult face and hands (MoS of 98). While the same scenarios for use by the whole family is not satisfactory, i.e. MoS less than 100.

The whole family calculation works with the assumption that if the specific application scenario is acceptable for toddlers (1-2 y.o), it is acceptable for the whole family.

Annual use considered for 240 days/years based upon Scenario 1 of the ASEM.

Scenario*	Skin Surface Area (cm^2)	Body weight (kg)	Reapplications (no. per day)	Annual use (days/year)	SED (mg/kg bw/d)	MoS
Face only (Toddlers)	500	13	2	240	0.99	68
Face + Hands (Toddlers)	900	13	2	240	1.78	38

Scenario*	Skin Surface Area (cm^2)	Body weight (kg)	Reapplications (no. per day)	Annual use (days/year)	SED (mg/kg bw/d)	MoS
Adult Face only	675	107	2	240	0.16	413
Adult Face + Hands	1875	107	2	240	0.45	149

*95th percentile for SSA body parts and total body weight (For Adult: average of male and female adult values combined)

Annual use considered for 365 days/years if sunscreen product containing oxybenzone is used every day.

Scenario*	Skin Surface Area (cm^2)	Body weight (kg)	Reapplications (no. per day)	Annual use (days/year)	SED (mg/kg bw/d)	MoS
Face only (Toddlers)	500	13	2	365	1.51	45
Face + Hands (Toddlers)	900	13	2	365	2.72	25
Adult Face only	675	107	2	365	0.25	272
Adult Face + Hands	1875	107	2	365	0.69	98

*95th percentile for SSA body parts and total body weight (For Adult: average of male and female adult values combined)

For these oxybenzone-containing sunscreen products to reach a satisfactory MoS (≥100) based on specific part of the body and for use by whole family vs adult only, the concentration of oxybenzone would need to be reduced as shown in the table below for different periods of use (240 & 365 days/year).

The concentration of oxybenzone that is low-risk in sunscreen products if applied to specific areas of the body every day.

Scenario*	Concentration (%) 240 d/yr	Concentration (%) 365 d/yr
Toddler Face only	6.8	4.4
Toddler Face + Hands	3.7	2.5
Adult Face only	>10	>10
Adult Face + Hands	>10	9.8

*95th percentile for SSA body parts and total body weight (For Adult: average of male and female adult values combined).

Recommendation

A MoS less than 100 was calculated using the ASEM. As a result, oxybenzone is not deemed to present a low risk to human health and safety when used at the highest maximum permitted concentration of 10% in therapeutic sunscreens.

To mitigate the risk from chronic exposure to oxybenzone in therapeutic sunscreens, it is recommended that oxybenzone is listed in the Poisons Standard. To manage the potential risks associated with oxybenzone it is recommended that that the entry restrict the use of oxybenzone in therapeutic sunscreens, giving consideration to the following:

OPTION 1

- Oxybenzone can be deemed low-risk and appropriate for use in general therapeutic sunscreens for daily use at a concentration up to 1%.

OPTION 2

- Specific use sunscreens are likely to be used differently by consumers, such as daily application year-round, compared with the use pattern for general sunscreens which are applied to larger parts of the body. Calculations for 240 days/year (based on ASEM scenario 1 for indoor workers) and 365 days/year exposure assumptions have been provided above.

- Oxybenzone can be deemed low-risk and appropriate for use in specific therapeutic sunscreens for daily use when:
  - Used by adults only;
  - Limited to face-only or face and hand application, not to the whole body; and
  - At a maximum concentration (9.8% to 10% of the product) depending on the types of products that are currently marketed and their directions for use.

OR

Oxybenzone can be deemed low-risk and appropriate for use in general therapeutic sunscreens for daily use by the whole family when:

- Limited to face-only or face and hand application, not to the whole body; and
- At a reduced maximum concentration (between 2.5% and 6.8% of the product), depending on the types of products that are currently marketed and their directions for use

Potential exposure of oxybenzone from other sources e.g. in cosmetics and cosmetic sunscreens should also be considered as well as use of specific warning statements or directions for use, and/or product packaging limitations to ensure appropriate use.

Phenylbenzimidazole sulfonic acid safety assessment

The safety of phenylbenzimidazole sulfonic acid was assessed based on the publicly available safety data from scientific literature, and the SCCP opinion (SCCP, 2006b).

Phenylbenzimidazole sulfonic acid was rapidly absorbed following oral administration in pregnant rats. The amount of absorption from the gastrointestinal tract was estimated to be 3 - 4%. There was no indication of accumulation in any of the organs investigated and phenylbenzimidazole sulfonic acid did not cross the blood/brain barrier. Phenylbenzimidazole sulfonic acid was mainly excreted though

urine and faeces in male rats and via the faeces in pregnant female rats following oral administration. No data were available on the metabolism of phenylbenzimidazole sulfonic acid.

Phenylbenzimidazole sulfonic acid was found to be of low acute toxicity in rats and mice (IP LD_{50} 1000 – 1500 mg/kg/day and the dermal LD_{50} is >3000 mg/kg bw in rats whereas oral LD_{50} in mice is >5000 mg/kg bw). There was no information available for acute inhalational toxicity. Phenylbenzimidazole sulfonic acid was not a skin or eye irritant in rabbits and did not cause skin sensitisation in guinea pigs. The NOAEL in a 13-week oral study in rats was established at 1000 mg/kg/day, the highest dose tested.

Phenylbenzimidazole sulfonic acid was not found to be genotoxic *in vitro* (Ames test and chromosome aberration test in human peripheral blood lymphocytes). No information was available for mutagenicity/genotoxicity *in vivo*. No carcinogenicity data on phenylbenzimidazole sulfonic acid were available.

No treatment-related findings were noted in a pre-natal developmental toxicity study in rats treated with phenylbenzimidazole sulfonic acid from gestation day 6 to 15 at doses up to 1000 mg/kg/day. The NOAEL for maternal and fetal toxicity was 1000 mg/kg/day. Phenylbenzimidazole sulfonic acid did not cross the blood brain barrier or the placenta following oral administration in rats.

An adjusted NOAEL of 40 mg/kg bw/day was calculated using the two report NOAELs (1000 mg/kg bw/day) to account for the low (4%) oral absorption as per SCCS calculations (SCCP, 2006b).

Exposure estimate and Margin of Safety for phenylbenzimidazole sulfonic acid

Phenylbenzimidazole sulfonic acid – standard parameters for the estimation of the systemic exposure dose

Parameter	Value
NOAEL (adjusted for low oral absorption)	40 mg/kg bw/day
Dermal absorption (DAp)	0.416 µg/cm^2
Highest concentration permitted to be used in Australian sunscreen products (C)	4 %

Estimated phenylbenzimidazole sulfonic acid SED and MoS using the Australian Sunscreen Exposure Model (ASEM)

ASEM method 2 (µg/cm²) MoS calculation

$$SED = ASEM_{(\text{method 2})} \times DA_a$$

$$= 336\ cm^2/kg\ bw/day \times 0.416\ \mu g/cm^2$$

$$= 140\ \mu g/kg\ bw/day = 0.140\ mg/kg\ bw/day$$

$$MoS = \frac{NOAEL\ (mg/kg\ bw/day)}{SED\ (mg/kg\ bw/day)} = \frac{40\ mg/kg\ bw/d}{0.140\ mg/kg\ bw/d} = \mathbf{286}$$

DA_a: Dermal Absorption

Recommendation

A MoS greater than 100 was calculated using the ASEM. As a result, phenylbenzimidazole sulfonic acid is deemed to present a low risk to human health and safety when used at the highest maximum permitted concentration of 4% in therapeutic sunscreens. No changes are recommended to the current permitted use.

Conclusion

Skin cancer is a major health issue in Australia. The Australasian College of Dermatologists recommends that daily sun protection should be used in Australia, particularly during the spring and summer months, where the UV index is often 3 or higher for nearly the entire day. In addition, the Cancer Council recommends Australians use SPF50 or SPF50+, broad-spectrum, water-resistant sunscreen. Given the widely recognised public health importance of sunscreens, Australians should continue to use sunscreens along with other sun protective behaviours when the UV index is 3 or more. The 5 SunSmart S's - slip, slop, slap, seek, slide are protective measures include seeking shade, wearing a hat, wearing protective clothing and eyewear and using sunscreen. This approach clearly supports the benefits of optimal sunscreen use, benefits which are substantial, and balanced against any theoretical risks.

Attachments

Attachment 1: Literature review search strategy

Search criteria (word input)

Keywords included either the chemical name, AAN or the INCI names, and “sunscreen” were used as the search items. Publications in last 15 years were searched (2008-2023). The following toxicological endpoints were included.

Nonclinical (toxicology) data:

- Dermal carcinogenicity
- Systemic carcinogenicity
- Developmental and reproductive toxicity (DART)
- Toxicokinetics
- Additional testing when data suggest a concern about other long-term effects, such as endocrine effects

Clinical data:

- Dermal irritation and sensitisation
- Phototoxicity and photoallergenicity testing
- Human maximal use bioavailability studies

Websites searched for the sunscreen active ingredients:

WHO:

- WHO: https://www.who.int/

USA:

- PubChem https://pubchem.ncbi.nlm.nih.gov
- GOLD FFX database / ChemWatch (TGA subscribed)
- FDA
- US EPA (www.epa.gov).
- NIOSH CDC https://www.cdc.gov/niosh/index.htm
- National Center for Toxicological Research (NCTR) https://ntp.niehs.nih.gov/nctr/
- National Toxicology program (NTP), U.S. Department of Health and Human Services https://ntp.niehs.nih.gov/publications/index.html.
- BUND (Federal Mnistry for the Environment, Nature Conservation, Building and Nuclear Safety)
- Comparative Toxicogenomics Database http://ctdbase.org/
- Consumer Product Information Database (cpid) https://www.whatsinproducts.com/. similar to and linked to PubChem.
- US EPA (United States Environmental Protection Agency) IRIS Assessments https://cfpub.epa.gov/ncea/iris_drafts/atoz.cfm
- Integrated Risk Information System (IRIS) https://www.epa.gov/iris
- ChemView https://chemview.epa.gov/chemview/
- Science Inventory https://cfpub.epa.gov/si/

UK:

- Cancer Research UK https://www.cancerresearchuk.org/

EU:

- Registered substances - Chemical property data search / European Chemicals Agency (ECHA)
- Scientific Committee on Consumer Safety (SCCS), European Commission https://op.europa.eu/en/
- SafetyNL; National Institute for Public Health and the Environment (RIVM), The Netherlands www.rivm.nl
- Coslng Database https://cosmeticseurope.eu/library/
- European Medicines Agency (EMA)
- OECD OECD Existing Chemicals Database https://hpvchemicals.oecd.org
- Environmental Protection Agency in Denmark www.mst.dk
- Nature Agency in Denmark www.nst.dk
- Swedish Chemicals Agency (KEMI) in Sweden www.kemi.se
- Environment Agency in Norway www.miljodirektoratet.no
- ANSES in France www.anses.fr
- The Environment Agency in the UK www.environment-agency.gov.uk
- ChemSec - International Chemical Secretariat www.chemsec.org
- Information Centre for Environment and Health www.forbrugerkemi.dk
- National Institute for Public Health and the Environment https://www.rivm.nl/en

Australia:

- AICIS
- Safe Work Australia - Hazardous Chemical Information System (HCIS) http://hcis.safeworkaustralia.gov.au/
- FSANZ

Canada:

- DRUGBANK / University of Alberta et al., Canada
- Health Canada

Non-Government:

- Environmental Working Group https://www.ewg.org/ (non-profit)
- Food Packaging Forum https://www.foodpackagingforum.org/
- International Toxicity Estimates for Risk (ITER) http://www.iter.tera.org/. similar to PubChem.
- Cosmetic Ingredient Review (CIR) https://www.cir-safety.org/

Attachment 2: List of endocrine activity modulation effects of commonly used UV filters

UV Filters	Endocrine disrupting effects	
Benzophenones	Estrogenic disrupting effects	Activation of ERα, ERβ; Inhibition of the activity of 17β-Estradiol; Induction of proliferation of MCF-7 cell; Induction of VTG in fathead minnow; Reduction of the uterine weight in immature Long-Evans rats.
	Androgenic disrupting effects	Antagonists of human AR transactivation; Repression of 4.5dihydrotestosterone-induced transactivational activity; Inhibition of testosterone formation in mice and rats.
	Disrupting effects toward other nuclear receptors	Inhibition of human recombinant TPO; Interference with THR; Inhibition of TPO activity in rats; Antagonists of PR
Camphor derivatives	Disrupting effects toward estrogen receptor	Activation of ERα, ERβ; Inhibition of the activity of 17β-Estradiol; Inhibition of testosterone formation in HEK-293 cells; Antagonist of Human AR.
	Disrupting effects toward androgen receptor	Repression of 4,5-dihydrotestosterone-induced transactivational activity; Inhibition of testosterone formation in HEK-293 cells; Antagonists of Human AR.
	Disrupting effects toward estrogen receptor	Antagonists of PR; Increase of PR mRNA levels in rats; Inhibition of the expression of PR protein in rats; Disturbance of the expression of membrane-associate PR in insects.
Cinnamate derivatives	Disrupting effects toward estrogen receptor	Activation of ERα; Inhibition of the activity of 17β-Estradiol; Induction of proliferation of MCF-7 cell; Reduction of uterine weight in rats; Induction of VTG in fish.
	Disrupting effects toward thyroid hormone receptor	Decrease of T4 levels; Inhibition of the conversion of T4 to triiodothyronine in rats.
	Disrupting effects toward other nuclear receptors	Antagonists of PR and AR; Inhibition of 4,5-dihydrotestosterone activity; Reduction of prostate and testicular weight in rats.

AR: androgen receptor; ER: estrogen receptor alpha; PR: progesterone receptor; T4: thyroxine; THR: thyroid hormone receptor; TPO: thyroid peroxidase; VTG: vitellogenin.
Source: Wang *et al.,* 2016

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Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	TGA	May 2025

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
Web: tga.gov.au

Reference/Publication D25-2148966

From: s22
To: s22
Cc: s22
Subject: RE: Updated sunscreens safety review for clearance [SEC=OFFICIAL]
Date: Thursday, 29 May 2025 5:19:05 PM
Attachments: image002.png
image003.png
image004.png
image005.gif
image006.png
image007.png

Thanks s22

TRIM workflow approved.

Kind regards,
s22

s22
Assistant Secretary (A/g)
Scientific Evaluation Branch
Medicines Regulation Division | Health Products Regulation Group
Australian Government, Department of Health, Disability and Ageing
T: s22 | E: s22 @health.gov.au

This email comes to you from Ngunnawal Country
Location: Fairbairn, ACT 2609
PO Box 100, Woden ACT 2606, Australia

The Department of Health, Disability and Ageing acknowledges First Nations peoples as the Traditional Owners of Country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

From: s22 @health.gov.au>
Sent: Wednesday, 28 May 2025 12:45 PM
To: s22 @health.gov.au>
Cc: s22 @health.gov.au>; s22
s22 @health.gov.au>
Subject: FW: Updated sunscreens safety review for clearance [SEC=OFFICIAL]

Hi s22

s22 has asked that I forward the updated Safety Review of the Seven Active Sunscreen Ingredients to you for clearance (D25-2148966).

As noted in the email below, the Safety Review of the Seven Active Sunscreen Ingredients (previously cleared by George) has been updated following discussions with the executive, CMES and the scheduling secretariate in early May. At this meeting it was concluded that the options included for scheduling consideration

should cover the whole population (children and adults) rather than just for adults as originally presented.

The updates to the document were to include additional exposure calculations and options to be considered for scheduling for the sunscreen ingredients homosalate and oxybenzone. I have attached a track changes version of the document showing the updates made.

Could you please approve the Trim workflow for this document? I will then forward it to s22 to progress with the scheduling process.

Please let me know if you need any further information.

Kind regards
s22

s22
Scientific Evaluation Branch
Medicines Regulation Division | Health Products Regulation Group
Australian Government, Department of Health, Disability and Ageing
T: s22 | E: s22 @health.gov.au

This email comes to you from Ngunnawal Country
Location: Fairbairn ACT
PO Box 100, Canberra ACT 2601, Australia

The Department of Health, Disability and Ageing acknowledges First Nations peoples as the Traditional Owners of Country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

From: s22 @health.gov.au>
Sent: Wednesday, 28 May 2025 12:14 PM
To: s22 @health.gov.au>
Cc: s22 @health.gov.au>
Subject: RE: Updated sunscreens safety review for clearance [SEC=OFFICIAL]

Hi s22

Crazy busy today and still have 4 policy papers to clear. As s22 A/g from tomorrow are you able to re-assign this to him. Better let him know...

Appreciated.

s22

s22
Scientific Evaluation Branch
TGA Chief Regulatory Scientist

Medicines Regulation Division | Therapeutic Goods Administration
Australian Government, Department of Health, Disability and Ageing
T: s22 | E s22 @health.gov.au
Location: Level 1, 27 Scherger Drive Fairbairn, ACT 2609
PO Box 100, Woden ACT 2606, Australia
The Department of Health and Aged Care acknowledges First Nations peoples as the Traditional Owners of Country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

From: s22 @health.gov.au>
Sent: Wednesday, 28 May 2025 11:59 AM
To: s22 @health.gov.au>
Cc: s22 @health.gov.au>
Subject: Updated sunscreens safety review for clearance [SEC=OFFICIAL]

Hi s22

The Safety Review of the Seven Active Sunscreen Ingredients document has been updated based on the discussions with the executive on 8 May and additional discussions with s22 .

(D25-2148966)

Specifically, we have:

- Updated the heading on the front cover to reflect new Departmental name;
- Clarified on pg 10 to highlight that Australians use higher amounts of sunscreen compared to other regions and therefore have used a tailored approach on assess the MoS of sunscreen ingredients;
- included additional calculations (for toddler scenarios) in the Homosalate (pg 48-52) and Oxybenzone (pg 59-61) safety assessment sections and updated the Recommendations for both of those to reflect the additional OPTIONS for Scheduling to consider.

Thank you to s22 from CMES for their work on this document.

Could you please approve the Trim workflow for this document. I will then forward it to s22 to progress with the scheduling process.

Kind regards
s22

s22

s22 [redacted]
Scientific Evaluation Branch

Medicines Regulation Division | Health Products Regulation Group
Australian Government, Department of Health, Disability and Ageing
T: s22 [redacted] | E: s22 [redacted] @health.gov.au

This email comes to you from Ngunnawal Country

Location: Fairbairn ACT
PO Box 100, Canberra ACT 2601, Australia

The Department of Health, Disability and Ageing acknowledges First Nations peoples as the Traditional Owners of Country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.