From: s22
To: SYME, Sarah; s22
Subject: FW: URGENT ACTION - ADVICE - DUE COB TODAY - FW: Briefing - Pre-meeting notice for homosalate, oxybenzone and benzophenone [SEC=OFFICIAL]
Date: Friday, 27 June 2025 3:12:18 PM
Attachments: image001.png

FYI – G2G from the boss.

s22 (Ms/ she/ her)

s22

Health Products Regulation Group
Australian Government, Department of Health, Disability and Ageing
☏: s22 | 💻: s2 @health.gov.au

This email comes to you from Ngunnawal Country
Location: 27 Scherger Drive Fairbairn, Level 2

I may send emails out of hours at a time that suits me. I look forward to receiving your response during your normal working hours.

The Department of Health, Disability and Ageing 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 all Elders both past and present.

From: LAWLER, Tony <Anthony.LAWLER@Health.gov.au>
Sent: Friday, 27 June 2025 3:11 PM
To: s22 @health.gov.au>
Cc: s22 @Health.gov.au>; BEDFORD, Chris <Chris.Bedford@health.gov.au>; s22 @health.gov.au>
Subject: RE: URGENT ACTION - ADVICE - DUE COB TODAY - FW: Briefing - Pre-meeting notice for homosalate, oxybenzone and benzophenone [SEC=OFFICIAL]

Thanks s22
Comfort level high.
Chris is across, Nick is nearby, and s22 and Sarah all over it.
Thanks
T

From: s22 @health.gov.au>
Sent: Friday, 27 June 2025 3:01 PM
To: LAWLER, Tony <Anthony.LAWLER@Health.gov.au>
Cc: s22 @Health.gov.au>; BEDFORD, Chris <Chris.Bedford@health.gov.au>; s22 @health.gov.au>
Subject: URGENT ACTION - ADVICE - DUE COB TODAY - FW: Briefing - Pre-meeting notice for homosalate, oxybenzone and benzophenone [SEC=OFFICIAL]
Importance: High

Hi Tony,

As I understand Sarah and s22 discussed with you this morning a pre-meeting notice which proposes scheduling the sunscreen ingredients homosalate, oxybenzone and benzophenone in the Poisons Standard has been drafted by s22 and the team (D25-2752198) and is ready for publication.

Noting the sensitivities around regulation of sunscreens, Sarah and s22 are seeking your comfort level and views on proceeding with publication of the pre-meeting notice, note they are not seeking clearance, and this has been sent to you and Chris simultaneously for consideration.

For your review and consideration of whether you wish the publishing to proceed. The plan is to publish, if agreed, the pre-meeting notice in the week starting 30 June 2025 (the regulations require a minimum 20 business-day consultation period after publication of the notice). Further detail is outlined in s22 email below.

s22

Appreciate your review and advice by COB today please.

Cheers,

s22

s22

s22

Health Products Regulation Group
Australian Government, Department of Health, Disability and Ageing
☏: s22 | 💻: s22 @health.gov.au

This email comes to you from Ngunnawal Country
Location: 27 Scherger Drive Fairbairn, Level 2

I may send emails out of hours at a time that suits me. I look forward to receiving your response during your normal working hours.

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From: SYME, Sarah <Sarah.Syme@health.gov.au>
Sent: Friday, 27 June 2025 2:51 PM
To: BEDFORD, Chris <Chris.Bedford@health.gov.au>; s22 s22 @health.gov.au>
Cc: s22 @health.gov.au>; s22 s22 @Health.gov.au>; s22 @health.gov.au>
Subject: FW: Briefing - Pre-meeting notice for homosalate, oxybenzone and benzophenone [SEC=OFFICIAL]

Hello Chris and s22

Sending this concurrently noting timing of Tony's leave. s22 and I briefly discussed this with him in a call this morning.

Please find below the proposed pre-meeting notice for sunscreen ingredients. I think the team has done a great job in balancing the different areas of discussion in the preamble. Not so much for clearance, but just confirming that both you, Chris, and Tony are comfortable with the direction before it is published.

s22

Thanks
S

From: s22 @health.gov.au>
Sent: Friday, 27 June 2025 11:58 AM
To: SYME, Sarah <Sarah.Syme@health.gov.au>
Cc: s22 @health.gov.au>
Subject: Briefing - Pre-meeting notice for homosalate, oxybenzone and benzophenone [SEC=OFFICIAL]

Sarah,

The draft pre-meeting notice which proposes scheduling the sunscreen ingredients homosalate, oxybenzone and benzophenone in the Poisons Standard is ready for publication (D25-2752198). Noting the sensitivities around regulation of sunscreens, I am seeking final views on proceeding with publication of the pre-meeting notice.
The scheduling proposals are based on the conclusions from the TGA Safety Review (D25-2148966) and the AICIS Evaluation statements on homosalate and benzophenone. A preamble provides context of the importance of sunscreen use in Australia and the reason for the

ingredients reviews – including international developments. It reinforces public health messaging stated in the medica release on continuing to use sunscreens.

The proposals are drafted similar to the approach for the paracetamol scheduling proposals in 2022 – presenting options which could be implemented separately or in combination (with modification) – instead of a single proposal. The proposals for homosalate and oxybenzone are limited 3 options each for simplicity. This is due to the TGA review calculations covering several use scenarios and that the product categories affected include therapeutic and cosmetic sunscreens. Only one option is presented for benzophenone as the risk management issues are simpler.

Due to the complex use patterns for homosalate and benzophenone, the options provide several regulatory approaches which are able to manage the potential risks of the substances. This provides industry and the public significant scope to provide views on implementing any of the proposed risk management controls.

We are targeting publication of the pre-meeting notice in the week starting 30 June 2025 (the regulations require a minimum 20 business-day consultation period after publication of the notice). There is some leeway noting that embargoed materials will be provided to some stakeholders.

The Joint ACCS-ACMS scheduling meeting to discuss these substances will be held on a half day in a date to be confirmed (9-11 Sep or 16-18 Sep). We have consulted the ACCS and ACMS Chairs and the Committee Support Unit on dates and will be polling Committee members for the optimal date.

As discussed previously, the TGA would be simultaneously publishing the following:

1. Publication **1 of 3** – Web publication request to come **from SEB**
    - Safety review of seven active sunscreen Ingredients (D25-2148966 – Publication ready version).
    - Safety review of benzophenone (D25-1519220 – Publication ready version).

2. Publication **2 of 3** – Web publication request to come **from REB**
    - Consultation hub, and eDM associated with the public consultation.
    - Pre-meeting public notice - Joint 41 - homosalate oxybenzone benzophenone - Sep 2025 (D25-2752198)

3. Publication **3 of 3** – Web publication request to come **from COMB**
    - Media Release (D25-1144490)
    - Landing Page (D25-932651)

4. Publication **3 of 3** – Distributed to select stakeholders but not published
    - Dear Healthcare Professional Letter (D25-1416719)
    - Consumer Leaflet (D25-1532815).

Regards

s22

[redacted] Scheduling and Chemicals Policy Section

Regulatory Practice and Support Division | Health Products Regulation Group
Regulatory Engagement Branch
Australian Government Department of Health, Disability and Ageing
T: s22 | E: s22 @health.gov.au

From: SYME, Sarah
To: HENDERSON, Nick; REBERA, Avi; BEDFORD, Chris; LANGHAM, Robyn
Cc: s22 s22 ;
Subject: RE: Media planning for sunscreens announcement [SEC=OFFICIAL]
Date: Monday, 30 June 2025 10:59:58 AM
Attachments: image002.png

Thank you – apologies, hadn't included her as she was on s22 original distribution list, but should have given her visibility that I'd sent it on.

S

From: HENDERSON, Nick <Nick.Henderson@health.gov.au>
Sent: Monday, 30 June 2025 10:58 AM
To: SYME, Sarah <Sarah.Syme@health.gov.au>; REBERA, Avi <Avi.Rebera@health.gov.au>; BEDFORD, Chris <Chris.Bedford@health.gov.au>; LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Cc: s22 @health.gov.au>; s22 s22 @Health.gov.au>; s22 @health.gov.au>; s22 @Health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>; s22 s22 @health.gov.au>
Subject: RE: Media planning for sunscreens announcement [SEC=OFFICIAL]

Thanks Sarah, I've copied in s22 who is acting for Avi Clarke

---

From: SYME, Sarah <Sarah.Syme@health.gov.au>
Sent: Monday, 30 June 2025 10:57 AM
To: REBERA, Avi <Avi.Rebera@health.gov.au>; BEDFORD, Chris <Chris.Bedford@health.gov.au>; HENDERSON, Nick <Nick.Henderson@health.gov.au>; LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Cc: s22 @health.gov.au>; s22 s22 @Health.gov.au>; s22 @health.gov.au>; s22 @Health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>
Subject: FW: Media planning for sunscreens announcement [SEC=OFFICIAL]

Hi all

FYI – please see below some information on the release of the sunscreens information.

Happy to discuss further as needed. The team has been working closely with MRD.

We're anticipating media attention, so will get some TPs / standards words prepared. You may also wish to get in touch with CHP Australia and Accord directly.

Thanks

S

From: s22 @health.gov.au>
Sent: Monday, 30 June 2025 10:53 AM
To: s22 @health.gov.au>; News <news@health.gov.au>
Cc: s22 @health.gov.au>; SYME, Sarah <Sarah.Syme@health.gov.au>; s22 @health.gov.au>; s22 @health.gov.au>; s22 @health.gov.au>; s22 @Health.gov.au>; TGA MEDIA <TGA.Media@health.gov.au>; s22 @health.gov.au>
Subject: Media planning for sunscreens announcement [SEC=OFFICIAL]

Hi s22 and team

The TGA will be publishing a range of materials relating to our sunscreen safety reviews and proposed regulatory controls on **Thursday 3 July** (see Trim links below). This has been approved by Prof Lawler and the MO has been advised.

COMB will be providing the media release, landing page and safety reviews to CHP Australia and Accord under embargo on Tuesday. All other external stakeholders will be sent an email post-publication.

Robyn Langham will be the TGA spokesperson. We previously discussed with you briefing other external experts, such as s47F Are you able to advise the best way to approach other spokespeople outside of the TGA? Are there any other journalist briefings you would recommend?

We'd also like your views on whether we should push the media release out via iSentia platform as well as our own channels? We're inclined to push out to as many channels as possible, so everyone has the information at the same time.

Once you've had a chance to review the materials below, we'd welcome your thoughts on what types of questions we can anticipate from journos, so that we can start to prepare our responses ahead of Thursday.

Links to materials:

- Media release: D25-1144490
- Landing page: D25-932651
- Pre-meeting public notice (homosalate, oxybenzone, benzophenone): D25-2752198
    - This will include a link to the public consultation
- Safety review of seven active sunscreen Ingredients: D25-2148966
- Safety review of benzophenone: D25-1519220
- Dear Healthcare Professional Letter: D25-1416719 – Not for publication
- Consumer Leaflet: D25-1532815 – Not for publication

Thanks!
s22

s22
Regulatory Education and Communication
Regulatory Engagement Branch
Regulatory Practice and Support Division | Health Products Regulation Group
Australian Government, Department of Health, Disability and Ageing
T: s22 | E: s22 @health.gov.au
Location: 27 Scherger Drive, Fairbairn
PO Box 100, Woden ACT 2606, Australia

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From: SYME, Sarah
To: BEDFORD, Chris; REBERA, Avi; HENDERSON, Nick; LANGHAM, Robyn
Cc: s22 s22
Subject: FW: Media planning for sunscreens announcement [SEC=OFFICIAL]
Date: Monday, 30 June 2025 11:19:47 AM
Attachments: image001.png

Hi all – an additional doc.

S

From: s22 @health.gov.au>
Sent: Monday, 30 June 2025 11:13 AM
To: s22 @health.gov.au>; News <news@health.gov.au>
Cc: s22 @health.gov.au>; SYME, Sarah <Sarah.Syme@health.gov.au>; s22 @health.gov.au>; s22 @health.gov.au>; s22 @health.gov.au>; s22 @health.gov.au>; s22 @Health.gov.au>; TGA MEDIA <TGA.Media@health.gov.au>; s22 s22 @health.gov.au>
Subject: RE: Media planning for sunscreens announcement [SEC=OFFICIAL]

Hi s22

One more document for your consideration – FAQs: D24-3900764

This has been prepared by COMB for reactive stakeholder enquiries but welcome your thoughts on these as well.

s22

From: s22
Sent: Monday, 30 June 2025 10:53 AM
To: s22 @health.gov.au>; News <news@health.gov.au>
Cc: s22 @health.gov.au>; SYME, Sarah <Sarah.Syme@health.gov.au>; s22 @health.gov.au>; s22 @health.gov.au>; s22 @health.gov.au>; s22 @Health.gov.au>; TGA MEDIA <TGA.Media@health.gov.au>; s22 s22 @health.gov.au>
Subject: Media planning for sunscreens announcement [SEC=OFFICIAL]

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Accord under embargo on Tuesday. All other external stakeholders will be sent an email post-publication.

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Links to materials:

- Media release: D25-1144490
- Landing page: D25-932651
- Pre-meeting public notice (homosalate, oxybenzone, benzophenone): D25-2752198
    - This will include a link to the public consultation
- Safety review of seven active sunscreen Ingredients: D25-2148966
- Safety review of benzophenone: D25-1519220
- Dear Healthcare Professional Letter: D25-1416719 – Not for publication
- Consumer Leaflet: D25-1532815 – Not for publication

Thanks!
s22

s22
s22 **Regulatory Education and Communication**
Regulatory Engagement Branch
Regulatory Practice and Support Division | Health Products Regulation Group
Australian Government, Department of Health, Disability and Ageing
T: s22 | E: s22 @health.gov.au
Location: 27 Scherger Drive, Fairbairn
PO Box 100, Woden ACT 2606, Australia

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From: s22
To: s22
Cc: s22
Subject: MR [SEC=OFFICIAL]
Date: Monday, 7 July 2025 5:06:00 PM
Attachments: TGA media release- Sunscreen MR_ Media.docx
image001.png
Importance: High

Hopefully, final version. Not all links included – if you could add. Let us know if OK

Thanks,
s22

s22
I Media and Events
Corporate Communication Branch
Australian Government, Department of Health, Disability and Ageing
T: s22 | E news@health.gov.au

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

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

Therapeutic Goods Administration

MEDIA RELEASE

TGA to consult on additional controls for some sunscreen ingredients

The Therapeutic Goods Administration (TGA) is recommending additional safeguards for two active ingredients and a by-product in sunscreens used in Australia, following its safety review into sunscreen ingredients. The review was prompted by developments overseas and the TGA's literature review of sunscreen ingredients

The TGA review proposes that some sunscreen products containing the active ingredients homosalate and oxybenzone, as well as the sunscreen by-product benzophenone, be reformulated to ensure sunscreens meet the highest standards of safety for prolonged and frequent use.

The review identified potential safety risks for oxybenzone and homosalate. However, the risks are only theoretical as the review was based on current sunscreen use patterns in Australia and information from animal studies.

A comprehensive public and stakeholder consultation will begin today to help determine the level these ingredients remain suitable for use in Australian sunscreens.

All sunscreens available in Australia are safe. The TGA is not recommending a change in the use of sunscreens, warnings, bans or recalls of any products.

The expert clinical advice remains that the benefits of all sunscreens available in Australia continue to far outweigh any risks. Australians are urged to continue using sunscreen.

Australia has the highest rates of skin cancer in the world with around 2,000 people dying each year from skin cancer, sunscreens help prevent sunburn and skin cancers. Australians should continue to protect themselves from the sun in five ways – using sunscreen, seeking shade and wearing protective clothing, hats and sunglasses.

Comprehensive information is available on the sunscreen ingredients page.

If you have any specific concerns about your health and sunscreen ingredients, please speak to your health provider.

Contact for members of the media:

- Email: news@health.gov.au
- Phone: (02) 6289 7400

From: s22
To: s22
Subject: Media release - edits [SEC=OFFICIAL]
Date: Monday, 7 July 2025 1:09:00 PM
Attachments: D25-1144490 Attachment D - MB25-000510 - Sunscreen Taskforce - TGA to consult on additional controls for sunscreen ingredients_RECS DRAFT MR_MEDIA.docx
image001.png
Importance: High

Hi s22

Can you give me a call when you have a moment

Thanks,
s22

s22
Assistant Director I Media and Events
Corporate Communication Branch
Australian Government, Department of Health, Disability and Ageing
T: 02 6289 7400 | E news@health.gov.au

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

Therapeutic Goods Administration

MEDIA RELEASE

TGA to consult on additional controls for some sunscreen ingredients

Day Month 2025

The Therapeutic Goods Administration (TGA) has conducted a review of active ingredients used in sunscreens and a sunscreen degradant, and is recommending additional safeguards for 2 ingredients and the degradant.

The TGA is not proposing a change in use of sunscreen, or any warnings, bans or recalls of any products. Australians are urged to continue using sunscreen.

All sunscreens available in Australia are safe. The expert clinical advice remains that the benefits of all sunscreens available in Australia continue to far outweigh any risks.

The benefits of sunscreen in preventing sunburn and skin cancers are well established. Australia has the highest rates of skin cancer in the world with around 2,000 people dying each year from skin cancer. Australians should continue to protect themselves from the sun in five ways – using sunscreen, seeking shade and wearing protective clothing, hats and sunglasses.

The TGA review recommends that some sunscreen products containing the active ingredients homosalate and oxybenzone be reformulated so they meet the highest standards of safety for prolonged and frequent use. It also recommends restricting the level of benzophenone allowable in sunscreens. Benzophenone can be found in very small amounts when the active ingredient octocrylene breaks down under certain conditions such as excessive temperatures.

A comprehensive public and stakeholder consultation will begin today to help determine at what level these chemicals remain suitable for use in Australian sunscreens.

The development of the Australian sunscreen exposure model, literature review and the subsequent reviews informed the TGA's decision to proceed to public consultation through the scheduling process.

Comprehensive information is available on the Sunscreen ingredients page.

If you have any specific concerns about your health and sunscreen ingredients, please speak to your doctor.

Contact for members of the media:

Commented [s2]: Is it possible to make this paragraph easier to understand? Most people won't know what you mean when you refer to "degradant".

Commented [s22]: Should this be included to allay any initial fears - The review was based on current sunscreen use patterns in Australia and information from animal studies, not human studies, and thus the risks we found are theoretical.

Commented [s2]: Web team: Link to public consultation

Field Code Changed

Commented [s22]: Web team: insert link to ASEM

Field Code Changed

Commented [s2]: Web team: Link to the Landing page

- Email: news@health.gov.au
- Phone: 02 6289 7400.

From: s22
To: s22
Cc: s22
Subject: FW: MR [SEC=OFFICIAL]
Date: Monday, 7 July 2025 5:28:00 PM
Attachments: TGA media release- Sunscreen MR_ Media.docx
image001.png
Importance: High

As per message.

From: s22
Sent: Monday, 7 July 2025 5:06 PM
To: s22 @Health.gov.au>; s22
s22 @Health.gov.au>
Cc: s22 @health.gov.au>
Subject: MR [SEC=OFFICIAL]
Importance: High

Hopefully, final version. Not all links included – if you could add. Let us know if OK

Thanks,
s22

s22
Assistant Director I Media and Events
Corporate Communication Branch
Australian Government, Department of Health, Disability and Ageing
T: 02 6289 7400 | E news@health.gov.au

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

Therapeutic Goods Administration

MEDIA RELEASE

TGA to consult on additional controls for some sunscreen ingredients

The Therapeutic Goods Administration (TGA) is recommending additional safeguards for two active ingredients and a by-product in sunscreens used in Australia, following its safety review into sunscreen ingredients. The review was prompted by developments overseas and the TGA's literature review of sunscreen ingredients

The TGA review proposes that some sunscreen products containing the active ingredients homosalate and oxybenzone, as well as the sunscreen by-product benzophenone, be reformulated to ensure sunscreens meet the highest standards of safety for prolonged and frequent use.

The review identified potential safety risks for oxybenzone and homosalate. However, the risks are only theoretical as the review was based on current sunscreen use patterns in Australia and information from animal studies.

A comprehensive public and stakeholder consultation will begin today to help determine the level these ingredients remain suitable for use in Australian sunscreens.

All sunscreens available in Australia are safe. The TGA is not recommending a change in the use of sunscreens, warnings, bans or recalls of any products.

The expert clinical advice remains that the benefits of all sunscreens available in Australia continue to far outweigh any risks. Australians are urged to continue using sunscreen.

Australia has the highest rates of skin cancer in the world with around 2,000 people dying each year from skin cancer, sunscreens help prevent sunburn and skin cancers. Australians should continue to protect themselves from the sun in five ways – using sunscreen, seeking shade and wearing protective clothing, hats and sunglasses.

Comprehensive information is available on the sunscreen ingredients page.

If you have any specific concerns about your health and sunscreen ingredients, please speak to your health provider.

Contact for members of the media:

- Email: news@health.gov.au
- Phone: (02) 6289 7400

From: s22
To: s22
Subject: FW: Media release - edits [SEC=OFFICIAL]
Date: Monday, 7 July 2025 4:45:00 PM
Attachments: image001.gif
image002.png
TGA media release- Sunscreen MR (003).docx

Does this helps.

From: s22
Sent: Monday, 7 July 2025 4:21 PM
To: s22 @Health.gov.au>
Subject: RE: Media release - edits [SEC=OFFICIAL]

Sorry had to restart computer

From: s2 @Health.gov.au>
Sent: Monday, 7 July 2025 2:29 PM
To: s22 @Health.gov.au>
Subject: RE: Media release - edits [SEC=OFFICIAL]

Hi s22

Thanks for your call. I have worked through the media release with a member of the sunscreen team, and we have come up with the attached. Please let me know if you think this messaging is more consistent and I will work for AS and FAS clearance ASAP.

Many thanks,

s22

s22
s22
Chief Medical Advisor Unit
Phone: s22
Email: s22 @health.gov.au
Therapeutic Goods Administration
Australian Government, Department of Health, Disability and Ageing
PO Box 100
Woden ACT 2606
www.tga.gov.au

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From: s22 @Health.gov.au>
Sent: Monday, 7 July 2025 1:09 PM
To: s22 @Health.gov.au>

Subject: Media release - edits [SEC=OFFICIAL]
Importance: High

Hi s22

Can you give me a call when you have a moment

Thanks,
s22

s22
s22 I Media and Events
Corporate Communication Branch
Australian Government, Department of Health, Disability and Ageing
T: 02 6289 7400 | E news@health.gov.au

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

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MEDIA RELEASE

TGA to consult on additional controls for some sunscreen ingredients

The Therapeutic Goods Administration (TGA) is recommending additional safeguards for two active ingredients and a by-product in sunscreens used in Australia, following its safety review into sunscreen ingredients.

[Insert here why review was conducted e.g. regularly conducted as we mention]

The TGA proposes that some sunscreen products containing the active ingredients homosalate and oxybenzone, as well as the sunscreen by-product benzophenone, be reformulated to ensure sunscreens meet the highest standards of safety for prolonged and frequent use.

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Contact for members of the media:

- Email: news@health.gov.au
- Phone: (02) 6289 7400

From: s22
To: s22
Subject: FW: Cleared MR - Sunscreen ingredient safety [SEC=OFFICIAL]
Date: Monday, 7 July 2025 12:17:24 PM
Attachments: [D24-4445890] Sunscreen Taskforce - TGA to consult on additional controls for sunscreen ingredients_RECS DRAFT MR.DOCX
image001.png

---

s22
Media and Events, Corporate Communication Branch
People, Communication & Parliamentary Division| Corporate Operations Group
Australian Government Department of Health, Disability and Ageing
T: s22 M: s22 | E: s22 @health.gov.au
Location: Sirius Building 3.N
GPO Box 9848, Canberra ACT 2601, Australia
Follow on: Twitter | Facebook | Pinterest | YouTube
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: Monday, 7 July 2025 12:14 PM
To: s22 @health.gov.au>
Cc: News <news@health.gov.au>
Subject: Cleared MR - Sunscreen ingredient safety [SEC=OFFICIAL]

Hi s22

Please find attached the cleared MR titled 'TGA to consult on additional controls for some sunscreen ingredients'. Please also find trim link for ease of reference: D24-4445890.

Please let me know if there is anything else you require.

Many thanks,

s22

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

Therapeutic Goods Administration

MEDIA RELEASE

TGA to consult on additional controls for some sunscreen ingredients

Day Month 2025

The Therapeutic Goods Administration (TGA) has conducted a review of active ingredients used in sunscreens and a sunscreen degradant, and is recommending additional safeguards for 2 ingredients and the degradant.

The TGA is not proposing a change in use of sunscreen, or any warnings, bans or recalls of any products. Australians are urged to continue using sunscreen.

Commented s22: Web team: For emphasis

The benefits of sunscreen in preventing sunburn and skin cancers are well established. Australia has the highest rates of skin cancer in the world with around 2,000 people dying each year from skin cancer. Australians should continue to protect themselves from the sun in five ways – using sunscreen, seeking shade and wearing protective clothing, hats and sunglasses.

The TGA review recommends that some sunscreen products containing the active ingredients homosalate and oxybenzone be reformulated so they meet the highest standards of safety for prolonged and frequent use. It also recommends restricting the level of benzophenone allowable in sunscreens. Benzophenone can be found in very small amounts when the active ingredient octocrylene breaks down under certain conditions such as excessive temperatures.

A comprehensive public and stakeholder consultation will begin today to help determine at what level these chemicals remain suitable for use in Australian sunscreens.

Commented s22 Web team: Link to public consultation

The development of the Australian sunscreen exposure model, literature review and the subsequent reviews informed the TGA's decision to proceed to public consultation through the scheduling process.

Commented s22: Web team: insert link to ASEM

Comprehensive information is available on the Sunscreen ingredients page.

Commented s22 Web team: Link to the Landing page

If you have any specific concerns about your health and sunscreen ingredients, please speak to your doctor.

Contact for members of the media:

- Email: news@health.gov.au
- Phone: 02 6289 7400.

From: s22
To: s22
Subject: CAn yuotake a quick read and than call me [SEC=OFFICIAL]
Date: Monday, 7 July 2025 3:08:00 PM
Attachments: s EDIT - Day Month 2025.docx
image001.png

Thanks,
s22

s22
Assistant Director I Media and Events
Corporate Communication Branch
Australian Government, Department of Health, Disability and Ageing
T: 02 6289 7400 | E news@health.gov.au

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

Day Month 2025

The Therapeutic Goods Administration (TGA) has conducted a review ~~of active ingredients used in~~ sunscreens used in Australia and ~~a sunscreen~~ degradant~~by-product~~, and is recommending additional safeguards for 2 ingredients and a by product.~~one the degradant.~~

All sunscreens available in Australia are safe, the TGA is not recommending a ~~proposing a~~ change in the use of sunscreens, ~~or any~~ warnings, bans or recalls of any products. ~~All sunscreens available in Australia are safe.~~ Australians are urged to continue using sunscreen.

The expert clinical advice remains that the benefits of all sunscreens available in Australia continue to far outweigh any risks.

~~All sunscreens available in Australia are safe. The expert clinical advice remains that the benefits of all sunscreens available in Australia continue to far outweigh any risks.~~

~~The benefits of sunscreen in preventing sunburn and skin cancers are well established.~~ Australia has the highest rates of skin cancer in the world with around 2,000 people dying each year from skin cancer, sunscreens help ~~in~~ prevent~~ing~~ sunburn and skin cancers. Australians should continue to protect themselves from the sun in five ways – using sunscreen, seeking shade and wearing protective clothing, hats and sunglasses.

The TGA review ~~recommends~~ proposes that some sunscreen products containing the active ingredients homosalate and oxybenzone and a sunscreen ingredient by-product benzophenone be reformulated so they meet the highest standards of safety for prolonged and frequent use. The review was based on current sunscreen use patterns in Australia and information from animal studies, not human studies, and thus the risks identified are theoretical.

It is the role of the TGA to monitor the safety of therapeutic products. All TGA approved products must meet the highest standard of safety, quality and efficacy.

~~It also recommends restricting the level of benzophenone allowable in sunscreens. Benzophenone can be found in very small amounts when the active ingredient octocrylene breaks down under certain conditions such as excessive temperatures.~~

A comprehensive public and stakeholder consultation will begin today to help determine the ~~at what~~ level these ~~chemicals~~ ingredient~~s~~ remain suitable for use in Australian sunscreens. ~~As part of our regulatory framework, the TGA can consider risk mitigation mechanisms such as scheduling where public submissions and expert advisory committee advice are taken into account.~~

The development of the Australian sunscreen exposure model, literature review and the subsequent reviews informed the TGA's decision to proceed to public consultation through the scheduling process.

If you have any specific concerns about your health and sunscreen ingredients, please speak to your doctor.

Comprehensive information is available on the Sunscreen ingredients page.

Commented s22 **:** Is it possible to make this paragraph easier to understand? Most people won't know what you mean when you refer to "degradant".

Formatted: Font: (Default) Arial, Underline

Formatted: Font: (Default) Arial, Underline, Strikethrough

Formatted: Font: (Default) Arial, Underline

Formatted: Font: (Default) Arial, Underline

Commented s22 Should this be included to allay any initial fears - The review was based on current sunscreen use patterns in Australia and information from animal studies, not human studies, and thus the risks we found are theoretical.

Commented s22 Web team: Link to public consultation

Field Code Changed

Commented s22 Web team: insert link to ASEM

Field Code Changed

Commented s22 **:** Web team: Link to the Landing page

~~If you have any specific concerns about your health and sunscreen ingredients, please speak to your doctor.~~

Contact for members of the media:

- Email: news@health.gov.au
- Phone: 02 6289 7400.

From: s22
To: s22
Subject: RE: Media release - edits [SEC=OFFICIAL]
Date: Monday, 7 July 2025 2:29:17 PM
Attachments: D25-1144490 Attachment D - MB25-000510 - Sunscreen Taskforce - TGA to consult on additional controls for sunscreen ingredients_RECS DRAFT MR_MEDIA - DG.docx
image002.gif
image003.png

Hi s22

Thanks for your call. I have worked through the media release with a member of the sunscreen team, and we have come up with the attached. Please let me know if you think this messaging is more consistent and I will work for AS and FAS clearance ASAP.

Many thanks,

s22

s22
s22
Chief Medical Advisor Unit
Phone: s22
Email: s22 @health.gov.au
Therapeutic Goods Administration
Australian Government, Department of Health, Disability and Ageing
PO Box 100
Woden ACT 2606
www.tga.gov.au

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: Monday, 7 July 2025 1:09 PM
To: s22 @Health.gov.au>
Subject: Media release - edits [SEC=OFFICIAL]
Importance: High

Hi s22

Can you give me a call when you have a moment

Thanks,
s22

s22
Assistant Director I Media and Events
Corporate Communication Branch
Australian Government, Department of Health, Disability and Ageing

T: 02 6289 7400 | E news@health.gov.au

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Australian Government

Department of Health, Disability and Ageing

Therapeutic Goods Administration

Therapeutic Goods Administration

MEDIA RELEASE

TGA to consult on additional controls for some sunscreen ingredients

Day Month 2025

The Therapeutic Goods Administration (TGA) has conducted a review of active ingredients used in sunscreens and a sunscreen ingredient ~~degradant~~by-product, and is recommending additional safeguards for 2 ingredients and the degradant.

The TGA is not proposing a change in use of sunscreen, or any warnings, bans or recalls of any products. All sunscreens available in Australia are safe. Australians are urged to continue using sunscreen. The expert clinical advice remains that the benefits of all sunscreens available in Australia continue to far outweigh any risks.

~~All sunscreens available in Australia are safe. The expert clinical advice remains that the benefits of all sunscreens available in Australia continue to far outweigh any risks.~~

The benefits of sunscreen in preventing sunburn and skin cancers are well established. Australia has the highest rates of skin cancer in the world with around 2,000 people dying each year from skin cancer. Australians should continue to protect themselves from the sun in five ways – using sunscreen, seeking shade and wearing protective clothing, hats and sunglasses.

The TGA review ~~recommends~~ proposes that some sunscreen products containing the active ingredients homosalate and oxybenzone and a sunscreen ingredient by-product benzophenone be reformulated so they meet the highest standards of safety for prolonged and frequent use. The review was based on current sunscreen use patterns in Australia and information from animal studies, not human studies, and thus the risks identified are theoretical.

It is the role of the TGA to monitor the safety of therapeutic products. All TGA approved products must meet the highest standard of safety, quality and efficacy.

~~It also recommends restricting the level of benzophenone allowable in sunscreens. Benzophenone can be found in very small amounts when the active ingredient octocrylene breaks down under certain conditions such as excessive temperatures.~~

A comprehensive public and stakeholder consultation will begin today to help determine at what level these chemicals remain suitable for use in Australian sunscreens. As part of our regulatory framework, the TGA can consider risk mitigation mechanisms such as scheduling where public submissions and expert advisory committee advice are taken into account.

Commented [redacted] Is it possible to make this paragraph easier to understand? Most people won't know what you mean when you refer to "degradant".

Formatted: Font: (Default) Arial, Underline

Formatted: Font: (Default) Arial, Underline

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Commented s22 Web team: Link to public consultation

Field Code Changed

The development of the Australian sunscreen exposure model, literature review and the subsequent reviews informed the TGA's decision to proceed to public consultation through the scheduling process.

If you have any specific concerns about your health and sunscreen ingredients, please speak to your doctor.

Comprehensive information is available on the Sunscreen ingredients page.

~~If you have any specific concerns about your health and sunscreen ingredients, please speak to your doctor.~~

Contact for members of the media:

- Email: news@health.gov.au
- Phone: 02 6289 7400.

Commented s22: Web team: insert link to ASEM

Field Code Changed

Commented s22 Web team: Link to the Landing page

From: s22
To: s22
Subject: RE: Media release - edits [SEC=OFFICIAL]
Date: Monday, 7 July 2025 4:20:00 PM
Attachments: image001.gif
image002.png
s EDIT MEDIA EDITS.docx

Sorry had to restart computer

From: s22 @Health.gov.au>
Sent: Monday, 7 July 2025 2:29 PM
To: s22 @Health.gov.au>
Subject: RE: Media release - edits [SEC=OFFICIAL]

Hi s22

Thanks for your call. I have worked through the media release with a member of the sunscreen team, and we have come up with the attached. Please let me know if you think this messaging is more consistent and I will work for AS and FAS clearance ASAP.

Many thanks,

s22

s22
s22
Chief Medical Advisor Unit
Phone: s22
Email: s22 @health.gov.au
Therapeutic Goods Administration
Australian Government, Department of Health, Disability and Ageing
PO Box 100
Woden ACT 2606
www.tga.gov.au

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From: s22 @Health.gov.au>
Sent: Monday, 7 July 2025 1:09 PM
To: s22 @Health.gov.au>
Subject: Media release - edits [SEC=OFFICIAL]
Importance: High

Hi s22

Can you give me a call when you have a moment

Thanks,
s22

s22
Assistant Director I Media and Events
Corporate Communication Branch
Australian Government, Department of Health, Disability and Ageing
T: 02 6289 7400 | E news@health.gov.au

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Day Month 2025

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The TGA review ~~proposes~~ proposes that some sunscreen products containing the active ingredients homosalate and oxybenzone and a sunscreen ~~ingredient~~ by-product benzophenone be reformulated so they meet the highest standards of safety for prolonged and frequent use.

Why was the review conducted what was the findings [similar to below – but shorter?

We released the outcome of the Australian Sunscreen Exposure Model (ASEM) public consultation in January 2025. We subsequently released a literature review of sunscreen ingredients in February 2025 as the first step in notifying the public that we were considering new evidence about the use of these ingredients, and advised that together these would inform our assessment of sunscreen ingredients.

Following comprehensive internal discussion and review, the TGA has finalised its safety review of 7 active sunscreen ingredients and a degradant. We have also prepared a pre-meeting public notice consultation paper that provides a number of options that we are seeking public comment on.

The review was based on current sunscreen use patterns in Australia and information from animal studies, not human studies, and thus the risks identified are theoretical.

A comprehensive public and stakeholder consultation will begin today to help determine the ~~at what~~ level these ~~chemicals~~ ingredient~~s~~ remain suitable for use in Australian sunscreens.

The development of the Australian sunscreen exposure model, literature review and the subsequent reviews informed the TGA's decision to proceed to public consultation through the scheduling process.

It is the role of the TGA to monitor the safety of therapeutic products. All TGA approved products must meet the highest standard of safety, quality and efficacy.

All sunscreens available in Australia are safe. The TGA is not recommending a ~~proposing a~~ change in the use of sunscreens, ~~or any~~ warnings, bans or recalls of any products. ~~All sunscreens available in Australia are safe.~~ Australians are urged to continue using sunscreen.

The expert clinical advice remains that the benefits of all sunscreens available in Australia continue to far outweigh any risks.

~~The benefits of sunscreen in preventing sunburn and skin cancers are well established.~~ Australia has the highest rates of skin cancer in the world with around 2,000 people dying each year from skin cancer, sunscreens help ~~in~~ prevent~~ing~~ sunburn and skin cancers. Australians should continue to protect themselves from the sun in five ways – using sunscreen, seeking shade and wearing protective clothing, hats and sunglasses.

~~The TGA review proposes that some sunscreen products containing the active ingredients homosalate and oxybenzone and a sunscreen ingredient by-product benzophenone be reformulated so they meet the highest standards of safety for prolonged and frequent use.~~

Commented s22 Is it possible to make this paragraph easier to understand? Most people won't know what you mean when you refer to "degradant".

Commented s22 : Web team: Link to public consultation

Commented s22 : Web team: insert link to ASEM

~~The review was based on current sunscreen use patterns in Australia and information from animal studies, not human studies, and thus the risks identified are theoretical.~~

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Commented [s22]: Web team: Link to public consultation

~~The development of the Australian sunscreen exposure model, literature review and the subsequent reviews informed the TGA's decision to proceed to public consultation through the scheduling process.~~

Commented [redacted]: Web team: insert link to ASEM

If you have any specific concerns about your health and sunscreen ingredients, please speak to your doctor. Comprehensive information is available on the Sunscreen ingredients page.

Commented [s22]: Web team: Link to the Landing page

Contact for members of the media:

- Email: news@health.gov.au
- Phone: 02 6289 7400.

From: s22
To: s22
Cc: s22
Subject: RE: MR [SEC=OFFICIAL]
Date: Monday, 7 July 2025 7:53:45 PM
Attachments: image003.png
[D25-1144490] Sunscreen Taskforce - TGA to consult on additional controls for sunscreen ingredients_RECS DRAFT MR.DOCX

Hi s22

Please find attached and trim link (D25-1144490) to the amended and cleared media release for sunscreen ingredient safety. Thank you for your input from a media perspective. Very much appreciated!

Many thanks,

s22

From: s22 @Health.gov.au>
Sent: Monday, 7 July 2025 5:29 PM
To: s22 @health.gov.au>
Cc: s22 @Health.gov.au>
Subject: FW: MR [SEC=OFFICIAL]
Importance: High

As per message.

From: s22
Sent: Monday, 7 July 2025 5:06 PM
To: s22 @Health.gov.au>; s22
s22 @Health.gov.au>
Cc: s22 @health.gov.au>
Subject: MR [SEC=OFFICIAL]
Importance: High

Hopefully, final version. Not all links included – if you could add. Let us know if OK

Thanks,
s22

s22
Assistant Director I Media and Events
Corporate Communication Branch
Australian Government, Department of Health, Disability and Ageing
T: 02 6289 7400 | E news@health.gov.au

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

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

Therapeutic Goods Administration

MEDIA RELEASE

TGA to consult on additional controls for some sunscreen ingredients

The Therapeutic Goods Administration (TGA) has conducted a review of sunscreen ingredients used in Australia and is recommending additional safeguards for 2 ingredients and a sunscreen ingredient by-product (degradant). The review was prompted by regulatory developments overseas, adoption of the Australian sunscreen exposure model and the TGA's scientific literature review of sunscreen ingredients.

Commented [s22]: Web team: insert link to ASEM

Commented [s22]: https://consultations.tga.gov.au/tga/proposed-model-for-assessing-sunscreen-ingredients/

Commented [s22]: Web team, link to literature search https://www.tga.gov.au/resources/publication/publications/literature-search-and-summaries-seven-sunscreen-active-ingredients

The TGA review proposes that some sunscreen products containing the active ingredients homosalate and oxybenzone, as well as the degradant benzophenone, be reformulated to ensure sunscreens meet the highest standards of safety for prolonged and frequent use.

The review identified potential safety risks for oxybenzone, homosalate and benzophenone. However, the risks are only theoretical as the review was based on information from animal studies extrapolated to current sunscreen use patterns in Australia.

A comprehensive public and stakeholder consultation will begin today to help determine the level in sunscreens at which these ingredients remain suitable for use in Australian sunscreens.

Commented [s22]: Web team: Link to public consultation

All sunscreens available in Australia are safe. The TGA is not recommending a change in the use of sunscreens, nor are there any warnings, bans or recalls of any products.

Commented [s22]: Media: Underlines for emphasis

The expert clinical advice remains that the benefits of all sunscreens available in Australia continue to far outweigh any risks. Australians are urged to continue using sunscreen.

The benefits of sunscreen in preventing skin damage and skin cancers are well established. Australia has the highest rates of skin cancer in the world with around 2,000 people dying each year from skin cancer. Sunscreens help prevent sunburn, skin damage and skin cancers. Australians should continue to protect themselves from the sun in five ways – using sunscreen, seeking shade and wearing protective clothing, hats and sunglasses.

Comprehensive information is available on the sunscreen ingredients page.

Commented [s22]: Web team: Link to landing page D25-932651

If you have any specific concerns about your health and sunscreen ingredients, please speak to your health provider.

Contact for members of the media:

- Email: news@health.gov.au
- Phone: (02) 6289 7400

From: News
To: s22
Cc: LANGHAM, Robyn; s22 ; News; s22 s22
Subject: RE: TGA MR - [SEC=OFFICIAL]
Date: Tuesday, 8 July 2025 10:37:45 AM
Attachments: image001.png image002.png

Thanks s22

Wanted to confirm as there have been significant changes to media release which were only approved by Robyn last night and sent to s22 this morning. I should have sent to s22 last night also when forwarding to the MO.

All good now though.

Thanks,
s22

s22
Assistant Director
Media and Events, Corporate Communication Branch
Australian Government, Department of Health, Disability
T: 02 6289 7400 | M s22 I E s22 @health.gov.au

The Department of Health, Disability and Ageing acknowledges First Nations peoples as the Traditional Owners of Country throughout Australia, and their 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: Tuesday, 8 July 2025 10:24 AM
To: s22 @Health.gov.au>; s22 s22 @health.gov.au>
Cc: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>; s22 s22 @Health.gov.au>; s22 @health.gov.au>; s22 s22 @health.gov.au>; News <news@health.gov.au>; s22 s22 @Health.gov.au>; s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>
Subject: RE: TGA MR - [SEC=OFFICIAL]

Hi s22

Publications are in progress. Apologies, my understanding was that advice had been provided

last week that the intended timeframe was from 10am today.

Regards
s22

s22
s22

Regulatory Engagement Branch

Regulatory Practice and Support Division | Health Products Regulation Group
Australian Government Department of Health, Disability and Ageing
T: s22 | E: s22 @health.gov.au

From: s22 @Health.gov.au>
Sent: Tuesday, 8 July 2025 10:22 AM
To: s22 @health.gov.au>
Cc: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>; s22 s22 @Health.gov.au>; s22 @health.gov.au>; s22 s22 @health.gov.au>; News <news@health.gov.au>; s22 s22 @health.gov.au>; s22 @Health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>; s22 s22 @health.gov.au>
Subject: RE: TGA MR - [SEC=OFFICIAL]

Thanks for the update.
MO fine with the release. Appreciate it if you could let us know in advance what time you intend to issue and publish.
Thanks,

s22

s22

Assistant Director
Media and Events, Corporate Communication Branch
Australian Government, Department of Health, Disability
T: 02 6289 7400 | M s22 I E s22 @health.gov.au

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From: s22 @health.gov.au>
Sent: Tuesday, 8 July 2025 10:15 AM

To: s22 @Health.gov.au>
Cc: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>; s22 s22 @Health.gov.au>; s22 @health.gov.au>; s22 s22 @health.gov.au>; News <news@health.gov.au>; s22 s22 @health.gov.au>; s22 @Health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>
Subject: RE: TGA MR - [SEC=OFFICIAL]

Hi s22

s22 has just advised the following: I have just had a discussion with s22 and s22 who have agreed to removed the 3rd paragraph of the media release. This has now been updated in TRIM and can proceed.

The updated version is attached.

Thanks
s22

From: s22 @Health.gov.au>
Sent: Tuesday, 8 July 2025 10:01 AM
To: s22 @health.gov.au>
Cc: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>; s22 s22 @Health.gov.au>; s22 @health.gov.au>; s22 s22 @health.gov.au>; News <news@health.gov.au>
Subject: RE: TGA MR - [SEC=OFFICIAL]
Importance: High

Hi s22

Please see updated media release to be issued today. It has been approved by Robyn and is currently with the MO s22 is reaching out to them this morning to ensure they are happy with it prior to distribution..
Note there is no link to *sunscreen ingredients* In the second last paragraph which I believe your team will add once final version is provided.

Thanks,
s22

s22
Media, Communication Branch

Australian Government, Department of Health and Aged Care
T: 02 6289 7400 | M: s22 I E: news@health.gov.au

From: s22 [redacted] @Health.gov.au>
Sent: Monday, 7 July 2025 7:54 PM
To: s22 [redacted] @Health.gov.au>
Cc: s22 [redacted] @health.gov.au>
Subject: RE: MR [SEC=OFFICIAL]

Hi s22 [redacted]

Please find attached and trim link (D25-1144490) to the amended and cleared media release for sunscreen ingredient safety. Thank you for your input from a media perspective. Very much appreciated!

Many thanks,

s22 [redacted]

From: s22 [redacted] @Health.gov.au>
Sent: Monday, 7 July 2025 5:29 PM
To: s22 [redacted] @health.gov.au>
Cc: s22 [redacted] @Health.gov.au>
Subject: FW: MR [SEC=OFFICIAL]
Importance: High

As per message.

From: s22 [redacted]
Sent: Monday, 7 July 2025 5:06 PM
To: s22 [redacted] @Health.gov.au>; s22 [redacted] s22 [redacted] @Health.gov.au>
Cc: s22 [redacted] @health.gov.au>
Subject: MR [SEC=OFFICIAL]
Importance: High

Hopefully, final version. Not all links included – if you could add. Let us know if OK

Thanks,
s22 [redacted]

s22 [redacted]
Assistant Director I Media and Events
Corporate Communication Branch
Australian Government, Department of Health, Disability and Ageing

T: 02 6289 7400 | E news@health.gov.au

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Sunscreen ingredients

[*Summary – meta description for site search and search engines*] We are considering regulatory changes for therapeutic sunscreens following a review of some active ingredients used in some sunscreen products.

[*Page intro*] We have conducted a review of some active ingredients used in sunscreens and a sunscreen degradant.

Our review recommends changes to sunscreen products that contain the active ingredients homosalate and oxybenzone, or a degradant (benzophenone) so they meet the highest standards of safety for prolonged and frequent use.

We have commenced public consultations on proposed scheduling changes for these chemicals to lower their permitted use in sunscreens.

We are not proposing a change in use of sunscreen, or any warnings, bans or recalls of any products. Australians are urged to continue using sunscreen.

Important [*callout box*]

You should continue to use sunscreen to protect against the sun's harmful ultraviolet (UV) rays.

Clinical advice remains unchanged - the benefits of sunscreen continue to outweigh any theoretical risks posed by some sunscreen chemicals.

<HYPERLINK> Safety review of seven sunscreen active ingredients

<HYPERLINK> Safety review of benzophenone

<HYPERLINK> Scheduling Public Notice

Commented [s22]: NOTE: Include HYPERLINKS to Ingredient Reviews and Scheduling Public Statement. Above the 'Related information'

Related information

[Item list (can contain external links to consultation hub)]

- **<HYPERLINK> - New Media Release**
- **Literature search and summaries of 7 sunscreen active ingredients**
- **Consultation: Australian Sunscreen Exposure Model (ASEM)**

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

Therapeutic Goods Administration

MEDIA RELEASE

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The TGA review proposes that some sunscreen products containing the active ingredients homosalate and oxybenzone, as well as the degradant benzophenone, be reformulated to ensure sunscreens meet the highest standards of safety for prolonged and frequent use.

A comprehensive public and stakeholder consultation will begin today to help determine the level in sunscreens at which these ingredients remain suitable for use in Australian sunscreens.

All sunscreens available in Australia are safe. The TGA is not recommending a change in the use of sunscreens, nor are there any warnings, bans or recalls of any products.

The expert clinical advice remains that the benefits of all sunscreens available in Australia continue to far outweigh any risks. Australians are urged to continue using sunscreen.

The benefits of sunscreen in preventing skin damage and skin cancers are well established. Australia has the highest rates of skin cancer in the world with around 2,000 people dying each year from skin cancer. Sunscreens help prevent sunburn, skin damage and skin cancers. Australians should continue to protect themselves from the sun in five ways – using sunscreen, seeking shade and wearing protective clothing, hats and sunglasses.

Comprehensive information is available on the sunscreen ingredients page.

If you have any specific concerns about your health and sunscreen ingredients, please speak to your health provider.

Contact for members of the media:

- Email: news@health.gov.au
- Phone: (02) 6289 7400

Commented [s22]: Web team: insert link to ASEM

Commented [s22]: https://consultations.tga.gov.au/tga/proposed-model-for-assessing-sunscreen-ingredients/

Commented [s22]: Web team, link to literature search https://www.tga.gov.au/resources/publication/publications/literature-search-and-summaries-seven-sunscreen-active-ingredients

Commented [s22]: Web team: Link to public consultation

Commented [s22]: Media: Underlines for emphasis

Commented [s22]: Web team: Link to landing page D25-932651

From: s22
To: s22
Cc: s22
Subject: Update on your web publishing request WEB-2194
Date: Thursday, 10 April 2025 5:03:44 PM

Please do not reply to this automated email as we will not receieve it.

Hi s22

Your web publishing request WEB-2194 has an approval outcome of Approved.

Approver name:
CLARKE, Avinash.

Approver comments:

If your request was approved it will be actioned by the Web Team.
If your request was rejected it will not be actioned.

You can check the status of your web publishing request at any time. You will be notified when the request has been actioned.

If an approved web publishing job is no longer required, please contact us at s22 @tga.gov.au.

Thank you.
Publishing Team

s22

E: t s22 @tga.gov.au

Web Experience Section
HPRG Digital Branch
Regulatory Practice and Support Division | Health Products Regulation Group
Australian Government, Department of Health and Aged Care
27 Scherger Drive, Level G, Fairbairn Business Park
FAIRBAIRN, ACT 2600

See the HPRG Service gateway for direct access to our services and resources

Need help writing Guidance? Check out our Guidance template and drafting guide.

The Department of Health and Aged Care acknowledges the Traditional Owners and Custodians 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
To: s22
Cc: s22 ; CLARKE, Avinash; s22
Subject: Web publishing request WEB-2194 is complete
Date: Tuesday, 8 July 2025 11:51:47 AM

Hi s22

Your web publishing request for WEB-2194 is now complete.

Title:
Publication 3 of 3 for Sunscreen ingredients reveiw

New or updated pages:
Please check any new or updated pages as soon as possible and let me know if there are any problems. Please note, you may need to refresh your browser or clear your browsing history to see changes:

Kind regards

s22

Publishing Team

s22

E: s22 @tga.gov.au

Web Experience Section
HPRG Digital Branch
Regulatory Practice and Support Division | Health Products Regulation Group
Australian Government, Department of Health and Aged Care
27 Scherger Drive, Level G, Fairbairn Business Park
FAIRBAIRN, ACT 2600

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From: s22
To: s22
Cc: s22
Subject: Your publishing request WEB-2194 has been assigned to a publisher
Date: Friday, 11 April 2025 10:40:54 AM

Hi s22

Re: Publication 3 of 3 for Sunscreen ingredients reveiw WEB-2194 has been assigned to s22 for publishing.

You will be notified when the job is complete.

You can check the status of your request at any time.

Please note, if you would like to cancel this job, you will need to ask your approver to reject the web publishing job.

If you have any questions, please contact us at s22 @tga.gov.au.

Publishing Team
s22
E: s22 @tga.gov.au
Web Experience Section

HPRG Transformation Branch
Regulatory Practice and Support Division | Health Products Regulation Group
Australian Government, Department of Health and Aged Care
27 Scherger Drive, Level 2 , Fairbairn Business Park
FAIRBAIRN, ACT 2600
Regulatory Engagement Branch

Service Gateway
Direct access to our services and resources
Need help writing guidance? Check out the Regulatory Guidance Toolkit

The Department of Health and Aged Care 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
To: s22 s22
Subject: RE: UPDATED TPs - RE: Sunscreen Comms Reference Group [SEC=OFFICIAL]
Date: Wednesday, 5 March 2025 10:04:04 AM
Attachments: image001.png
image002.png
Sunscreen-ingredients-review-landing-page-version-2.0_3.3.2025.docx

---

Hi all

As agreed at our last meeting, I'm sending you a draft email that I'll circulate to the Sunscreen Communication Reference Group. If you could please review the email asap.

s22 – if you could also please add the attached web landing page into Trim with your other documents? (with thanks to s22 for drafting)

Thanks all

Hi all

We are re-activating the Sunscreen Communication Reference Group ahead of the anticipated mid-April publication of the safety review report and public consultation for the scheduling process.

The updated materials, approach and messaging align with the medical experts' input provided at the December meeting chaired by Robyn Langham.

We are specifically seeking your review and feedback on the following documents:

1. DRAFT Media Release - D24-4445890
2. DRAFT Landing Page – Trim link s22
3. Talking Points – D25-846157

Please send your comments or tracked changes by **COB Date** s22

We apologise for the short turnaround, however, the team needs to get Executive approval and package up for a ministerial brief.

The following documents/links are provided as reference:

1. DRAFT Min Brief - D25-803060
2. DRAFT Communication Strategy - D24-4058884
3. FINAL Dear Healthcare Professional Letter (final review by Robyn underway) - D24-4437749
4. Summary of Sunscreen Roundtable Discussion from Robyn - D25-555355
5. TGA's literature review

6. ASEM consultation results

Many thanks
s22

From: s22 @health.gov.au>
Sent: Wednesday, 26 February 2025 6:06 PM
To: s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 @Health.gov.au>
Cc: s22 @health.gov.au>; s22 @health.gov.au>; s22 @Health.gov.au>; s22 @Health.gov.au>
Subject: UPDATED TPs - RE: Sunscreen Comms Reference Group [SEC=OFFICIAL]
Importance: High

Hi All, Please see the updated Talking Points document in TRIM now: D25-846157

From: s22 @health.gov.au>
Sent: Wednesday, 26 February 2025 3:21 PM
To: s22 @health.gov.au>; s22 s22 @Health.gov.au>
Cc: s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>; s22 s22 @Health.gov.au>; s22 @Health.gov.au>
Subject: FW: Sunscreen Comms Reference Group [SEC=OFFICIAL]
Importance: High

Hi s22

We wanted to bring you both back into the 'sunscreen ingredients' conversation ahead of consulting with the broader Sunscreens Comms Reference Group.

Things have moved on a bit since we last spoke about this. You would have seen that the TGA's literature review was published; however, without active promotion we are not aware of it being picked up by the media or public. We expect interest to take-off with the publication of the safety review and announcement of the public consultation for proposed scheduling changes, anticipated in mid April.

With s22 departure, we are now working directly with the lovely s22 and s22. Ahead of the public announcement, the team are working to get the core materials finalised for a Min Brief. You can see the email chains below for reference.

The advice from the expert medical committee hosted by Robyn Langham was that we should not be advising the public to change their current practices regarding sunscreen use. Providing public information relating to sunscreen use on specific body parts (hands and face) was also not recommended. Further thought still needs to be given to messaging relating to infants/children and pregnant women.

Taking this all into account, we wondered if the current 'landing page' is providing too much content/information ahead of the public consultation where much of the detail still needs to be worked through and finalised. While it's important that we are clear and transparent, providing too much detail before things are settled may add to the confusion and lead to unintended consequences (such as people stopping using sunscreen). To illustrate, I have highlighted in yellow some of the phrasing that I think will need further work or is not yet settled on the draft landing page (listed below).

Instead, could we consider creating a 'Sunscreen ingredients' hub, similar to what we did through the rescheduling process for MDMA and psilocybine? The page itself would just provide a short intro that then links through to the scheduling public consultation, safety report, literature review, ASEM and media release.

Over time, we would add additional resources – noting the HPRG Executive has agreed that my team to create a range of resources tailored to GPs / HCPs / schools / carers / childcare centres, etc that we can get the language user tested before publication.

For reference, here are the current documents that are currently still under development and review:

Document list:

1. DRAFT Min Brief - D25-803060
2. DRAFT Communication Strategy - D24-4058884
3. DRAFT Dear Healthcare Professional Letter (final review by Robyn underway) - D24-4437749
4. DRAFT Media Release - D24-4445890
5. DRAFT Landing Page - D24-3900764
6. Talking Points (sent with recent Min Brief MB25-000207) – ~~Attached~~ - D25-846157

Once you've digested, let's have a chat – perhaps Thursday or Friday?

Thanks
s22

From: s22 [redacted] @Health.gov.au>
Sent: Wednesday, 26 February 2025 10:43 AM
To: s22 [redacted] @health.gov.au>
Subject: FW: Sunscreen Comms Reference Group [SEC=OFFICIAL]
Importance: High

I've made some changes to the media release. Over to you

From: s22 [redacted] @health.gov.au>
Sent: Monday, 24 February 2025 4:55 PM

To: s22 @health.gov.au>; s22 s22 @health.gov.au>
Cc: s22 @tga.gov.au>; s22 @health.gov.au>; s22 @Health.gov.au>
Subject: RE: Sunscreen Comms Reference Group [SEC=OFFICIAL]
Importance: High

Hi All,

I have drafted the Min Brief for the publication and updated/commented on the draft media release. And currently updating the Landing page, as much as possible, should be ready for your consideration tomorrow.
Will work on the TPs next, however I'm attaching the TPs sent around with the most recent Min Brief – The new one will essentially be an extension of these.

Document list:

1. DRAFT Min Brief - D25-803060
2. DRAFT Dear Healthcare Professional Letter (final review by Robyn underway) - D24-4437749
3. DRAFT Media Release - D24-4445890
4. DRAFT Landing Page - D24-3900764
5. Talking Point (sent with recent Min Brief MB25-000207) – Attached

s22 : Please feel free to update documents 3 and 4 in liaison with the Web Team and circulate to the Sunscreen Comms Reference Group (SCRG) for review/comments.

We plan to finalise the Min brief and the relevant documents by 7 March so ideally we would want the **SCRG feedback by 5 March**, if possible.

Thanks and Regards

s22

From: s22 @health.gov.au>
Sent: Friday, 21 February 2025 5:35 PM
To: s22 @health.gov.au>; s22 s22 @health.gov.au>
Cc: s22 @tga.gov.au>; s22 @health.gov.au>; s22 @Health.gov.au>
Subject: RE: Sunscreen Comms Reference Group [SEC=OFFICIAL]

Thanks s22

I been in an editing track today so I have already had a look-see. The comms strategy is good – I have added one comment about the messaging.
I have looked at the draft media release (D24-4445890) and added several comments for consideration though I see there will also need to be work done to align with the draft landing page. My team won't have much capacity to start drafting the scheduling pages until after the March advisory committee meetings.

Regards
s22

s22
Director – Scheduling and Chemicals Policy Section

Regulatory Practice and Support Division | Health Products Regulation Group
Regulatory Engagement Branch
Australian Government Department of Health and Aged Care
T: s22 | E: s22 @health.gov.au

From: s22 @health.gov.au>
Sent: Friday, 21 February 2025 4:57 PM
To: s22 @health.gov.au>; s22 s22 @health.gov.au>
Cc: s22 @tga.gov.au>; s22 @health.gov.au>; s22 @Health.gov.au>
Subject: RE: Sunscreen Comms Reference Group [SEC=OFFICIAL]

Afternoon all

I understand from s22 that s22 will be sending through some documents soon.

This afternoon, I have updated the Communication Strategy: D24-4058884 but I haven't reviewed or made changes to any of the corresponding content as yet. I'll wait until I see s22 latest versions.

For the Comms Strategy, I've removed most of the key messages as they were getting bogged down in detail (but you can still them if you check an earlier revision). It would make more sense for us to wordsmith the actual content then spend too much time on a document that won't be published. I've also removed all the resolved comments so we can start with a fresh document.

Let's chat more next week. Have a good weekend.

s22

From: s22 @health.gov.au>
Sent: Thursday, 13 February 2025 9:23 AM
To: s22 @health.gov.au>; s22

s22 @health.gov.au>
Cc: s22 @tga.gov.au>; s22 @health.gov.au>;
s22 @Health.gov.au>
Subject: RE: Sunscreen Comms Reference Group [SEC=OFFICIAL]

Thanks s22 and s22

Yes I was planning to include both of you to the same meeting, but went separately on the email

I'll send out a meeting invite shortly.

s22

From: s22 @health.gov.au>
Sent: Wednesday, 12 February 2025 6:11 PM
To: s22 @health.gov.au>
Cc: s22 @tga.gov.au>; s22 @health.gov.au>;
s22 @Health.gov.au>; s22 @health.gov.au>
Subject: RE: Sunscreen Comms Reference Group [SEC=OFFICIAL]

Hi s22

Thanks for reaching out. I note you've also reached out to s22 re scheduling timeframes. s22 and I work very closely together (in the same branch) so there may be value in combining this kick off meeting to discuss timeframes for both comms and scheduling.

I can also update you on what was discussed/agreed at HPRG Exec meeting.

Happy to meet tomorrow or Friday.

Cheers
s22

From: s22 @health.gov.au>
Sent: Wednesday, 12 February 2025 1:46 PM
To: s22 @health.gov.au>
Cc: s22 @tga.gov.au>; s22 @health.gov.au>
Subject: RE: Sunscreen Comms Reference Group [SEC=OFFICIAL]
Importance: High

Hi s22

Hope you are well.

I'm just reaching out, leading from s22 request to assist with the updates the Sunscreens Comms documents in preparation for the forthcoming Scheduling public notice/release planned for April 2025.

Essentially, we would need to run the Comms documents (including the Safety reviews from Tox (once finalised)) past the Ministers Office as part of a Min Publication brief prior to the Scheduling publication in April. This puts us in a bit of a time squeeze to get the relevant documents updated and acknowledged/reviewed by the Sunscreen Comms Reference Group by the end of February 2025 (ideally).
Once these are finalised we will attach them to the Min Brief for consideration by the MO which is planned to be sent out no later than Mid-March 2025 (at this stage).

I hope you got some clarity on the resources for preparation during your Monday meeting?

Can we perhaps meet and discuss the plan to circulate and finalise the Comms documents by end of February. Happy to meet tomorrow or Friday to discuss.

Regards,
s22

From: s22 @health.gov.au>
Sent: Friday, 7 February 2025 4:48 PM
To: s22 @health.gov.au>; s22 @tga.gov.au>
Cc: s22 @health.gov.au>
Subject: RE: Sunscreen Comms Reference Group [SEC=OFFICIAL]

Hi there s22

Well done on getting through step 1!

Your email is great timing. My team is presenting our quarterly report to HPRG Executive on Monday and as part of that meeting I was hoping to seek some guidance around the types of resources we should be preparing in advance of the next tranche of public information. I am keen for us to develop materials for all audiences and to have these tested. We do have some budget remaining for this type of activity. I will let you know how the conversation goes on Monday.

Many thanks
s22

From: s22 @health.gov.au>
Sent: Friday, 7 February 2025 4:44 PM
To: s22 @health.gov.au>; s22

s22 @tga.gov.au>
Cc: s22 @health.gov.au>
Subject: Re: Sunscreen Comms Reference Group [SEC=OFFICIAL]

Hi s22

Thank you for your invaluable assistance with the web news that was released on Tuesday. Despite a busy week, we are pleased to report that everything is under control.

With the disbandment of the Sunscreen Taskforce, s22 and I are now balancing the sunscreen project alongside our BAU in CMES. However, progress is promising. We will be working closely with Tox, the CMA's office and Scheduling to synchronise the publication of the safety reviews with the Scheduling public consultation.

Earlier this week, I forwarded you the Summary of Sunscreen Roundtable Discussion from Robyn (D25-555355). Could you please start the ball rolling again for the communication strategy (D24-4058884) and landing page (D24-3900764) updates to incorporate the clinical advice from the CMA? The Taskforce has previously revised these documents to use more consumer-friendly language based on the reference group's feedback.

We would greatly appreciate your team's expertise in refining the clinical advice for community release.

Please let us know if you encounter any issues or would like to discuss further. As always, happy to chat on the phone if it's easier!

Have a lovely weekend,
s22

s22
s22 **Complementary Medicines Evaluation Section**
Complementary and OTC Medicines 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, Gulgana Level 1 South East
PO Box 100, Woden ACT 2606, Australia
Gulgana First Aid Officer: On-site Tuesdays and Thursdays

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: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Sent: Wednesday, October 23, 2024 12:21 PM
To: s22 @health.gov.au>
Cc: HENDERSON, Nick <Nick.Henderson@health.gov.au>; CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>
Subject: Re: Sunscreen Comms Reference Group [SEC=OFFICIAL]

Hi Ali,

I am worried that there are a couple of critical issues that have not been addressed.

- there is a pressing need for clinically relevant toxicity advice - something that i think, on my reading of the current tox documents, will change the message that can be provided to consumers. As mentioned, this function can be fulfilled by MO review +/- ACM input as needed.

- the language in the media report is too complex for the community. Given the overlap with work done in other parts of the Department, this message should be constructed in consultation with the Department Comms team. At yesterday's meeting, it was the clear message from the Dept Comms person s22 , that the proposed messages are too complex for community release.

The time pressured approach the ability to provide a robust regulatory approach that has the interests of community safety at heart.

happy to discuss

robyn

From: s22 @health.gov.au>
Sent: Wednesday, October 23, 2024 11:32 AM
To: s22 @health.gov.au>; LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>; s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 @Health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>; s22 @health.gov.au>; s22 s22 @Health.gov.au>; s22 @health.gov.au>; CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>
Cc: s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 @Health.gov.au>; s22 @Health.gov.au>
Subject: Sunscreen Comms Reference Group [SEC=OFFICIAL]

Dear Colleagues,

Thank you for your feedback.

As advised yesterday, we've revised the communication strategy (D24-4058884) and landing page (D24-3900764) to use more consumer-friendly language and address your suggestions. **Please review and provide any comments or tracked changes by Monday next week.**

We have not updated the media release or the Dear Healthcare Professional letter yet. Once the landing page wording is finalised, and we have more specific consumer advice we can give for these ingredients, we'll complete the other documents.

As advised yesterday, please see how US publications have discussed issues about sunscreen safety regarding these ingredients (noting they have not made a final decision and they are still calling for data):

- US FDA FAQs about sunscreen changes. See 'Q: Should consumers only use sunscreens with zinc oxide and/or titanium dioxide?'.
- Also see this US FDA article, which answers the question ' This is a complex area of medicine and policy right now, to say the least. As a trained health care provider and the director of CDER's Office of Nonprescription Drugs, what do you want the public to know about sunscreen?'.
- The American Academy of Dermatology Association has advice about 'Are sunscreens safe'.

Best regards,

s22
s22
Director – Sunscreen Taskforce
Complementary & OTC Medicines Branch
Medicines Regulation Division | Health Products Regulation Group
Australian Government Department of Health and Aged Care
T: s22 | E: s22 @health.gov.au
Location: Level 1, 27 Sherger Drive, Fairbairn 2609
PO Box 100, Canberra ACT 2601, Australia

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Sunscreen ingredients

[*Summary – meta description for site search and search engines*] We are considering regulatory changes for therapeutic sunscreens following a review of active ingredients used in some sunscreen products.

[*Page intro*] We are considering potential regulatory changes for therapeutic sunscreens following a TGA review of active ingredients used in some sunscreen products.

Our review found theoretical risks from frequent exposure to some substances found in some sunscreens over a person's lifetime.

These substances are:

- homosalate
- oxybenzone
- benzophenone.

We have commenced public consultations on potential scheduling changes for these chemicals to lower their permitted use in sunscreens.

We are not proposing a ban on these substances or recalling any sunscreen products.

Important [*callout box*]

You should continue to use sunscreen to protect against the sun's harmful ultraviolet (UV) rays.

Recent clinical advice has confirmed that the benefits of sunscreen continue to far outweigh any theoretical risks.

Related information

[Item list (can contain external links to consultation hub)]

- **TGA publishes literature review of sunscreen ingredients**
- **Literature search and summaries of 7 sunscreen active ingredients**
- **Consultation: Australian Sunscreen Exposure Model (ASEM)**

From: s22
To: s22
Subject: FW: Sunscreen Comms Reference Group - Input on updated materials by COB 6 March [SEC=OFFICIAL]
Date: Thursday, 6 March 2025 5:13:50 PM
Attachments: image001.png
image002.png
image003.png
image006.png

Hey all – see below s22 email cover note.

I plan to look at all the feedback tomorrow

Cheers
s22

From: s22 @health.gov.au>
Sent: Thursday, 6 March 2025 5:08 PM
To: s22 @health.gov.au>
Cc: s22 @Health.gov.au>; s22
s22 @Health.gov.au>; s22 @Health.gov.au>
Subject: RE: Sunscreen Comms Reference Group - Input on updated materials by COB 6 March [SEC=OFFICIAL]

Hi s22
I've reviewed and marked some changes in track on the TRIM records. Appreciate a lot of people are adding their 2c.

My main query is to ensure (if possible) we aren't saying there are 'theoretical risks' in sunscreen use, as I fear that will embolden anti-sunscreen fear merchants to drive down sunscreen use. I've removed this from the media release and queried its inclusion on the webpage.

I'm not sure who the talking points are for, but I'm guessing they're for internal use. I've sent through draft TPs for potential Ministerial use previously.

Thank you for keeping us briefed and included in this process, it is much appreciated. We aren't able to brief our campaign partner Cancer Council Australia on this impending announcement as they are also sunscreen manufacturers (through a third party), but we would appreciate advice on when we can discuss this with them. The mid-April timing suits the campaign, as we will be off-air at this time.

Thanks
s22

s22
Director – Communication and Partnerships
National Cancer Screening Programs | Cancer, Hearing and Chronic Conditions
Australian Government, Department of Health and Aged Care

GPO Box 9848, Canberra ACT 2601

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

From: s22 @health.gov.au>
Sent: Wednesday, 5 March 2025 2:33 PM
To: s22 @health.gov.au>; s22 s22 @health.gov.au>; LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>; s22 s22 @Health.gov.au>; s22 @health.gov.au>; s22 @Health.gov.au>; CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>; s22 s22 @Health.gov.au>
Cc: s22 @health.gov.au>; s22 s22 @industrialchemicals.gov.au>; s22 s22 @Health.gov.au>; s22 @Health.gov.au>; s22 s22 @Health.gov.au>; s22 @health.gov.au>; s22 s22 @Health.gov.au>; s22 @health.gov.au>; SYME, Sarah <Sarah.Syme@health.gov.au>
Subject: Sunscreen Comms Reference Group - Input on updated materials by COB 6 March [SEC=OFFICIAL]

Hi all

We are re-activating the Sunscreen Communication Reference Group ahead of the anticipated mid-April publication of the safety review report and public consultation for the scheduling process.

The updated materials, approach and messaging align with the medical experts' input provided at the December meeting chaired by Prof Robyn Langham.

We are specifically seeking your review and feedback on the following documents:

1. DRAFT Media Release - D24-4445890
2. DRAFT Landing Page – D25-932651
3. Talking Points – D25-846157

Please send your comments or tracked changes by **COB 6 March 2025**.

We apologise for the short turnaround, however, the team needs to get Executive approval and package up for a ministerial brief due early next week.

The following documents/links are provided as reference:

1. DRAFT Min Brief - D25-803060
2. DRAFT Communication Strategy - D24-4058884
3. FINAL Dear Healthcare Professional Letter - D24-4437749
4. Summary of Sunscreen Roundtable Discussion from Robyn - D25-555355
5. TGA's literature review
6. ASEM consultation results

Many thanks
s22

From: s22 @health.gov.au>
Sent: Friday, 8 November 2024 8:47 AM
To: s22 @health.gov.au>; s22 @health.gov.au>; LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>; s22 @health.gov.au>; s22 @health.gov.au>; s22 @Health.gov.au>; s22 @health.gov.au>; s22 @health.gov.au>; s22 @health.gov.au>; s22 @Health.gov.au>; s22 @health.gov.au>; CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>
Cc: s22 @health.gov.au>; s22 @industrialchemicals.gov.au>; s22 @Health.gov.au>; s22 @Health.gov.au>; s22 @health.gov.au>; s22 @Health.gov.au>; s22 @health.gov.au>; s22 @Health.gov.au>; s22 @health.gov.au>
Subject: UPDATE: Sunscreen Comms Reference Group [SEC=OFFICIAL]

Dear Colleagues,

I hope you are well. I wanted to thank you for your input into the draft sunscreen communications so far and update you on our progress.

As mentioned in our last meeting, we were seeking clinical advice to inform our communications and activities. We are now planning to formally seek advice from clinical experts during the Advisory Committee on Medicines meeting from 4-6 December. After this, we will update the communications and discuss taking this issue to the joint medicines and chemical scheduling meeting in June 2025.

Therefore, we will not need to conduct any more work on the communications until we receive this advice. We will return to the reference group for a review of the updated communications in the new year.

In the meantime, if we receive any media enquiries, we may return to you for advice to ensure we maintain a consistent message.

Please note I will be on extended leave from 22 November – my colleague s22 will be leading this work in my absence. Please don't hesitate to give me a call before then if you wish to discuss.

Warm regards,

s22

s22
Director – Sunscreen Taskforce
Complementary & OTC Medicines Branch
Medicines Regulation Division | Health Products Regulation Group
Australian Government Department of Health and Aged Care
T: s22 | E: s22 @health.gov.au
Location: Level 1, 27 Sherger Drive, Fairbairn 2609
PO Box 100, Canberra ACT 2601, 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: LANGHAM, Robyn
To: s22 [redacted]; CLARKE, Avinash; s22 [redacted]
Cc: s22 [redacted]; SYME, Sarah
Subject: Re: Sunscreen Comms Reference Group - Input on updated materials by COB 6 March [SEC=OFFICIAL]
Date: Thursday, 6 March 2025 6:47:06 PM
Attachments: image001.png
D25-846157 Talking points - MB25-xxxxx - Min Brief for release of safety review of sunscreen ingredients - Mar 2025-RL.DOCX

Hi s22 [redacted]. hope all is well..

couple of things (and apologies, TRIM would not let me amend the documents)

1. would be good to discuss the minute (just to make sure we can send to both GP Colleges..) it would also be worth disseminating to other peak bodies, but we can discuss.

2. also, have a suggestion to the second paragraph of the media release (D24-4445890)

The TGA is not proposing a change in use of sunscreen, or any warnings, or bans or recalls of any products. Australians are urged to continue using sunscreen.

really to reinforce the importance of not stopping use.. the paragraph currently starts with the words 'ban'..

3. Landing page; D25-932651
   I agree with s22 [redacted] that the following paragraph can be deleted

   'Our review found theoretical risks from frequent exposure to some substances found in some sunscreens over a person's lifetime.

   These substances are:

   homosalate

   oxybenzone

   benzophenone.'

4. Landing page; D25-932651
   I would also repeat the statement as written above..
   The TGA is not proposing a change in use of sunscreen, or any warnings, or bans or recalls of any products. Australians are urged to continue using sunscreen.
5. Landing page; D25-932651
   call-out box - 'Recent clinical advice has confirmed that the benefits of sunscreen continue to far outweigh any theoretical risks.'
   This implies that there is information that we have only just learned.. i would suggest

we recraft this as..
'Clinical advice remains unchanged - the benefits of sunscreen continue to outweigh any theoretical risks posed by some sunscreen chemicals'

6. finally, the talking points i have made some suggested changes.. we need to say right at the start that sunscreens are safe. I have attached this document (tracked) noting that i cannot save any changes into TRIM for this document.

thanks again for all of your work on this.

robyn

From: s22 @health.gov.au>
Sent: Wednesday, March 5, 2025 2:32 PM
To: s22 @health.gov.au>; s22 s22 @health.gov.au>; LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>; s22 s22 @Health.gov.au>; s22 @health.gov.au>; s22 @Health.gov.au>; CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>; s22 s22 @Health.gov.au>
Cc: s22 @health.gov.au>; s22 s22 @industrialchemicals.gov.au>; s22 s22 @Health.gov.au>; s22 @Health.gov.au>; s22 s22 @Health.gov.au>; s22 @health.gov.au>; s22 s22 @Health.gov.au>; s22 @health.gov.au>; SYME, Sarah <Sarah.Syme@health.gov.au>
Subject: Sunscreen Comms Reference Group - Input on updated materials by COB 6 March [SEC=OFFICIAL]

Hi all

We are re-activating the Sunscreen Communication Reference Group ahead of the anticipated mid-April publication of the safety review report and public consultation for the scheduling process.

The updated materials, approach and messaging align with the medical experts' input provided at the December meeting chaired by Prof Robyn Langham.

We are specifically seeking your review and feedback on the following documents:

1. DRAFT Media Release - D24-4445890

2. DRAFT Landing Page – D25-932651
3. Talking Points – D25-846157

Please send your comments or tracked changes by **COB 6 March 2025**.

We apologise for the short turnaround, however, the team needs to get Executive approval and package up for a ministerial brief due early next week.

The following documents/links are provided as reference:

1. DRAFT Min Brief - D25-803060
2. DRAFT Communication Strategy - D24-4058884
3. FINAL Dear Healthcare Professional Letter - D24-4437749
4. Summary of Sunscreen Roundtable Discussion from Robyn - D25-555355
5. TGA's literature review
6. ASEM consultation results

Many thanks
s22

From: s22 @health.gov.au>
Sent: Friday, 8 November 2024 8:47 AM
To: s22 @health.gov.au>; s22 s22 @health.gov.au>; LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>; s22 s22 @Health.gov.au>; s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 s22 @Health.gov.au>; s22 @health.gov.au>; CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>
Cc: s22 @health.gov.au>; s22 s22 @industrialchemicals.gov.au>; s22 s22 @Health.gov.au>; s22 @Health.gov.au>; s22 s22 @health.gov.au>; s22 @Health.gov.au>; s22 s22 @health.gov.au>; s22 s22 @Health.gov.au>; s22 @health.gov.au>
Subject: UPDATE: Sunscreen Comms Reference Group [SEC=OFFICIAL]

Dear Colleagues,

I hope you are well. I wanted to thank you for your input into the draft sunscreen communications so far and update you on our progress.

As mentioned in our last meeting, we were seeking clinical advice to inform our communications and activities. We are now planning to formally seek advice from clinical experts during the

Advisory Committee on Medicines meeting from 4-6 December. After this, we will update the communications and discuss taking this issue to the joint medicines and chemical scheduling meeting in June 2025.

Therefore, we will not need to conduct any more work on the communications until we receive this advice. We will return to the reference group for a review of the updated communications in the new year.

In the meantime, if we receive any media enquiries, we may return to you for advice to ensure we maintain a consistent message.

Please note I will be on extended leave from 22 November – my colleague s22 will be leading this work in my absence. Please don't hesitate to give me a call before then if you wish to discuss.

Warm regards,

s22

s22
Director – Sunscreen Taskforce
Complementary & OTC Medicines Branch
Medicines Regulation Division | Health Products Regulation Group
Australian Government Department of Health and Aged Care
T: s22 | E: s22 @health.gov.au
Location: Level 1, 27 Sherger Drive, Fairbairn 2609
PO Box 100, Canberra ACT 2601, Australia

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Attachment C

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Is sunscreen still safe to use?

Yes sunscreen is still safe to use. The benefits of sunscreen in preventing sunburn and skin cancers are well established and sun protection should remain a priority.

- The TGA remains committed to safeguarding public health so 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.~~
- We are closely monitoring international developments, and have conducted~~ing~~ our own comprehensive literature review of a number of common active ingredients used in Australian sunscreens~~, and considering all available scientific information~~.
- While ~~some components of~~certain ingredients in some sunscreens currently marketed in Australia may have minor, theoretical risks associated with frequent use over one's lifetime, their use is safe. Their use is considered even more important when balanced against the dangers of prolonged sun exposure and the increased risk of skin cancer.
- We are working with the relevant stakeholders to address any ~~our~~ concerns ~~and that~~ the safety of the Australian public remains our priority. This ensures the public can use sunscreen bought in Australia with confidence.
- Note that sunscreen is just one of the ways we can protect against skin cancer amongst other protection mechanisms via clothing coverage, seeking shade and wearing sunglasses.

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Why has the TGA done safety reviews of sunscreen ingredients:

- In 2019, the Food and Drug Administration (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.
- T~~t~~he 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.
- In response to the interest by the US FDA~~.~~, ~~T~~the TGA ~~conducted and is~~ have ~~finalising~~published the outcomes of the public consultation to the Australian Sunscreen Exposure Model (ASEM) and a literature review, as communicated to you in MB24-002706 and MB25-00207 in January and February 2025, respectively.

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Attachment C

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- A safety review was also undertaken by the TGA for a degradant chemical resulting from an active sunscreen ingredient in 2023 via the low-negligible risk changes public consultation.

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- The TGA have finalised a comprehensive safety ~~review~~ assessment of these common sunscreen ingredients found in Australia using the literature review and adopting the ASEM ~~and have established a Sunscreen Taskforce to prioritise and advance this work. 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~~.
- ~~Five ingredients were assessed as low risk.~~
- ~~A safety risk was~~The assessment identified some literature that reference risks associated with~~for~~ homosalate, oxybenzone and benzophenone as they can be systemically absorbed after application to the skin.
    - the currently available evidence for endocrine disrupting properties of homosalate and oxybenzone is inconclusive, and at best equivocal based on non-clinical studies. There have been no clinical studies examining endocrine disruption in humans.

Talking points on medical advice from ~~CMO~~TGA's Chief Medical Advis~~e~~or:

- At the expert stakeholder roundtable held 18 December 2024, there was ~~a~~ unanimous agreement that supporting the use of sunscreens ~~is~~ to prevent skin cancers should be the forefront of any messaging or campaign. Any messaging that advises reduction or avoidance would result Australians ~~in the risk of~~ avoiding sunscreen use, with the subsequent risk of excess skin cancer in the community.
- The group advised that there was no clear evidence to bring about a change in practice at this time. There was support for an ongoing measured regulatory approach, ensuring an ongoing message of the safety and utility of sunscreens.
- ~~Regarding advice to infants and pregnant women, the group recommended moderating the advice in a balanced approach, and that providing clear and correct advice in the first instance will avoid the need to dispel myths down the track. The benefits of sunscreen application to avoid skin cancer, maintaining Vitamin D levels through sun exposure outweighs the non-definitive theoretical risk of harm currently.~~
- ~~The group also advised that messaging from all sectors should be aligned, and that advice to apply to certain body parts only would result in a reduced and harmful use of sunscreen. There was also a request for new educational resources for primary care.~~

What are the next steps for these safety reviews~~.~~?

- The government (TGA and AICIS) ~~is proposing~~proposes that ~~the~~ any potential risks identified in these safety reviews be managed ~~by including~~

Attachment C

homosalate, oxybenzone and benzophenone in the Poisons Standard through the standard Scheduling process.

- The Scheduling process allows affected industry stakeholders, healthcare professionals, including sponsors and manufacturers of both primary and secondary sunscreensand interested stakeholders, to provide feedback and suggestions in a single consultation process, rather than multiple consultations from different regulators.
- In Australia, there are two categories of sunscreens:
  - Primary sunscreens (those that are primarily intended for UV protection) are regulated as therapeutic goods by the TGA.
  - 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 by AICIS and ACCC.
- The sScheduling process is the preferred risk the management measure, because:
  - It is applicable to both primary and secondary sunscreens.
  - It uniformly and concurrently ensures the safety of conventional sunscreens and cosmetics containing sunscreen ingredients.

Talking points on communication strategy:

- The TGA intends to make a public statement about the public release of the safety reviews.
- The TGA has developed a communication strategy to support dissemination of accurate and balanced information to minimise any impacts on public confidence in sunscreens during the Scheduling public consultation process. The strategy includes a media release, webpage with FAQs about the safety review and sunscreen safety, and social media posts.
- A Sunscreen Communication Reference Group has been formed, including representatives from HPRG and Primary and Community Care Group. The reference group will review and coordinate communication activities so that communication is balanced and engages with the public, industry and relevant organisations (such as the Australasian College of Dermatologists and Cancer Council Australia).

If needed:

- 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.

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Formatted: Right
Commented s22 [redacted], do you mind reviewing content covered under this sub-heading?
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- ~~This was followed by the publication of a US FDA proposed rule in 2019 elaborating the requirement for testing and labelling of sunscreens by manufacturers~~
- ~~The rule divided the 16 active ingredients approved in USA into three categories:~~
  - ~~Category I (GRASE)~~
  - ~~Category II (not GRASE)~~
  - ~~Category III (additional data needed)~~
- ~~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.~~

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- ~~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.~~
- The TGA is committed to safeguarding public health and places a high priority on ~~takes~~ the safety of sunscreen ingredients ~~very seriously~~.

From: s22
To: s22
Cc: s22 s22
Subject: RE: UPDATED PUBLICATION DATE 8 JULY 2025 - RE: Publication Schedule for Sunscreen Ingredients Project [SEC=OFFICIAL]
Date: Tuesday, 8 July 2025 1:01:21 PM
Attachments: image001.png
image002.png
image004.png
image005.png

Hi s22

The media release and associated pages have been published. I will be sending the subscription email out shortly.

Media release: TGA to consult on additional controls for some sunscreen ingredients | Therapeutic Goods Administration (TGA)

Kind Regards,

s22
Web Experience Developer – Web Experience Section
HPRG Digital Brach

Regulatory Practice and Support Division | Health Products Regulation Group
Australian Government, Department of Health, Disability, and Ageing
E: s22 @health.gov.au
Location: Gulgana Building, Fairbairn
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: Tuesday, 8 July 2025 10:18 AM
To: s22 @tga.gov.au>; s22 @health.gov.au>; s22 @Health.gov.au>; s22 s22 @Health.gov.au>
Cc: s22 @health.gov.au>; s22 s22 @Health.gov.au>; s22 @Health.gov.au>; s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>
Subject: RE: UPDATED PUBLICATION DATE 8 JULY 2025 - RE: Publication Schedule for Sunscreen Ingredients Project [SEC=OFFICIAL]

Thanks s22

Regards

s22

s22
Acting Assistant Secretary

Regulatory Engagement Branch

Regulatory Practice and Support Division | Health Products Regulation Group
Australian Government Department of Health, Disability and Ageing
T: s22 | E: s22 @health.gov.au

From: s22 @tga.gov.au>
Sent: Tuesday, 8 July 2025 10:15 AM
To: s22 @health.gov.au>; s22 @health.gov.au>; s22 @Health.gov.au>; s22 s22 @Health.gov.au>; s22 @tga.gov.au>
Cc: s22 @health.gov.au>; s22 s22 @Health.gov.au>; s22 @Health.gov.au>; s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>
Subject: RE: UPDATED PUBLICATION DATE 8 JULY 2025 - RE: Publication Schedule for Sunscreen Ingredients Project [SEC=OFFICIAL]

Thanks s22

I have updated the media release draft to reflect the changes made in TRIM. I will publish the media release after all the other sunscreen pages have been published.

Please let me know if you need anything else.

Thank you.

Kind Regards,

s22
Web Experience Developer – Web Experience Section
HPRG Digital Brach

Regulatory Practice and Support Division | Health Products Regulation Group
Australian Government, Department of Health, Disability, and Ageing
E: s22 @health.gov.au
Location: Gulgana Building, Fairbairn
PO Box 100, Woden ACT 2606, Australia

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From: s22 @health.gov.au>
Sent: Tuesday, 8 July 2025 10:03 AM
To: s22 @health.gov.au>; s22 s22 @Health.gov.au>; s22 @Health.gov.au>; s22 @tga.gov.au>
Cc: s22 @health.gov.au>; s22 s22 @Health.gov.au>; s22 @Health.gov.au>; s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>
Subject: RE: UPDATED PUBLICATION DATE 8 JULY 2025 - RE: Publication Schedule for Sunscreen Ingredients Project [SEC=OFFICIAL]
Importance: High

Hi all,

I have just had a discussion with Gaelene, Sharon and Kartik who have agreed to removed the 3rd paragraph of the media release. This has now been updated in TRIM and can proceed.

Regards
s22

s22
Acting Assistant Secretary

Regulatory Engagement Branch

Regulatory Practice and Support Division | Health Products Regulation Group
Australian Government Department of Health, Disability and Ageing
T: s22 | E: s22 @health.gov.au

From: s22
Sent: Tuesday, 8 July 2025 9:53 AM
To: s22 @health.gov.au>; s22 s22 @Health.gov.au>; s22 @Health.gov.au>; s22 @tga.gov.au>
Cc: s22 @health.gov.au>; s22 s22 @Health.gov.au>; s22 @Health.gov.au>; s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>
Subject: RE: UPDATED PUBLICATION DATE 8 JULY 2025 - RE: Publication Schedule for Sunscreen Ingredients Project [SEC=OFFICIAL]
Importance: High

Dear Colleagues,

I would like the publication of the **media release to be paused**. The internal review of the socials

message has picked up changes in the media release we weren't aware which needs additional discussion.

Please contact me if there are questions. I am trying to get this resolved ASAP.

Regards
s22

s22
Acting Assistant Secretary

Regulatory Engagement Branch

Regulatory Practice and Support Division | Health Products Regulation Group
Australian Government Department of Health, Disability and Ageing
T: s22 | E: s22 @health.gov.au

From: s22 @health.gov.au>
Sent: Monday, 7 July 2025 4:44 PM
To: s22 @Health.gov.au>; s22 s22 @health.gov.au>; s22 @Health.gov.au>; TGA s22 @tga.gov.au>
Cc: s22 @health.gov.au>; s22 s22 @Health.gov.au>; s22 @Health.gov.au>; s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>; s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>
Subject: RE: UPDATED PUBLICATION DATE 8 JULY 2025 - RE: Publication Schedule for Sunscreen Ingredients Project [SEC=OFFICIAL]

Thanks s22 for filling out the last web request details.

WEB TEAM: Please note publication time is **10.00 am AEST**, so all the different areas in the Department are ready to respond when media/enquiries come in.

I'll be on-site as well, and available via mobile, if required. My mobile s22

Thanks,
s22

s22
Director (A/g) – Complementary Medicines Evaluation Section
Complementary and OTC Medicines Branch
Medicines Regulation Division | Health Products Regulation Group
Australian Government, Department of Health, Diability and Ageing
T: s22 | E: s22 @health.gov.au
Location: Fairbairn, Gulgana Level 1 South East

PO Box 100, Woden ACT 2606, Australia

Gulgana First Aid Officer: On-site Tuesdays and Thursdays

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: Monday, 7 July 2025 3:21 PM
To: s22 @health.gov.au>; s22 @health.gov.au>; s22 @Health.gov.au>; s22 @tga.gov.au>
Cc: s22 @health.gov.au>; s22 @Health.gov.au>; s22 @Health.gov.au>; s22 @health.gov.au>; s22 @health.gov.au>; s22 @health.gov.au>; s22 @health.gov.au>; s22 @health.gov.au>; s22 @health.gov.au>
Subject: RE: UPDATED PUBLICATION DATE 8 JULY 2025 - RE: Publication Schedule for Sunscreen Ingredients Project [SEC=OFFICIAL]

Hello everyone

Just to update, the pre-meeting consultation document and the consultation hub and eDM are ready expect for the links to the safety reviews. I have submitted a request to publish the landing page for consultation of TGA website (D25-2826766 ; not to confuse with the Consultation hub which we can publish ourselves). I think the sequence of events will be

1. Publication 1 of 3 - Safety reviews are published by the web team
2. Publication 2 of 3 – publication of pre-meeting public notice (PMPN) calling for submissions on proposed scheduling changes
   a. I update the PMPN (D25-2752198) with links to the safety review (published under 1) and open the consultation with the PMPN embedded. The PMPN is published only in the consultation hub and not published separately on TGA website.
   b. Web team publishes the landing page for consultation (D25-2826766) on TGA website with links to the specific consultation (published under 2(a) above)
      Note: This step can happen immediately after the publication of safety reviews. However public will see that the consultation is not open until we publish.
   c. I send out the eDMs for consultation on the PMPN.
3. Publication 3 of 3 – media release and landing page – *can happen before or parallel to 2 (publication of the PMPN)*

Let me know of any comments or concerns. I will be in office tomorrow and can also be contacted on s22

Regards
s22

From: s22 @health.gov.au>
Sent: Tuesday, 1 July 2025 3:37 PM
To: s22 @health.gov.au>; s22 s22 @Health.gov.au>; s22 @tga.gov.au>
Cc: s22 @health.gov.au>; s22 s22 @Health.gov.au>; s22 @Health.gov.au>; s22 @health.gov.au>; s22 s22 @Health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>; s22 s22 @health.gov.au>
Subject: UPDATED PUBLICATION DATE 8 JULY 2025 - RE: Publication Schedule for Sunscreen Ingredients Project [SEC=OFFICIAL]
Importance: High

Hi all,

Sorry to put a spanner in the works.

There has been a change to the publication date. The UPDATED date of publication is now **8 July 2025**.

Please note that the sequence of publishing is critical.

Please note there is a change in the TRIM link in the SEB Web request WEB-2198 (Highlighted below) as there were further changes are clearance was re-sought.

1. Publication **1 of 3** – Web publication request to come **from SEB** (Web request WEB-2198)
- Safety review of seven active sunscreen Ingredients (D25-2148966 – Publication ready version).
- Safety review of benzophenone (D25-1519220 – Publication ready version).

2. Publication **2 of 3** – Web publication request to come **from REB** (REB will progress with this web request on their end)
- Pre-meeting publication notice.

3. Publication **3 of 3** – Web publication request to come **from COMB** (Web request WEB-2194)
- Media Release (D25-1144490)
- Landing Page (D25-932651)

Apologies for any inconvenience caused,
s22

From: s22 @health.gov.au>
Sent: Monday, 30 June 2025 8:56 PM
To: s22 @Health.gov.au>; s22 s22 @health.gov.au>; s22 @tga.gov.au>
Cc: s22 @health.gov.au>; s22 s22 @Health.gov.au>; s22 @Health.gov.au>; s22 @health.gov.au>; s22 @Health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 @health.gov.au>
Subject: Re: JUNE UPDATE - RE: Publication Schedule for Sunscreen Ingredients Project [SEC=OFFICIAL]

Hi s22

That one is in progress. We also have to prepare the consultation hub as well. We'll let s22 know when it's ready to go.

Regards
s22

Sent from Workspace ONE Boxer
On 30 June 2025 at 20:13:28 AEST, s22 @Health.gov.au> wrote:

> Hi s22
>
> Thanks so much for this update. When I checked this afternoon, we did not have a web request for Publication **2 of 3** – Pre-meeting publication notice, which I note was to come from REB.
>
> I meant to call you to discuss today but time got away. It would be great if you could liaise directly with the web publishing team s22 about this so we can ensure everything happens at the right time.
>
> Warm regards,
> s22
>
> s22 **(she/her)**
> Acting Director, HPRG Web Experience Section
> HPRG Digital Branch
> Regulatory Practice and Support 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: Gulgana Building
PO Box 100, Woden ACT 2606, Australia

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From: s22 @health.gov.au>
Sent: Monday, 30 June 2025 2:47 PM
To: s22 @Health.gov.au>; s22 s22 @Health.gov.au>; s22 @health.gov.au>; s22 @health.gov.au>; TGA Website s22 @tga.gov.au>
Cc: s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 @Health.gov.au>; s22 @health.gov.au>; s22 s22 @Health.gov.au>; s22 s22 @health.gov.au>; s22 s22 @health.gov.au>
Subject: RE: JUNE UPDATE - RE: Publication Schedule for Sunscreen Ingredients Project [SEC=OFFICIAL]

Hi Web Team and Web publication team,

Following our web requests submitted in April, we've now received confirmation that senior executives are comfortable for the process to proceed, and the Ministerial Office has been briefed accordingly:

- It is now planned to publish the pre-meeting notice in the week starting 30 June 2025 (the regulations require a minimum 20 business-day consultation period after publication of the notice). This precedes discussion at a special Joint meeting of the Advisory Committee of Chemicals Scheduling (ACCS) and Advisory Committee on Medicines Scheduling (ACMS) being organised for a date in September (tentatively a day on 9-11 or 16-18 September).

Our current aim is to publish the following on Thursday, 3 July 2025. Should there be any changes to this timeline, we will ensure your teams are informed as soon as practicable. Please note that the sequence of publishing is critical.

Please note there is a change in the TRIM link in the SEB Web request WEB-2198 (Highlighted below) as there were further changes are clearance was re-sought.

2. Publication **1 of 3** – Web publication request to come **from SEB** (Web request WEB-2198)

- Safety review of seven active sunscreen Ingredients (D25-2148966 – Publication ready version).
- Safety review of benzophenone (D25-1519220 – Publication ready version).

3. Publication **2 of 3** – Web publication request to come **from REB** (REB will progress with this web request on their end)

- Pre-meeting publication notice.

4. Publication **3 of 3** – Web publication request to come **from COMB** (Web request WEB-2194)

- Media Release (D25-1144490)
- Landing Page (D25-932651)

Please don't hesitate to reach out should you need further assistance or clarification.

Kind regards,
s22

s22
Director (A/g) – Complementary Medicines Evaluation Section
Complementary and OTC Medicines Branch
Medicines Regulation Division | Health Products Regulation Group
Australian Government, Department of Health, Diability and Ageing
T: s22 E: s22 @health.gov.au
Location: Fairbairn, Gulgana Level 1 South East
PO Box 100, Woden ACT 2606, Australia
Gulgana First Aid Officer: On-site Tuesdays and Thursdays
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
Sent: Tuesday, 15 April 2025 10:48 AM
To: s22 @Health.gov.au>; s22 s22 @Health.gov.au>; s22 @health.gov.au>
Cc: s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 @Health.gov.au>; s22 @health.gov.au>; s22 s22 @health.gov.au>; s22 s22 @health.gov.au>
Subject: UPDATE - RE: Publication Schedule for Sunscreen Ingredients Project [SEC=OFFICIAL]
Importance: High

UPDATE: Potential change in plans – PLEASE HOLD OFF THE PUBLICATIONS

Dear Web team

PLEASE PUT A HOLD ON THE BELOW PUBLICATIONS AS THE SENIOR EXECs DISCUSS A POTENITAL CHANGE IN THE OVERALL PROCESS.

Regards
s22

Dear Web team

Thank you once again for meeting with us recently to discuss a plan ahead.

As promised, please find below the list of documents scheduled for publication as part of the overall sunscreen ingredients project, along with the scheduling public consultation (via Citizen Space). These documents are listed in the proposed order of publication:

4. Publication **1 of 3** – Web publication request to come **from SEB** (Web request WEB-2198)

- Safety review of seven active sunscreen Ingredients (D25-1519215 – Publication ready version).
- Safety review of benzophenone (D25-1519220 – Publication ready version).

5. Publication **2 of 3** – Web publication request to come **from REB**

- Web page associated with the scheduling public consultation.

6. Publication **3 of 3** – Web publication request to come **from COMB** (Web request WEB-2194)

- Media Release (D25-1144490)
- Landing Page (D25-932651)

I hope this information assists in planning the publication process.

Please do not hesitate to contact me if you require any further information.

Regards

s22

s22
Senior Evaluator – Complementary Medicines Evaluation Section
Complementary and OTC Medicines Branch
Medicines Regulation Division | Health Products Regulation Group
Australian Government, Department of Health and Aged Care
T: s22 | E: s22 @health.gov.au
Location: Level 1, 27 Scherger Drive, Fairbairn ACT
PO Box 100, Woden ACT 2606, Australia

-----Original Appointment-----
From: s22 @health.gov.au>
Sent: Friday, 28 March 2025 3:03 PM
To: s22 ;
s22
Subject: Sunscreen ingredients web publishing [SEC=OFFICIAL]
When: Monday, 7 April 2025 3:30 PM-4:00 PM (UTC+10:00) Canberra, Melbourne, Sydney.
Where: Microsoft Teams Meeting

Hi all

We are starting to finalise all of the elements that will need to be published in parallel for the Sunscreen ingredients work.

s22 we wanted to have a chat with you both about the best way to compile the request, given there will be multiple branches/approvers involved.

Cheers
s22

[SEC=OFFICIAL]

From: CLARKE, Avinash
To: s22 [redacted]
Cc: s22 [redacted]; VUCKOVIC, George
Subject: Fwd: Sunscreen Safety Report - FOI Release [SEC=OFFICIAL]
Date: Monday, 3 February 2025 10:32:02 AM
Attachments: image001.png
Summary of sunscreen roundtable discussion Deb182024.docx
Expert stakeholder roundtable - TGA"s toxicology review of sunscreen ingredients - Attendance report 12-18-24.csv

---

FYI

Sent from Workspace ONE Boxer
---------- Forwarded message ----------

From: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Date: February 3, 2025 at 10:22:47 AM GMT+11
Subject: Re: Sunscreen Safety Report - FOI Release [SEC=OFFICIAL]
To: CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>
Cc: s22 [redacted] @Health.gov.au>, s22 [redacted] @Health.gov.au>

attached..

i have included the file from the Teams meeting of attendees.. let me know if you need info about the expertise of each invitee.

There is also some commentary included in the Teams meeting. - hope i have incorporated all.

Robyn

From: CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>
Sent: Sunday, February 2, 2025 10:33 PM
To: LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>
Cc: s22 [redacted] @Health.gov.au>; s22 [redacted] @Health.gov.au>
Subject: RE: Sunscreen Safety Report - FOI Release [SEC=OFFICIAL]

Hi Robyn,

Any chance we can get that summary of the expert stakeholder roundtable on sunscreen ingredients (ideally tomorrow AM) – even if it is in draft and not finalised. Be useful to include relevant advice in talking points and min brief.

Thanks!

A

Avinash Clarke

02 5132 1436

From: HENDERSON, Nick <Nick.Henderson@health.gov.au>
Sent: Friday, 31 January 2025 11:26 AM
To: s22 @Health.gov.au>; LAWLER, Tony <Anthony.LAWLER@Health.gov.au>
Cc: CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>; VUCKOVIC, George <George.VUCKOVIC@Health.gov.au>
Subject: RE: Sunscreen Safety Report - FOI Release [SEC=OFFICIAL]

Ok

Avi and George, we'll need to have TPs and comms (including web content) ready by COB Monday. I advised the MO this morning we will also provide Min Brief with key points, this will need to go to MO COB Monday as well

---

From: s22 @Health.gov.au>
Sent: Friday, 31 January 2025 11:25 AM
To: HENDERSON, Nick <Nick.Henderson@health.gov.au>; LAWLER, Tony <Anthony.LAWLER@Health.gov.au>
Cc: CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>; VUCKOVIC, George <George.VUCKOVIC@Health.gov.au>
Subject: RE: Sunscreen Safety Report - FOI Release [SEC=OFFICIAL]

s22 confirmed with me this morning that the deadline is Monday.

From: HENDERSON, Nick <Nick.Henderson@health.gov.au>
Sent: Friday, 31 January 2025 11:23 AM
To: s22 @Health.gov.au>; LAWLER, Tony <Anthony.LAWLER@Health.gov.au>

Cc: CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>; VUCKOVIC, George <George.VUCKOVIC@Health.gov.au>
Subject: RE: Sunscreen Safety Report - FOI Release [SEC=OFFICIAL]

Thanks s22

I understood the deadline was Tuesday/Wednesday?

From: s22 @Health.gov.au>
Sent: Friday, 31 January 2025 10:44 AM
To: LAWLER, Tony <Anthony.LAWLER@Health.gov.au>; HENDERSON, Nick <Nick.Henderson@health.gov.au>
Subject: Sunscreen Safety Report - FOI Release [SEC=OFFICIAL]

Hi both,

- 4 documents will be released on Monday, 3 February 2025
- minimal redactions (principally limited to "deliberative content" by way of internal comments on drafts).

Regards

s22

Regulatory Legal Services Division (16 - 31 January 2025)

Regulatory Legal Services Division | Health Products Regulation Group | Therapeutic Goods Administration

Australian Government, Department of Health and Aged Care

T: s22 | E: Grant.Moodie@health.gov.au

Location: Level 15, 595 Collins Street, Melbourne 3000

PO Box 100, Woden ACT 2606, Australia

[SEC=OFFICIAL]

Summary of roundtable discussion

TGA's risk assessment of sunscreen ingredients

11.00am- 1pm, Wednesday 18 December 2024

Teleconference

Chair: Professor Robyn Langham AM

Attendees: see attached

Agenda item 1: Welcome and introductions

Professor Langham opened the meeting. The list of attendees is included at Attachment 1.

Agenda item 2: Sunscreen risk assessment- current status and possible future direction

- Professor Langham presented on the risk management of sunscreen chemicals in Australia.
- It was reiterated that skin cancer is a major health issue in Australia. The age-standardised rate of melanoma in Australia increased from 46 cases per 100,000 persons in 2000 to an estimated 55 cases per 100,000 persons in 2021.
- It was noted that the TGA undertook a review of sunscreen ingredients following regulatory changes progressed by the FDA in 2019, with a single change to maximum concentration of one chemical by the EMA in 2022.
- An overview of the AICIS review of homosalate was provided.
- It was noted that the TGA conducted two recent reviews;
    - The first review led to the development of the Australian Sunscreen Exposure Model (ASEM). The ASEM was proposed to provide a standardised method for calculating sunscreen exposure, reducing discrepancies in risk assessments. It was developed to align with Australian conditions (i.e. high UV light levels) and consumer practices (i.e. outdoor lifestyle), ensuring sunscreens are safe and effective when used as directed. The TGA undertook extensive targeted pre-public consultation between May-July 2024 to develop the ASEM and public consultation again between July and August 2024. There was broad in-principle support from this consultation for the adoption of the ASEM for estimating therapeutic sunscreen exposure for ingredient risk assessments.
    - The second review is the risk assessment of seven chemicals in Australian sunscreens, the Draft Risk Assessment of 7 Active Sunscreen Ingredients, noting a theoretical risk with two of the seven chemicals from the extensive literature review and with the application of the ASEM to allow for a local contextualisation.

Following a brief overview of the proposed next steps, including a proposed scheduling change to limit concentrations of the chemicals in question in therapeutic sunscreens, the proposed messaging was also presented, forming the basis of the subsequent roundtable discussion.

Agenda item 3: Roundtable discussion

The group felt that the work undertaken was thorough and detailed. There was concern that the term 'low risk' was not one that the public would readily understand in applying to their own context.

There was discussion on the utility of the ASEM (particularly with respect to calculation of surface area), and some questions regarding the specifics of the PK analysis of some chemicals in the draft document.

There was a clear and consistent view of the group that supporting the use of sunscreens to prevent skin cancers should be front and centre of any campaign. Any messaging that advises reduction or avoidance would result in the risk of shunning sunscreen.

The advice from the group was that there was no clear evidence to bring about a change in practice at this time. There was support for an ongoing measured regulatory approach, ensuring an ongoing message of the safety and utility of sunscreens. A number of examples and approaches concerning sunscreen use were shared, particularly Queensland Health and also a strong social media presence.

Further discussion regarding advice to infants and pregnant women were discussed. Advice was on softening the advice from an absolute, particularly with respect to advice for pregnant women. Providing clear and correct advice in the first instance will avoid the need to dispel myths down the track. Advice was on providing a balanced approach (avoiding skin cancer, maintaining Vitamin D levels through sun exposure rather than advice to avoid using sunscreen when pregnant because of a minimal theoretical risk of harm)

The group also gave clear advice that messaging from all sectors should be aligned, and that advice to apply to certain body parts only would result in a reduced and harmful use of sunscreen. There was also a request for new educational resources for primary care.

Prof Langham concluded the meeting by thanking all those present for their time and efforts, with an undertaking to keep the group informed of ongoing work.

Document 23

1. Summary

Meeting title	Expert stakeholder roundtable - TGA's toxicology review of sunscreen ingredients
Attended participants	22
Start time	12/18/24, 10:46:41 AM
End time	12/18/24, 1:00:57 PM
Meeting duration	2h 14m 16s
Average attendance time	1h 47m 7s

2. Participants

Name	First Join	Last Leave	In-Meeting Duration	Email	Participant ID (UPN)	Role
[redacted]	12/18/24, 10:55:43 AM	12/18/24, 12:59:34 PM	2h 3m 51s	[redacted]@Health.gov.au	[redacted]@Health.gov.au	Presenter
Robyn Langham (Unverified)	12/18/24, 10:56:05 AM	12/18/24, 12:59:29 PM	2h 3m 24s			Presenter
[redacted]	12/18/24, 10:58:05 AM	12/18/24, 12:59:21 PM	2h 1m 15s	[redacted]@health.gov.au	[redacted]@health.gov.au	Presenter
[redacted]	12/18/24, 10:58:27 AM	12/18/24, 12:59:18 PM	2h 51s	[redacted]@health.gov.au	[redacted]@health.gov.au	Presenter
[redacted]	12/18/24, 11:01:49 AM	12/18/24, 12:59:19 PM	1h 57m 30s	[redacted]@Health.gov.au	[redacted]@Health.gov.au	Presenter
Brian Priestly (Unverified)	12/18/24, 11:01:49 AM	12/18/24, 12:59:22 PM	1h 57m 32s			Presenter
[redacted]	12/18/24, 11:01:50 AM	12/18/24, 12:59:21 PM	1h 57m 30s	[redacted]	[redacted]	Presenter
Liang Joo Leow (External)	12/18/24, 11:01:53 AM	12/18/24, 12:59:24 PM	1h 57m 31s	[redacted]	[redacted]	Presenter
Liang Joo Leow (Unverified)	12/18/24, 11:01:54 AM	12/18/24, 12:59:31 PM	1h 57m 37s			Presenter
Joanne muller (Unverified)	12/18/24, 11:01:55 AM	12/18/24, 12:59:21 PM	1h 57m 26s			Presenter
[redacted]	12/18/24, 11:01:58 AM	12/18/24, 12:18:13 PM	1h 16m 14s	[redacted]	[redacted]	Presenter
Monika Janda (External)	12/18/24, 11:02:06 AM	12/18/24, 12:59:20 PM	1h 57m 14s	[redacted]	[redacted]	Presenter
Amanda Gwee (External)	12/18/24, 11:02:11 AM	12/18/24, 12:59:19 PM	1h 57m 8s	[redacted]	[redacted]	Presenter
[redacted]	12/18/24, 11:02:39 AM	12/18/24, 12:59:25 PM	42m 35s	[redacted]@Health.gov.au	[redacted]@Health.gov.au	Presenter
[redacted]	12/18/24, 11:03:24 AM	12/18/24, 12:59:17 PM	1h 55m 53s	[redacted]@health.gov.au	[redacted]@health.gov.au	Presenter
Debra Kennedy (External)	12/18/24, 11:04:24 AM	12/18/24, 12:59:27 PM	1h 55m 3s	[redacted]	[redacted]	Presenter
Dr Michael Bonning (Unverified)	12/18/24, 11:05:45 AM	12/18/24, 12:59:18 PM	1h 53m 32s			Presenter
Melissa Eastgate	12/18/24, 11:06:14 AM	12/18/24, 12:59:18 PM	1h 53m 3s	[redacted]	[redacted]	Presenter
Euan Walpole	12/18/24, 11:07:05 AM	12/18/24, 12:59:19 PM	1h 52m 14s	[redacted]	[redacted]	Presenter
Darren Roberts (Sydney LHD)	12/18/24, 11:08:38 AM	12/18/24, 12:59:23 PM	1h 50m 44s	[redacted]	[redacted]	Presenter
Ju Oei (South Eastern Sydney LHD)	12/18/24, 11:16:09 AM	12/18/24, 12:59:24 PM	1h 43m 15s	[redacted]	[redacted]	Presenter
[redacted]	12/18/24, 12:35:46 PM	12/18/24, 1:00:57 PM	25m 11s	[redacted]@health.gov.au	[redacted]@health.gov.au	Presenter

3. In-Meeting Activities

Name	Join Time	Leave Time	Duration	Email	Role
[redacted]	12/18/24, 10:55:43 AM	12/18/24, 12:59:34 PM	2h 3m 51s	[redacted]@Health.gov.au	Presenter
Robyn Langham (Unverified)	12/18/24, 10:56:05 AM	12/18/24, 12:59:29 PM	2h 3m 24s		Presenter
[redacted]	12/18/24, 10:58:05 AM	12/18/24, 12:59:21 PM	2h 1m 15s	[redacted]@health.gov.au	Presenter
[redacted]	12/18/24, 10:58:27 AM	12/18/24, 12:59:18 PM	2h 51s	[redacted]@health.gov.au	Presenter
[redacted]	12/18/24, 11:01:49 AM	12/18/24, 12:59:19 PM	1h 57m 30s	[redacted]@Health.gov.au	Presenter
Brian Priestly (Unverified)	12/18/24, 11:01:49 AM	12/18/24, 12:59:22 PM	1h 57m 32s		Presenter
[redacted]	12/18/24, 11:01:50 AM	12/18/24, 12:59:21 PM	1h 57m 30s	[redacted]	Presenter
Liang Joo Leow (External)	12/18/24, 11:01:53 AM	12/18/24, 12:59:24 PM	1h 57m 31s	[redacted]	Presenter
Liang Joo Leow (Unverified)	12/18/24, 11:01:54 AM	12/18/24, 12:59:31 PM	1h 57m 37s		Presenter
Joanne muller (Unverified)	12/18/24, 11:01:55 AM	12/18/24, 12:59:21 PM	1h 57m 26s		Presenter
[redacted]	12/18/24, 11:01:58 AM	12/18/24, 12:18:13 PM	1h 16m 14s	[redacted]	Presenter
Monika Janda (External)	12/18/24, 11:02:06 AM	12/18/24, 12:59:20 PM	1h 57m 14s	[redacted]	Presenter
Amanda Gwee (External)	12/18/24, 11:02:11 AM	12/18/24, 12:59:19 PM	1h 57m 8s	[redacted]	Presenter
[redacted]	12/18/24, 11:02:39 AM	12/18/24, 11:36:03 AM	33m 23s	[redacted]@Health.gov.au	Presenter
[redacted]	12/18/24, 12:50:12 PM	12/18/24, 12:59:25 PM	9m 12s	[redacted]@Health.gov.au	Presenter
[redacted]	12/18/24, 11:03:24 AM	12/18/24, 12:59:17 PM	1h 55m 53s	[redacted]@health.gov.au	Presenter
Debra Kennedy (External)	12/18/24, 11:04:24 AM	12/18/24, 12:59:27 PM	1h 55m 3s	[redacted]	Presenter
Dr Michael Bonning (Unverified)	12/18/24, 11:05:45 AM	12/18/24, 12:59:18 PM	1h 53m 32s		Presenter
Melissa Eastgate	12/18/24, 11:06:14 AM	12/18/24, 12:59:18 PM	1h 53m 3s	[redacted]	Presenter
Euan Walpole	12/18/24, 11:07:05 AM	12/18/24, 12:59:19 PM	1h 52m 14s	[redacted]	Presenter
Darren Roberts (Sydney LHD)	12/18/24, 11:08:38 AM	12/18/24, 12:59:23 PM	1h 50m 44s	[redacted]	Presenter
Ju Oei (South Eastern Sydney LHD)	12/18/24, 11:16:09 AM	12/18/24, 12:59:24 PM	1h 43m 15s	[redacted]	Presenter
[redacted]	12/18/24, 12:35:46 PM	12/18/24, 1:00:57 PM	25m 11s	[redacted]@health.gov.au	Presenter

From: s47F
To: s22 ;s47F
s47F ;s22 ;s47F
s47F HENDERSON, Nick; CLARKE, Avinash;s22
s22 ;
s47F
s47F s22
Cc: s22 ; LANGHAM, Robyn;s22
Subject: Re: Expert stakeholder roundtable - TGA"s risk assessment of sunscreen ingredients [SEC=OFFICIAL]
Date: Wednesday, 18 December 2024 5:53:17 PM
Attachments: image001.png
MkJxeXVFTStwdHV4ZHFaNkpMZmNhdz09.pdf
parisi2003.pdf
vernez2012.pdf

Articles I mentioned this morning, three as file attachments and one as a link:

https://www.researchgate.net/figure/Skin-surface-area-of-body-parts-expressed-as-a-fraction-of-total-body-surface-area-and_tbl2_23475459

Liang Joo

From: s22 @health.gov.au>
Sent: Tuesday, 17 December 2024 10:26
s47F
s22 @health.gov.au>;s47F
s47F
s47F HENDERSON, Nick <Nick.Henderson@health.gov.au>; CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>;s22
s22 @health.gov.au>;s22 @health.gov.au>;
s22 @health.gov.au>;s22 @health.gov.au>;
s22 @Health.gov.au>;s22 @Health.gov.au>;
s22 @Health.gov.au>;s47F
s47F
s47F
s47F
s47F s22
s22 @health.gov.au>;s22 @health.gov.au>
Cc:s @health.gov.au>;s22
s22 @health.gov.au>; LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>;
s22 @Health.gov.au>
Subject: Expert stakeholder roundtable - TGA's risk assessment of sunscreen ingredients [SEC=OFFICIAL]

Dear all,

Thank you for confirming your participation in tomorrow's expert roundtable discussion regarding TGA's risk assessment of sunscreen ingredients.

Date- Wednesday 18 December 2024, 11am – 1pm

Venue - All external experts are attending the meeting virtually via Microsoft Teams. The meeting link can be found within the TGA calendar invite.

Papers- All relevant papers are available on GovTeams, available at Meeting Papers. You should have access to five documents:

- Agenda
- Roundtable paper- TGA risk assessment of sunscreen ingredients
- Attachment 1- Australian Sunscreen Exposure Model
- Attachment 2- Risk Assessment of Seven Active Sunscreen Ingredients (Working Copy)
- Attachment 3- Benzophenone Risk Assessment (Working Copy)

DOIs- Please ensure you have submitted your DOI paperwork prior to attendance.

If you require assistance with accessing the documents or entering the meeting tomorrow, please feel free to contact me directing via email at s22 @health.gov.au or via phone on s22 .

I look forward to meeting you all tomorrow.

Kind regards,
s22

s22
Senior Policy Officer/Director
Chief Medical Adviser Unit
He Regulation Group
T: s22 | E: s22 @health.gov.au
Location: 27 Scherger Drive, Level 2
PO Box 100, Canberra ACT 2601, Australia

The Department of Health and Aged Care 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 all Elders both past and present.

Supplement-
Photoprotection

Cutaneous solar ultraviolet exposure and clinical aspects of photodamage

Claire Battie, Michèle Verschoore

L'Oréal Research and Innovation, France

Address for correspondence:
Claire Battie, 5-29 quai Aulagnier - 92665 Asnieres Sur Seine, France.
E-mail: cbattie@rd.loreal.com

ABSTRACT

Solar ultraviolet (UV) radiation reaching the earth is a combination of UVB (290–320 nm) and UVA (320–400 nm) wavelengths. Since UVA is less energetic than UVB, UVB has long been thought to be the factor responsible for the damaging effects of solar radiation. But with modern tools such as *in vitro* models, it has been proven that UVA plays a major role. The objective of this review is to show how skin may be exposed to UV light and to highlight the clinical aspects of UV-induced skin damages with the respective contribution of UVB or UVA. Even if UVA is less energetic than UVB, it is more abundant and penetrates deeper into the skin, reaching as far as the dermis. Various factors also influence skin exposure to UV light: the latitude, season, and time of the day. Acute as well as chronic sun exposure induces short- and long-term clinical damages. Erythema and pigmentation are immediate responses of normal human skin exposed to UV radiation. The long-term effects are photoaging and photocarcinogenesis. In particular, UVA appears to play a major role in the deterioration of dermal structure leading to the photoaged appearance of the skin.

Key words: Photoaging, photocarcinogenesis, pigmentation, ultraviolet

CUTANEOUS UV EXPOSURE

Solar radiation reaching the skin

The solar spectrum includes several wavebands ranging from the very short cosmic rays to very long radio waves and beyond. Solar radiation reaching the surface of the earth, and thereby the surface of our skin, contains infrared (700-2500 nm), visible (400-700 nm), and ultraviolet radiation (UVR) (290-400 nm). UVR is invisible.

Although UVR represents less than 9% of the total solar irradiance between 290 and 2500 nm received on the earth's surface,[1] the UV photons have the greatest biological impact. More precisely, there are three categories of UVR. UVC rays (100-290 nm) are the shortest in wavelength and are filtered out by the ozone layer. In contrast, UVB rays (290-320 nm) and UVA (320-400 nm) reach the earth's surface and are responsible for cutaneous photobiological events. UVA can be further subdivided into longer wavelengths, UVA1 (340-400 nm), and shorter wavelengths, UVA2 (320-340 nm).[2]

UVB radiation reaches the earth in relatively low amounts (about 0.5% of solar spectral irradiance at ground level, integrated over 290-2500 nm range) and is highly energetic. In contrast, UVA rays are lower in energy, but they are at least 20 times more abundant. 95% of UV rays reaching the ground level are UVA.[1]

Various factors influencing skin exposure to solar ultraviolet rays

The solar UV irradiance highly varies because it depends on geo-orbital and environmental parameters.

Geo-orbital parameters include latitude, date of the year, and hour of the day.[3,4] All these factors are

Access this article online	
Quick Response Code:	Website: www.ijdvl.com
	DOI: 10.4103/0378-6323.97350

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related to the height of the sun in the sky, and hence the pathway of beam of sunlight through the atmosphere. Because of the elliptical orbit of the earth around the sun, the distance between the sun and the earth varies by about 3.4% over the year. This results in a variation of about 7% in intensity and in slightly higher levels of UVR in summer in the southern than in the northern hemisphere. Both the quality (spectrum) and the quantity (intensity) of terrestrial UVR vary with sun's elevation above the horizon, or solar altitude. The solar altitude depends on the time of the day, day of the year, and geographic location (latitude and longitude). On a summer day, the UV energy received (daily dose) includes approximately 3.5% UVB and 96.5% UVA.[5] UV irradiance is greater for both UVA and UVB with decreasing latitude.[3]

Figure 1 shows the variation of UVB and UVA irradiance during a clear summer day in South of France. Balasaraswathy *et al.* also showed that both the UVA and UVB reached a peak between 11.30 a.m. and 1.30 p.m. in Coimbatore, India.[6] In addition, this study highlighted the fact that UVB radiation was much lower than UVA radiation in the morning and in the evening.

The dose of UVR reaching the skin also depends on the season. UVB irradiance is much higher in summer than in winter at a given site. UVA irradiance is less affected by seasons and decreases to a lesser extent in winter.[3] In Coimbatore, compared to average irradiance between March and October, UVB was lower in November, December, January, and February by 24%, 40%, 19%, and 12%, respectively, and UVA was lower by 13%, 22%, 18%, and 13%, respectively.[6]

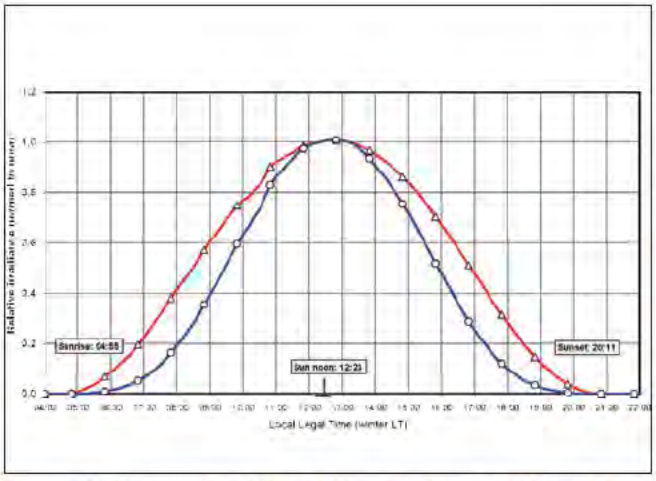

Figure 1: Variations of UVB (blue line) and UVA (red line) irradiances along a clear summer day in south of France

Environmental parameters can also influence UV exposure. They include the ozone total column and the ozone vertical atmospheric profile, clouds, pollutants, dusts, aerosols, and albedo (reflection of UVR from the ground).[7] Absorption by ozone, in addition to cutting off UVC radiation, has a dramatic influence on the amount of UVB radiation reaching the ground.[8-13] As aerosols and dusts are less concentrated at high altitudes, UV irradiance values are higher in a mountain location than at the sea level. Finally, a highly reflecting environment, such as white sand, fresh snow or, to a lesser extent, white broken clouds acting as reflectors, can significantly increase UV irradiance.[14]

Furthermore, the main part of UVA radiation is not absorbed by standard glass: car windows, verandas, conservatories, and windows in general fail to protect against UVA as they do from UVB radiation because the glass short cut-off wavelength is about 320 nm. Thus, high UVA doses may be received while erythemal UVB is filtered out.

The contribution of diffuse UVR is also important and should not be underestimated. Indeed, a recent study suggests that diffuse irradiation may explain a large part of the cumulative annual exposure dose.[15]

Solar ultraviolet penetration throughout the skin

70% of UVB radiation that reaches the skin is absorbed by the stratum corneum, 20% reaches viable epidermis, and only 10% penetrates the upper part of the dermis. On the other hand, UVA radiation is partly absorbed by the epidermis, but 20-30% of it reaches deep dermis. Thus, UVA rays are more penetrating than UVB ones. The major chromophores that determine the depth of penetration are nucleic acids, aromatic amino acids, and melanin. So, UVB has a major action on the epidermis and UVA can also target the dermis [Figure 2].

CLINICAL ASPECTS OF UV-INDUCED SKIN DAMAGE

Short-term effects

Sunburn (erythema) and suntan (pigmentation) are the immediate responses of normal human skin exposed to UVR.

Erythema

Erythema (sunburn) is the most familiar symptom

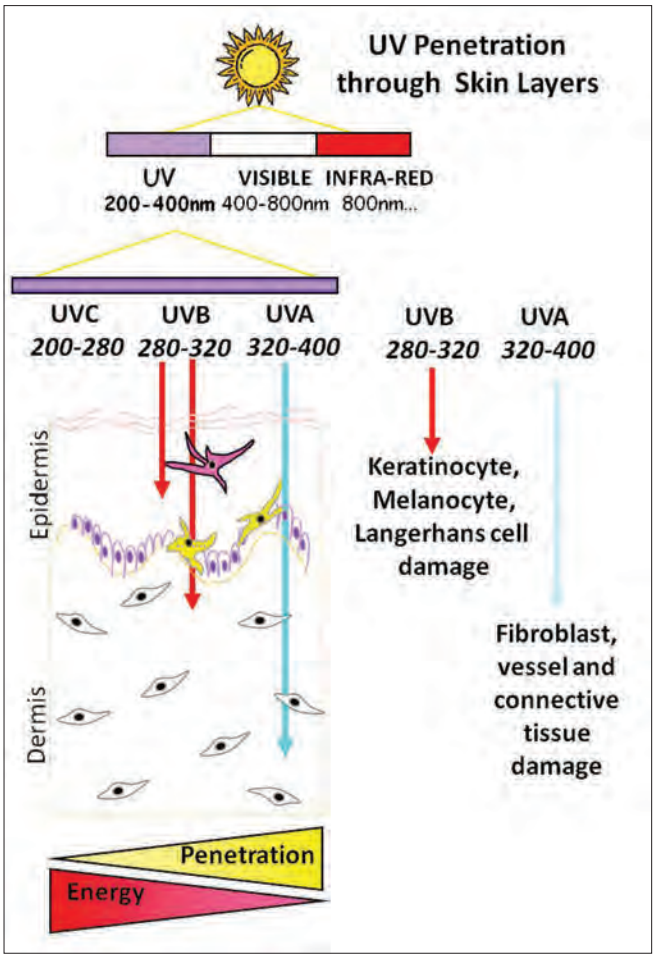

Figure 2: Diagram showing depth of UV penetration into the skin and photon-associated energy according to wavelength: UVA penetrates deeper

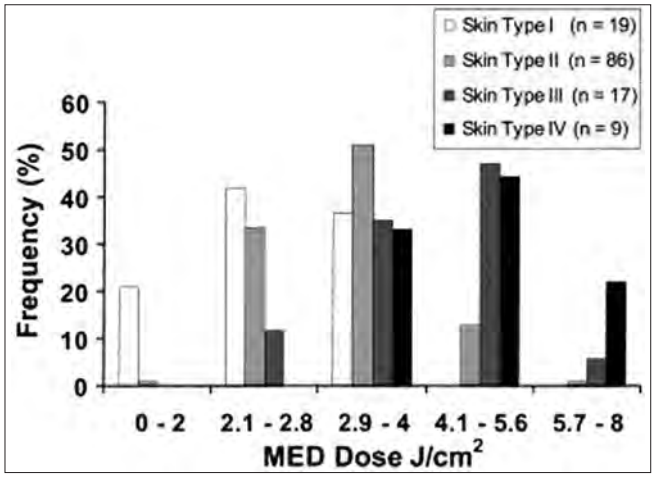

Figure 3: Distribution of MED with SSR filter in skin types I-IV. These data show a considerable overlap, especially in the mid-dose range (from 19)

associated with UVR overexposure. It is an acute skin inflammatory reaction associated with redness. The erythemal reaction to UVR depends on the wavelength range. Increasing wavelength decreases considerably the erythemal effectiveness. UVB, particularly at 307 nm, is the most effective waveband for eliciting erythema in the human skin. UVA radiation is 1000-fold less potent in producing skin erythema.

UVB-induced erythema is a delayed response. It reaches a peak at 6-24 h depending on the dose,[16] with erythema, pruritus, and pain in sun-exposed areas. This erythema fades over a day or longer, depending on the dose and the skin type.[17] In skin type I, it may last longer compared to skin type III or IV.[4] UVA-induced erythema contributes to at least 15% of total sun-induced erythema.[18] The minimal erythema dose (MED) is defined as the UVB dose that induces minimally perceptible or detectable erythema. This biological value obviously varies from one subject to another. It depends on the skin phototype as well as the skin color typing and body area. MED increases with higher skin type.[19] Since most Indians have Fitzpatrick skin phototypes III-V, they obviously have a higher MED than Caucasian skin. It is nevertheless important to note that there is a considerable overlap of MED between skin phototypes, especially in the mid-dose range [Figure 3]. Similarly, people involved in outdoor occupation have a higher MED as compared to people involved in indoor occupation.

Later changes include hyperkeratosis (increased scaling), acanthosis (epidermal thickening), disorganization and misalignment of keratinocytes, dermal vascular ectasia, and mononuclear perivascular infiltration.

Pigmentation

Sun exposure induces the UVA and UVB pigmentation phenomena. UVA-induced changes in color begin with an immediate darkening of the skin due to photo-oxidation of pre-existing melanin [immediate pigment darkening (IPD)].[18,20] In skin types III and IV, this pigmentation may appear within a short single exposure to UVA (dose less than 6 J/cm).[21] A partial fading occurs rapidly within 1 h after the end of exposure. As it decreases, the pigmentation progressively loses its blue component within 2 h post-exposure. The phenomenon is more prominent in darkly pigmented individuals and it does not protect the skin against the effects of UVB radiation.[4]

Following exposure to UVA doses higher than about 10 J/cm^2, a stable residual pigmentation is observed after the transient part of IPD has faded out. This

pigmentation [persistent pigment darkening (PPD)] remains detectable for a few days or weeks, depending on the UVA dose applied and this is particularly seen in skin with phototypes III or IV.[21] It is also due to melanin photo-oxidation. A minimal PPD dose is about 15 J/cm^2 and represents somewhat less than the UVA dose received over 1 h of exposure to a quasi-zenithal sun.[22]

The neo-melanization or delayed pigmentation is characterized by a visible brown pigmentation in UV-exposed skin, which represents an increase in epidermal melanin content. It becomes visible after about 72 h. An acute erythemogenic dose of UVB is necessary to induce delayed pigmentation. Both UVA and UVB can cause tanning, but UVA is less effective.

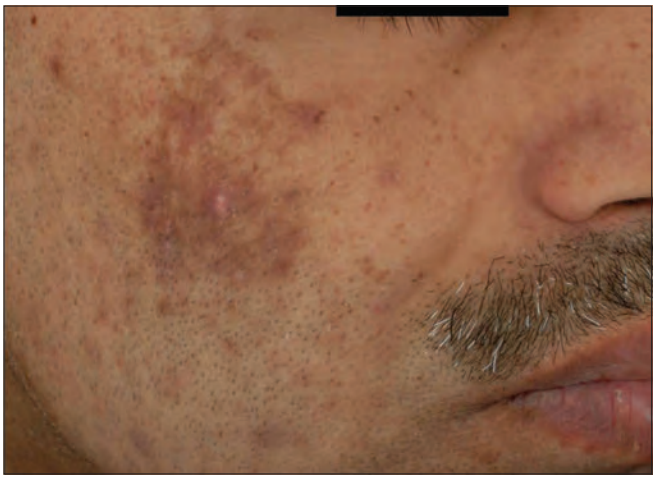

Figure 4: Melasma of the face in an Indian man (Courtesy: Prof. Ortonne)

However, melanization produced by cumulative UVA exposures appears to be much longer lasting (several months or even a year) than that acquired with UVB exposures.

UVB pigmentation phenomena result in a homogeneous color, which can bring some natural protection. On the contrary, UVA pigmentation is not protective, as shown by the absorbance spectra of UVA-induced pigmentation which is under 0 from 290 to 400 nm.[23]

UV-pigmentation can lead to irregular pigmentation and hyperpigmented areas. In particular, melasma [Figure 4], post-inflammatory pigmentation, and actinic lentigines are associated with exposure to UVR.[24]

Pigmented changes are the major sign of skin photoaging in Asians.[25-27] An ethnic group-related variation in melanosome distribution was reported,[28-32] showing a mix of individual (about 60%) and aggregated (about 40%) melanosomes in Asian skin, whereas aggregated melanosomes (85%) prevail in European skin.[32,33] The density and highly variable size of melanosomes in Asian skin could account for the irregular, spotty pigmentation associated with photoaging. It is also known that in darker-skinned individuals, UVA induces greater pigmenting effects than UVB.[34]

Long-term effects: Photoaging and photocarcinogenesis

Photoaging

The damage caused to the skin by chronic sun exposure differs in many respects from natural aging. Photoaged skin is characterized by numerous clinical signs, fine

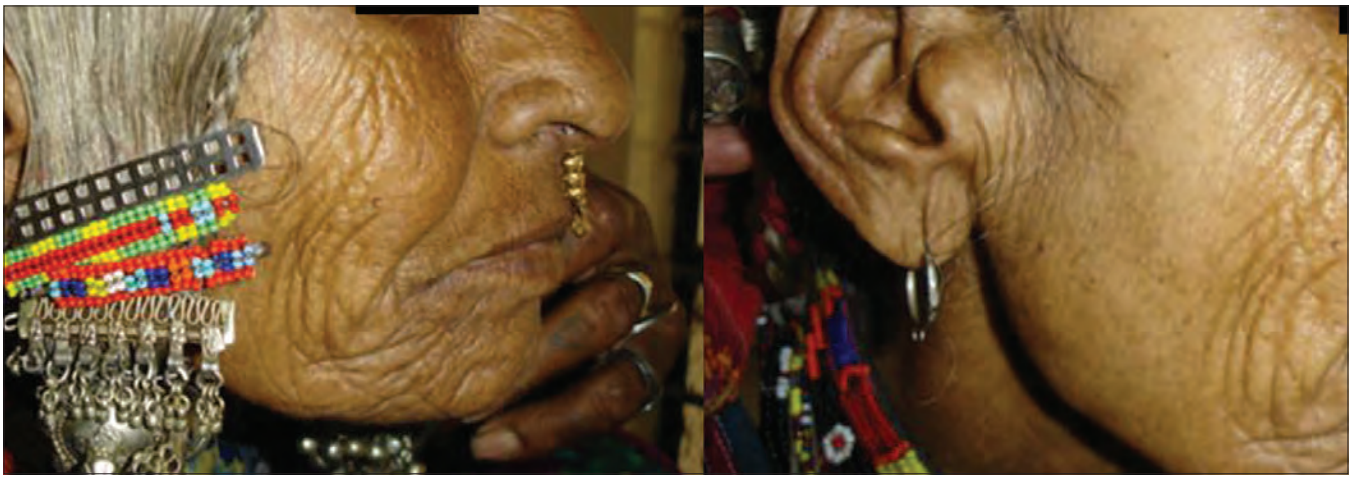

Figure 5: A 70-year-old Indian woman –Sun-protected versus sun-exposed skin (Courtesy: Prof. Inamadar)

and coarse wrinkling, laxity, leathery appearance, mottled pigmentation reflected by lentigines, fragility, impaired wound healing, and telangiectasias. [Figure 5] clearly illustrates this impact of sun exposure on skin.

Histologic and ultrastructural studies have revealed that the major alterations in photoaged skin are found in the connective tissue (dermis).[35-37] Damage induced by UVR is primarily reflected by an impaired collagen fibril network and accumulation of abnormal, amorphous, elastin-containing material.[38] Increased lysozyme staining on abnormal elastic fibers from sun-damaged skin has been reported.[39] As lysozyme at high concentrations inhibits the activity of collagenase and elastase, it prevents the elastic fibers component from proteolysis. Greater deposition follows repeated UVA exposure. In actinically damaged skin, there is also a loss of collagen associated with change in collagen composition (i.e. an increase in collagen III/collagen I ratio). There is a significant correlation between reduced level of type I collagen and the severity of photodamage in human skin.[40]

Since collagen fibrils and elastin are responsible for the firmness and resilience of skin, their disarrangement induced by photoaging process causes the skin to look older.[41,42]

While the roles of UVB and UVA wavelengths in the photoaging process are not fully understood, it is known that UVA radiation contributes significantly to long-term deterioration of the dermal structure and clinical signs of photoaging.[43] In particular, repeated exposures to UVA induce alterations within the dermal compartment, which correlate with early damage occurring during photoaging.[44] An *in vivo* study showed that using repeated low doses of solar simulated radiation (SSR) for 6 weeks induces the production of some of the major alterations observed and/or participating in the long-term photoaging process (e.g. reduced level of type I collagen precursor, increased lysozyme deposit on elastic fibers). This study also demonstrated the efficacy of a daily broad-spectrum photoprotection in preventing some of those biological endpoints.[45]

Photocarcinogenesis

Sunlight overexposure is involved in increasing the risk of skin cancer since DNA represents one of its biological targets. Indeed, DNA alteration can affect many cellular functions and can lead to mutations and genetic instability. Unlike UVB which directly impacts DNA, UVA toxicity mainly depends on indirect mechanisms in which reactive oxygen species (ROS) are generated through the activation of endogenous photosensitizers present in skin, triggering the genotoxic effects. Thus, repetitive low-dose UVA is capable of eliciting DNA damage. Evidence for the generation of oxidative damage in cultured cells, and even in skin biopsy specimens, has been accumulating in recent years; several reports have described the induction of transient DNA breakage after UVA exposure. Purines and pyrimidines can be modified by ROS. One of the best studied lesions is 8 oxo-dG, which results from the oxidation of the guanine moiety. This 8 oxo-dG lesion was shown to be premutagenic and it is suspected to be involved in the photocarcinogenic process initiated by sunlight.[46]

Regarding the clinical data, there is strong evidence to support the direct role of sunlight exposure in the development of skin cancers, especially non-melanoma skin cancers (NMSCs), squamous cell carcinoma (SCC), and basal cell carcinoma (BCC).[47] These cancers occur more frequently on the head, neck, arms, and hands, which are the skin areas most frequently exposed to UVR. Actinic keratoses (AK), which are precancerous lesions, are also frequent in these body sites.About 5-20% of these lesions progress to SCC. Lightly pigmented individuals (skin types I or II) are more prone to NMSC than those with deeply pigmented skin.[48] Conventional wisdom has it that the incidence of all varieties of skin cancers is lower among Indians due to the protective effects of melanin. Nevertheless, a recent Indian review showed that there are indirect indications that NMSCs may be on the rise in India.[49]

Unlike NMSC, the direct association with UV exposure is still under investigation for cutaneous malignant melanoma. Severe sunburn episodes during childhood may cause the development of melanoma on sun-exposed areas. A recent Australian study tends to prove that melanoma may be preventable by regular sunscreen use in adults.[50]

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Lower body anatomical distribution of solar ultraviolet radiation on the human form in standing and sitting postures

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Abstract

Humans undertake their daily activities in a number of different postures. This paper aims to compare the anatomical distribution of the solar erythemal UV to human legs for standing and sitting postures. The exposure ratios to the legs (ratio of the UV exposure to a particular anatomical site compared to the ambient) have been measured with UV dosimeters for standing and sitting postures of a manikin. The exposure ratios for the legs ranged from 0 to 0.75 for the different anatomical sites for the sitting posture in summer (December through February) compared to 0.14 to 0.39 for the standing posture. In winter (June through August) the exposure ratios ranged from 0.01 to 0.91 for sitting to 0.17 to 0.81 for standing. For the anterior thigh and shin, the erythemal UV exposures increased by a factor of approximately 3 for sitting compared to standing postures. The exposure ratios to specific anatomical sites have been multiplied by the ambient erythemal UV exposures for each day to calculate the annual exposures. The annual erythemal exposures to the anterior thigh and ankle were predicted to be higher than 800 MED for humans sitting outdoors each day between noon and 13:00 h Australian Eastern Standard Time (EST). For humans standing outdoors during this time, the annual erythemal UV exposure averaged over each leg site was 436 MED, whereas, the averaged annual erythemal UV exposure was 512 MED for the sitting posture. Similarly, the annual erythemal UV exposure averaged over each of the sites was 173 MED for humans standing outdoors between 09:00 h EST and noon each Saturday morning and 205 MED for humans sitting outdoors during this time. These results show that there is increased risk of non-melanoma skin cancer and malignant melanoma to the lower body if no UV preventative strategies are employed while in a sitting posture compared to a standing posture.

Keywords: UV; Erythemal; Posture; Standing; Sitting

1. Introduction

The solar UV exposures to selected human anatomical sites, for example the wrist and shoulder during normal daily activities have been measured using personal UV dosimeters [1–5]. Additionally, previous researchers have employed polysulphone dosimeters to determine the distribution of solar erythemal UV exposure to the human body in predominantly upright positions (for example, Refs. [4,6]).

Numerical models based on the exposure ratio or the ratio of the exposure to a specific anatomical site compared to that to a horizontal plane are used for the calculation of longer term UV exposures to humans [7,8]. Exposure ratios for predominantly upright postures have been measured (for example, Refs. [6,9,10]). Annual solar UV exposures have been calculated using these exposure ratios. This is necessary for aetiological studies of skin cancer and other sun-related disorders and to determine the damaging influence of solar UV radiation.

Previous research has determined the dependence of the spectral biologically effective solar UV irradiances on sun-normal and horizontal planes [11]. The receiver orientation influences the solar UV exposures. Surfaces orientated in a sun-normal plane may receive up to 27% higher erythemal UV exposures. Humans undertake their daily activities in a number of different postures. For example walking and gardening have very different postures, although both activities are undertaken outdoors. Consequently, it is necessary to measure exposure ratios for human anatomical sites for postures other than predominantly upright. Exposure ratios have been reported for

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different postures in full sun for the upper leg [12]. However, more data are required for other sites of the leg. This is important in a number of settings for humans. Examples are spectators at sporting events, participants at sporting events, parents and friends as spectators at junior sports and people confined to wheelchairs. This paper compares the differences in the anatomical distribution of the erythemal UV exposures to the lower half of the body during sitting and standing postures.

2. Materials and methods

2.1. UV dosimetry

The erythemal UV [13] exposures to specific human anatomical sites were measured using UV dosimetry techniques utilizing polysulphone film [14]. The polysulphone film was placed into a 25×25-mm plastic holder with an approximate 1 cm^2 central aperture. The polysulphone dosimeters were cast and fabricated by the authors at the University of Southern Queensland, Australia. The optical absorbance of the polysulphone film at 330 nm changes as a result of UV exposure causing degradation. The pre- and post-solar UV exposure optical absorbance of the polysulphone film was measured at 330 nm in a spectrophotometer (model UV 1601, Shimadzu, Kyoto, Japan). The pre- and post-exposure optical absorbance of the dosimeters was measured at four sites over the dosimeters in order to minimise the effects of surface variations and thickness changes over the surface of the film. Changes in optical absorbance following exposure were standardized by measuring the post exposure absorbance of all the dosimeters after a period of more than 24 h following exposure. The overall error associated with polysulphone UV dosimetry is of the order of 10% [15].

The dosimeters were calibrated in units of MED (minimum erythemal dose). This was achieved through the exposure of a series of dosimeters on a horizontal plane near a calibrated erythemal UV meter (UV-Biometer, model 501, Solar Light, Philadelphia, PA, USA). The MED is defined as the UV exposure producing barely perceptible erythema after 8–24 h following UV exposure [7]. The erythemal UV meter provides the integrated erythemal UV for each 15-min interval. The series of calibration dosimeters were exposed between 09.00 h Australian Eastern Standard Time (EST) and noon. The broadband UV meter was calibrated on a seasonal basis through the direct comparison of recorded solar irradiances between the meter and a UV spectroradiometer. The calibration provided 1 MED as equivalent to 216 J m^{-2}. The spectroradiometer has calibration traceable to the UV standard based at the National Standards Laboratory, CSIRO, Lindfield, Australia.

2.2. UV exposure distribution

Polysulphone dosimeters were placed on a manikin at each of the following sites: left thigh anterior and posterior, right thigh anterior and posterior, left shin anterior and posterior, right shin anterior and posterior. The manikins were used in this study as ethical issues, such as overexposure to solar UV prevented the use of humans as subjects in a series of experiments. Previous researchers (for example, Refs. [6,9]) have employed manikins in the measurement of solar UV exposures to the human body. The manikins with the attached polysulphone dosimeters were deployed in an open sports field between 09:00 h EST and noon at a sub-tropical latitude in Toowoomba (latitude 27.5°S and 693 m above sea level), Australia. For this location, the surface albedo of the grass was approximately 5% and the nearest buildings were more than 30 m away from the experiment site. For each exposure period, two dosimeters were exposed in full sun on a horizontal plane for the calculation of the exposure ratios. The exposure ratios to specific anatomical sites vary with the seasons due to the different solar zenith angles and atmospheric conditions, consequently, for this research, a set of measurements was made in the southern hemisphere summer and a set in the winter.

In this experiment, two manikins were used. The first set of UV exposure measurements consisted of one manikin in an upright position and the other manikin sitting on a chair, with both exposed to full sun conditions. The manikins were sufficiently spaced from each other so that there no was no mutual shading. Both manikins were rotated clockwise by 90° every 15 min to minimise any directional effects, such as over exposure to one site, and also to replicate the effect of human random orientation to the sun when outdoors. Previous comparisons of the UV received by rotating manikins and humans undertaking normal outdoor activities have shown that the UV exposures to the manikin cheek, hand and thigh provide a good approximation of the UV exposures to these sites on humans [16]. The manikin UV measurements overestimate the exposures to the shoulder and sternum and underestimate the exposure to the lumbar spine and upper arm, probably due to a tendency of humans to stoop forward and outstretch the arms and a preference to turn away from the direct sun. In this case, it was impractical to place the manikins on a rotating platform, so they were manually rotated every 15 min. The second set of exposures consisted of the manikins each in a standing and sitting position in tree shade. The manikins were again moved clockwise 90° throughout the exposure period and also moved to follow the shade cast by the tree, in a similar manner to humans.

The dates of the exposures in the summer were 26 and 27 February 2001 for the two postures in the full sun and in tree shade, respectively. This was repeated in the winter on 21 June and 1 August for the two postures in the full

sun and in tree shade, respectively. The ranges of solar zenith angles between 09:00 h EST and noon were 19–48° and 45–66° in summer and winter, respectively.

The tree species used in this study was a *Cinnamomum camphora*. The denseness of the tree canopy was estimated by measuring the reduction of the irradiances in the visible waveband in the tree shade compared to the visible irradiances in full sun, using a similar technique to Parisi et al. [17]. The shade was not dense shade with sun flecks in the shade. The irradiances measured in the tree shade were 15% of those in the sun.

2.3. Scenarios

To quantify the differences in the annual UV exposures for the two postures to each site UV(S), a numerical model based on previous models [7,8] has been employed as follows:

$$\mathrm{UV(S)} = \sum_i \mathrm{ER}_i(\mathrm{S})\mathrm{AE}_i \quad (1)$$

where AE_i is the ambient erythemal UV exposures on an unshaded horizontal plane for the *i*th day and that has been summed over each 15-min interval of the day, $\mathrm{ER}_i(\mathrm{S})$ is the exposure ratio for each site during the *i*th day. The exposure ratios for each respective site in summer and winter have been linearly interpolated to provide those for the intermediate days. This assumes these days have similar atmospheric parameters such as ozone levels and cloud cover.

With this model, various hypothetical scenarios for the UV exposures can be considered, as follows:

- Scenario 1: A group of the population who spends time between noon and 13:00 h EST outdoors in full sun for each day of the year in an upright posture, either standing or walking with the remainder of the time of day spent indoors. This scenario is designed to represent indoor workers who spend the lunch hour outdoors standing or walking.
- Scenario 2: The same group of the population as scenario 1 who spend the lunch hour sitting outdoors in full sun. This scenario is designed to estimate indoor workers who spend a lunch hour outdoors in a sitting posture while relaxing or eating lunch.
- Scenario 3: A population group who spends the time between 09:00 h EST and noon on each Saturday morning outdoors in full sun in an upright posture and spends the remainder of the time indoors. This scenario is used to reflect the situation for indoor workers who spend a morning each weekend, playing an outdoor sport where they are mainly in an upright posture, for example cricket or baseball.
- Scenario 4: A population group who spends the time between 09:00 h EST and noon on each Saturday morning outdoors in full sun in a sitting position and spends the remainder of the time indoors. The time spent outdoors may be as spectators at their children's or friends' weekend sporting activities or as spectators at major sporting events.
- Scenario 5: The same group as scenario 1, except they spend the time either standing or sitting in tree shade either as a sport's spectator or relaxing.
- Scenario 6: The same group as scenario 4, except they spend the time either standing or sitting in tree shade.

Analysis of these scenarios are important due to the skin damage resulting from intermittent UV exposures on relatively unprotected skin.

3. Results

3.1. UV exposure distribution

The erythemal UV exposures between 09:00 h EST and noon to the six sites on the lower body for the 3-h exposure period in summer are shown in Table 1 for each of the two postures in full sun. For the anterior thigh and shin, the exposure increased by a factor of approximately three for sitting compared to standing. In comparison, the exposure dropped to zero for the posterior thigh due to this site being between the leg and the chair, and the chair acting as a shading device for this site. The exposure was reduced by a factor of 10 for the posterior shin while sitting. This is due to the shading to this site by the top of the chair and the upper part of the leg. The exposure to the posterior ankle for this posture was reduced by a factor of approximately 2 due to partial shading of this site by the higher parts of the leg. The exposures for the standing and sitting postures in the tree shade are provided for comparison in the final two columns. In the tree shade, the sitting/standing ratio is 1.6 for the anterior thigh and 1.4 for the anterior ankle. Again the exposure to the posterior thigh is negligible. The differences compared to full sun

Table 1
Comparison of the erythemal UV exposures to the lower body for the standing and sitting postures in sun and tree shade in summer between 09:00 and 12:00 h EST

	Erythemal UV exposure (MED)			
	Sun		Tree shade	
	Standing	Sitting	Standing	Sitting
Anterior thigh	3.5	10.1	2.2	3.5
Posterior thigh	2.8	0.0	1.9	0.1
Anterior shin	2.3	6.8	2.0	3.8
Posterior shin	5.4	0.5	2.1	1.1
Anterior ankle	5.6	9.5	2.8	3.9
Posterior ankle	4.3	2.3	2.2	1.4

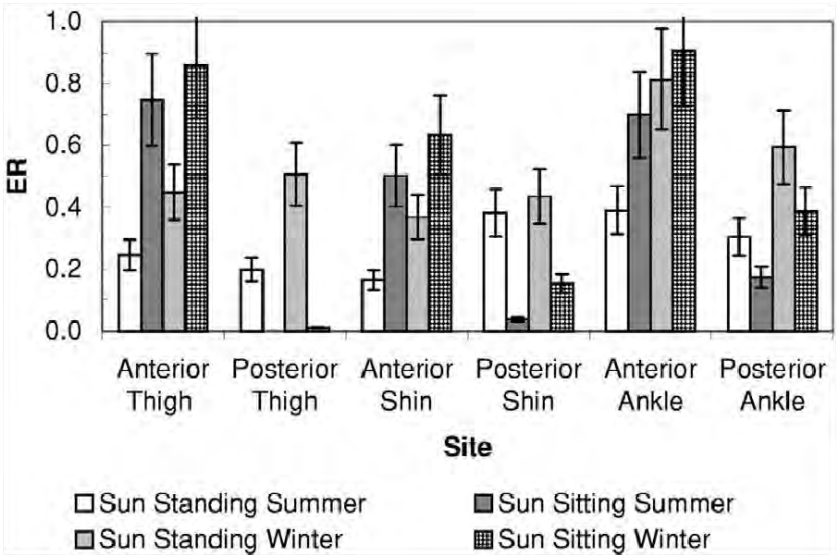

Fig. 1. Exposure ratios (ER) for the human leg sites while standing and sitting in full sun for summer and winter.

are due to blocking of the direct component and the high relative proportion of diffuse radiation in tree shade [18].

The exposure ratios for the two postures in full sun in summer and winter for each of the sites are shown in Fig. 1. Error bars are shown as ±20% and are calculated as the accumulation of the ±10% error in the polysulphone measurements. As expected from the relative exposures in Table 1, the exposure ratios for the anterior thigh, shin and ankle for the sitting posture are higher than those for the standing posture. Conversely, the exposure ratios are lower for the posterior of the thigh, shin and ankle in the sitting posture. The corresponding exposure ratios for the tree shade are provided for comparison in Fig. 2. Again the highest exposure ratios for the sitting posture are to the anterior of the thighs, shins and ankles. The exposure ratios in the tree shade for these sites are generally half of those in the sun. In comparison, the exposure ratios for the standing posture in both the sun and the shade vary less across each of the sites.

3.2. Scenarios

The annual erythemal UV exposures for the group of the population who spend an hour outdoors between noon and 13:00 h EST for each day of the year with the remainder of the time spent indoors are shown in Fig. 3 for scenarios 1 and 2. For the sitting posture the highest annual exposures were to the anterior thigh and anterior ankle with annual

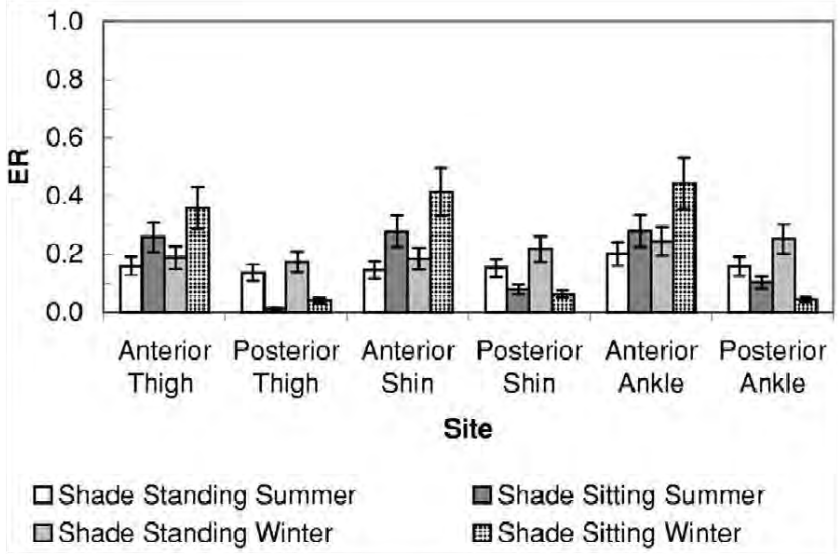

Fig. 2. Exposure ratios (ER) for the human leg sites while standing and sitting in tree shade for summer and winter.

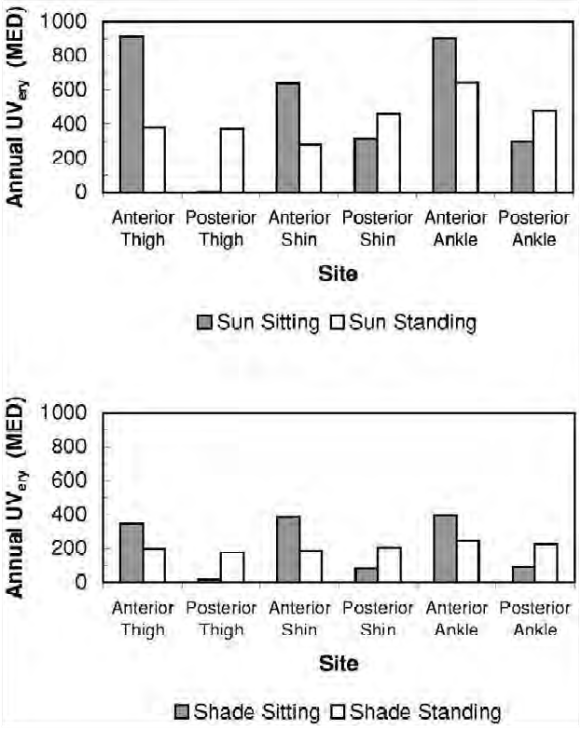

Fig. 3. Annual erythemal UV (UVery) exposures between noon and 13:00 h EST in full sun for the standing and sitting postures of scenarios 1 and 2 and in tree shade for the standing and sitting postures of scenario 5.

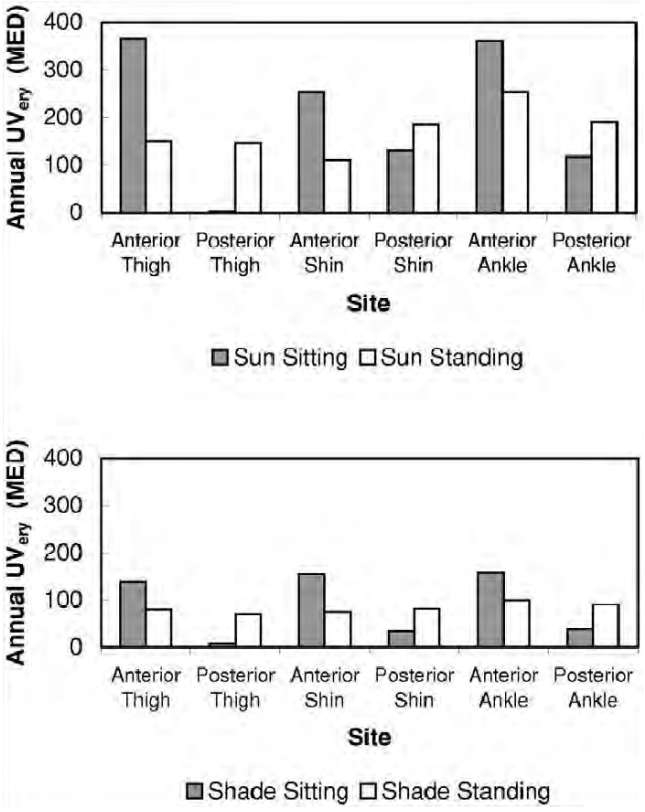

Fig. 4. Annual erythemal UV (UVery) exposures for each Saturday between 09:00 h EST and noon in full sun for the standing and sitting postures of scenarios 3 and 4 and in tree shade for the standing and sitting postures of scenario 6.

exposures higher than 800 MED. These exposures are higher than those for the standing postures for the corresponding sites due to the angle of the anterior of the thigh being on approximately a horizontal plane for sitting and the anterior of the ankle being on approximately 45° to the horizontal. The exposures to the anterior of the shin are also higher for sitting compared to those for standing. This is due to the shin being at an angle between the vertical and 45° to the vertical. This places the shin at an angle that is closer to the normal to the sun, causing the higher exposure. Fig. 3 also provides the annual erythemal UV exposures for scenario 5. The highest exposures are between 300 and 400 MED.

Fig. 4 provides the annual erythemal UV exposures for the group of the population who spends each Saturday morning between 09:00 h EST and noon outdoors as either sport's participants or spectators. The annual exposures are in excess of 350 MED to the anterior of the thigh and the ankle. Fig. 4 also provides the annual exposures for scenario 6 with the highest exposures of approximately 150 MED.

4. Discussion

The anatomical distribution to the lower body of the solar erythemal UV has been compared for the standing and sitting postures of a manikin. The exposure to each site was dependent on the particular anatomical site orientation. This distribution over the body has been measured for solar zenith angles between 19° and 48° in summer and between 45° and 66° in winter. The exposure ratios for all sites measured ranged from 0 to 0.75 for the sitting posture in summer compared to 0.14 to 0.39 for the standing posture. In winter the exposure ratios ranged from 0.01 to 0.91 for sitting to 0.17 to 0.81 for standing. Solar UV exposures in the tree shade were found also to be dependent on the body posture; however, the range of exposure ratio values was less than that for full sun. The exposure ratios will not be the same for trees of canopy density different to the one used in this project due to the differing diffuse component of trees with a higher canopy density. However, the exposure ratios for the tree were provided to highlight the change in exposure ratios for the case when the relative proportion of diffuse UV is increased relative to the direct component.

The annual erythemal exposures to the anterior of the thigh and ankle were higher than 800 MED to each site for scenario 2. Averaged over each day, this is over 2 MED for the 1-h period of exposure outdoors. These are in excess of occupational exposure limits for UV exposure [19]. The erythemal UV exposures to different population groups have been previously measured at this location by

other researchers [3]. The median of the daily erythemal UV exposures to the shoulder for outdoor workers, school children and home workers during normal daily activities were 3.0, 1.5 and 1.2 MED. At a similar latitude, daily erythemal exposures of 3 to 5 MED have been measured to the shoulder and chest of lifeguards, school grounds staff and physical education teachers [4]. For the standing posture of scenario 1, the annual erythemal UV exposure averaged over each site was 436 MED, whereas the averaged annual erythemal UV exposure was 512 MED for the sitting posture of scenario 2. Similarly, the annual erythemal UV exposure averaged over each of the sites was 173 MED for the standing posture of scenario 3 and 205 MED for the sitting posture of scenario 4. Skin acclimatization such as skin thickening and pigmentation would lead to considerable lower cumulative MEDs. Long-term dosimetry does not take into account dynamic changes in skin sensitivity; however, it provides information on the relative exposures to each site for each posture. These exposures averaged over each site are higher for the sitting posture due to the receiver orientations of the sitting posture. In comparison for the tree shade, there are also differences in the exposures for the standing and sitting postures, however the differences are not as high as for full sun exposure.

The UV distribution over a human varies with solar zenith angle, atmospheric composition and ground albedo. However, in this project, the exposures from 09:00 h EST to noon in both summer and winter take into account solar zenith angles between 19° and 66° in clear sky conditions. Nevertheless, further research is required to collect data on the exposure ratios for each month of the year and different atmospheric conditions and surface albedo. Additionally, humans sit in a variety of different postures and the exposure ratios may possibly vary for different sitting postures. The results presented are for one sitting posture only. Nevertheless, they provide a first order of magnitude evaluation of the differences in the exposure ratios and differences in UV exposures. Further research is required to quantify the exposure ratios for possible different sitting postures.

This research has shown that people outdoors in a sitting posture will receive higher exposures to the legs compared to people in a standing posture if no UV preventative strategies are employed. Additionally, the exposures to some specific leg sites increases by approximately a factor of three. Spectators at sporting events, people sitting outdoors relaxing and people that are confined to wheelchairs will have increased risk of non-melanoma skin cancer and malignant melanoma if no protective measures against over exposure to solar UV radiation, such as clothing or sunscreen are employed.

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Anatomical exposure patterns of skin to sunlight: relative contributions of direct, diffuse and reflected ultraviolet radiation

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Summary

Background The dose response between ultraviolet (UV) exposure patterns and skin cancer occurrence is not fully understood. Sun protection messages often focus on acute exposure, implicitly assuming that direct UV radiation is the key contributor to the overall UV exposure. However, little is known about the relative contribution of the direct, diffuse and reflected radiation components.

Objective To investigate solar UV exposure patterns at different body sites with respect to the relative contribution of the direct, diffuse and reflected radiation.

Methods A three dimensional numerical model was used to assess exposure doses for various body parts and exposure scenarios of a standing individual (static and dynamic postures). The model was fed with erythemally weighted ground irradiance data for the year 2009 in Payerne, Switzerland. A year round daily exposure (08:00 17:00 h) without protection was assumed.

Results For most anatomical sites, mean daily doses were high (typically 6·2 14·6 standard erythemal doses) and exceeded the recommended exposure values. Direct exposure was important during specific periods (e.g. midday during summer), but contributed moderately to the annual dose, ranging from 15% to 24% for vertical and horizontal body parts, respectively. Diffuse irradiation explained about 80% of the cumulative annual exposure dose. Acute diffuse exposures were also observed during cloudy summer days.

Conclusions The importance of diffuse UV radiation should not be underestimated when advocating preventive measures. Messages focused on avoiding acute direct exposures may be of limited efficiency to prevent skin cancers associated with chronic exposure.

Solar ultraviolet (UV) radiation is one of few environmental exposures that can both cause and protect against diseases. While UV exposure can prevent diseases of vitamin D insufficiency, it can cause eye diseases and is responsible for 50–90% of all skin cancers.[1] Each year, excessive sun exposure leads to an estimated 60 000 premature skin cancer deaths worldwide, the majority of these being melanomas, the most dangerous cutaneous neoplasm.[2] Although epithelial skin cancer is less lethal than melanoma, it is the most common cancer among fair-skinned people with an annual burden of approximately 13 million new cases worldwide: 10 million basal cell carcinomas (BCCs) and 2·9 million squamous cell carcinomas (SCCs).[2]

The dose-response between UV exposure patterns and skin cancer occurrence is not yet fully understood. SCC is predominantly induced by chronic (cumulative) sun exposure, leaving outdoor workers and elderly people at greater risk.[3–5] Melanoma[6] has been associated with intermittent sun exposure, whereas both prolonged cumulative exposure and intermittent exposure appear to be responsible for BCC development.[7,8] The steady rises in skin cancer rates over the past 50 years concur with the gradual increase in outdoor leisure activities, vacation in sunny areas, and changing clothing habits favouring exposure of larger skin surfaces.[4,9,10]

For a given individual, the anatomical distribution of UV exposure is highly heterogeneous, poorly correlated to ground irradiance, and depends on the time of exposure and orientation to the sun.[11] Variations in UV doses received across individuals are even greater as they are strongly influenced by

behavioural and host factors such as posture, orientation to the sun, skin complexion, clothing and other sun-protective behaviours.[12 14] For a given individual and weather condition, exposure of anatomical sites ranges from 13% to 76% of the exposure to the vertex of the head.[15] Occupational exposures beyond 100% of the ground global irradiance have been measured on some anatomical sites in outdoor workers.[16,17]

Sun-protection messages often focus on direct UV radiation and short-term, acute exposure (avoidance of erythema), implicitly assuming that direct UV radiation is the key contributor to the overall UV exposure. However, little is known regarding the relative contribution of the direct, diffuse and reflected UV radiation to the anatomical exposure as individual dosimetric measurement cannot separate the three radiation components. Recent investigations of UV doses received by body parts unexposed to direct sunlight have suggested the importance of diffuse radiation.[18,19] UV irradiance measured in the shade (in Australia) during a short time-period was sufficient to cause erythema and UV doses measured on the lower leg of cyclists showed that a potentially shaded anatomical site can receive half the dose of the maximally exposed sites.[20]

A recently developed three-dimensional (3D) numerical model (Simulating UV Exposure, SimUVEx) based on broadband detector information can quantify individual exposure patterns with separate computation for each radiation component.[21] Our objectives were to model daily and yearly solar UV exposure patterns with respect to the relative contribution of direct, diffuse and reflected components, and to investigate site-specific UV exposure for each radiation component.

Materials and methods

Modelling tool

Sun exposure patterns were investigated through numerical simulation using the SimUVEx model. SimUVEx predicts the dose and anatomical distribution of UV exposure received on the basis of ground irradiation and morphological data. 3D computer graphics techniques are used to compute the interaction between a virtual manikin, depicted as a triangle mesh surface constituted of 4000 meshes, and the incoming solar radiation. Direct, diffuse and reflected (reflection from ground) components are computed separately for 45 body sites. The amount of solar energy received by each triangle is calculated, taking into account the three radiation components and shading from other body parts. The principles and a validation of the SimUVEx model in field conditions have been detailed previously.[21]

Ground irradiance source

Five input parameters are required by the model: direct irradiance (W m^{-2}), diffuse irradiance (W m^{-2}), ground reflected irradiance (W m^{-2}) and sun position [defined by its azimuth p(t) and zenith d(t) angles]. Measurements performed at the MeteoSwiss Payerne station (46·815°N, 6·944°E, altitude 491 m) were used. The Payerne facility is part of the Baseline Surface Radiation Network of the World Meteorological Organization, World Climate Research Program.[22] Ambient direct, diffuse and reflected UV irradiance are measured concomitantly every minute at this facility using broadband UV radiometers (Biometer 501A; Solar Light, Glenside, PA, U.S.A.) with filters mimicking the erythemal response (erythemally weighted irradiance).[23] Four broadband radiometers were used for measuring global, direct, diffuse and reflected radiation, respectively. Instruments measuring direct and diffuse components are mounted on sun-trackers (within a collimator for direct and under a shading disc for diffuse), while the one measuring the reflected component is turned upside down. These broadband radiometers undergo strict quality assurance procedures including regular calibrations traceable to the European Ultraviolet Calibration Centre.[24] The calibration technique accounts for differences between the spectral response of the filter and the theoretical erythemal action spectrum. The overall uncertainty of the measurement is estimated at 10%.

Irradiance data treatment

Ground irradiance data collected for the entire year 2009 were used in this study (525 600 measurements). Data were first checked for missing or aberrant values (e.g. maintenance of the measuring device): 2483 (0·5%) and 386 (< 0·1%) missing/aberrant values were found for direct and diffuse measurements, respectively. Ground global irradiance was used to recalculate most of the missing/aberrant values, while the remaining values (35 measurements on 22 September 2009) were reconstructed using measurements from the closest day of similar meteorological conditions (23 September 2009). Data were treated and analysed using Stata/IC 11.0 (StataCorp LP, College Station, TX, U.S.A.).

Implementation

The virtual manikin represented an adult male standing with arms down, which was found to be the predominant posture among outdoor construction workers due to their frequent changes in activity and movements.[17] Exposure scenarios under various conditions were compared for this body posture.

Simulations were first run for a daily outdoor activity performed between 08:00 and 17:00 h without shading or protective clothing. To account for the dynamic body orientation (due to walking or turning), the manikin was rotated between each simulation step. We used a simulation step of 1 min and a step rotation of 24° corresponding to four full rotations per hour.

Table 1 summarizes the various exposure scenarios investigated (environmental conditions with static or dynamic body orientations).

Table 1 Conditions and scenarios of simulations

Scenario	Exposure period	Exposure time	Weather	Body orientation	No. simulations	Related Figure and Table
1	Whole year 2009	08:00 17:00 h, daily dose	Any	Dynamic, step rotation 24°	365	Fig. 1a c, Table 2
2	Summer day, 13 June 2009	08:00 17:00 h, 15-min dose	Cloudless	Dynamic, step rotation 24°	36	Figs 2a and 3a
3	Autumn day, 7 October 2009	08:00 17:00 h, 15-min dose	Cloudless	Dynamic, step rotation 24°	36	Fig. 2b
4	Winter day, 19 December 2009	08:00 17:00 h, 15-min dose	Cloudless	Dynamic, step rotation 24°	36	Fig. 2c
5	Summer day, 15 June 2009	08:00 17:00 h, 15-min dose	Cloudy	Dynamic, step rotation 24°	36	Fig. 2d
6	Summer day, 13 June 2009	08:00 17:00 h, 15-min dose	Cloudless	Static orientation	36	Fig. 3b

Results

Overall exposure

The daily doses for each radiation component and some selected body parts are given in Table 2. The computed daily doses assumed an unprotected skin and year-round exposure (weekends included) so that results indicate upper dose estimates.

The mean daily doses, between 6·2 and 14·6 standard erythemal doses (SED, 100 J m^{-2}) were high and exceeded both the International Commission on Non-ionizing Radiation Protection exposure threshold (0·3 SED)[25] and the minimal erythema dose for skin types II and III (2·5–3·0 SED),[26] the most common phototypes in fair-skinned populations. Horizontal body parts, such as top of shoulder, exhibited the highest exposure doses, about 90% of that measured at ground level. For most anatomical sites, exposure was about half the ambient total dose. The strongest attenuation was observed for vertical and curved body sections such as the back of the hand (6·2 SED) and the face (6·7 SED) which were exposed to 38% and 41% of the ambient total dose (16·3 SED), respectively.

Yearly exposure patterns

Reflected radiation bore a negligible contribution (< 0·1–3%) and most of the total UV exposure came from diffuse and direct irradiation. However, a substantial contribution of reflected radiation occurred on specific days in winter (snow-covered ground). For instance, a maximum daily dose of 2·1 SED was measured for the face (Table 2). Reflection also showed a larger anatomical variability (ratio of about 9 between sites of lowest and highest absolute doses) than diffuse or direct radiation.

A substantial contribution of direct irradiation occurred only during specific time periods and for some body locations. It can represent > 50% of the total dose at (around) summer midday, for instance. Exposure to direct irradiation was,

Table 2 Daily exposure (erythemally weighted) dose by body site and component of ultraviolet radiation

	Total (SED)[a]			Diffuse (SED)			Direct (SED)			Reflection (SED)		
	Mean	5 95 percentile[b]	Max	Mean	5 95 percentile	Max	Mean	5 95 percentile	Max	Mean	5 95 percentile	Max
Body site												
Face	6·7	0·89 14·1	16·0	5·5	0·77 11·1	13·5	1·0	< 0·01 3·5	4·8	0·21	0·01 1·3	2·1
Neck	10·0	1·3 22·2	25·5	8·0	1·1 16·1	19·6	1·9	< 0·01 6·9	10·0	0·13	< 0·01 0·83	1·4
Top of shoulder	14·6	1·6 34·5	41·5	11·1	1·5 22·4	27·2	3·5	< 0·01 13·4	20·1	0·03	< 0·01 0·16	0·26
Shoulder (right)	9·3	1·2 20·6	23·8	7·5	0·1 15·1	18·3	1·7	< 0·01 6·3	9·2	0·15	< 0·01 0·94	1·5
Centre back	7·1	0·94 15·0	16·9	5·8	0·81 11·8	14·3	1·1	< 0·01 3·8	5·1	0·20	0·01 1·3	2·1
Torso	8·2	1·1 17·5	19·7	6·6	0·93 13·4	16·3	1·3	< 0·01 4·7	6·6	0·18	0·01 1·1	1·8
Forearm (right)	7·1	0·95 14·8	16·8	5·8	0·81 11·8	14·4	1·1	< 0·01 3·7	4·9	0·20	0·01 1·3	2·0
Back of hand (right)	6·2	0·82 12·7	14·4	5·1	0·71 10·2	12·4	0·87	< 0·01 3·0	3·9	0·22	0·01 1·4	2·3
Upper leg (front right)	7·3	0·97 15·3	17·4	6·0	0·84 12·2	14·8	1·1	< 0·01 3·8	5·0	0·19	0·01 1·3	2·0
Calf (right)	7·1	0·95 14·8	16·7	5·9	0·82 11·9	14·4	1·1	< 0·01 3·6	4·6	0·20	0·01 1·3	2·1
Ground irradiance	16·3	2·3 36·2	47·6	11·8	0·23 22·2	29·0	5·3	0·03 15·8	27·9	0·40	0·04 0·65	4·2

[a]1 SED (standard erythemal dose) = 100 J m^{-2}. [b]5 95 percentile: range between the 5th and 95th percentiles.

however, strongly attenuated by shading from other body parts, a decrease in the sun zenithal angle (early or late in the day, seasonal changes), and cloudiness. These factors explain the low overall contribution of direct irradiation to the yearly cumulative dose. On average, direct irradiation amounted to 24% of the yearly dose for horizontal surfaces. For vertical and curved body parts, its contribution was less: 19% for the neck and shoulders and 15% for the face.

Diffuse irradiation explained about 80% of the yearly exposure dose, and was the main contributor to average exposure. This varied only slightly across anatomical variations, ranging from 76% for top of shoulder to 82% for vertical or curved body parts (e.g. face, centre back, forearm, legs). The daily exposure doses by time of year and the relative contribution from each type of irradiation for the face, neck and top of shoulder are shown in Figure 1. These anatomical sites were of special interest because they are often left uncovered, have various orientations and have been associated with BCC and SCC (at least for the face and neck).

Differences in seasonal patterns of exposure across body parts are apparent in Figure 1. Both the direct and diffuse irradiation exhibited a marked yearly cycle, the former being stronger than the latter. In particular, the increase in daily dose for neck and top of shoulder during summer led to daily exposures up to 40 SED. This marked yearly cycle is due to seasonal change in solar zenith angle.[27] In addition, at Payerne, cloudiness can be frequent, which impacts most on direct radiation. On average, the neck was 31% less exposed than the top of shoulder on cloudy winter days. The decrease in direct exposure for vertical body parts explained why facial exposure was lower than both neck and top of shoulder exposure. Interestingly, diffuse exposure was also 50% lower for the face compared with top of shoulder. This decrease was due to the fact that vertical body parts 'see' a smaller part of the sky than horizontal body sites.

These site-specific exposure patterns led to differences in the relative contribution of diffuse and direct exposures as well as in 'peak' periods for total exposure. For the top of shoulder, for instance, about 81% of the yearly dose occurred between 1 April and 15 September, and 27% of this exposure came from direct irradiation. For the face, the same percentage of yearly dose occurred between 15 March and 30 September, and only 16% of this exposure was due to direct irradiation.

Daily exposure patterns

Further investigations were performed for specific days, better to understand exposure patterns and their influencing factors. We used the face, which is normally exposed year-round, as a reference to illustrate the results and facilitate comparisons.

Weather and seasonal changes

As shown in Figure 2a–c, seasonal variation impacted mostly exposure intensity. The relative contribution from direct and diffuse radiation during cloudless days in summer and autumn followed a bell-shaped pattern. In winter, although the bell-shaped pattern was still perceptible, attenuation was more pronounced and direct radiation became marginal. On cloudless days with snow-covered ground (Fig. 2c), reflection from the ground rose dramatically and became the dominant source of

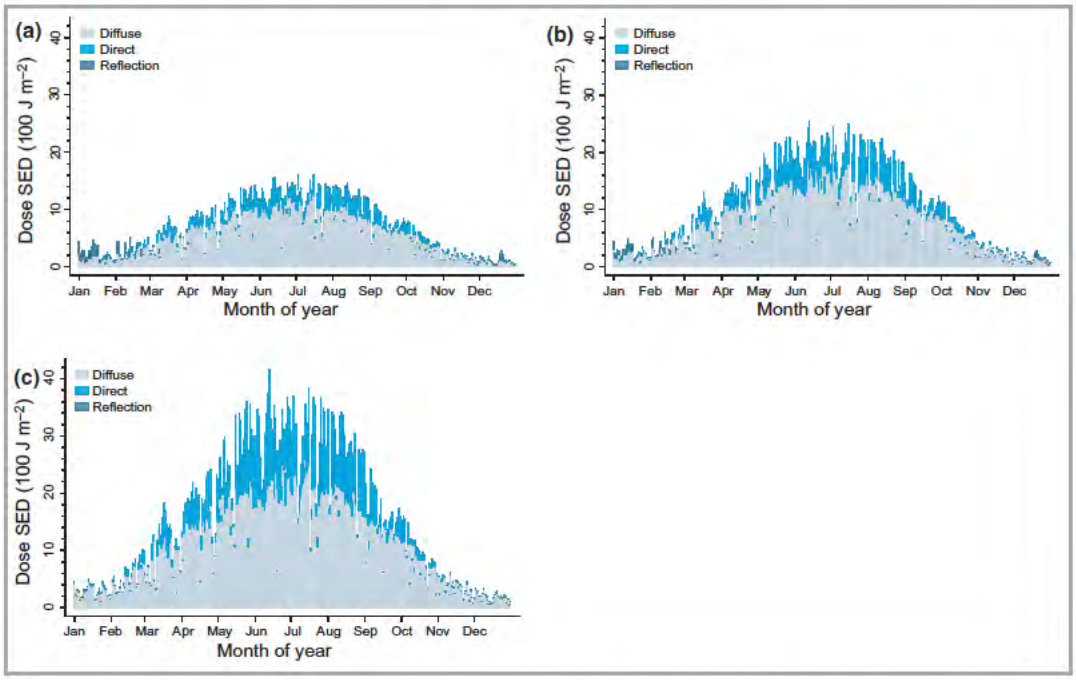

Fig 1. Components of ultraviolet exposure, expressed as daily doses over a whole calendar year for an adult man standing with arms down for the (a) face, (b) neck and (c) top of shoulder. SED, standard erythemal dose.

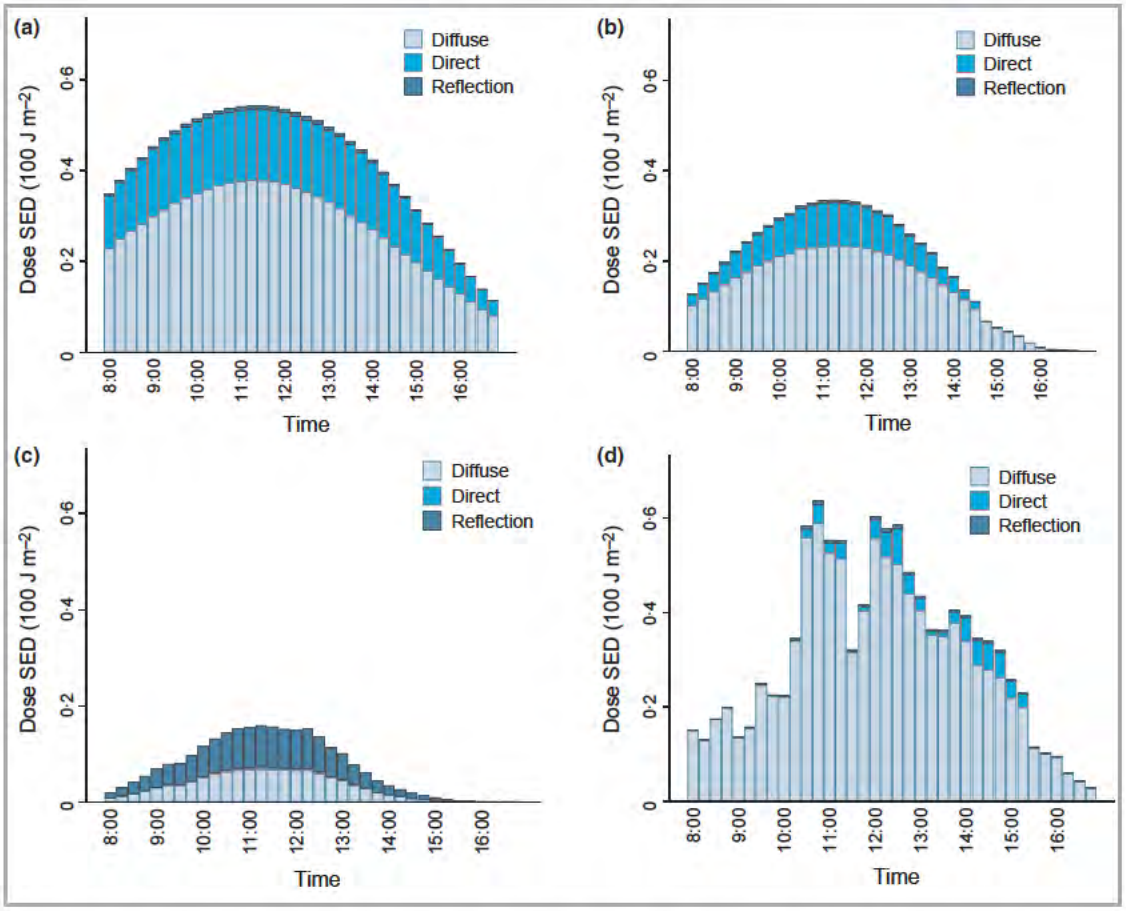

Fig 2. Daily pattern for face exposure during (a) a clear summer day (13 June 2009), (b) a clear autumn day (7 October 2009), (c) a clear winter day (19 December 2009) and (d) a cloudy summer day (15 June 2009). SED, standard erythema dose.

UV exposure (> 50% of total exposure) for vertical body parts (face, chest). On cloudy days, exposure pattern was erratic because both radiation intensity and the relative contribution of diffuse and direct radiation were affected by the weather. The exposure profile on a cloudy summer day is presented in Figure 2d. Direct exposure was marginal and limited to short spells, and most of the total exposure (93% on average) stemmed from diffuse radiation. On a cloudless summer day (Fig. 2a), face exposure was estimated to be 15·6 SED, with a diffuse contribution of 67% or 10·6 SED (maximum 15-min dose 0·40 SED) whereas 2 days later (Fig. 2d), face exposure was 11·9 SED, but with a diffuse contribution of 11·1 SED (maximum 15-min dose 0·6 SED). The observed increase in diffuse radiation was most probably due to cloudiness. Indeed, meteorological data for these 2 days indicated < 3% difference in ozone total column values and a negligible change in sun zenithal angle.

Static vs. dynamic exposure

Dynamic (rotating orientation) and static postures resulted in markedly different daily exposure patterns. Direct exposure, which depended on shading and light incidence angle, was strongly affected by dynamic aspects while no variations were observed in diffuse contributions. Dynamic and static situations for the same day (13 June 2009) are compared in Figure 3 for selected body sites. In a dynamic situation, the frequent orientation changes had an 'averaging' effect on total body exposure. In a static situation, variations in anatomical exposure due to shading or incidence angle were exacerbated, leading to localized and short-term overexposures. Static/dynamic changes affected both the daily dose and the exposure pattern over time. In a dynamic situation, shoulder exposure between 08:00 and 17:00 h exhibited a typical bell-shaped curve. In a static situation, the exposure profile was shifted to the right, moving the peak exposure period from 11:30 to 12:15 h. Moreover, lower back exposure exhibited a local minimum between 10:30 and 12:30 h because of shading from the head and centre chest.

Discussion

This study, combining detailed ground irradiance data and numerical modelling, has investigated for the first time UV exposure of various human body sites with specific quantification of direct, diffuse and reflected radiation. Overall,

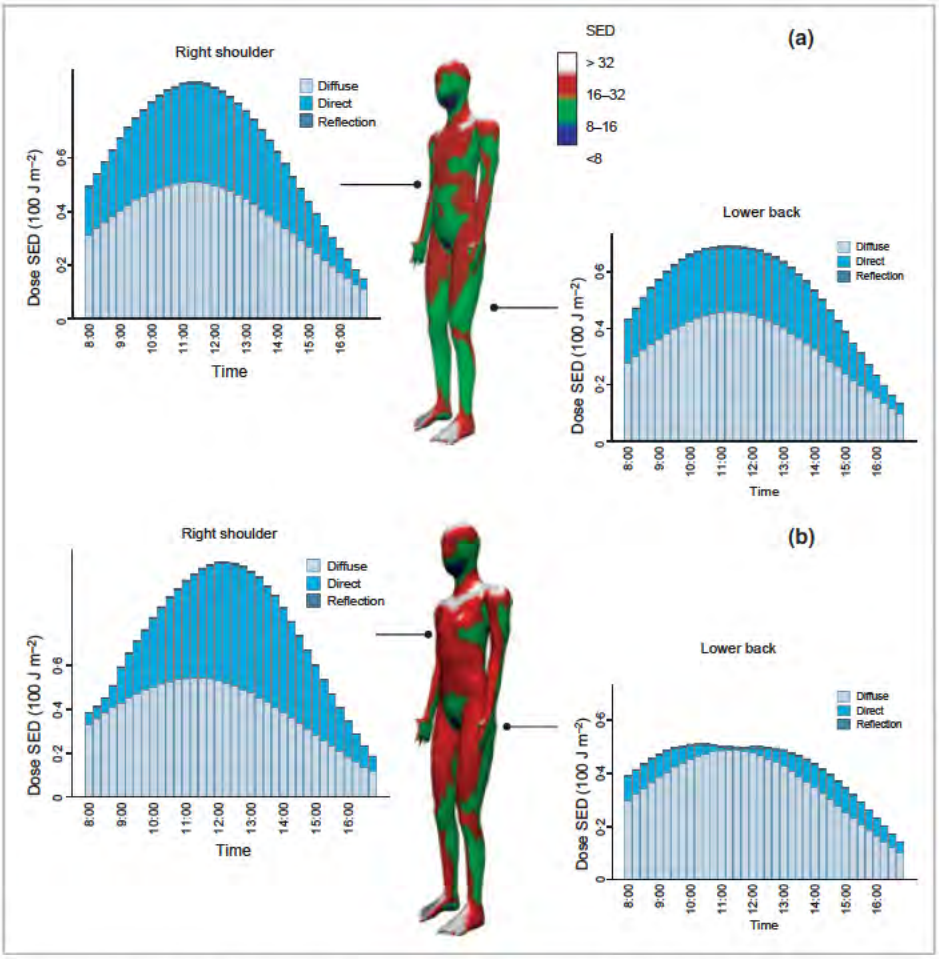

Fig 3. Anatomical distribution of daily dose and ultraviolet exposure pattern for two body locations (13 June 2009): shoulder (left) and lower back (right). (a) Dynamic situation; (b) static situation. SED, standard erythema dose.

site-specific exposure ranged from 38% to 90% of the total ambient UV dose and the various orientations of body parts led to different distributions of anatomical exposure across radiation components. Diffuse radiation appeared to be the main source of annual UV exposure (75–85% of total exposure) while direct radiation was a major contributor to the dose received around peak UV irradiance hours, especially in summer and for horizontally oriented anatomical sites (e.g. top of the head), or for a static posture. Reflected radiation was overall negligible (< 3% of total exposure) except on specific cloudless situations in the presence of a highly reflective surface, such as snow-covered ground.

SimUVEx, as any model, bears some limitations due to its underlying simplifying hypotheses.[21] First, diffuse and reflected radiation were assumed to be almost isotropic. The daily cycle of diffuse radiation may be less symmetrical in clear-sky situations as some anisotropy of the diffuse component can then be expected (higher radiance in the region near the sun). Reflection from ground partly covered by snow in winter is also a typical anisotropic situation. Such days are, however, infrequent and provide a modest contribution to the overall exposure. Second, the model simulated year-round exposure of unprotected skin. While this overestimates real exposure, this provides an upper annual (potential) exposure and leaves room to predict attenuating effects of sun-protection scenarios. Further, comparisons (in %) are unaffected by these absolute UV exposure estimates. Third, results pertain to a standing posture (with arms down). Although this posture is predominant in outdoor construction workers,[17] outdoor occupations and leisure activities characterized by other prevailing postures may experience different patterns of site-specific UV exposure.

Our estimates of global anatomical UV exposure (the sum of the direct, diffuse and reflected components) were in line with studies based on rotating manikins and on living subjects. The proportion of ground irradiance received by the face (about 41% in our study), the dorsum of hand (38%) and the calf (44%) concurred with manikin-based measures.[15,28,29] Our predicted exposure patterns also agreed with absolute dosimetric measurements such as wrist exposure of gardeners in Denmark (0·4–3·8 SED daily)[30] or arm and back exposures in vineyard workers in Italy[31] (arm and back: 2·0–10·3 and 3·0–14·5 SED, respectively, depending on season). Occasional large discrepancies occurred for a given anatomical site even across studies of similar designs. For instance, dosimetric

assessment of shoulder exposure from a manikin was 85–90% of the value at the vertex of the head according to Wright *et al.*[15] and 66–75% according to Diffey.[29] SimUVEx yielded a ratio of ambient exposure of 57% for the shoulder but of 90% for the top of shoulder. This difference illustrates the effect of the measurement/computation technique. While dosimetry only captures UV exposure locally, an anatomically detailed model can also average exposure over the whole shoulder area and explains apparently conflicting results.

Our results suggest a very large contribution of diffuse UV radiation to total sun exposure, with a lesser than expected contribution of direct sunlight. Situations where a high direct radiation was predicted typically corresponded to potential risk situations of acute episodes of overexposure. These high-risk situations are generally covered in sun-protection messages; similarly, people are aware of the increased UV irradiation near snow, sand or water due to reflection. Conversely, the importance of diffuse radiation, albeit the main contributor to an individual's total UV exposure, does not appear to be adequately conveyed in current prevention practices. Our results question the effectiveness of recommendations such as avoiding 'peak' hours or seeking shade regarding the subsequent risk of long-term UV-induced damage, such as nonmelanocytic lesions. This is particularly true for vertically oriented surfaces such as the chronically exposed face, for which diffuse exposure explained most of the yearly dose, or for cloudy summer days where UV radiation remains high and is substantially higher than on sunny days in other seasons. In the same way as a cloudy sky can provide a false sense of UV protection, shading only reduces the portion of 'visible' sky and thereby offers a partial protection against diffuse radiation. Sun-protection messages could be better tailored, particularly towards outdoor workers, to include long-term risk associated with a regular exposure to suberythemal UV doses, and inform them of the increased risk of erythema when sun exposed in a static posture. Information about the limited protection offered by clouds (especially in summer) and shade in some situations should also be emphasized.

What's already known about this topic?

- Melanoma is predominantly associated with acute sun exposure, squamous cell carcinoma with chronic sun exposure, and basal cell carcinoma with both intermittent and cumulative sun exposure.
- The dose-response between ultraviolet (UV) exposure patterns and skin cancer occurrence is, however, not fully understood.

What does this study add?

- The contribution of specific UV radiation components (direct, diffuse and reflected radiation) to the anatomical dose is investigated for the first time using a numerical model.
- As input the model uses ground irradiance observational data collected over a complete year.
- Understanding exposure patterns with respect to radiation component is essential, better to target prevention.

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Skin Exposure to Aliphatic Polyisocyanates in the Auto Body Repair and Refinishing Industry: III. A Personal Exposure Algorithm

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Objectives: Isocyanate skin exposure may play an important role in sensitization and the development of isocyanate asthma, but such exposures are frequently intermittent and difficult to assess. Exposure metrics are needed to better estimate isocyanate skin exposures. The goal of this study was to develop a semiquantitative algorithm to estimate personal skin exposures in auto body shop workers using task-based skin exposure data and daily work diaries. The relationship between skin and respiratory exposure metrics was also evaluated.

Methods: The development and results of respiratory exposure metrics were previously reported. Using the task-based data obtained with a colorimetric skin exposure indicator and a daily work diary, we developed a skin exposure algorithm to estimate a skin exposure index (SEI) for each worker. This algorithm considered the type of personal protective equipment (PPE) used, the percentage of skin area covered by PPE and skin exposures without and underneath the PPE. The SEI was summed across the day (daily SEI) and survey week (weekly average SEI) for each worker, compared among the job title categories and also compared with the respiratory exposure metrics.

Results: A total of 893 person-days was calculated for 232 workers (49 painters, 118 technicians and 65 office workers) from 33 auto body shops. The median (10th–90th percentile, maximum) daily SEI was 0 (0–0, 1.0), 0 (0–1.9, 4.8) and 1.6 (0–3.5, 6.1) and weekly average SEI was 0 (0–0.0, 0.7), 0.3 (0–1.6, 4.2) and 1.9 (0.4–3.0, 3.6) for office workers, technicians and painters, respectively, which were significantly different ($P < 0.0001$). The median (10th–90th percentile, maximum) daily SEI was 0 (0–2.4, 6.1) and weekly average SEI was 0.2 (0–2.3, 4.2) for all workers. A relatively weak positive Spearman correlation was found between daily SEI and time-weighted average (TWA) respiratory exposure metrics ($\mu g\,NCO\,m^{-3}$) ($r = 0.380, n = 893, P < 0.0001$) and between weekly SEI and TWA respiratory exposure metrics ($r = 0.482, n = 232, P < 0.0001$).

Conclusions: The skin exposure algorithm developed in this study provides task-based personal daily and weekly average skin exposure indices that are adjusted for the use of PPE. These skin exposure indices can be used to assess isocyanate exposure–response relationships.

Keywords: auto body refinishing; exposure assessment; exposure modeling; hexamethylene diisocyanate; isocyanates; PPE; skin exposure; task-based exposure metrics

INTRODUCTION

Isocyanates, highly reactive chemicals used to manufacture polyurethane paints, foams and other products, remain a major cause of occupational asthma, especially in end-use settings such as auto body repair shops. Isocyanate exposure assessment and control has focused primarily on respiratory exposures, but skin exposure likely can also contribute to sensitization and asthma (Bello *et al.*, 2007a; Redlich and Herrick, 2008). The auto body industry uses

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isocyanates, primarily hexamethylene diisocyanate and isophorone diisocyanate, as the hardener component in polyurethane coatings, which typically contain <1% volatile monomers and >99% non-volatile polyisocyanates (Bello *et al.*, 2002, 2007b). Assessing skin exposure to isocyanates in the auto body repair setting presents a significant challenge. The methodologies for assessing isocyanate skin exposure are limited, and further complicated by the nature of auto body repair work, which involves a variety of sporadic tasks, numerous different isocyanate products in multiple small shops and inconsistent use of personal protective equipment (PPE).

The Survey of Painters and Repairers of Autobodies by Yale (SPRAY) study investigating isocyanate dose–response relationships initially focused on respiratory exposures (Redlich *et al.*, 2001; Sparer *et al.*, 2004; Woskie *et al.*, 2004). It was not feasible to obtain detailed exposure data on each auto body shop worker to evaluate exposure–response relationships. Thus, a task-based exposure algorithm was developed, using task-based measured airborne concentrations, daily diaries of tasks performed and use of PPE, to assess personal isocyanate inhalation exposures (Woskie *et al.*, 2004, 2008).

With increased awareness of the potential risks of isocyanate skin exposure and demonstration of skin exposure in a pilot study (Liu *et al.*, 2000), SPRAY was expanded to include evaluation of isocyanate skin exposures using qualitative and quantitative methodologies (Liu *et al.*, 2007; Bello *et al.*, 2008). SWYPE™ colorimetric indicators (CLI, Des Plains, IL, USA) were validated as a tool for isocyanate skin exposure and used to assess task-based skin exposures in auto body shop workers following painting and non-painting tasks (Liu *et al.*, 2007). These colorimetric indicator pads, which measure the aliphatic total isocyanate groups, were used to evaluate isocyanate contamination on skin surfaces exposed during auto body repair tasks or underneath gloves, paint suits or a respirator. A more limited quantitative skin exposure assessment was also conducted in 22 of the 35 SPRAY shops using similar wipe pads, which were analyzed for the total isocyanate group content with the National Institute for Occupational Safety and Health (NIOSH) 5525 method (Bello *et al.*, 2008).

This paper describes the development of a (semi-quantitative) algorithm to estimate personal skin exposures (daily and weekly) for an epidemiologic study of auto body shop workers. To account for the variable work pattern in auto body shops, task-based skin exposure data and daily work diaries that included tasks and use of PPE were used to estimate an individual skin exposure metric. The qualitative indicators described above were used in this algorithm rather than the quantitative wipe data due to the larger number of qualitative samples obtained in all surveyed shops and the greater range of tasks sampled. This individual daily and weekly skin exposure index (SEI) was compared to previously developed respiratory exposure metrics (Woskie *et al.*, 2008) to evaluate their relationships and will be used in future analyses to estimate the contribution of skin (as well as respiratory) isocyanate exposures to immunologic, respiratory and other outcomes in the SPRAY epidemiologic study.

MATERIALS AND METHODS

Auto body shop work process and task-based skin exposure assessment

The skin exposure assessment supplemented the ongoing SPRAY study. Study design, study population and work processes are described in previous publications (Redlich *et al.*, 2001; Sparer *et al.*, 2004; Woskie *et al.*, 2004; Liu *et al.*, 2007; Woskie *et al.*, 2008). Briefly, auto body shop work can be classified as painting and non-painting tasks, including paint mixing, spray painting (sealer, primer, base and clear coatings), grinding, sanding, polishing, compounding (use of abrasive compounds to grind the surface layers) and management or office work. As previously described, task-based skin exposure was evaluated in 124 auto body shop workers from 35 shops using colorimetric indicators (Liu *et al.*, 2007). Both unprotected skin areas and skin under the protection of PPE were evaluated following painting and non-painting tasks using SWYPE™ and Permea-Tec™ colorimetric indicators (CLI). Briefly, the SWYPE™ color indicators were used to wipe unprotected skin areas and skin areas covered by a half-facepiece cartridge respirator (skin areas covered by a dust mask or a full-facepiece respirator were not evaluated). The Permea-Tec™ patches were placed on thumb, index and middle fingers and the palm center to evaluate isocyanate breakthrough of gloves and on the right chest or inner clothing to evaluate the breakthrough of protective clothing. Wipes that changed color after a task were recorded as positive and the percent positive (we have previously used the term 'rate of positive samples') was calculated as the number of positive samples divided by the total samples for each task.

To identify the daily tasks with possible isocyanate skin exposures, all tasks each SPRAY auto body participant (n = 232 workers) performed daily were evaluated, using the work diary checklists that had been developed for estimating personal respiratory exposures as previously described (Sparer *et al.*, 2004; Woskie *et al.*, 2008). Briefly, these diaries were obtained on each SPRAY worker during four consecutive workdays (Monday through Thursday) when medical evaluations were performed, noting what tasks a worker had performed and the type of PPE

used (if any) every ½ h. Tasks with possible skin exposures were identified based on the task-percent of positive samples obtained from the colorimetric indicators.

Semiquantitative algorithm

Results from task-based qualitative skin wipe sampling with and without use of PPE and the daily work diaries were used to develop the skin exposure algorithm. The fraction of the surface area of each body part protected by PPE (coverall, gloves and respirator) over the total surface area that can be exposed was also taken into account. Spray painters might wear T-shirts with hands, forearms, face and neck exposed. When gloves were used, as indicated in the diary, the hands were covered; when a half-facepiece respirator was worn, a large part of the face was covered. If a nylon or Tyvek suit was used as indicated in the diary, the arms and neck were covered. Reference values for the fractional surface area of body parts likely to be exposed in an auto body workplace were used as a weighting factor in the algorithm.

Reference values for skin areas of body parts were obtained from the burn management algorithm in the 'Lund–Browder' charts in Figure 129-1 of Wolf and Prnitt (2008). The surface areas of body parts with potential isocyanate exposure (hands, forearms, face and neck) were expressed as a fraction of the total body surface area: both hands 0.05 (2×0.025; i.e. each hand makes up 2.5% of the total body skin surface area), forearms 0.06 (2×0.03), face 0.035 (face area is approximately half of the head area or $0.07/2 = 0.035$) and the neck area 0.02 (Table A-1, OECD, 1997). The total fractional surface area of hands, forearms, face and neck is 0.165 or 16.5% of the total body surface area.

These data were used to develop a semiquantitative SEI that estimated daily and weekly isocyanate skin exposure for each worker (see Results and Table 3 for more details on skin surface areas and calculations).

Statistical analysis

All data analysis was conducted using SAS® (Statistical Analysis Software, Version 9.13; SAS Institute, Cary, NC, USA). The qualitative wipe sampling data and work diary data were merged with the sample and shop information by shop and sample IDs. Personal daily SEI data were calculated for all SPRAY participants for each day and averaged for all survey days during the survey week (Monday through Thursday) as the weekly SEI. SEI data were checked for normality. Descriptive statistics (median, 10th–90th percentile, maximum) were calculated for daily SEI and weekly average SEI by self-reported job title (painter, technician and office worker). A Kruskal–Wallis rank sum chi-square test was performed to test the differences in daily SEI and weekly average SEI among the three job groups. Box plots were made for daily and weekly SEIs by job title. A correlation analysis was also performed on the daily and weekly SEIs with daily and weekly respiratory exposure indices (μg NCO m^{-3}) using Spearman's rank correlation coefficients.

RESULTS

The percent of skin positive samples for different spray painting and paint-related tasks performed without PPE and using PPE are shown in Tables 1 and 2, respectively, based on our prior qualitative assessment of skin exposure (Liu *et al.*, 2007). For the exposure algorithm, some tasks were combined, either because they were not significantly different from each other and/or because the diary information did not permit use of subcategories within a task. For example, percent positive for several paint-related tasks were combined, as the tasks were brief and frequently performed within the same ½ h time period in the diaries (Table 1). Similarly for percent positive under gloves, all painting tasks were combined into 'spray painting' (Table 2). For a few tasks that were not qualitatively sampled both with and without PPE, percent positive for related or similar tasks were used. For example, the percent positive for gun cleaning with non-protected hands was assumed to be the same as that for the painting task without gloves that occurred right before the spray gun was cleaned (Table 1).

A semiquantitative SEI was developed that estimated a body surface area- and PPE use-weighted sum of positive skin exposure events for paint-related tasks. After the SEI was calculated for each painting, mixing, gun cleaning and paint-related and non-paint-related task, they were added together as the daily SEI. SEIs from all workdays were then averaged as the weekly SEI for each worker. For non-paint-related task, a 0% positive was used based on our findings for

Table 1. Percent of positive samples for unprotected skin used in the algorithm

Task	Number of samples (total = 220)	Number of positive samples (%)
Spray painting		
Priming/sealing	51	14 (27)
Clear coating	84	38 (45)
Paint mixing	23	10 (43)
Spray gun cleaning	0	(27 or 45)[a]
Paint-related[b]	52	12 (23)

[a]Percent positive was not measured for this task. It was assumed similar to that of the painting task without gloves done right before the gun cleaning.
[b]Including sanding, buffing, compounding and polishing tasks.

Table 2. Percent of positive samples for protected skin used in the algorithm

PPE type/task	Number of samples (total = 181)	Number of positive samples (%)
Under gloves		
Spray painting	65	15 (23)
Paint mixing	41	3 (7)
Spray gun cleaning	5	4 (80)
Paint-related[a]	0	(7)[b]
Under respirator		
Spray painting	27	0 (0)
Under coverall		
Spray painting	43	1 (2)

[a]Including sanding, buffing, compounding and polishing tasks.
[b]Percent positive was not measured under gloves for these tasks, which was assumed similar to that in paint mixing under gloves.

these tasks (0 positive per 50 samples, Liu Y, Stowe MH, Bello D, Sparer J, Gore RJ, Cullen MR, Redlich CA, Woskie SR, unpublished data).

For spray painting tasks where exposures involve the whole body, the general model for SEI is defined as follows:

$$\mathrm{SEI} = \sum_{i=1} \mathrm{TE}(P)\{1 - \{[(\mathrm{FS_{hand}})(G)(\mathrm{GP})] + [(\mathrm{FS_{forearm}})(C)(\mathrm{CP})] + [(\mathrm{FS_{face+neck}})(R)(\mathrm{RP})]\}\}_I, \quad (1)$$

where i = task type (1, …, I); TE = total number of isocyanate task events (each ½ h counted as one event) per day from the work diary; P = task-based average percent of skin positive samples when no PPE was used (27% for priming/sealing; 45% for clear coating. See Table 1 last column); $\{1-\{[(\mathrm{FS_{hand}})\ (\mathrm{G})(\mathrm{GP})] + [(\mathrm{FS_{forearm}})\ (\mathrm{C})\ (\mathrm{CP})] + [(\mathrm{FS_{face\ +\ neck}})\ (\mathrm{R})\ (\mathrm{RP})]\}\}$ = the decrease in the SEI based on the amount of skin surface area covered by PPE (FS) and the PPE protection fraction (GP, CP and RP). When no PPE is worn G or C or R = 0 so the applicable term drops out. When PPE is worn G or C or R =1; and FS = fraction of potentially exposed skin surface area that could be covered by PPE during the task event (i.e. total normalized area of hands, forearms, face and neck equals 1). Specific values for surface areas of body part are given in Table 3.

$\mathrm{FS_{face\ +\ neck}}$ = fraction of the surface area of face and neck covered by a respirator that varies by respirator type.

A half-facepiece respirator covers ~22% of the face surface area only, so $\mathrm{FS_{face\ +\ neck}} = (0.212 \times 0.22 + 0.121 \times 0) = 0.05$.

A full-facepiece respirator (cartridge, powered air-purifying respirator or tight-fitting and loose-fitting supplied air respirators) covers essentially all of the face but none of the neck, so $\mathrm{FS_{face\ +\ neck}} = (0.212 \times 1 + 0.121 \times 0) = 0.212$. A supplied air respirator with hood covers both the face and neck, so $\mathrm{FS_{face\ +\ neck}} = (0.212 \times 1 + 0.121 \times 1) = 0.333$.

Table 3. Skin surface area of body parts expressed as a fraction of total body surface area and total exposed area ($\mathrm{FS_{hand,\ forearm\ and\ face\ and\ neck}}$) used in the algorithm

Body part type	Body part surface area as a fraction of total body area[a]	Fraction of potentially exposed skin area that could be covered by PPE[b]
Hands (both)	0.05	0.303
Forearms (both)	0.06	0.364
Face and neck	0.055	0.333
Face	0.035	0.212
Neck	0.02	0.121
Sum of fractions	0.165	1.000

[a]Based on Lund–Browder charts in Figure 129-1 of Wolf and Prnitt (2008).
[b]Fraction of potentially exposed skin area that could be covered by PPE is the [body part surface area fraction/sum of total fractions (0.165)]. This is a body part fraction normalized to the surface area available for exposure since each body part can be exposed during a task, but can also be covered by PPE, such as a respirator, gloves or coveralls.

G, C, R = use of PPE 0 = no 1 = yes for gloves, coveralls, respirator; GP = glove protection (percent negative) = 1 − percent positive under gloves for spraying with any type of isocyanate paint = 1 − 0.23 (see Table 2); CP = coverall protection (percent negative) = 1 − percent positive under coverall for spraying with any type of isocyanate paint = 1 – 0.02 (see Table 2); and RP = respirator protection (percent negative) = 1 − percent positive under respirator for all isocyanate spraying = 1 − 0 (see Table 2).

For the following diary tasks: mixing of isocyanate-containing paint, spray gun cleaning and other paint-related tasks such as dry and wet sanding, the exposure was simplified to involve the hands only. Equation (1) is reduced to equation (2):

$$\mathrm{SEI} = \mathrm{FS_{hand}} \sum_{i=1} \mathrm{TE}(P)\{1 - [(G)(\mathrm{GP})]\}_I, \quad (2)$$

where TE, G and $\mathrm{FS_{hand}}$ are defined as in equation (1); P = task-based average percent of skin positive samples from Table 1—mixing isocyanate paints = 43%, other isocyanate paint-related tasks (sanding) = 23% and gun cleaning had no samples, therefore use the percent positive for the type of paint sprayed in the same ½ h as gun cleaning (if more than one type paint, use highest percent positive; if no paint, look at previous ½ h) and GP = glove protection (percent negative) = 1 − percent positive under gloves (see Table 2).

When there was a single task during the ½ h, that task P was used. If there were multiple tasks during the ½ h, the highest P was used for that ½ h. For each worker on each day, the SEI was the sum of SEIs

from all tasks (SEI_{day}); for each worker for each week, the total SEI was the sum of the SEI_{day} from 4 days (Monday through Thursday).

Daily SEIs were then calculated for all 232 SPRAY workers (49 painters, 118 technicians and 65 office workers) from 33 auto body shops, resulting in 893 person-days (245 days for office workers, 458 days for body technicians and 190 days for painters) based on presence during the study week as recorded in the diary, using this algorithm. The daily SEI ranged from 0 to 6.1, and the 10th–90th percentile range was 0–3.5. The median (10th–90th percentile, maximum) daily SEI was 0 (0–0, 1.0), 0 (0–1.9, 4.8) and 1.6 (0–3.5, 6.1) for office workers, technicians and painters, respectively. There was a significant difference in daily SEI between job titles (Kruskal–Wallis rank sum chi-square = 332.6, df = 2, $P < 0.0001$), with painters having the highest daily SEIs and office workers the lowest SEIs, as shown in Fig. 1. Box plots of daily SEI by job title showed a range of SEIs for each job category with considerable overlap between technicians and painters (Fig. 1) and no skin exposure for most office workers, as expected.

Each worker's weekly average SEI was also calculated for Monday to Thursday (Fig. 2), with similar differences between job categories. The weekly average SEI ranged from 0 to 4.2 and the 10th–90th percentile ranged from 0 to 3.0 with a median value of 0.2 for all workers. Weekly average SEI was 0 (0–0.0, 0.7), 0.3 (0–1.6, 4.2) and 1.9 (0.4–3.0, 3.6) for office workers, technicians and painters, respectively. There was also a significant difference in SEI between job titles (Kruskal–Wallis rank sum chi square = 118.7, df = 2, $P < 0.0001$), with painters having the highest SEIs. Box plots of weekly average SEI by job title were similar to daily SEI, showing a range of skin exposures, with considerable overlap between technicians and painters (Fig. 2).

The skin exposure indices estimated for individual workers were compared to the respiratory exposures (μg NCO m^{-3}) estimated for the same workers using the quantitative task-based exposure algorithm previously developed (Woskie *et al.*, 2008), in order to evaluate the relationship between air and skin exposure levels. Daily SEI and the daily time-weighted average (TWA) air concentration (μg NCO m^{-3}) were weakly correlated ($r = 0.380$; $P < 0.0001$), as shown in Fig. 3. As expected, there is a general positive trend between SEI and the respiratory exposure. However, there are clearly workers with minimal daily isocyanate respiratory exposure and high daily skin exposure indices and vice versa. The weekly average SEI and the weekly TWA air concentration (μg NCO m^{-3}) were similarly correlated ($r = 0.482$; $P < 0.0001$), as shown in Fig. 4.

DISCUSSION

Despite growing concerns about the role of skin exposure in isocyanate sensitization and asthma, methods to evaluate isocyanate skin exposures remain very limited, and skin exposure assessment has rarely been incorporated into occupational epidemiologic studies of isocyanate-exposed workers (Petsonk *et al.*, 2000; Pronk *et al.*, 2006; Bello *et al.*, 2007a). This paper is the third in the series describing isocyanate skin exposures in auto body shops (Liu *et al.*, 2007; Bello *et al.*, 2008). It describes the development of a task-based skin exposure algorithm to estimate daily and weekly isocyanate skin exposures for each auto body shop worker, based on task-based qualitative isocyanate skin exposure data and daily work diaries obtained

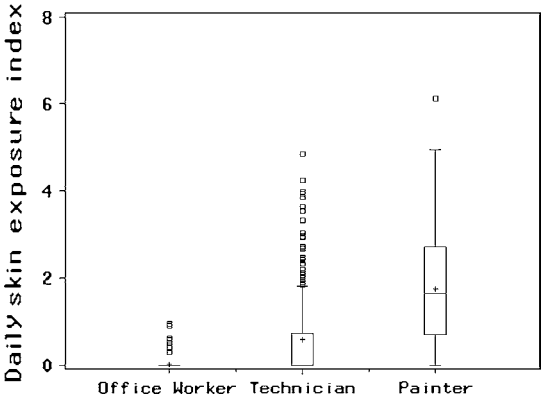

Fig. 1. Distribution of daily isocyanate SEI by job category ($n = 893$ worker days). The top of box plots represents the upper quartile (75%tiles), the bottom represents the lower quartile (25%tile), the middle line represents the median (50%tile) and '+' indicates the arithmetic mean. The top bar (whisker) is the maximum value and lower bar is the minimum value which are not outliers. The squares outside the top bar indicate outliers.

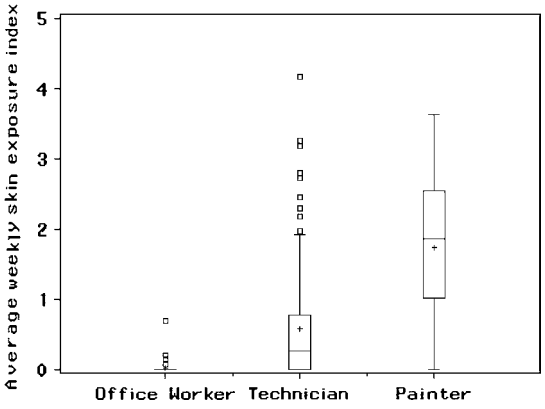

Fig. 2. Distribution of weekly isocyanate average SEI by job category ($n = 232$ workers). See Fig. 1 for the interpretation of box plots.

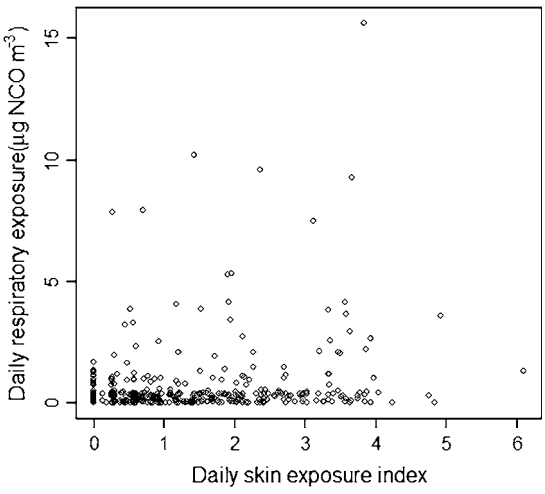

Fig. 3. Relationship between daily SEI and daily respiratory exposure to isocyanates (μg NCO m^{-3}), $n = 893$ worker days.

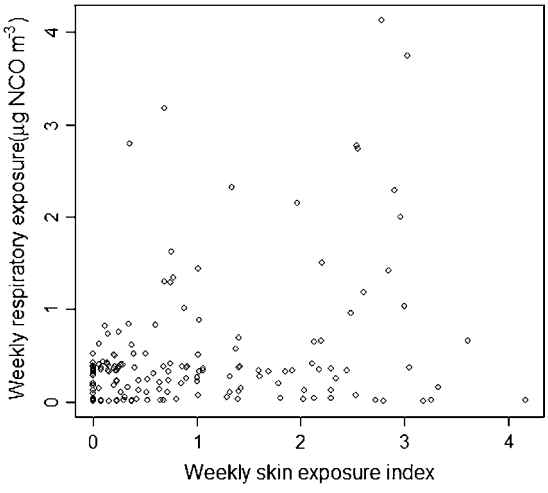

Fig. 4. Relationship between weekly average SEI and weekly average respiratory exposure to isocyanates (μg NCO m^{-3}), $n = 232$ workers.

as part of the SPRAY study (Redlich *et al.*, 2001; Sparer *et al.*, 2004; Woskie *et al.*, 2004).

Individual skin exposures were quite variable, with painters and technicians having the highest exposures and skin exposure was uncommon among office workers. An important finding is that individual skin and respiratory exposure indices, although related, are not highly correlated ($r = 0.38$ for daily exposure). Not unexpectedly, painters have the highest skin exposure, as tasks such as spray painting can have relatively high respiratory and skin isocyanate exposures, which can be modified by factors such as the use of PPE (Woskie *et al.*, 2004; Liu *et al.*, 2006, 2007). However, it is notable that worker isocyanate skin exposures cannot be reliably estimated from respiratory exposure. Isocyanate skin exposures were variable and also relatively high in some technicians as well as painters, consistent with tasks such as mixing or sanding that can have relatively high isocyanate skin exposure (Table 1) and relatively low respiratory exposure (Woskie *et al.*, 2008). Wet sanding in particular is a task that seldom has any respiratory exposure (water is used for sanding), but has relatively high skin exposure (45%). This weak correlation between individual skin and respiratory exposure indices should enable evaluation of the contribution of both respiratory and skin exposure to health-related end points. Pronk *et al.* (2006) found that skin and airborne exposures were closely correlated. However, the skin exposure assessment in their study was based only on hand exposure (estimated from glove extraction), did not take into account use of PPE or exposure to other body parts such as arms, face and neck and only included spray painters and spray tasks.

The skin exposure algorithm reported here has several strengths. Importantly, it is task based. Isocyanate exposures commonly occur in small end-use settings such as auto body shops, where workers perform a number of different job tasks, frequently with irregular work patterns, leading to sporadic and variable isocyanate exposures (Sparer *et al.*, 2004). Task-based exposure assessment can assess exposures in a range of tasks and, when combined with a work diary, can estimate individual worker exposure (Warren *et al.*, 2006; Woskie *et al.*, 2008). The task-based isocyanate skin exposure used for this algorithm was based on a relatively large number of skin exposure samples (>400), obtained on all major auto body shop tasks with potential isocyanate skin exposure using qualitative colorimetric indicators that have previously been validated (Liu *et al.*, 2007). Detailed daily work diaries obtained on each worker enabled estimation of a daily and weekly personal SEI for each worker, incorporating frequency and duration of exposure during a variety of different tasks.

Another strength of this skin exposure algorithm is that total body skin exposure was estimated and the individual SEIs were adjusted for the use of PPE (respirator, gloves and protective clothing) and the protection achieved. This adjustment was possible since isocyanate skin exposure was evaluated on different body parts (e.g. hands/face) with and without PPE for most tasks and individual PPE use was recorded in the diaries. Thus, the estimated SEI takes into account the use and effectiveness of the PPE worn. Importantly, the daily and weekly average isocyanate SEIs were compared with the comparable quantitative respiratory TWA exposure metrics. The relatively weak correlation between individual skin and respiratory exposures will enable future analyses to determine whether skin and respiratory exposures independently contribute to isocyanate asthma or other end points such as immunologic markers.

Skin exposure assessment is much less developed than respiratory exposure assessment (Schneider *et al.*, 2000; Vermeulen *et al.*, 2002). Several limitations of the skin exposure algorithm should be noted. For one, the SEI depends on the accuracy of the qualitative skin wipes. These wipes have been validated in comparison with quantitative wipes but also have limitations, as previously noted, including less sensitivity than quantitative wipes and probable underestimation of skin exposure (Liu *et al.*, 2007). The percent of skin exposure for different tasks was based on the percent positive qualitative wipes for each task and did not differentiate color intensity or concentration of exposure, which can vary for any task (Liu *et al.*, 2007). The SEI is thus based on exposure fraction and is an index, rather than a quantitative estimate that can be expressed as μg NCO per surface area. As noted above, the quantitative wipe results were not used due to the more limited number of quantitative samples that could be obtained and analyzed. Pronk *et al.* (2006) used a glove extraction method to evaluate dermal hand exposures during spray painting. Tape stripping has been used to evaluate skin exposure in a single spray painter, but has not yet been utilized to estimate exposure in a larger number of workers (Fent *et al.*, 2006). Petsonk *et al.* (2000) used questionnaire data to evaluate skin spotting as an indicator of isocyanate skin exposure, but did not confirm or quantify isocyanate skin exposure. Other skin exposure approaches such as theoretical modeling, observational methods or expert judgment have not to our knowledge been applied to isocyanates (Schneider *et al.*, 2000; Vermeulen *et al.*, 2002; van Wendel de Joode *et al.*, 2005). Biomarkers of isocyanate exposure are not specific for skin exposure and have shown variable associations with exposure (Pronk *et al.*, 2006; Bello *et al.*, 2007a). Thus, despite limitations, the task-based skin algorithm developed in this article likely provides the most comprehensive approach to-date to estimate individual worker isocyanate skin exposure.

Sampling under PPE was determined largely by what PPE was worn by the workers. Gloves worn were predominantly latex despite the recommendation of using nitrile by the paint manufacturers. For respirators, we assessed exposures under half-facepiece respirators with organic vapor cartridges and prefilters as these were most commonly worn (Sparer *et al.*, 2004; Liu *et al.*, 2006). We did not take wipe samples under dust masks, powered air-purifying respirators and full-facepiece supplied air respirators, which were infrequently used. Using the percent positive under half-facepiece cartridge respirators to calculate the SEI for other respirator types might have introduced bias. For underneath protective clothing, the algorithm neither evaluates the type of protective clothing worn by workers (nylon suits versus Tyvek etc.) nor does it account for short-sleeved versus long-sleeved work shirts among those not wearing PPE clothing.

Other limitations relate to the accuracy of the work diary, and how representative the survey week was of more long-term exposure. Efforts were made with the shop management to select a survey week that represented a typical work week, but work could be variable from week to week.

Despite these limitations, this skin exposure algorithm is the first attempt we are aware of that provides the most comprehensive approach to estimate individual worker isocyanate skin exposure based on field isocyanate skin exposure data.

In summary, the skin exposure algorithm developed in this study provides task-based daily and weekly average worker SEIs that are adjusted for individual use of PPE. Comparison of individual worker SEIs with TWA respiratory exposures (μg NCO m^{-3}) estimated for the same workers using a task-based algorithm showed a relatively weak positive correlation. The application of the isocyanate skin exposure metric developed here to the SPRAY epidemiologic study is essential, but is beyond the scope of this article. Extensive analysis of the relative contribution of isocyanate skin and respiratory exposures and other risk factors in the SPRAY study will be presented separately.

FUNDING

US National Heart, Lung and Blood Institute/National Institutes of Health (1R01-HL62932); National Institute for Occupational Safety and Health/Centers for Disease Control and Prevention (1R01OH03457); National Institute of Environmental Health Sciences (K24-ES00355) to C.A.R.

Acknowledgements—We thank shop management and workers, whose participation and support made this study possible.

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From: s47F
To: s22
Subject: RE: Expert stakeholder roundtable - TGA"s risk assessment of sunscreen ingredients [SEC=OFFICIAL]
Date: Wednesday, 18 December 2024 9:40:27 PM
Attachments: image001.png
image002.png
image003.jpg
image004.png
Percutaneous sunscreens Roberts with Q and A.pdf

Hi s22

For information, attached is a talk by Mike Roberts an Emeritus Professor at UQ. He has been working in this field for decades, and more recently with the FDA on their sunscreen assessments. Details of that presentation is here:
Please find a PDF copy of my presentation entitled *Percutaneous absorption of sunscreens and other consumer products*. And that I gave as the Plenary speaker at the *"Innovations in Dermatological Sciences Conference"* held remotely on September 27 and 28, Center for Dermal Research Rutgers, The State University of NJUSA 2023.
He might be willing to provide input to the TGA response if this is useful or desired.

Thanks
s47F

s47F

From: s22 @health.gov.au>
Sent: Tuesday, 17 December 2024 11:02 AM
To: s47F
Cc: s47F
Subject: RE: Expert stakeholder roundtable - TGA's risk assessment of sunscreen ingredients [SEC=OFFICIAL]

Hi s47F

You NSW Health Teams should work.

You will need to go into the 'document section'.

Let me know if you have further issues.

Many thanks
s22

From: s47F
Sent: Tuesday, 17 December 2024 10:57 AM
To: s22 @health.gov.au>
Cc: s47F
Subject: RE: Expert stakeholder roundtable - TGA's risk assessment of sunscreen ingredients [SEC=OFFICIAL]

Hi s22

My GovTEAMS channel for "Sunscreen Expert Working Group" is empty.

That said, I am using NSW Health Teams and not UNSW. I prefer NSW Health, but if I need to change to UNSW please let me know so I can look into how to log into that

Thanks
s47F

From: s22 @health.gov.au>
Sent: Tuesday, 17 December 2024 10:26 AM
To: s47F s22
s22 @health.gov.au>; s47F
s47F ; HENDERSON, Nick <Nick.Henderson@health.gov.au>; CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>; s22
s22 @health.gov.au>; s22 @health.gov.au>; s22 @health.gov.au>; s22
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s47F
s47F s22 @health.gov.au>; s22
s22 @health.gov.au>
Cc: s @health.gov.au>; s22 @health.gov.au>; LANGHAM, Robyn
<Robyn.LANGHAM@Health.gov.au>; s22 @Health.gov.au>
Subject: Expert stakeholder roundtable - TGA's risk assessment of sunscreen ingredients [SEC=OFFICIAL]

Dear all,

Thank you for confirming your participation in tomorrow's expert roundtable discussion regarding TGA's risk assessment of sunscreen ingredients.

Date- Wednesday 18 December 2024, 11am – 1pm

Venue - All external experts are attending the meeting virtually via Microsoft Teams. The meeting link can be found within the TGA calendar invite.

Papers- All relevant papers are available on GovTeams, available at Meeting Papers. You should have access to five documents:

- Agenda
- Roundtable paper- TGA risk assessment of sunscreen ingredients
- Attachment 1- Australian Sunscreen Exposure Model

Attachment 2- Risk Assessment of Seven Active Sunscreen Ingredients (Working Copy)

- Attachment 3- Benzophenone Risk Assessment (Working Copy)

DOIs- Please ensure you have submitted your DOI paperwork prior to attendance.

If you require assistance with accessing the documents or entering the meeting tomorrow, please feel free to contact me directing via email at s22 @health.gov.au or via phone on s22 .

I look forward to meeting you all tomorrow.

Kind regards,
s22

s22
Senior Policy Officer/Director
Chief Medical Adviser Unit
He Regulation Group
T: s22 E: s22 @health.gov.au
Location: 27 Scherger Drive, Level 2
PO Box 100, Canberra ACT 2601, Australia

The Department of Health and Aged Care 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 all Elders both past and present.

Percutaneous absorption of sunscreens and other consumer products

Michael Roberts

University of Queensland, Brisbane &
University of South Australia, Adelaide
AUSTRALIA

THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

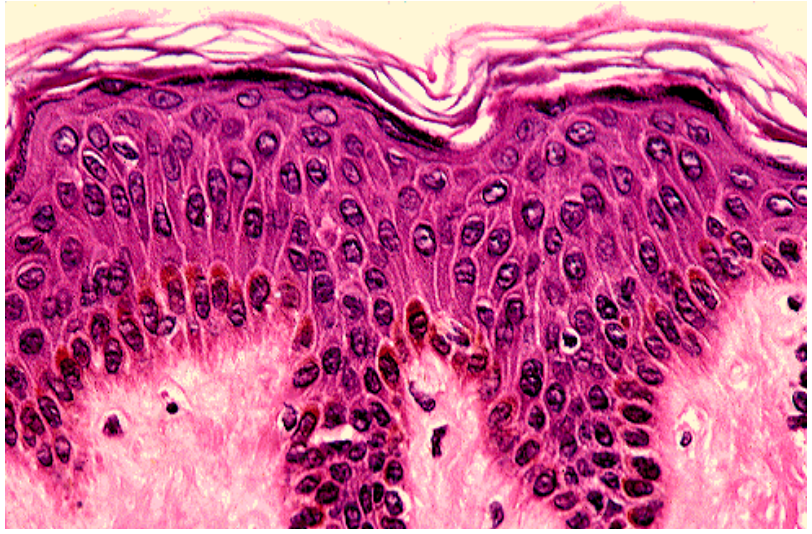
The Institute
basil hetzel institute for medical research

UniSA

TRI
TRANSLATIONAL RESEARCH INSTITUTE
AUSTRALIA

Percutaneous absorption of sunscreens and other consumer products outline

- Why this area captivated me
- Topical products growth, range and opportunities
- Organic sunscreen percutaneous absorption
- NSAID products
- Nanozinc oxide sunscreens
- FDA psoriasis study
- Dermal Open Flow Microperfusion



My introduction into topical product development

Pharmacy student (B Pharm,1970) captivated by Star Trek, history & compounding

Reid Building where learned compounding

Building and University of Adelaide adjacent to Torrens River

Dr. "Bones" McCoy inoculates Star Trek (1966–1969) crew with a needle-free hypospray

Galen's Cerate (cold cream)

Cetyl esters wax	12.5g
White beeswax	12.0g
Almond oil	56.0g
Sodium Borate USP; Borax BP	0.5g
Stronger rose water	2.5mL
Rose Oil	0.2 mL
Purified water qs to	100g

GALEN – Experimenter in Compounding (131-201 AD) Thom (1952).
https://collections.nlm.nih.gov/catalog/nlm:nlmuid-101416748-img

Cold cream APF

White beeswax	17g
Liquid paraffin	45g
Borax	1g
Purified water	37mL

"Cooling" water-repellent cream

Calamine lotion APF & BP

Calamine	15g
Zinc oxide	5g
Bentonite, sterilized	3g
Sodium citrate	0.5g
Liquified phenol	0.5mL
Glycerol	5 mL
Purified water	to 100mL

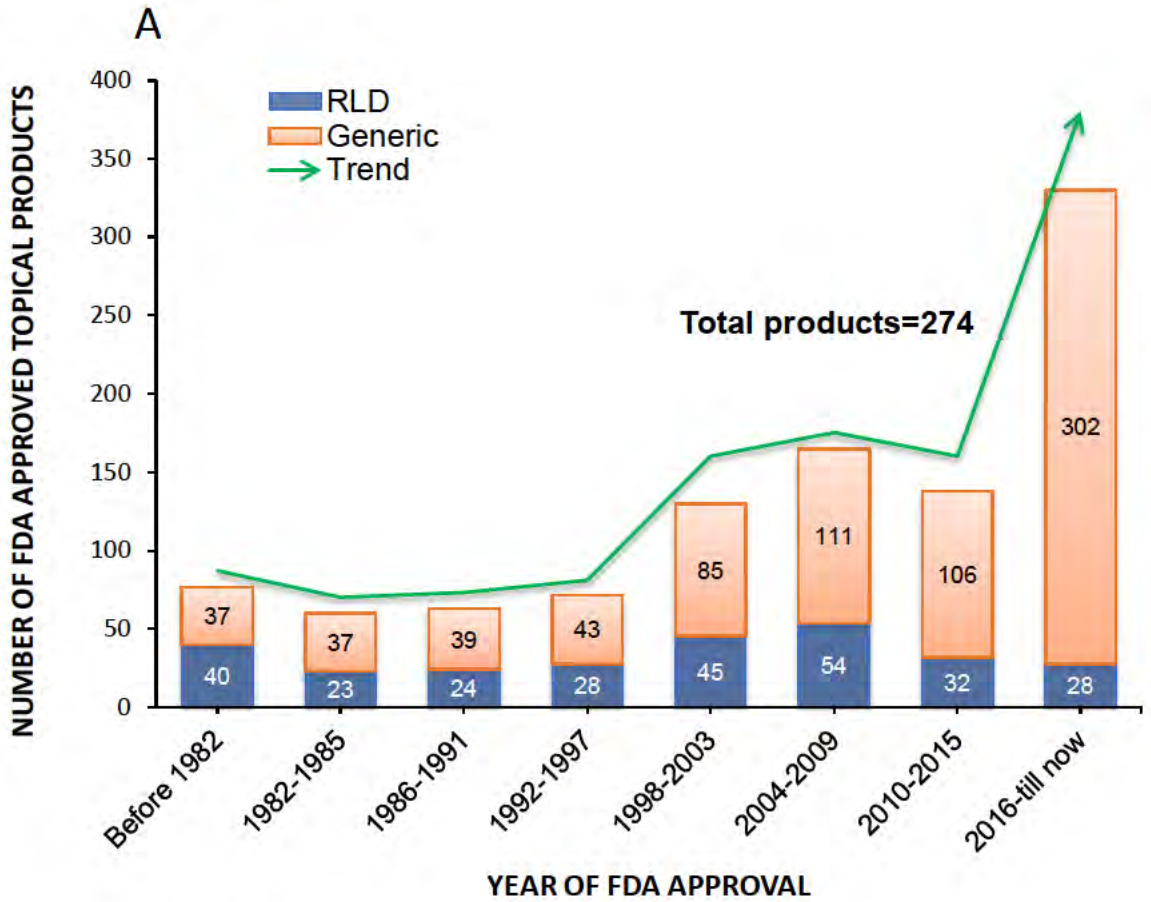
Soothing and protective agent

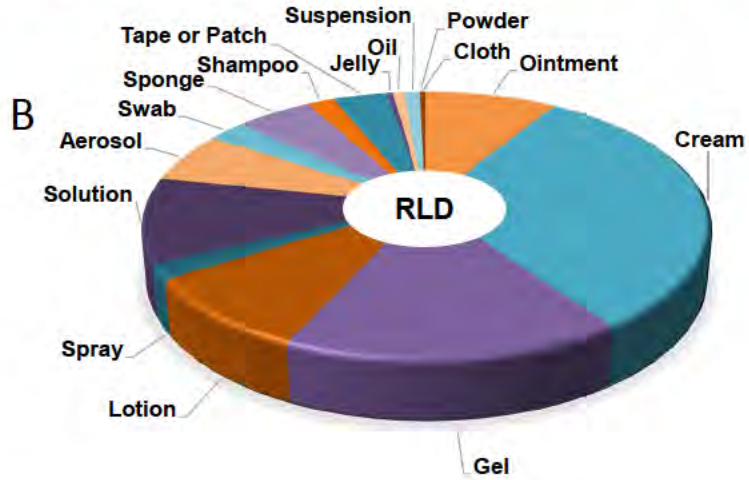
Methyl salicylate liniment APF

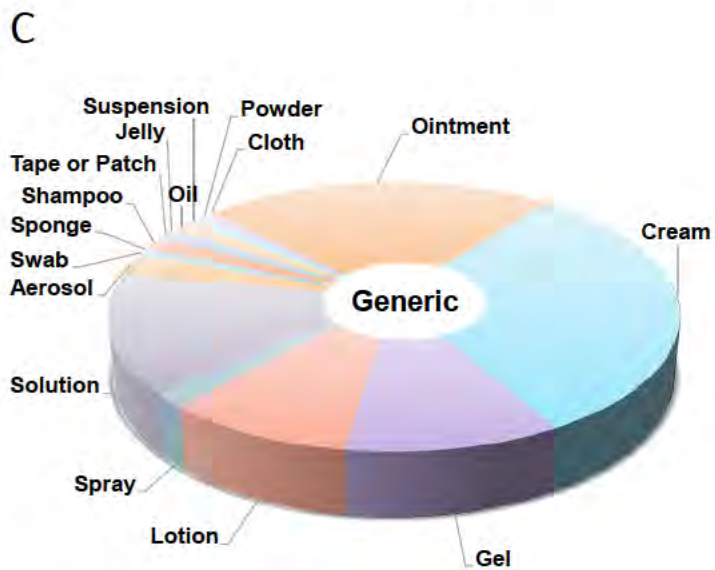
Methyl salicylate	25mL
Arachis oil to	100mL

Soothing and protective agent

From that time, an exponential growth in FDA approved generic topical products (A), with, today, a wide range of different RLD (B) and generics (C)







A key question that follows is which product for when?

Total products=770

Roberts MS.et al. Topical drug delivery. Adv Drug Deliv Rev. 2021 Oct;177:113929.

These products are used to target various local sites – a key question we will seek to address in this talk is how well is this achieved?

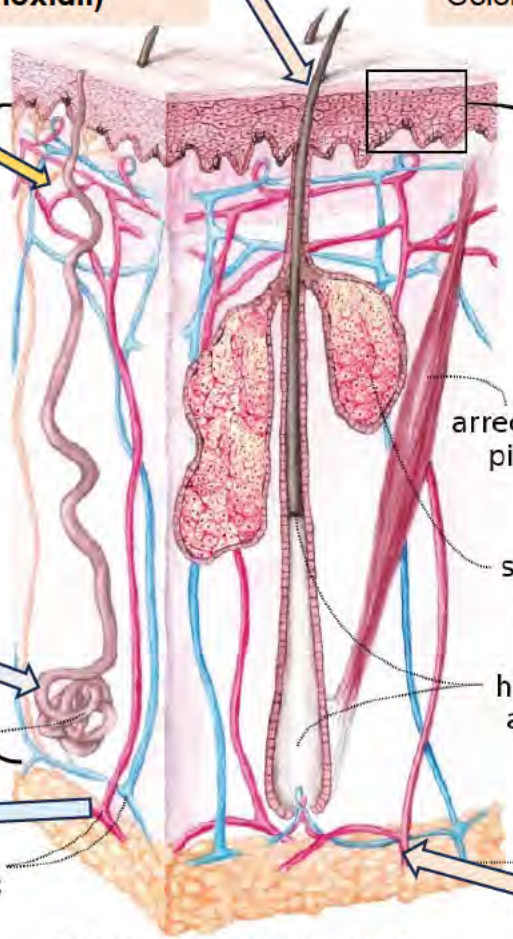
Follicular delivery
Anti-acne (erythromycin)
Anti-dandruff (zinc pyrithione)
Anti-infectives (fusidic acid)
Hair restorers (minoxidil)

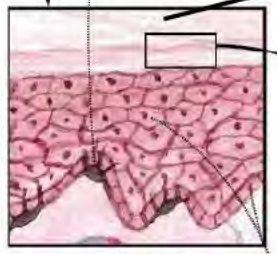
Sensorial
Cold cream - evaporation
Feel – grittiness, fluidity
Smell
Color

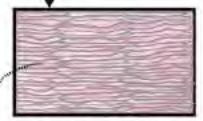
Surface & SC delivery
Anti-infectives
Moisturising & drying cosmetics
Insect repellents
Organic sunscreens (oxybenzone)
'Physical' sunscreens (ZnO, TiO2

Dermal delivery
Local anaesthetics
Vasoconstrictor
Collagen suppl.

In this talk, we focus on agents in bold







Viable epidermis delivery
Corticosteroids
Retinoids
Immunomodulators
Whiteners
Re-pigmentation
Vaccines

Sweat gland delivery
Antiperspirants

Systemic delivery
Nicotine, nitroglycerin etc

Subcutaneous & deeper delivery
NSAIDs

Flynn GL, Roberts MS. Physical and biophysical foundations of pharmacy practice: Issues in drug delivery, HathiTrust, 2015. Fig. 1 p694 drawn by Anna Vlaminck.

Surface & stratum corneum delivery- sunscreens

Ultraviolet (UV) radiation effects

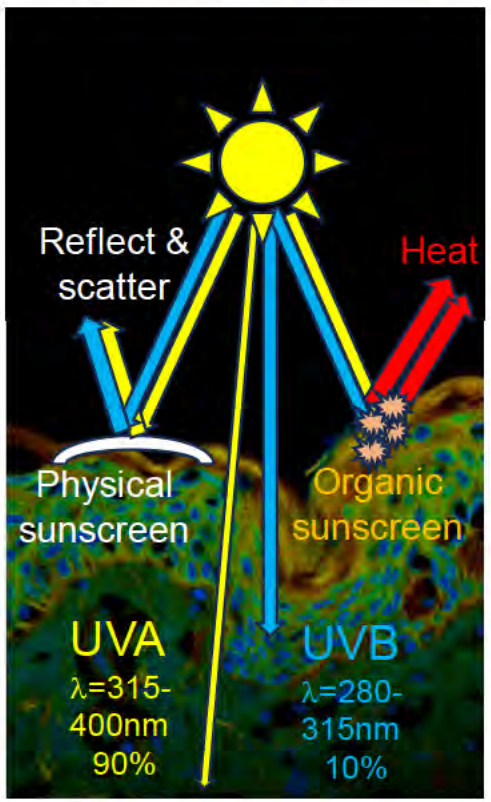
- UVB → new melanin pigment & thicker epidermis → ± sunburn & tanning.
- UVA activates existing melanin pigment → transitory tan. Deeper penetration → long-term skin damage & premature ageing.
- UV light + skin cells →free radicals → indirectly cause DNA mutations → promote skin cancer

(Actinic keratoses; Basal cell carcinoma, BCC; squamous cell carcinoma, SCC; melanoma)

16 Sunscreens approved by FDA

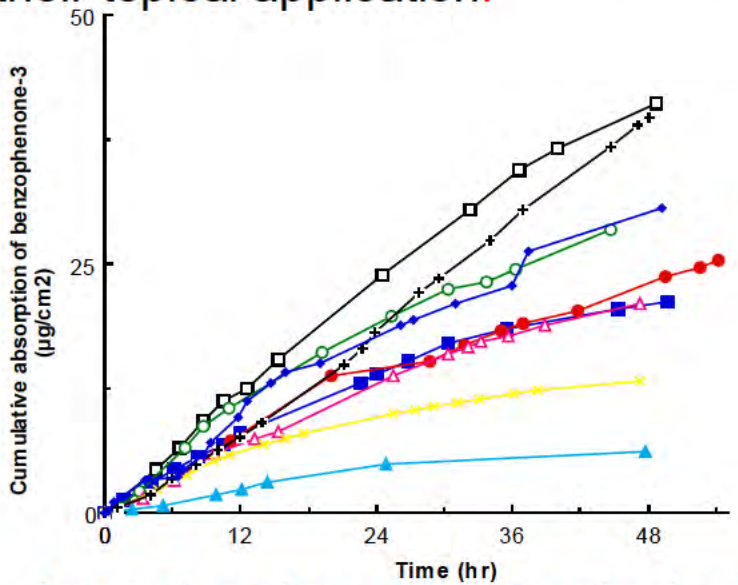
8 in common use

- **6 Organic** (avobenzone, homosalate, octinoxate, octisalate, octocrylene, oxybenzone)
- **2 Physical** (titanium dioxide and zinc oxide)



Desirable sunscreen does not penetrate into skin beyond stratum corneum nor into systemic circulation

In 1997, we measured excretion of sunscreens in urine of volunteers after their topical application.



- Amount oxybenzone absorbed over 10h is 1 - 2% applied amount.
- No apparent absorption of other sunscreens

Hayden et al Lancet 1997

Organic sunscreen percutaneous absorption

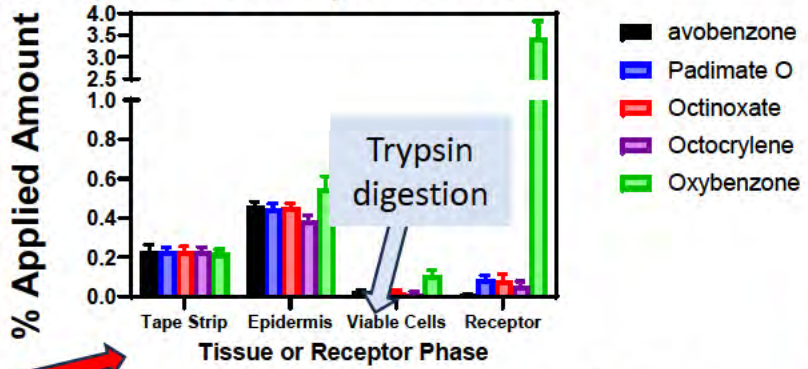
Dosing and Analysis of Human Epidermis in vitro.

- Heat separated epidermal membranes from human female abdominal skin were mounted in horizontal Franz-type diffusion cells (surface area~1.3 cm^2)
- Receptor phase of 4% bovine serum albumin in phosphate buffer pH 7.4 maintained at 35 ° C and continuously agitated with a magnetic stirrer.
- Acetonitrile extraction & HPLC analysis

Sunscreen Toxicity Testing in Human Epidermal Keratinocyte Cultures (HEKs)

- HEKs from neonatal foreskins (dispase/trypsin)
- DNA Synthesis based on uptake of [3H]-thymidine into HEK cultures & scintillation counting
- Data fitted to 3 parameter logistic function to generate $E_{max}(\%)$, IC_{50} (μM) and shape factor
- IC_{50} (μM) adjusted for 40 X difference between cell culture and receptor phase protein to yield viable epidermal equivalent $IC_{50,\,ve}$ (μM)

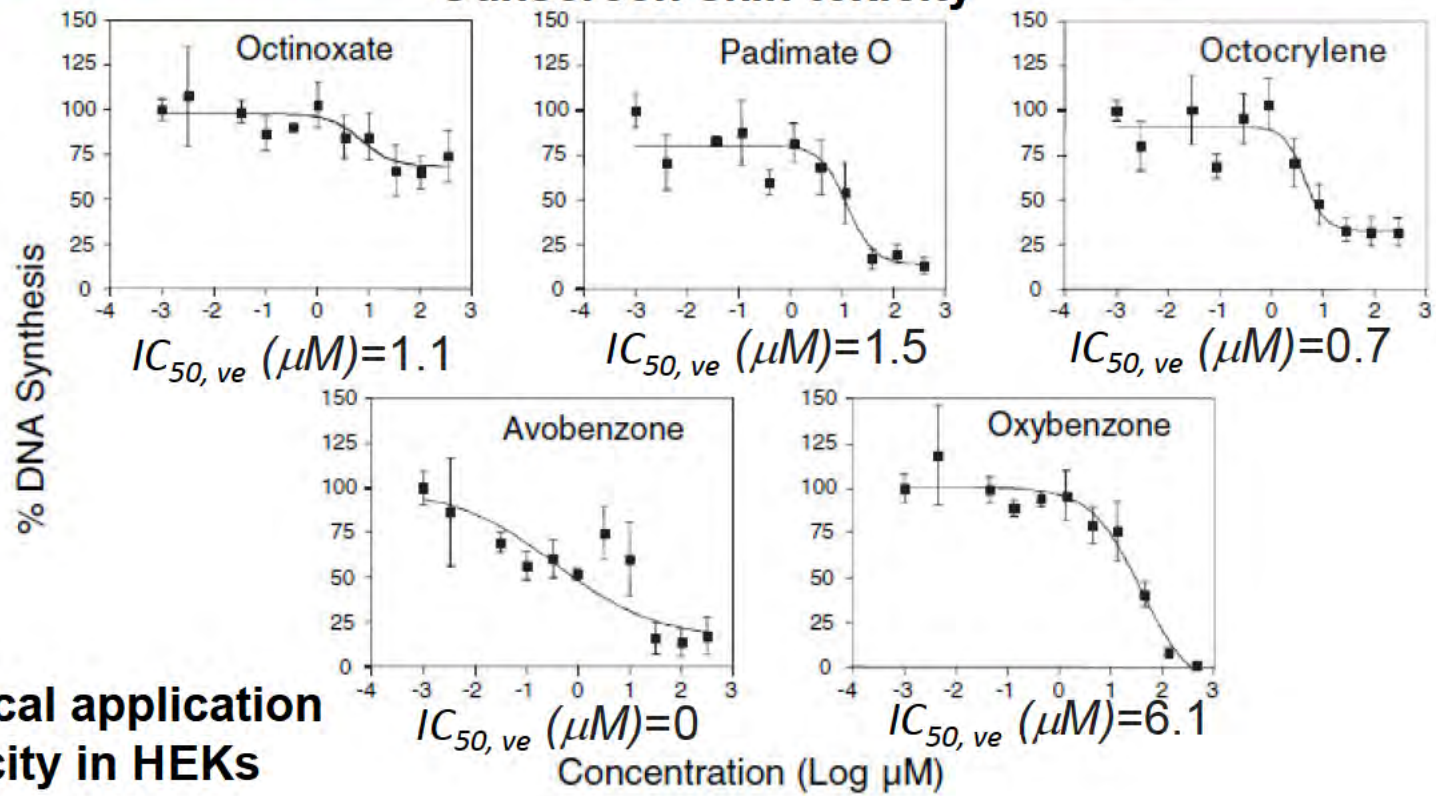
Sunscreen skin permeation



X2 after surface clean

Hayden et al. Skin Pharmacol Physiol 2005;18:170–174

Sunscreen skin toxicity



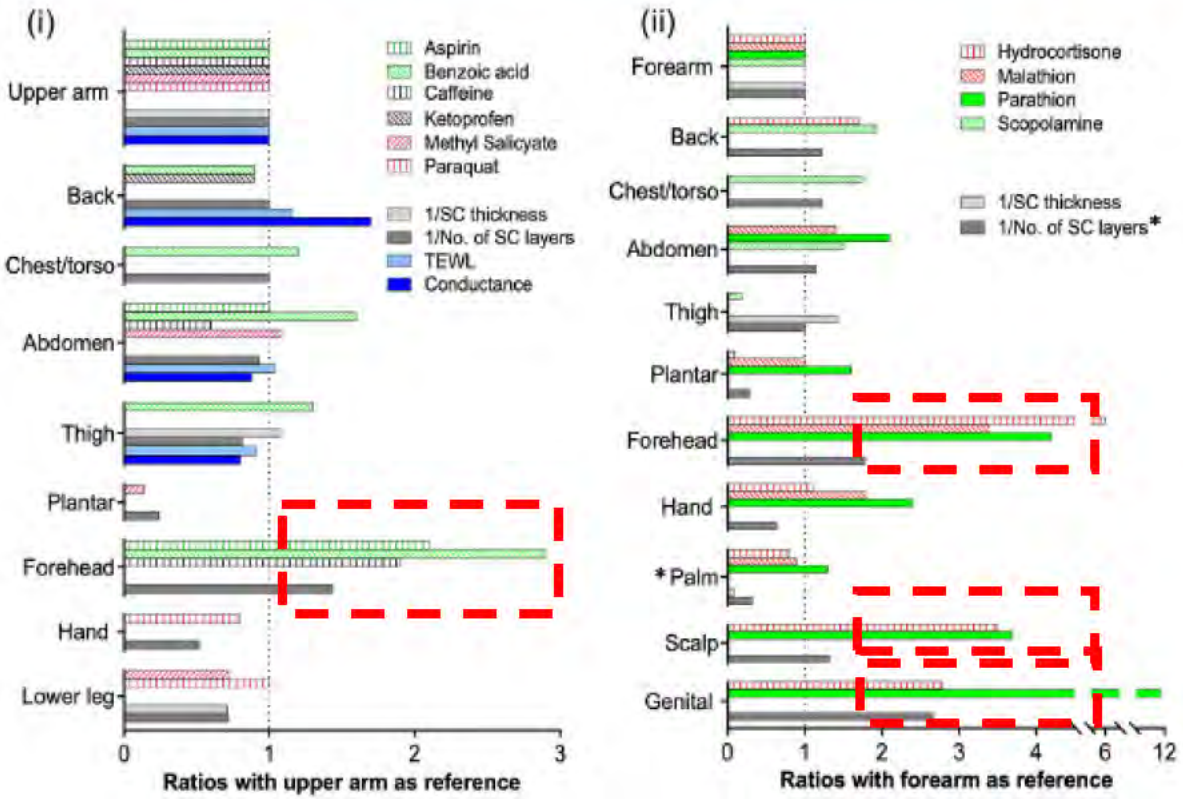
Sunscreen levels in viable epidermis after topical application to intact skin well below those causing toxicity in HEKs

To what extent are these findings applicable to other skin types?

Body site

- Shared findings with local cosmetic manufacturer
- Removed oxybenzone from sunscreen products
- Observed that their face irritation complaints disappeared.

Relative systemic absorption to different body sites after topical application,

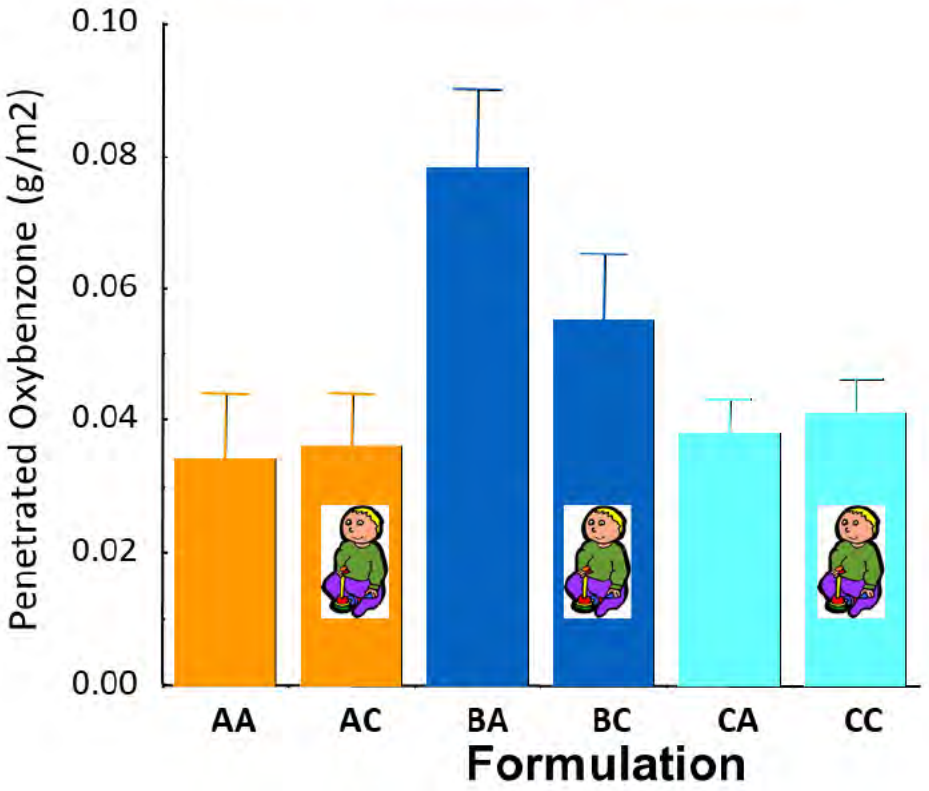


Liu et al J Control Rel 334 (2021) 37–51

Age

- And how do children's formulations differ from adults? Are they safer?
- There is little difference in skin absorption of actives

Human skin penetration of oxybenzone

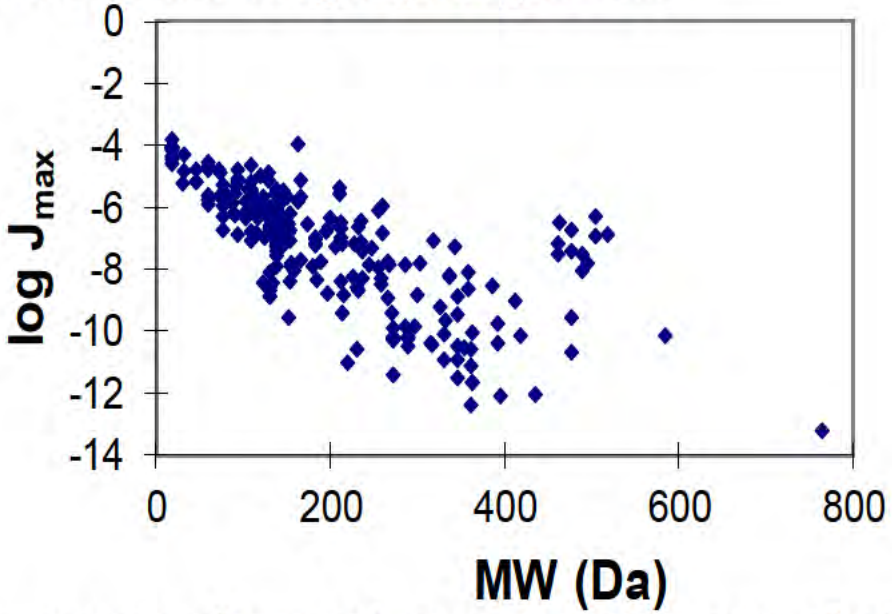


Jiang et al, Br J Clin Pharmacol 1999

And why does oxybenzone have more profound skin (stratum corneum, SC) absorption than other actives?

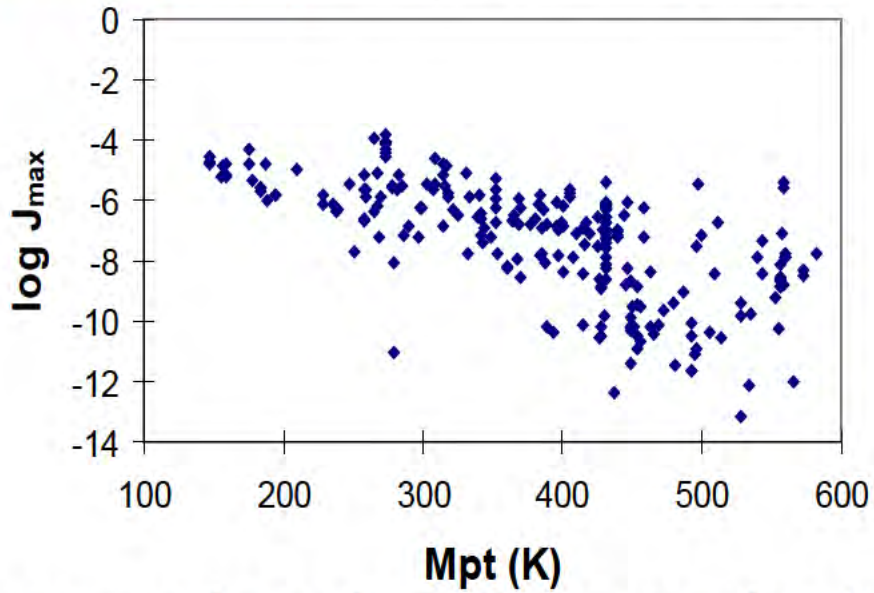
General principle: Maximum flux for an active through the SC = $\frac{Solubility_{sc} Diffusivity_{sc}}{SC\ pathlength}$

The major determinant for the **SC diffusivity** of most actives is its **molecular size**, as represented by its molecular weight (MW), N=278



The commonly used **sunscreens are similar in MW** (Da): avobenzone, 310.4; homosalate, 262.3; octinoxate, 290.4; octisalate (octyl salicylate), 250.3; octocrylene, 361.5; oxybenzone, 228.2

A key determinant of **SC solubility** of any active is its **melting point,** as represented by MP, N=278



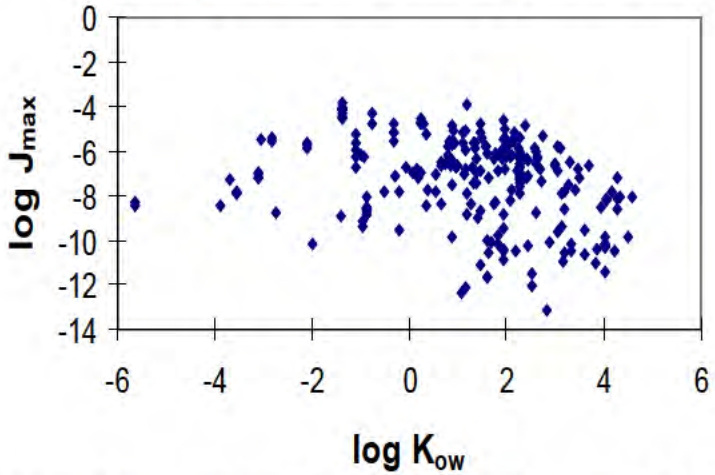
The commonly used sunscreens are also **similar in MP** (Da): avobenzone, 187.1; homosalate, <248.1; octinoxate, 248.1; octisalate (octyl salicylate), 266.1; octocrylene, 263.1; oxybenzone, 211.1

Magnusson et al. J Invest Dermatol. 2004 Apr;122(4):993-9

And why does oxybenzone have more profound skin (stratum corneum, SC) absorption than other actives?

General principle: Maximum flux for an active through the SC = $\frac{Solubility_{sc} Diffusivity_{sc}}{SC\ pathlength}$

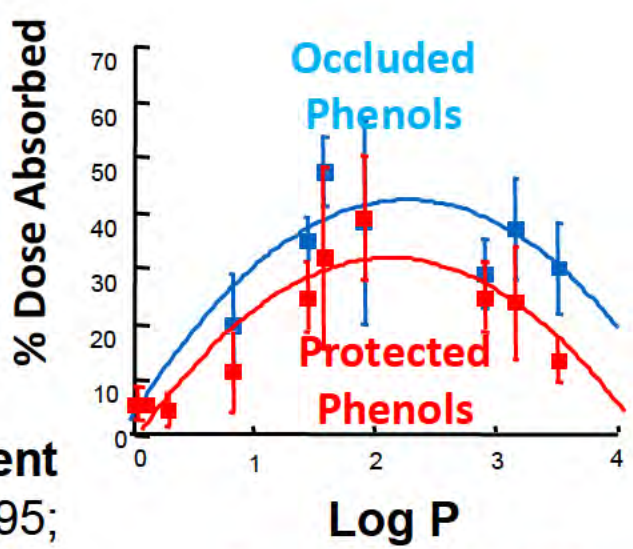
The second key determinant of **SC solubility** of an active is its affinity for SC as defined by logarithm of the octanol-water partition coefficient (**log P**) as a surrogate (N=278)



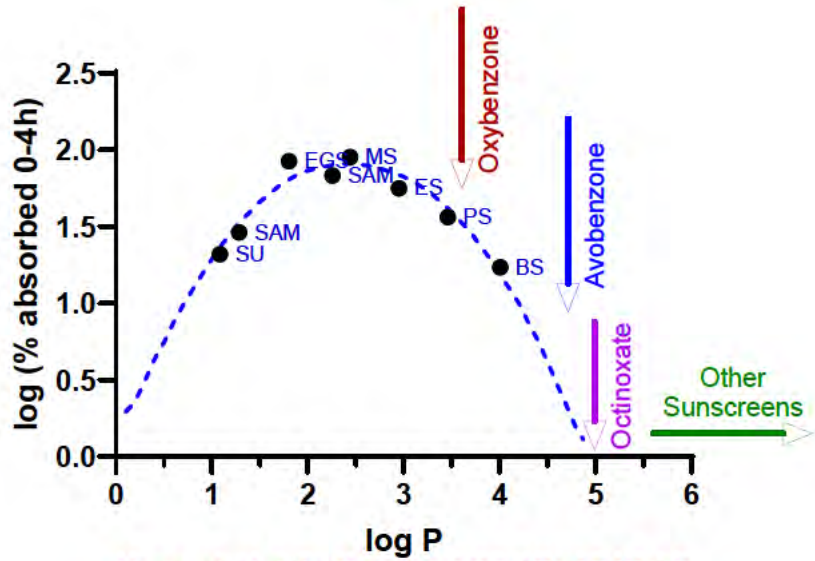
The commonly used sunscreens are quite **different in log P**: avobenzone, 4.51; homosalate, 5.95; octinoxate, 6.1; octisalate (octyl salicylate), 5.93; octocrylene, 6.78; oxybenzone, 3.79

Magnusson et al. J Invest Dermatol. 2004 Apr;122(4):993-9

- Zhang et al *Pharm Res* 2009 Aug;26(8):1974-85 have shown D_{sc} is relatively constant for a series of phenols with a similar *MW,* Log J_{max} is proportional to log S_{sc} and parabolic in log *P.*
- A number of other studies have shown a relatively tight parabola for actives with a similar MW.



Bucks, PhD Thesis, 1980

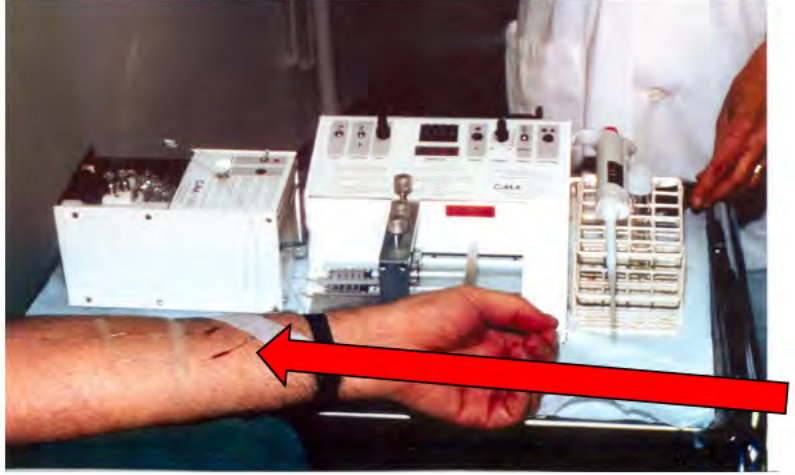


Yano et al. Life Sci 1986;39(12):1043-50.

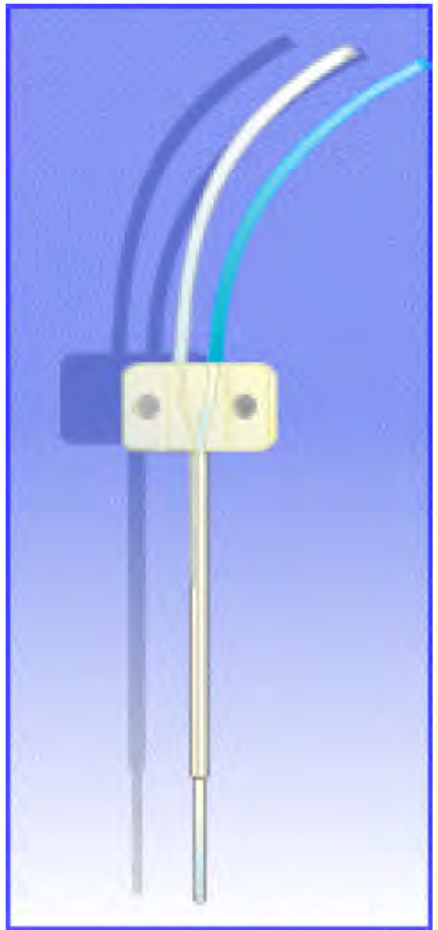
Hence, oxybenzone has greatest propensity to and shows the greatest systemic absorption after topical application

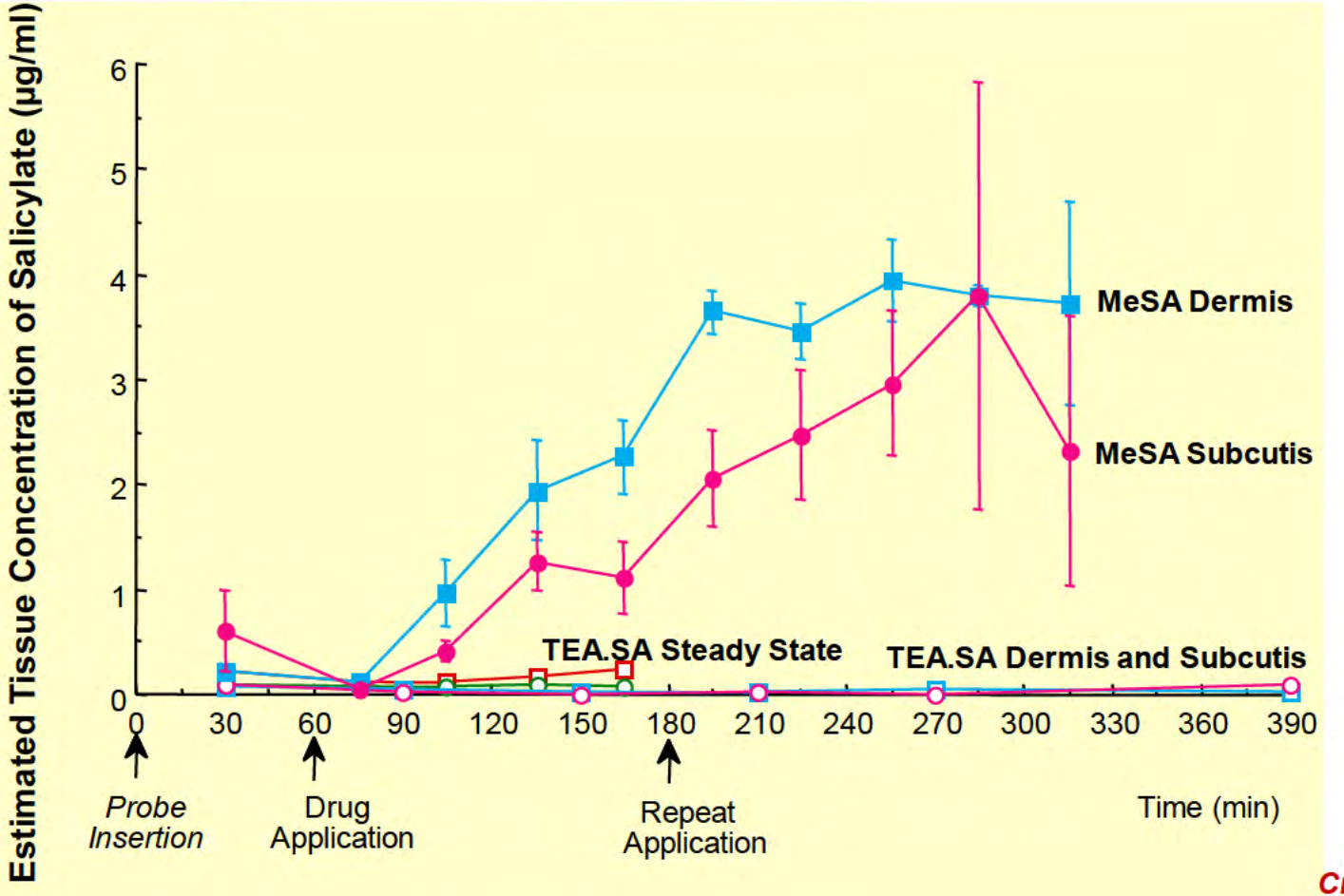
Micro-dialysis

Proving tissue penetration of Dencorub & non-irritating analgesic cream?



Microdialysis probes in skin

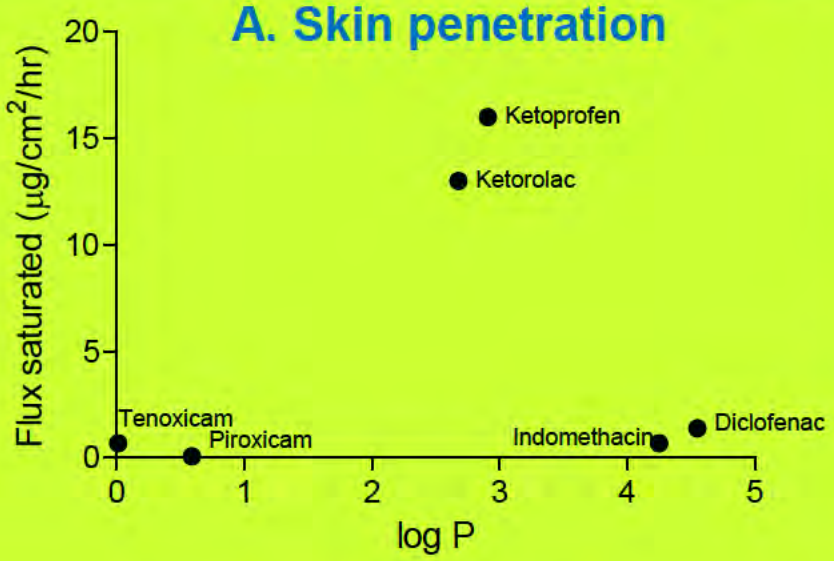




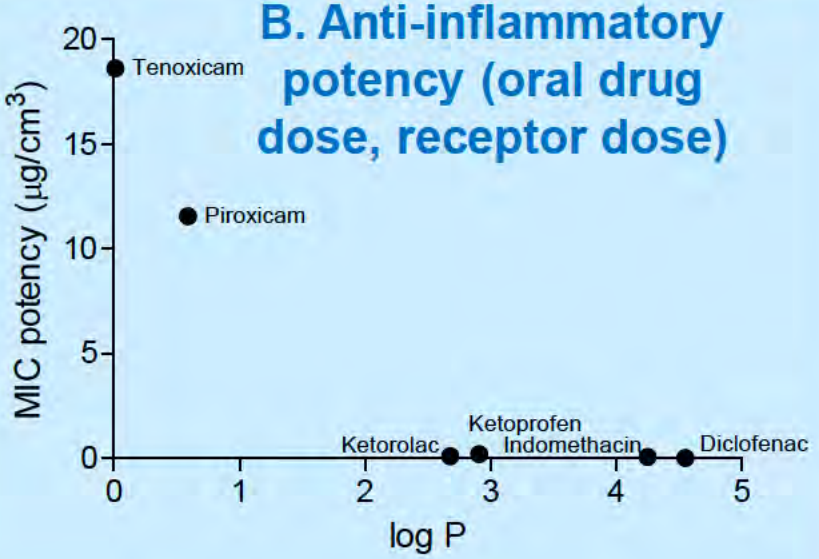
Cross et al Lancet 1997

Product efficacy of topical NSAIDs

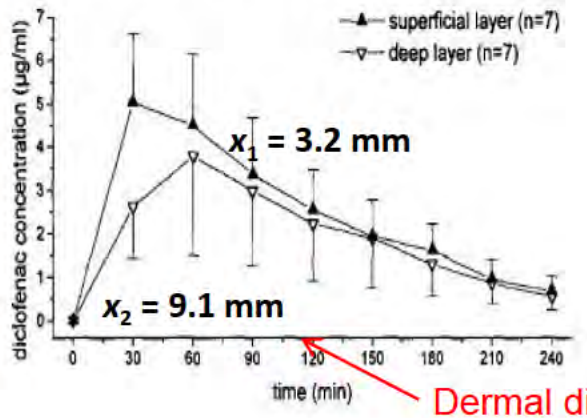
A. Skin penetration



B. Anti-inflammatory potency (oral drug dose, receptor dose)

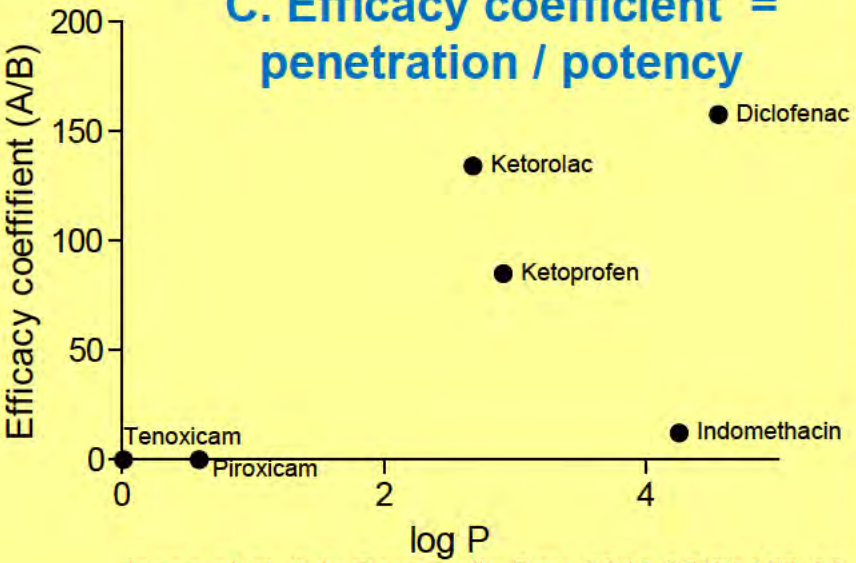


Skin microdialysis diclofenac

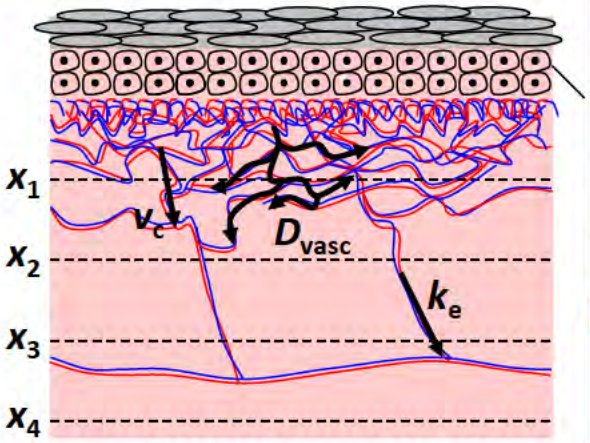


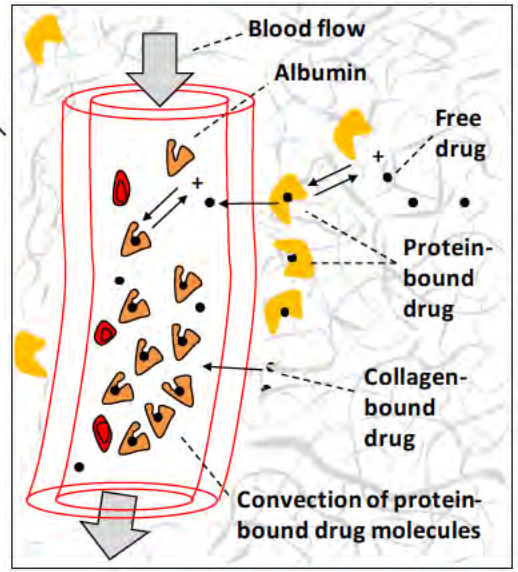
Dermal diffusion prediction

C. Efficacy coefficient = penetration / potency



Jepps et al. Adv Drug Deliv Rev. 2013 65(2):152-68.





Convective transport of plasma protein bound drugs in dermis describes shallow NSAID concentration - distance profile

Dancik et al.Br J Clin Pharmacol. 2012 Apr;73(4):564-78.

Sunscreen formulation and percutaneous absorption

There are a range of sunscreen formulations, with lotions, milks, creams and oils most useful for dry skin; gels and sprays for hairy skin, roll-ons, sticks and makeup for face and sprays for children.

J Robinson https://pharmaceutical-journal.com/article/infographics/science-of-sunscreen

FDA have a made a number of comments helpful in sunscreens use https://www.fda.gov/drugs/understanding-over-counter-medicines/sunscreen-how-help-protect-your-skin-sun

A recent clinical trial analysed plasma concentrations of sunscreens after various topical applications. Results below.

	Geometric Mean Maximum Plasma Concentration,CV (%), ng/mL			
	Lotion	Aerosol Spray	Nonaerosol Spray	Pump Spray
Avobenzone	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)	5.8 (77.4)	4.6 (97.6)
Octinoxate	NA	NA	7.9 (86.5)	5.2 (68.2)

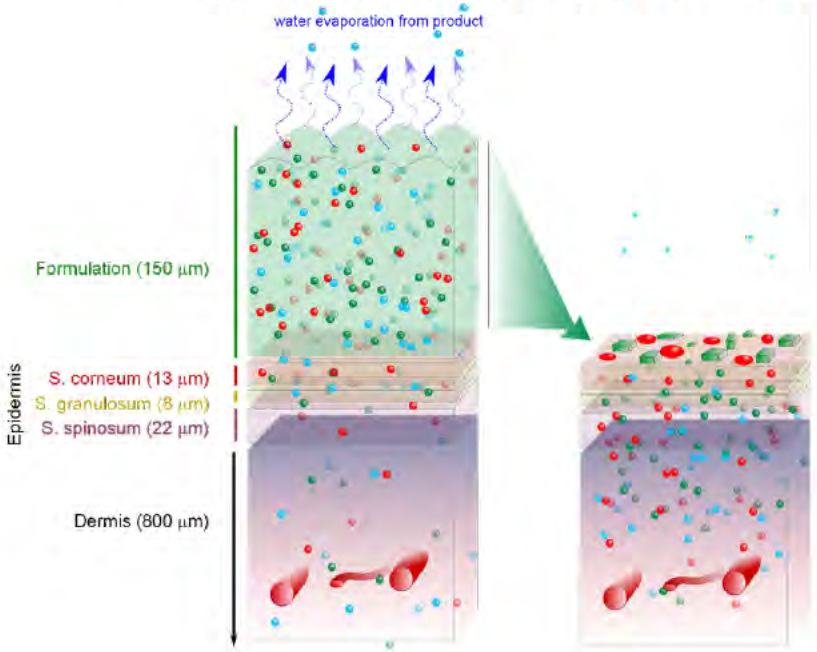
Matta et al. Effect of Sunscreen Application on Plasma Concentration of Sunscreen Active Ingredients: A Randomized Clinical Trial. JAMA. 2020 Jan 21;323(3):256-267.

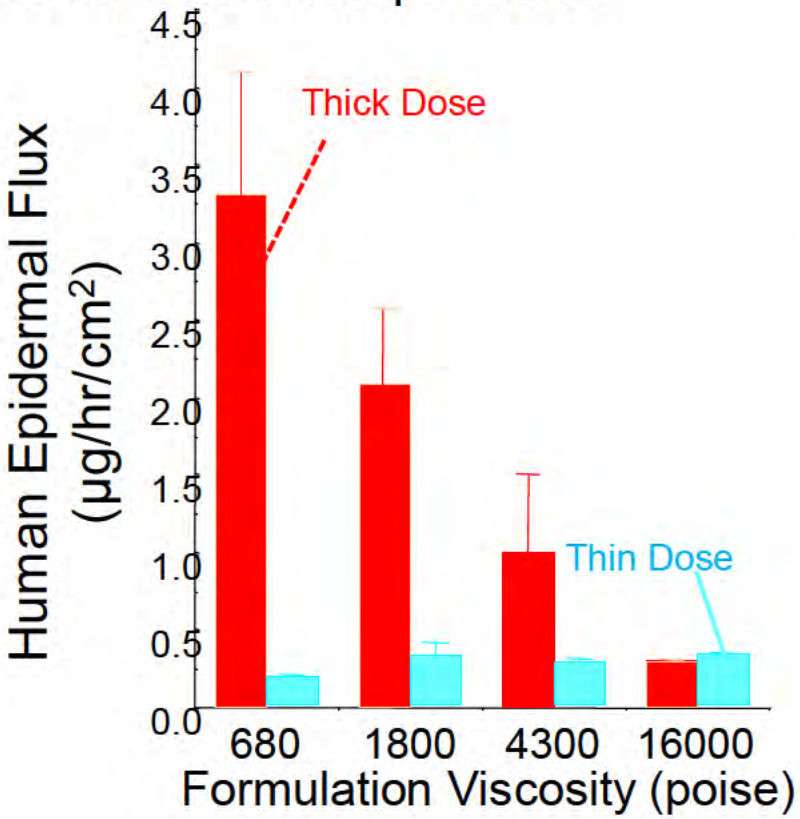
A couple of observations:

- Consistent with our earlier observations and projections, oxybenzone concentrations are an order of magnitude more than the other sunscreen concentrations
- Plasma concentrations are relatively independent of formulation, consistent with being a maximum flux

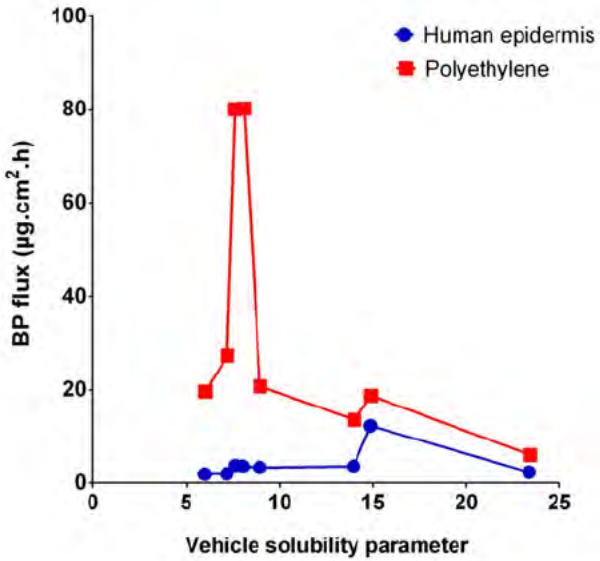
Our experience with sunscreen formulations

Impact of product thickness and viscosity on human epidermal permeation of oxybenzone for thick and thin products





Oxybenzone (BP3) half maximal flux from different solvents



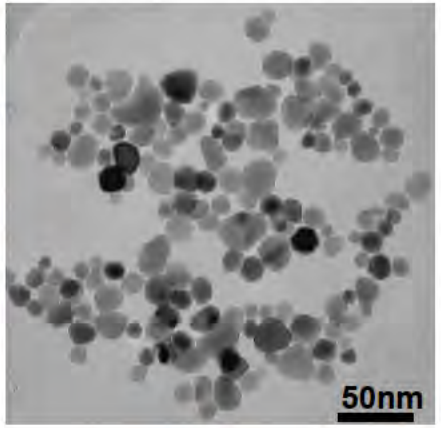
Jiang et al, 1997

Similar results for octyl salicylate

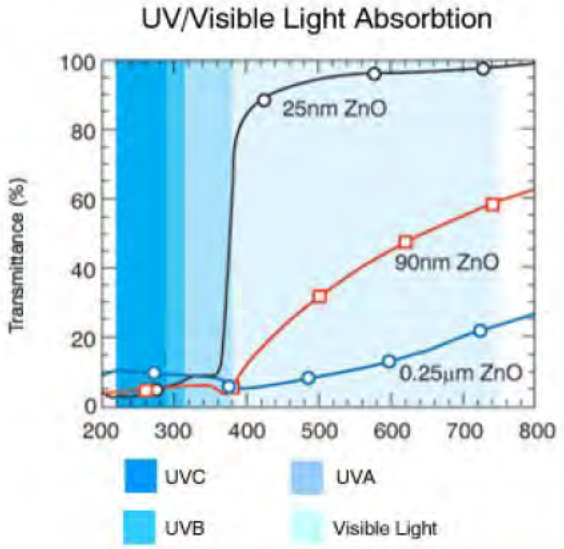
To be complete on organic sunscreens, we should note that concerns have been raised about their safety and effects on **endocrine, reproductive, developmental, and cancer-related outcomes, as well as environmental harm**.

Cross et al. J Invest Dermatol. 2001 Jul;117(1):147-50.

In vitro studies of zinc penetration from ZnO nanoparticles applied to human skin

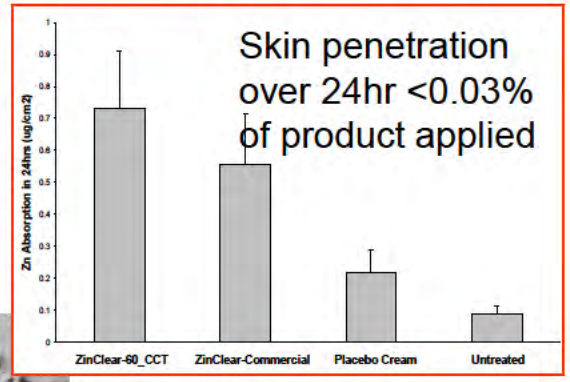


TEM of coated ZnO

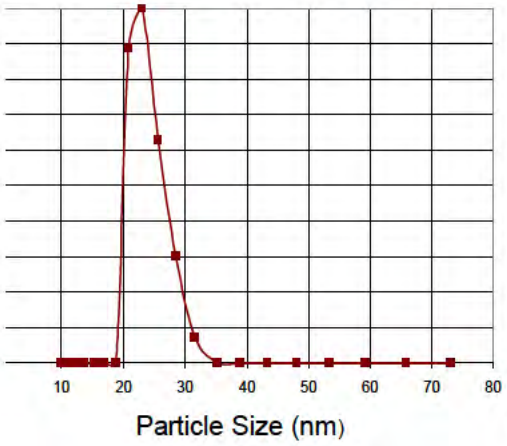


Spectral transmittance in aqueous solution

- Epidermal membrane in Franz cells with PBS & DC-30 2%
- ZinClear o/w sunscreen & placebo for 24 hr
- Zn assayed by ICP-MS after acidifying solution



Skin penetration over 24hr <0.03% of product applied



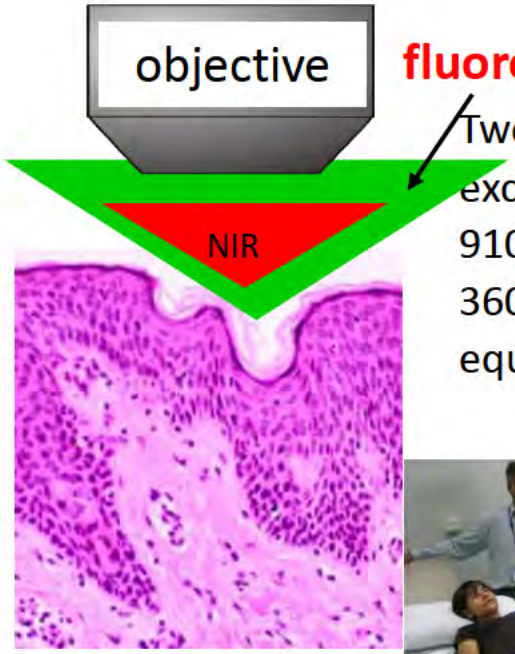
PCS size distribution

Cross et al Skin Physiol Pharmacol, 2007

TEM

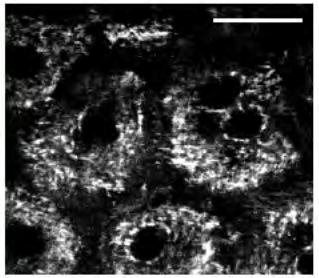
BUT! Study is not *in vivo*

In vivo: Non-invasive spectral imaging of human skin - DermaInspectTM

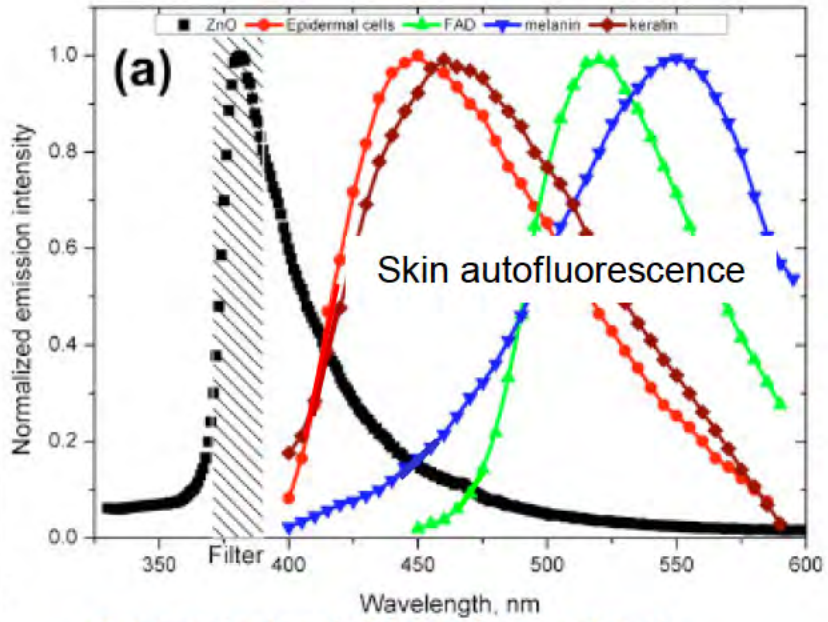


fluorescence

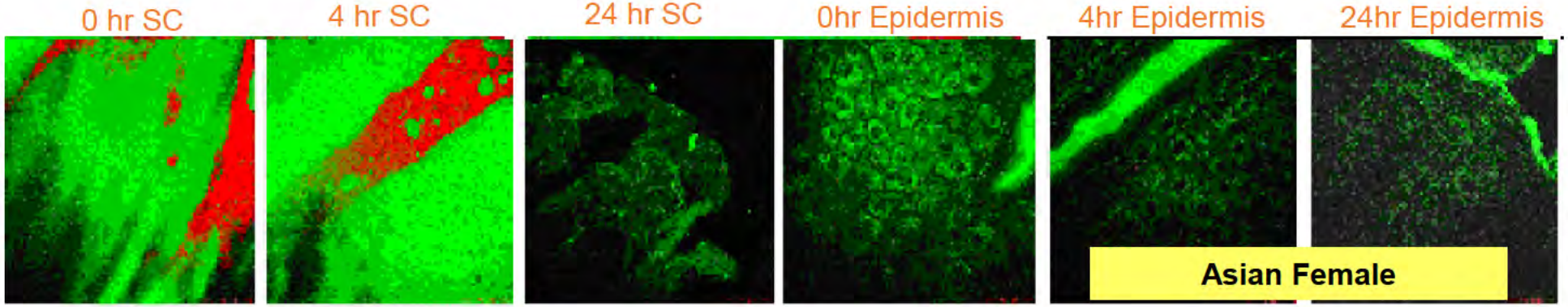
Two-photon fluorophore excitation with <2mW, fs, 720-910 nm pulses (Mai Tai) I.e. ~ 360 to 455nm confocal equivalent



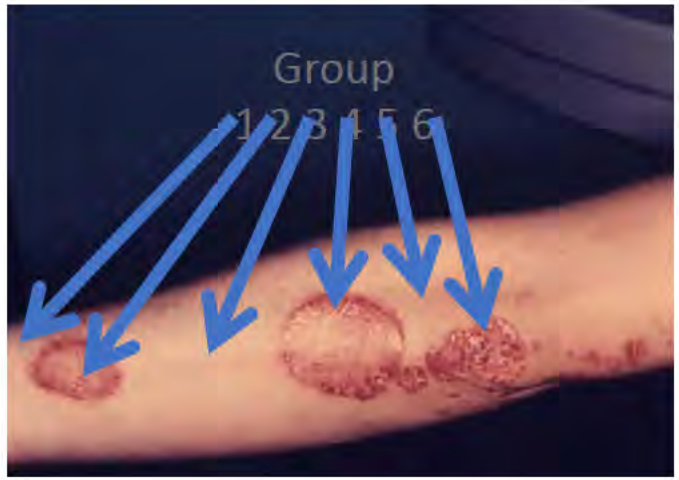
Penetration of sunscreen of Nano-zinc oxide in vivo



Computerised filter wheel added

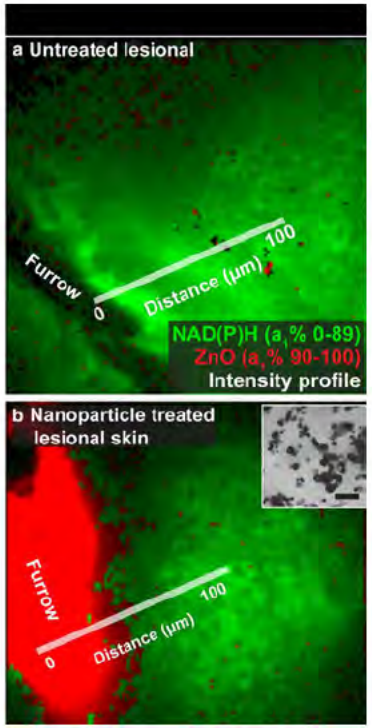


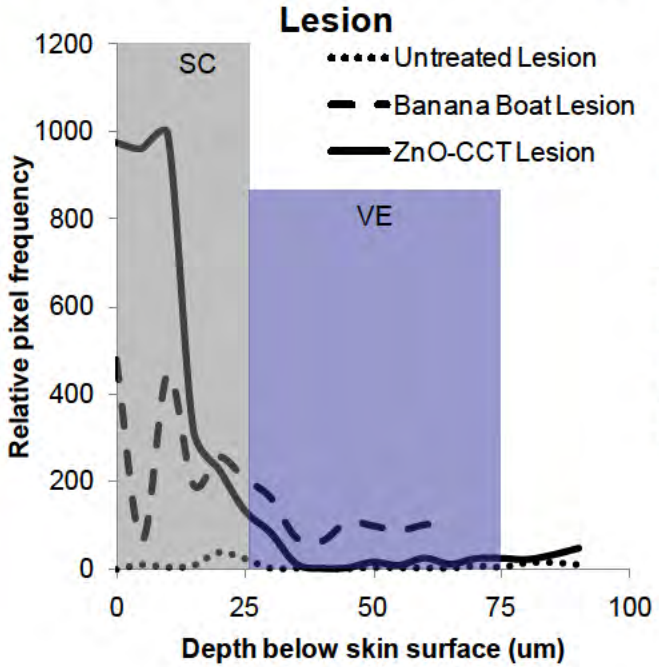
Multiphoton Tomography to assess nano-ZnO penetration into psoriasis

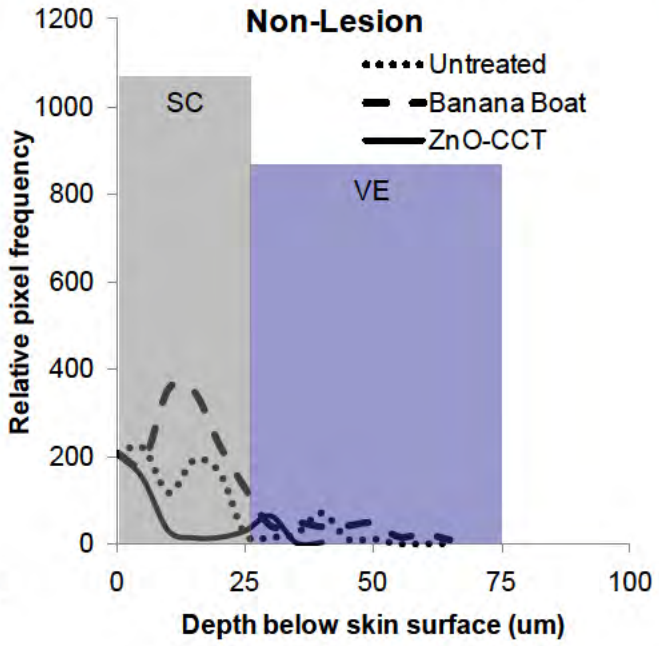


- Skin was left untreated or treated for 2 hours with 20 mg/cm^2
- MPT-FLIM was used to take optical biopsies (236x236x100 µm^3, each 2 µm thick sections) from:

1. Untreated non-lesion; 2. Untreated lesion; 3. Banana Boat treated non-lesion
4. Banana Boat treated lesion; 5. ZnO-NP CCT treated non-lesion; 6. ZnO-NP CCT treated lesion



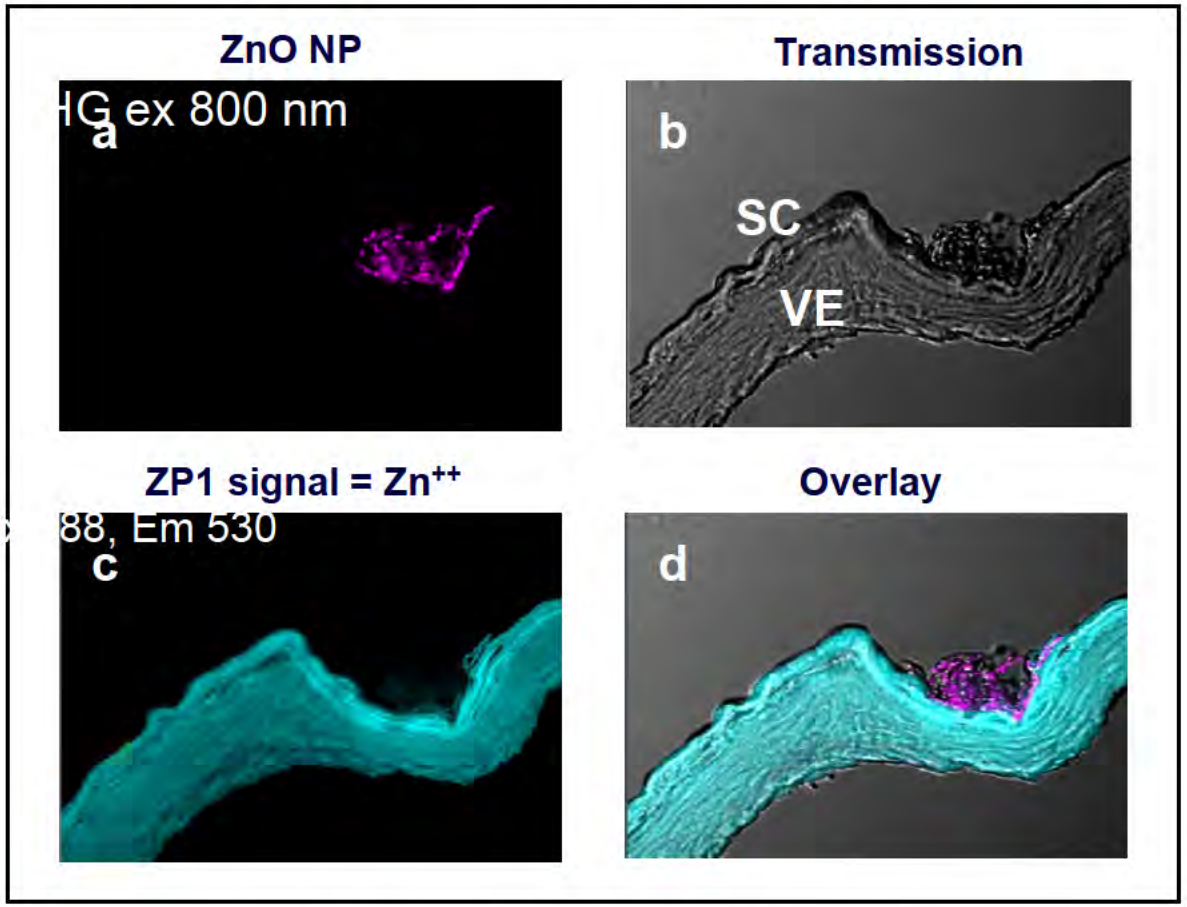


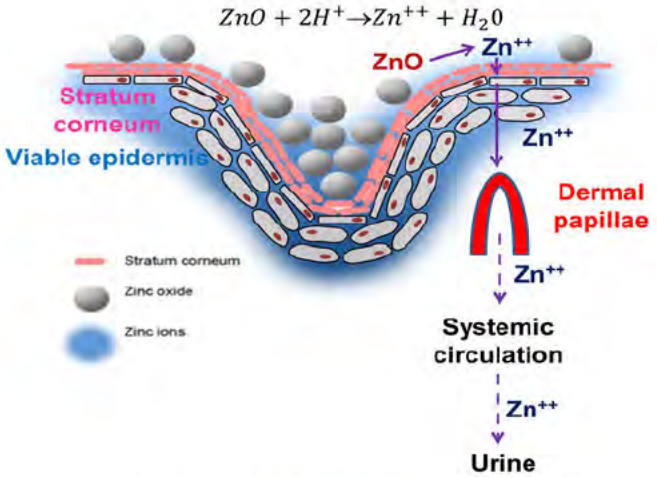


Tarl Prow is now a professor at UniSA, here with his Research Fellow Dr Miko Yamada.

What happens to nano zinc oxide in human skin?

10 % wt nanoZnO in CCT applied to HSE for 48 h





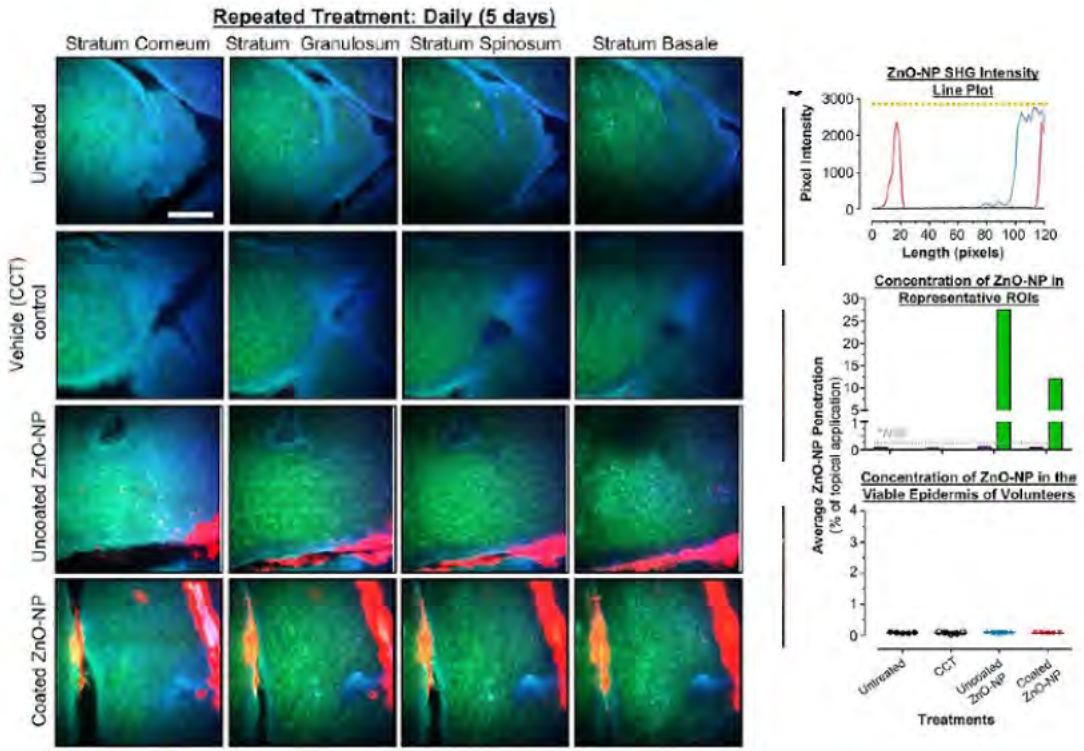
Amy Holmes

AM Holmes et al., *ACS Nano* **2016**, 10, 1810−1819

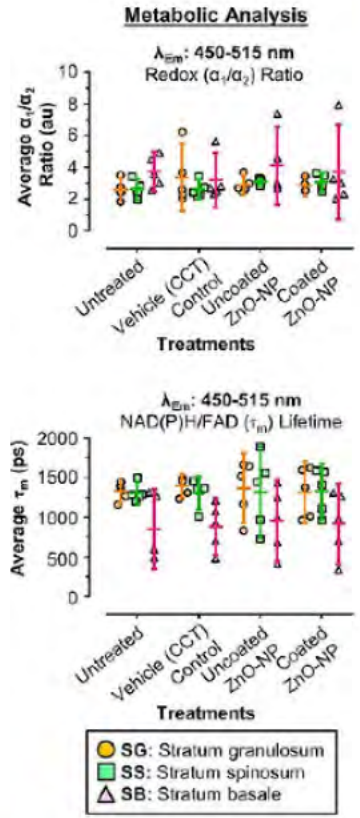
Likely basis for systemic Zn increases after topical ZnO to volunteers under in use conditions (Gulson et al.)

Safe use of zinc oxide nanoparticle sunscreens in humans *in vivo*

Lack Of Skin Penetration



Lack of Cellular Toxicity



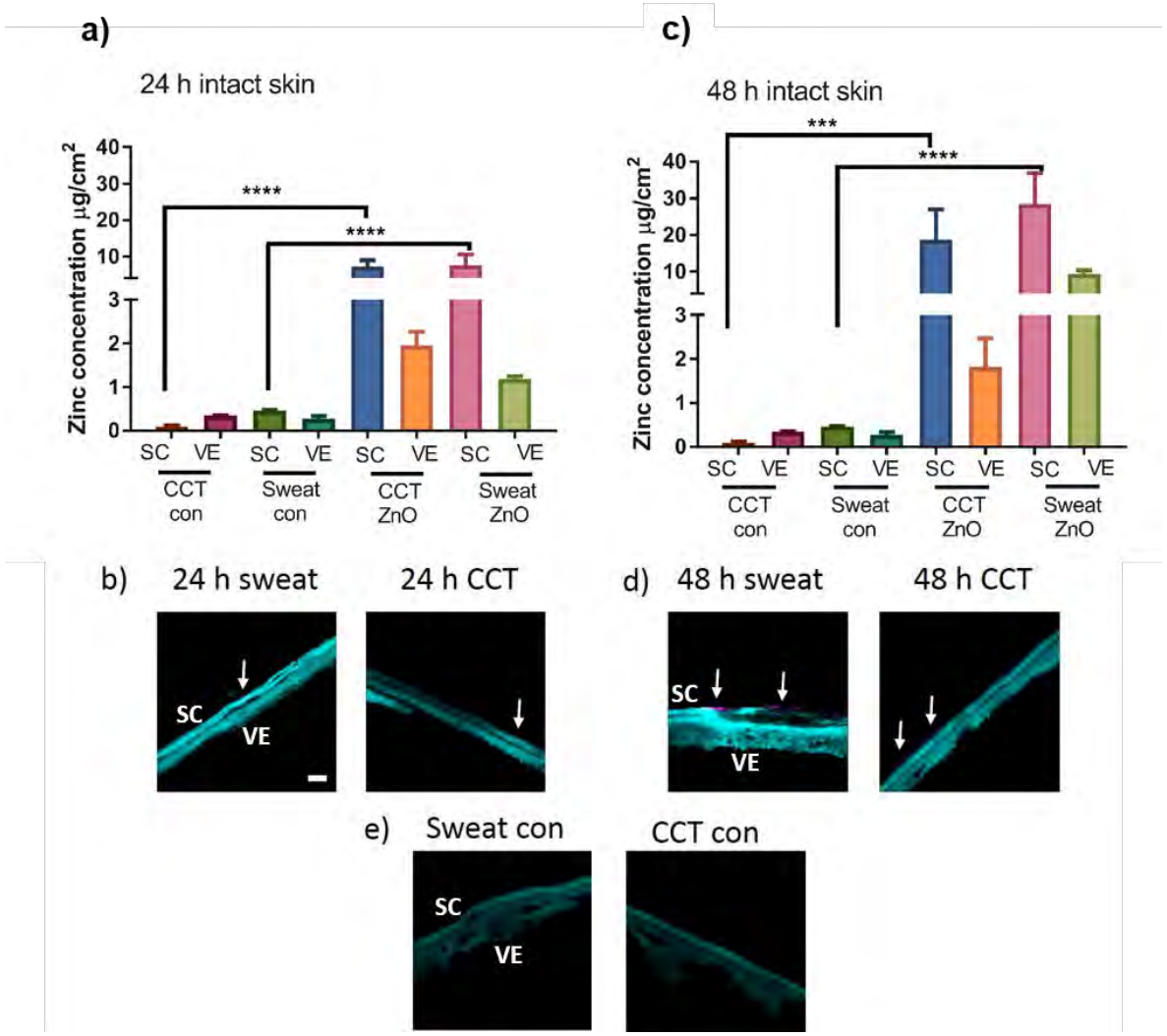
Mohammed J Invest Dermatol 2019

Message that topical zinc oxide nanoparticles are safe

What about the effect of human sweat?

Australian Synchrotron

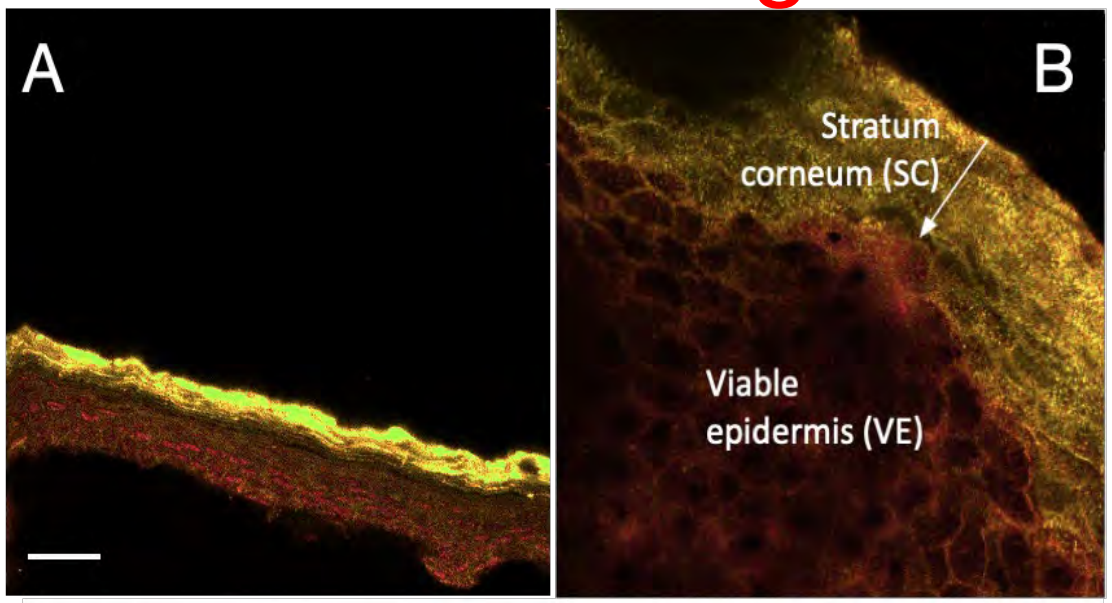
ZnO application to intact skin

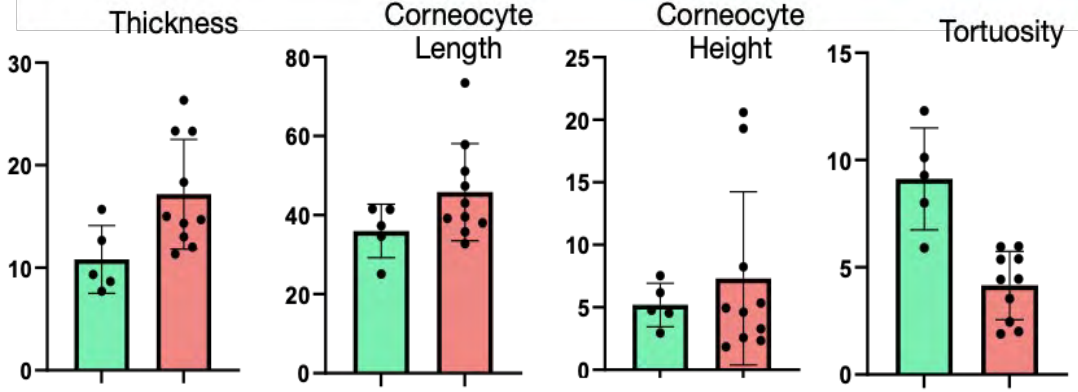


- When applying ZnO NPs to the skin the greatest variable of Zn skin penetration is application time rather than the vehicle when applied to intact skin
- The pH of sweat is ~4.6-5.2 therefore the acidic electrolyte solution increases dissolution of ZnO NPs and thus increases the zinc concentration within the skin after 48 h
- Zinc concentrations were determined using synchrotron X-ray fluorescence microscopy
- Note *ex vivo* - non-viable

Holmes et al. ACS Appl Bio Mater. 2020 Jun 15;3(6):3640-3647

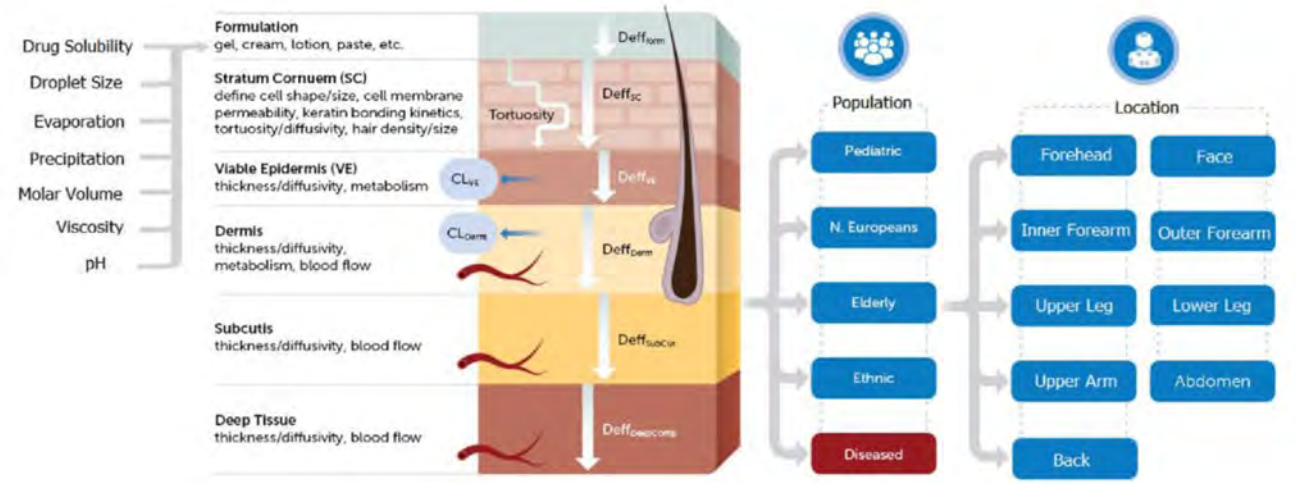
FDA Grant U01FD006521: Simcyp dermal PBPK modeling - diseased skin physiology





Nile red fluorescence microscopy of healthy (A) and psoriatic (B) skin showing major thickening of the epidermis and dermis. (C): image analysis reveals quantitative differences in cellular-level features between healthy (green) and psoriatic skin (red). All dimensions in μm.

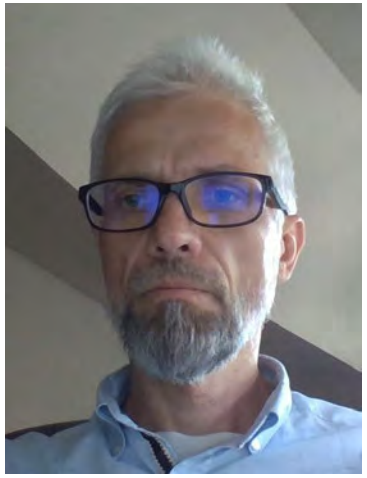
Bottom-up skin pharmacokinetics and response



THE TEAM

FDA Grant U01FD006521: Simcyp dermal PBPK modeling - diseased skin physiology

Sebastian Polak CERTARA



James Clarke CERTARA

Michael Roberts UQ UniSA

Jeff Grice UQ

Eleftheria Tsakalozou FDA

THE TEAM

Manasa Voleti CERTARA

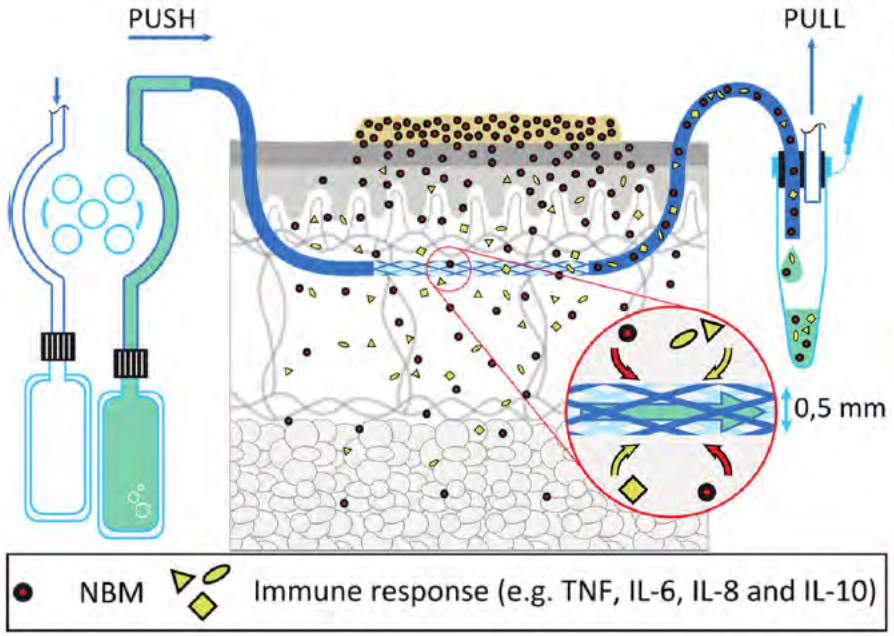
Sean Mangion UniSA

Lorraine Mackenzie UniSA

Joshua Dalton UniSA

Karthika Natarajan FDA

Suitability of dOFM for in vivo assessment of topical drug products!

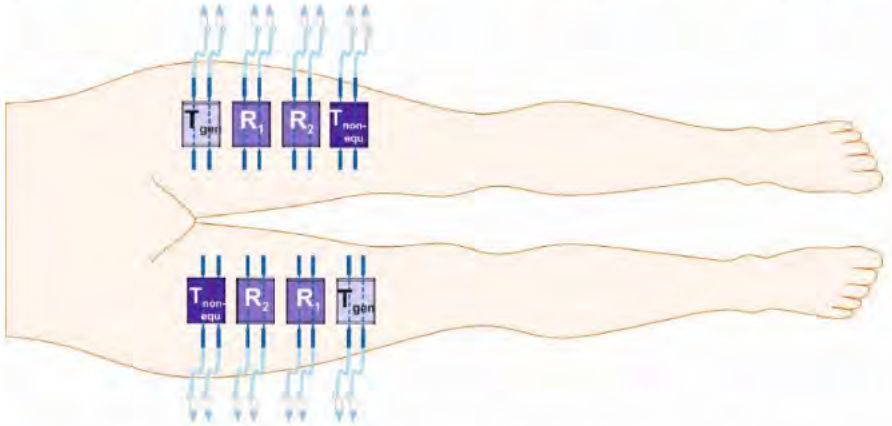


dOFM pivotal BE verification study

➔ ***medium hydrophilic and medium protein-bound API***

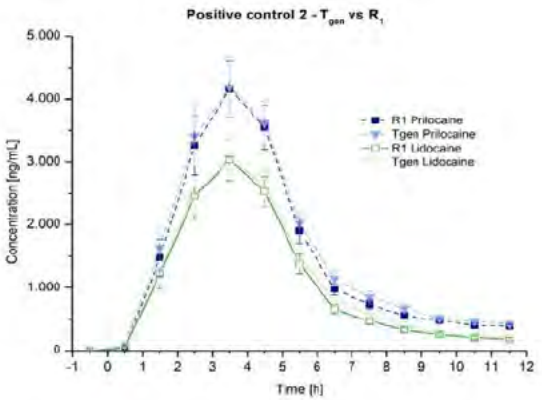
- 20 healthy subjects
- Reference Drug (R): EMLA ® cream
- US-FDA Approved Generic (T_{gen}): Fougera® cream
- Test Product ($T_{non-eqv.}$): Oraquix ® gel
- Drug dosing for 3 hours
- 24 hours dOFM sampling time
- 16 dOFM probes per subject
- BE calculated by using SABE

Clinical study outline - lidocaine/prilocaine low dose

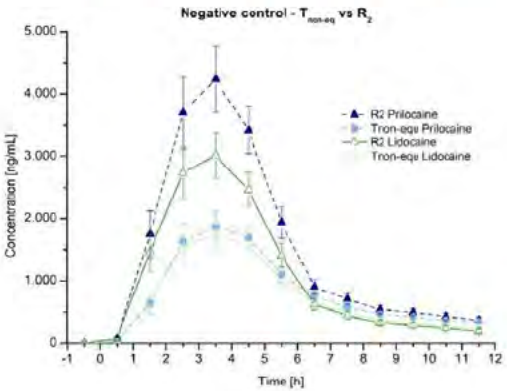


R_1/R_2	15mg/cm² EMLA® topical cream (Actavis Pharma Inc., US)
$T_{non-equ}$	15 mg/cm² Oraqix periodontal gel (Dentsply Detrey GmbH, Germany)
T_{gen}	15 mg/cm² Lidocaine 2.5% and Prilocaine 2.5% cream (E. Fougera & Co, US)

US-FDA approved generic vs. R (EMLA)



Non-BE drug vs. EMLA



https://croservices.joanneum.at/
frank.sinner@joanneum.at

Thank you to those who shared in this work over the years and not mentioned earlier - especially…

Adelaide

Brisbane

I also thank the US FDA and our collaborators for their support and in doing so point out that "The views expressed in this presentation do not reflect the official policies of the Food and Drug Administration, or the Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government."

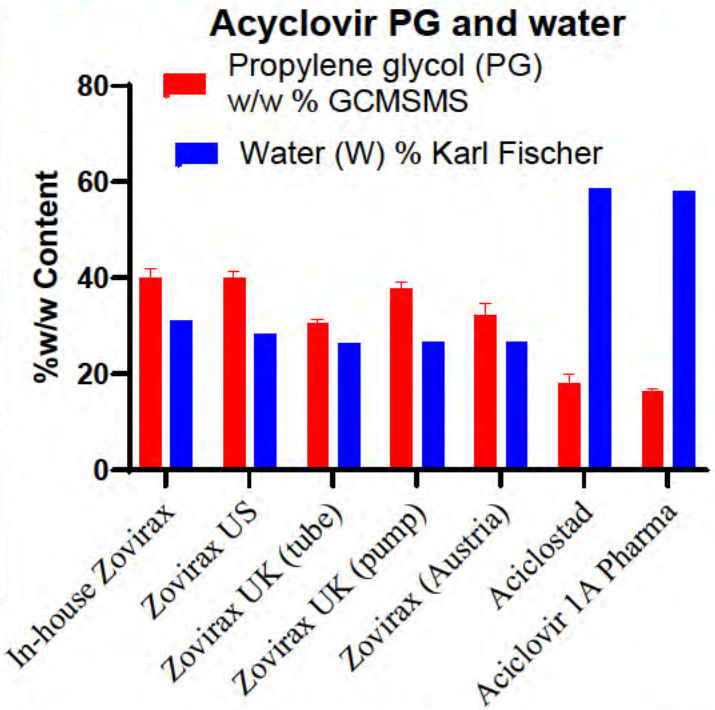
Q. You mentioned topical product thickness and viscosity as impacting on sunscreen percutaneous absorption.
What are the other topical product design issues one should be aware of?

FDA project: topical acyclovir dose forms - Q1, Q2 and Q3 for & performance (IVPT)

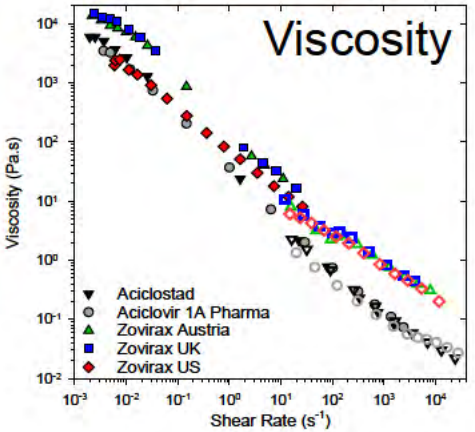
Q1 Same Composition

Zovirax (USA)	Zovirax (UK)	Zovirax (Austria)	Aciclostad (Austria)	Aciclovir-1A (Austria)
Water	Water	Purified water	Water	Water
Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol
Mineral oil	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Viscous Paraffin
White petrolatum	White soft paraffin	White Vaseline	White Vaseline	White Vaseline
Cetostearyl alcohol	Cetostearyl alcohol	Cetostearyl alcohol	Cetyl alcohol	Cetyl alcohol
SLS	SLS	SLS		
Poloxamer 407	Poloxamer 407	Poloxamer 407		
	Dimethicone 20	Dimethicone 20	Dimethicone	Dimethicone
	Arlacel 165	Glyceryl Mono Stearate	Glyceryl Mono Stearate	Glyceryl Mono Stearate
	Arlacel 165	Polyoxyethylene stearate	Macrogol stearate	Polyoxyethylene stearate

Q2 At same Concentrations



Q3 With same icro-structure



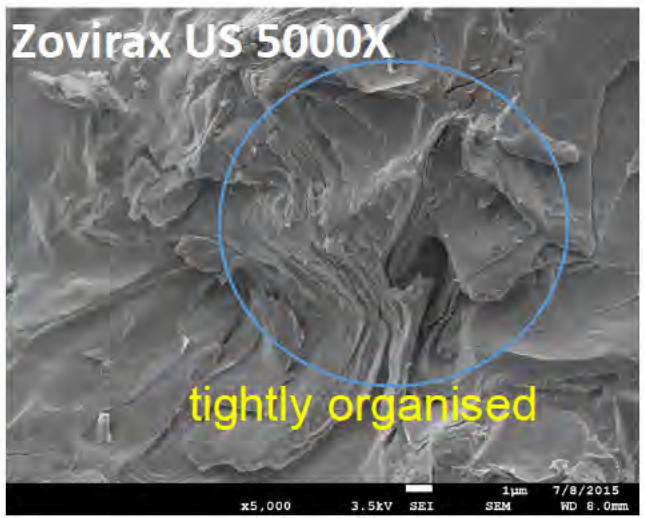
Q3 Micro-structure continued

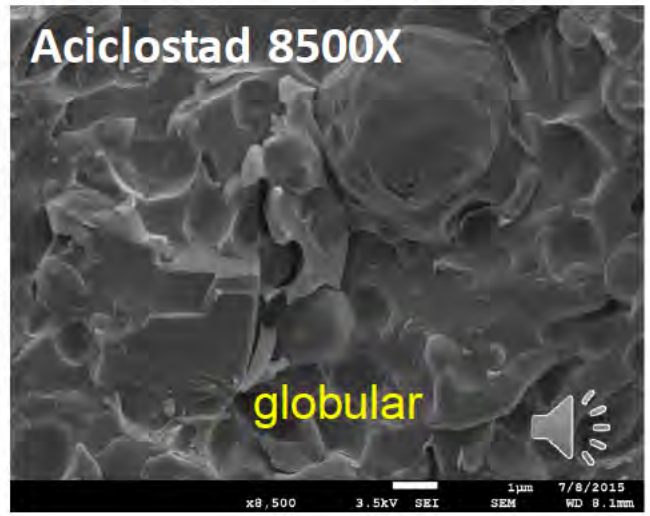
Acyclovir particle size

Products	d10 (µm)	d50 (µm)	d90 (µm)
Zov. US	3.63	6.92	16.60
Zov AU	4.00	8.30	29.00
Zov UK (P)	4.00	7.82	18.88
Zov UK (T)	3.52	6.22	19.35
Zov Austria	4.61	8.26	18.34
Aciclostad	2.72	4.38	9.72
Acyclovir 1A Pharma	1.91	2.90	6.24

Also differences in phase volumes, solids

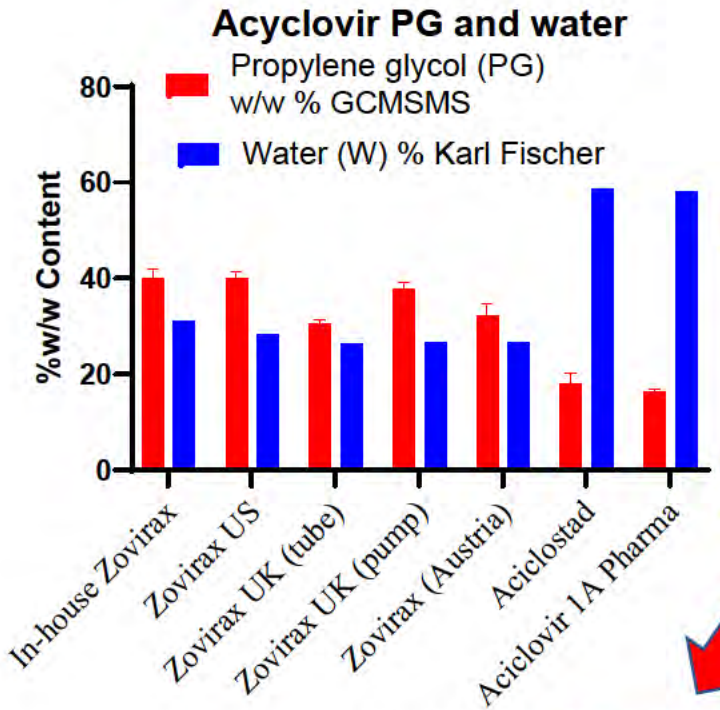
Product fabric by SEM





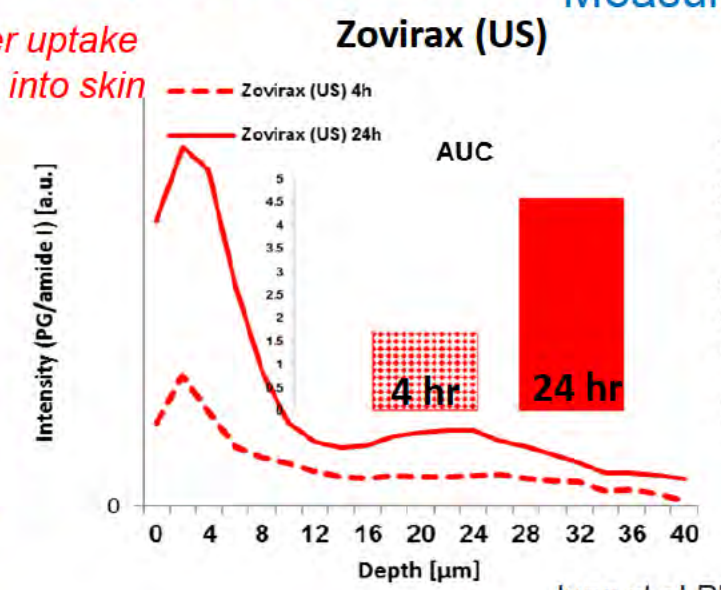
But it is not just Q1, Q2 & Q3 in design. Testing should show translation into product performance?

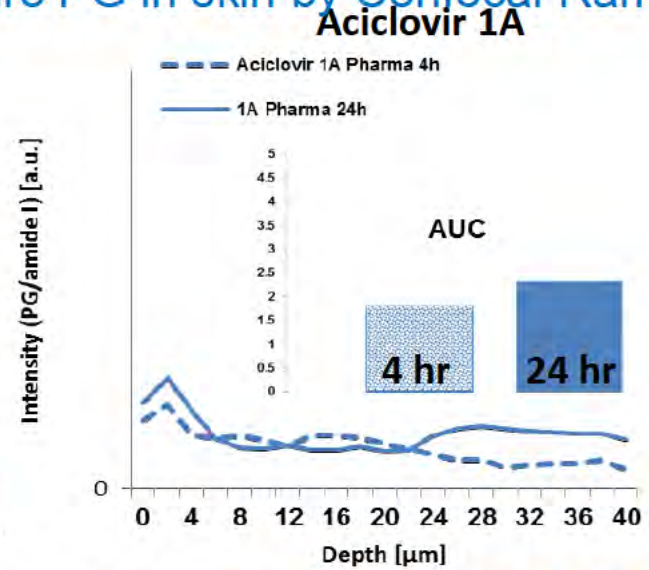
Measure PG in skin by Confocal Raman



Zovirax (US) has 2.5 times PG & half water content of Aciclovir 1A*

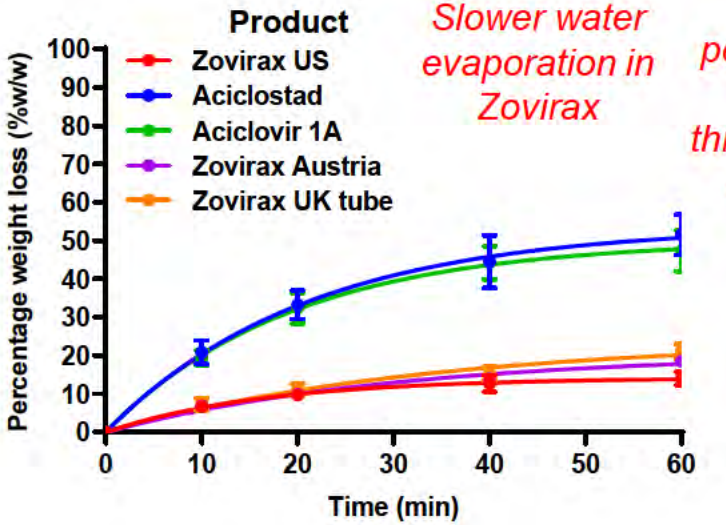
Faster uptake of PG into skin





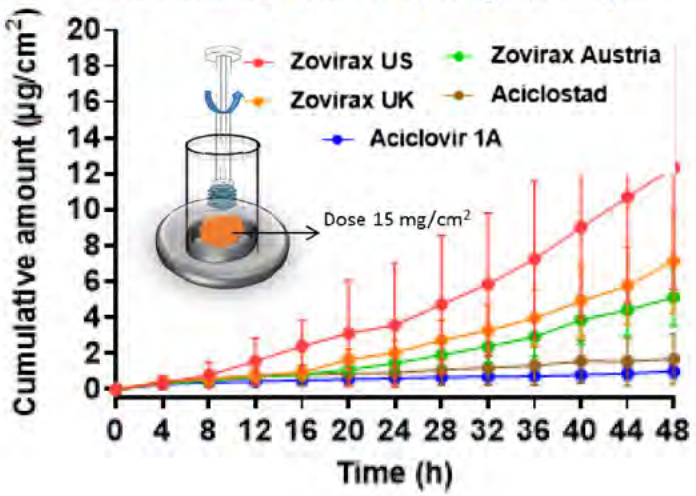
Jung et al Pharm Res 2022: 10.1007/s11095-022-03245-7

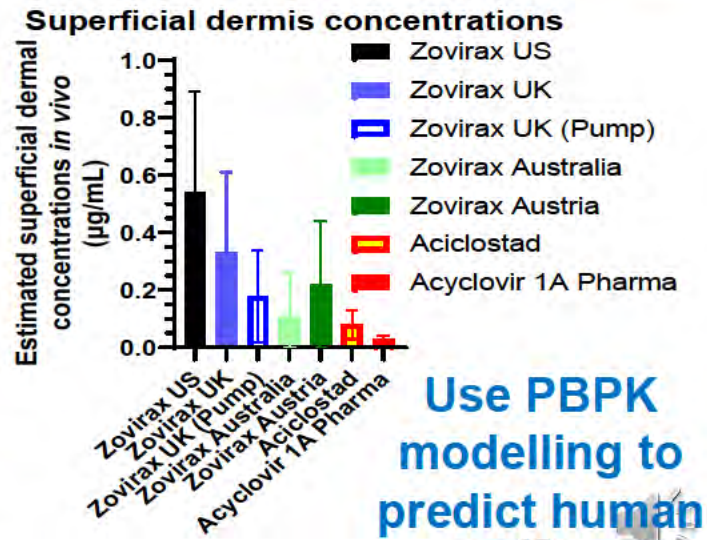
Slower water evaporation in Zovirax



Faster permeation of acyclovir through human epidermis

Our group applied 15mg/cm² accurately with a syringe plunger





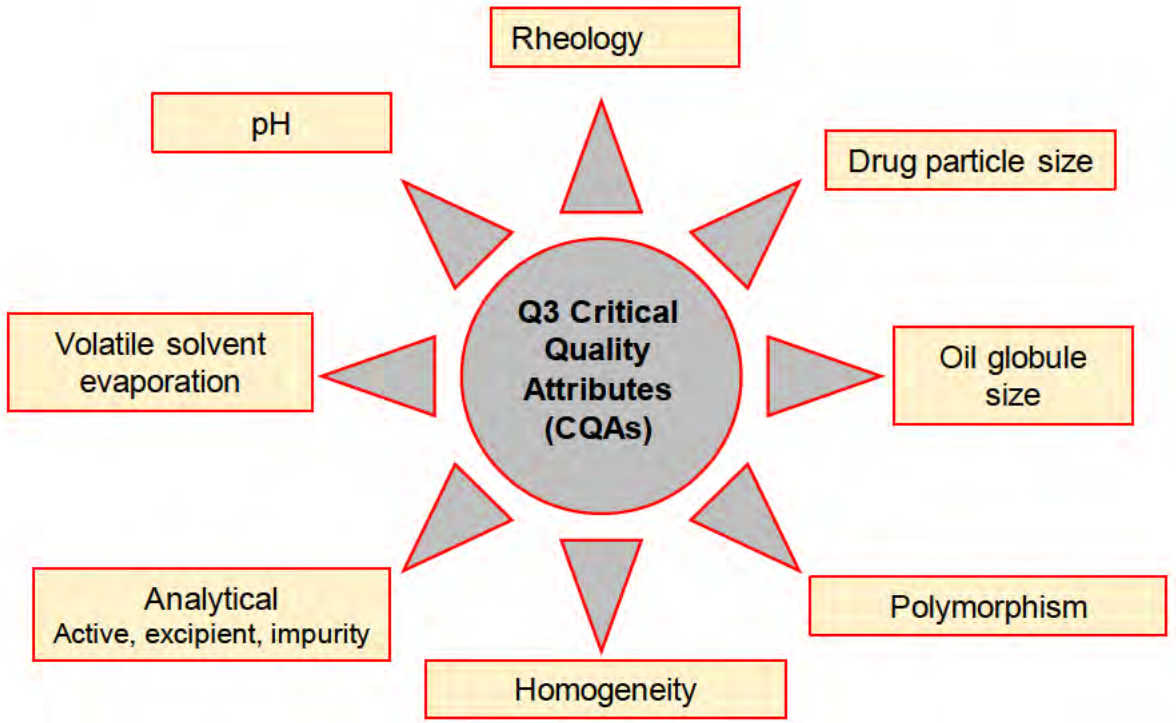
Use PBPK modelling to predict human *In Vivo*

Q. As a follow-on to the question on topical product design issues, which ones matter most?

However, recognise there are potential failure modes in product formulation

Ingredient & Formulation Variables

- Formulation variables
- Manufacturing variables
- Packaging



Failure Modes

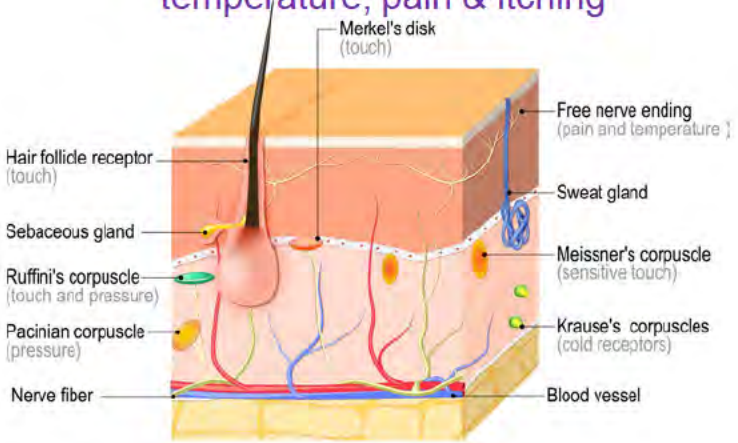
- Physical stability
- Chemical stability
- Performance and compliance

Q. Are you able elaborate more on why sensorial effects are important and how your group is assessing them/

I would suggest that a third potential failure mode is not recognising sensory perceptions associated with topical products – the placebo & nocebo effects

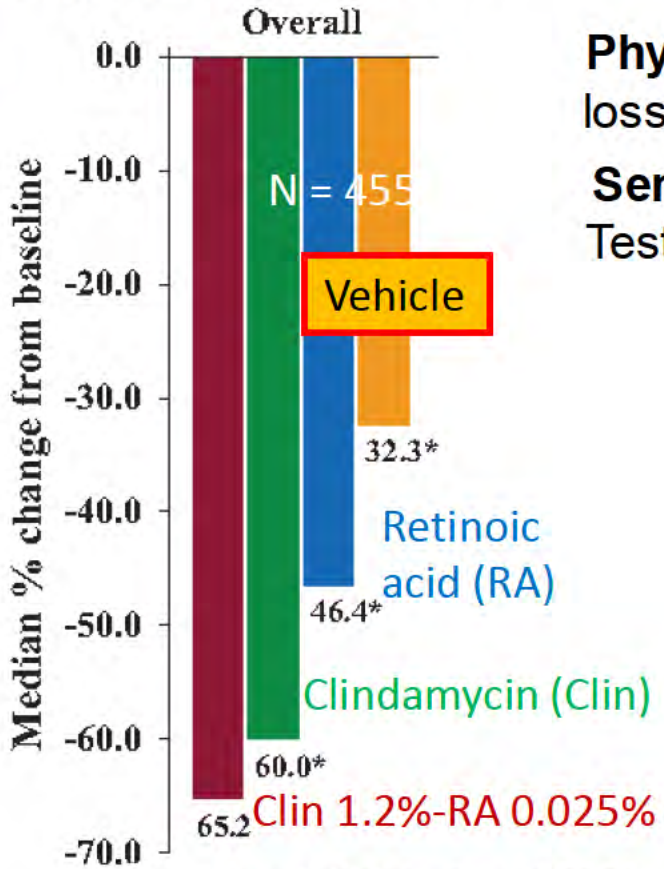
Vania Leite, Brazil

Sensory receptors in the skin
For pressure, vibration, temperature, pain & itching



Reproduced with permission of Tetiana Zhabska / Alamy Stock Vector

Pivotal Phase III change in inflammatory acne vulgaris after 12 weeks.



* p<0.0001; † p=0.0002 vs Clin-RA

Dreno Eur J Dermatol 2014; 24(2): 201-9

FDA 1U01FD006700: Sensorial and Functional Characteristics of Topical Formulations

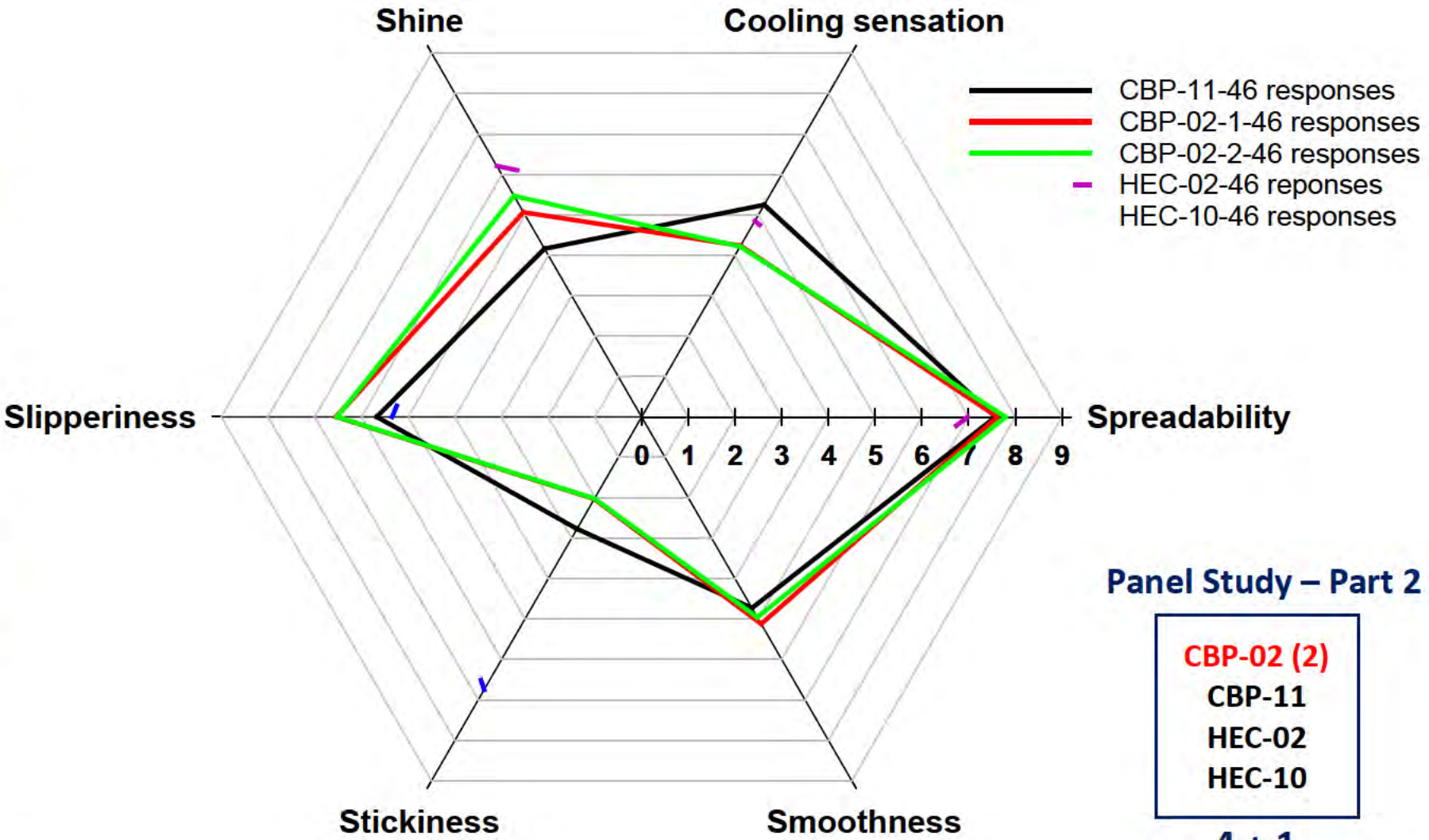
Physical quality – rheology, hydration, water activity, loss on drying, particle size, tribology, texture analysis

Sensory testing by Temporal Dominance Sensitivity Test with focus groups led by Y Mohammed & V Leite

Panel study:Part 2. All attributes – 46 Responses

Composition (%w/w)	HEC-02	HEC-10
Hydroxyethyl cellulose	2.2	2.2
Alcohol	20	20
Propylene glycol	15	**30**
2-Phenoxyethanol	0.8	0.8
Water	62	47

Composition (%w/w)	CBP-02	CBP-11
Carbopol 980	**0.25**	0.5
Ethanol	-	**35**
Propylene glycol	15	15
Methyl paraben	0.1	0.1
Propyl paraben	0.03	0.03
Triethanolamine	q.s.	q.s.
Water	84.62	49.21



Panel Study – Part 2

CBP-02 (2)
CBP-11
HEC-02
HEC-10

4 + 1

From: s22 [redacted]
To: Ju-Lee Oei
Subject: RE: Expert stakeholder roundtable - TGA"s risk assessment of sunscreen ingredients [SEC=OFFICIAL]
Date: Tuesday, 17 December 2024 11:57:13 AM
Attachments: image002.png
image003.png
image004.png
image005.jpg
image006.png
image007.png
Agenda.docx
Attachment 1 Australian Sunscreen Exposure Model - ASEM Calculations Microsoft Excel file - 2 July 2024 (3).xlsx
Attachment 2 Risk Assessment of Seven Active Sunscreen Ingredients - WORKING COPY.docx
Attachment 3 Benzophenone risk assessment - WORKING COPY (002).docx
Copy of D24-4721790 Sunscreen roundtable meeting - planning.xlsx
Roundtable paper- Therapeutic Goods Administration (TGA) risk assessment of sunscreen ingredients.docx

---

Dear Julee,

I am sharing the documents via email to ensure you have access. Please note the documents are confidential and should not be shared.

Kind regards,
s22 [redacted]

From: Ju-Lee Oei <j.oei@unsw.edu.au>
Sent: Tuesday, 17 December 2024 10:37 AM
To: s22 [redacted]@health.gov.au>
Subject: Re: Expert stakeholder roundtable - TGA's risk assessment of sunscreen ingredients [SEC=OFFICIAL]

REMINDER: Think before you click! This email originated from outside our organisation. Only click links or open attachments if you recognise the sender and know the content is safe.

Dear s22 [redacted]
I can't access the documents – says accessed denied
Could you help?
Kind regards
Julee

Ju-Lee Oei

Neonatologist
Royal Hospital for Women, Randwick NSW

Visiting Medical Officer
Murrumbidgee Local Health District Drug and Alcohol NSW

Conjoint Professor
School of Paediatrics
Faculty of Medicine and Health
University of New South Wales
Randwick NSW Australia

Honorary Affiliate
NHMRC Clinical Trials Centre
University of Sydney
Camperdown NSW Australia

Editor in Chief
Journal of Paediatrics and Child Health
Email: j.oei@unsw.edu.au or Ju-lee.oei@sydney.edu.au

From: s22 [redacted] @health.gov.au>
Date: Tuesday, 17 December 2024 at 10:28
To: Jo Muller s47F [redacted] s47F [redacted] s47F [redacted] s47F [redacted] s47F [redacted], s22 [redacted] @health.gov.au>, s47F [redacted] Ju-Lee Oei s47F [redacted], Debra Kennedy (Redirection) s47F [redacted], HENDERSON, Nick <Nick.Henderson@health.gov.au>, CLARKE, Avinash <Avinash.CLARKE@Health.gov.au>, s22 [redacted] @health.gov.au>, s22 [redacted] @health.gov.au>, s22 [redacted] @health.gov.au>, s22 [redacted] @health.gov.au>, s22 [redacted] @Health.gov.au>, s22 [redacted] @Health.gov.au>, s22 [redacted] @Health.gov.au>, s47F [redacted] s47F [redacted] Melissa Eastgate s47F [redacted], s47F [redacted] Amanda Gwee s47F [redacted], s22 [redacted] @health.gov.au>, s22 [redacted] s22 [redacted] l@health.gov.au>
Cc: s22 [redacted] @health.gov.au>, s22 [redacted] s22 [redacted] @health.gov.au>, LANGHAM, Robyn <Robyn.LANGHAM@Health.gov.au>, s22 [redacted] @Health.gov.au>
Subject: Expert stakeholder roundtable - TGA's risk assessment of sunscreen ingredients [SEC=OFFICIAL]

Dear all,

Thank you for confirming your participation in tomorrow's expert roundtable discussion regarding TGA's risk assessment of sunscreen ingredients.

Date- Wednesday 18 December 2024, 11am – 1pm

Venue - All external experts are attending the meeting virtually via Microsoft Teams. The meeting link can be found within the TGA calendar invite.

Papers- All relevant papers are available on GovTeams, available at Meeting Papers. You should have access to five documents:

- Agenda
- Roundtable paper- TGA risk assessment of sunscreen ingredients
- Attachment 1- Australian Sunscreen Exposure Model
- Attachment 2- Risk Assessment of Seven Active Sunscreen Ingredients (Working Copy)
- Attachment 3- Benzophenone Risk Assessment (Working Copy)

DOIs- Please ensure you have submitted your DOI paperwork prior to attendance.

If you require assistance with accessing the documents or entering the meeting tomorrow, please feel free to contact me directing via email at s22 @health.gov.au or via phone on s22 s22

I look forward to meeting you all tomorrow.

Kind regards,
s22

s22
s22
Chief Medical Adviser Unit
He Regulation Group
T: s22 | E: s22 @health.gov.au
Location: 27 Scherger Drive, Level 2
PO Box 100, Canberra ACT 2601, Australia

The Department of Health and Aged Care 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 all Elders both past and present.

Sunscreen ingredient risk assessment

Expert Stakeholder Roundtable

Wednesday, 18 December 2024

11 am – 1 pm

27 Scherger Drive, Fairbairn, ACT (TGA office)

Virtual attendance welcome

Agenda

Time	***Session***	***Presenter***
11.00 – 11.10 am	Welcome and Introductions	Professor Robyn Langham
11.10 – 11.50 am	Sunscreen risk assessment –current status and possible future direction. **Paper to follow**	Professor Robyn Langham
11.50 – 12.50 pm	Roundtable discussion	All
12.50 – 1 pm	Next Steps and Closing Remarks	Professor Robyn Langham

Australian Sunscreen Exposure Model (ASEM)

The Australian Sunscreen Exposure Model (ASEM) is proposed to accurately calculate sunscreen use that accounts for the diverse needs of Australians and integrates the expected sunscreen application practices that align with current Australian recommendations, rather than utilising international models that do not. This ensures that sunscreen ingredients are evaluated for safety based on how they are, and recommended to be, used in Australia today.

The objective of this approach is to affirm the safety of sunscreen ingredients, considering the highest plausible sunscreen use throughout the year, for the most sensitive population. To achieve this, the ASEM proposes 6 theoretical exposure scenarios, each representing a broad spectrum of regular sunscreen usage patterns across different demographics across Australia (see Tab 3. Scenarios). These scenarios provide the highest estimated daily sunscreen exposure, to calculate maximum safe concentration of a sunscreen ingredient using the SED and MoS formulas.

Tab 2. ASEM calculations
Outlines the formulae used to caclulate the estimated daily sunscreen exposure for each scenario and consequently the estimated highest daily sunscreen exposure.

Tab 3. Scenarios
Describes the 6 ASEM scenarios, including clothing use, exposed skin that sunscreen is applied to, sunscreen reapplication rates, and use throughout the year.
The scenarios are used in the ASEM calcullations in Tab 2

Tab 4. Body Weight data
Describes the Australian representative bodyweights for adults, children and adolescents used in the the ASEM calcullations in Tab 2

Tab 5. Skin Surface Area data
Describes the Australian representative skin surface area data for different parts of the body, different age groups and under different scenarios used in the the ASEM calculations in Tab 2. Calculations and notes are also provided, e.g. SSA for the face in the absence of specific data (use of 'half a head' SSA value).

Corrections
Stakeholders are encouraged to advise the TGA if there are any errors in the data or calculations.

Variables used to calculate estimated daily sunscreen exposure for each scenario

Scenario	1	2	3	4	5	6
***AF* (application frequency)**	2	2	2 or 3*	3	3	3
***Duration* (days)**	240	240	240	240	26	26
***AT* (Averaging time, days)**	365	365	365	365	365	365
***Appl Rate* (application rate, mg/cm2)**	2	2	2	2	2	2

*3 applications for toddler (1-<2 yo)/(2-<3 yo) and 2 applications for other children

SSA (skin surface area exposed to sunscreen, m^2, 95th)	1	2	3	4	5	6
Toddler (1-<2 yo)	-	-	0.20	-	0.20	-
Toddler (2- <3 yo)	-	-	0.21	-	0.22	-
Preschool student (3- <6 yo)	-	-	0.33	-	0.33	-
Primary school student (6 - <11 yo)	-	-	0.47	-	0.48	-
Secondary school student (11- <16 yo)	-	-	0.67	-	0.69	2.06
Adult	0.26	1.09	-	0.76	0.65	2.43

Bw_t (body weight linked to SSA, kg95th)	1	2	3	4	5	6
Toddler (1-<2 yo)	-	-	13	-	13	-
Toddler (2- <3 yo)	-	-	17	-	17	-
Preschool student (3- <6 yo)	-	-	36	-	36	-
Primary school student (6 - <11 yo)	-	-	58	-	58	-
Secondary school student (11- <16 yo)	-	-	83	-	83	83
Adult	107	107	-	107	107	107

Notes:

$Appl\ Rate$, SSA, AF, $Duration$, Bw_t and AT are variables used to calculate the estimated daily sunscreen exposure for each scenario.

Where:

Appl Rate	Application rate of product (2 mg/cm²) (Sunscreen Standard)
SSA	Surface area of skin sunscreen applied to (cm²) per application
AF	Application Frequency (applications/day)
Dura ion	Annual Use (days)
Bw_t	Body weight linked to SSA (kg)
AT	Averaging time (365 days)

Calculation for estimated daily sunscreen exposure for each scenario

Daily sunscreen exposure (Method 1, mg/kg bw/day)	1	2	3	4	5	6
Toddler (1-<2 yo)	N.A.	N.A.	607	N.A.	66	N.A.
Toddler (2- <3 yo)	N.A.	N.A.	487	N.A.	55	N.A.
Preschool student (3- <6 yo)	N.A.	N.A.	237	N.A.	39	N.A.
Primary school student (6 - <11 yo)	N.A.	N.A.	211	N.A.	35	N.A.
Secondary school student (11- <16 yc	N.A.	N.A.	211	N.A.	36	106
Adult	63	267	N.A.	279	26	97

N.A. Not Applicable

Daily sunscreen exposure Method 2 (cm²/kg bw/day)	1	2	3	4	5	6
Toddler (1-<2 yo)	N.A.	N.A.	303	N.A.	33	N.A.
Toddler (2- <3 yo)	N.A.	N.A.	244	N.A.	28	N.A.
Preschool student (3- <6 yo)	N.A.	N.A.	119	N.A.	19	N.A.
Primary school student (6 - <11 yo)	N.A.	N.A.	105	N.A.	18	N.A.
Secondary school student (11- <16 yo)	N.A.	N.A.	105	N.A.	18	53
Adult	31	134	N.A.	140	13	48

N.A. Not Applicable

Formulae

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

$$ASEM\ (method\ 2) = \frac{SSA\ \times\ AF\ \times\ Duration}{Bw_t\ \times\ AT}$$

Notes:

Method 1 is used if the dermal absorption is based on he percentage of the ingredient dermally absorbed (%).

Method 2 is used if the dermal absorption is based on he absolute amount of the ingredient that is bioavailable (µg/cm²).

Calculation for highest estimated daily sunscreen exposure

Method 1 (mg/kg bw/day)	Scenarios 4+6	Scenarios 3+5	Scenarios 3+6
Toddler (1-<2 yo)	N.A.	673	N.A.
Toddler (2- <3 yo)	N.A.	543	N.A.
Preschool student (3- <6 yo)	N.A.	276	N.A.
Primary school student (6 - <11 yo)	N.A.	246	N.A.
Secondary school student (11- <16 yo	N.A.	N.A.	317
Adult	376	N.A.	N.A.

Method 2 (cm²/kg bw/day)	Scenarios 4+6	Scenarios 3+5	Scenarios 3+6
Toddler (1-<2 yo)	N.A.	336	N.A.
Toddler (2- <3 yo)	N.A.	271	N.A.
Preschool student (3- <6 yo)	N.A.	138	N.A.
Primary school student (6 - <11 yo)	N.A.	123	N.A.
Secondary school student (11- <16 yo)	N.A.	N.A.	158
Adult	188	N.A.	N.A.

Formula:

$$ASEM_{highest\ estimated\ daily\ sunscreen\ exposure} = ASEM_{scenario\ a} + ASEM_{scenario\ b}$$

Notes:

The TGA has calculated the sunscreen exposure for each ASEM scenarios, and combined the weekday and weekend scenarios to provide a yearly realistic exposure:

- For adults, a combination of Scenarios 4 and 6.
- For secondary school children, a combination of Scenarios 3 and 6.
- For other children, including toddlers, pre-school, and primary school children, a combination of Scenarios 3 and 5.

To derive the es imated daily sunscreen exposure, Scenarios 3 and 5 for toddlers aged 1 to 2 years old provided the highest estimated daily sunscreen exposure. Therfore the can be caculated as below:

- ASEM (method 1) Scenario 3 + Scenario 5 = 607 + 66 = **673 mg/kg bw/day**
- ASEM (method 2) Scenario 3 + Scenarios 5 = 303 + 33 = **336 cm²/kg bw/day**

Body weight data used in ASEM calculations

Age groups	Body weight* (95th percentile, Kg)
Toddler (1 - <2 yo)	13
Toddler (2 - <3 yo)	17
Preschool student (3 - <6 yo)	36
Primary school student (6 - <11 yo)	58
Secondary school student (11 - <16 yo)	83
Adults**	107

* Data based on enHealth (2012) Table 2.2.1 and E2 for body weights for Adults (≥18 years), adolescents and children.

** enHealth reports male and female 95th percentile body weight data, which has been averaged.

Skin surface area of individual body parts (Adult, 95th percentile, m^2)

Body part (Adult)	Male 95th	Female 95th
Head	0.15	0.12
Trunk (incl neck)	1.10	0.85
Upper extremities	0.47	0.35
Arms	0.40	0.27
Upper arms	0.22	NR
Forearms	0.20	NR
Hands	0.13	0.11
Lower extremities	0.97	0.88
Legs	0.85	0.76
Thighs	0.52	0.48
Lower legs	0.32	0.29
Feet	0.16	0.15
Total BSA	**2.52**	**2.33**

* Data based on enHeal h (2012), Table 3.2.3 and 3.2.5 for skin surface area of body parts for Adults, adolescents and children. It is based on rounded data from US EPA (2009, Tables 7-11 and 7-12).

Note: NR: Not Reported, data for upper arms and forearms were not reported in US EPA (2009)

Skin surface area of individual body parts (Child, 95th percentile, m^2)

Body part (Child)	Toddler (1-<2 yo)	Toddler (2- <3 yo)	Preschool student (3- <6 yo)	Primary school student (6 - <11 yo)	Secondary school student (11- <16 yo)
Head	0.1	0.1	0.13	0.19	0.19
Trunk	0.22	0.27	0.3	0.51	0.69
Arms	0.08	0.08	0.14	0.19	0.27
Hands	0.04	0.04	0.06	0.07	0.11
Legs	0.14	0.16	0.26	0.41	0.65
Feet	0.04	0.05	0.07	0.11	0.16
Total SSA	**0.61**	**0.7**	**0.95**	**1.48**	**2.06**

* Data based on enHealth (2012), Table 3.2.5 for skin surface area of body parts for Adults, adolescents and children. It is based on rounded data from US EPA (2008, Tables 7-2).

Note: Data are for both sexes combined.

Skin surface area exposed to sunscreen used to calculate estimated daily sunscreen exposure per scenario for Adults (m^2)

ASEM Scenario	Male 95th	Female 95th	Person 95th
Scenario 1	0.28	0.23	0.26
Scenario 2	1.17	1.00	1.09
Scenario 4	0.83	0.69	0.76
Scenario 5	0.69	0.61	0.65
Scenario 6	2.52	2.33	2.43

Notes: Person 95th body weight is the average of male and female 95th body weight
Nil SSA data for neck alone, therefore SSA for neck is estimated to be '0'
Nil SSA data for hat coverage, or face alone, therefore SSA estimated to be 'half head'
Upper extremities SSA include upper arms + lower arms or arms, and hands
Lower extremities SSA include thighs + lower legs or legs, and feet
Trunk SSA includes chest, abdomen and pelvis areas.

Skin surface area exposed to sunscreen used to calculate estimated daily sunscreen exposure per scenario for Children (m^2)

ASEM Scenario	Toddler (1-<2 yo)	Toddler (2- <3 yo)	Preschool student (3- <6 yo)	Primary school student (6 - <11 yo)	Secondary school student (11- <16 yo)
Scenario 3	0.20	0.21	0.33	0.47	0.67
Scenario 5	0.20	0.22	0.33	0.48	0.69
Scenario 6	N.A.	N.A.	N.A.	N.A.	2.06

Notes: Nil SSA data for neck alone, therefore SSA for neck is estimated to be '0'
Nil SSA data for hat coverage, or face alone, therefore SSA estimated to be 'half head'

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Risk Assessment of Seven Active Sunscreen Ingredients

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

Version 1.0 XXXX 2024

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 Toxicology risk assessment 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 tox risk assessment 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.

The two main issues considered in this toxicology risk assessment were the evidence for the ability of these ingredients to penetrate the skin to become available to viable cells systemically and the potential toxicity exerted by them, all in the setting of the new Australian Sunscreen Exposure Model (ASEM), a model developed to better represent sunscreen use in the Australian context. The ASEM has been used to calculate the highest risk estimate (Margin of Safety), by modelling the average daily sunscreen exposure for high use of therapeutic sunscreens when applied long-term to the face and body by children and adults.

Based on the data available for these ingredients, a Margin of Safety (MoS) was determined for each of the ingredients using the ASEM. The data and assumptions developed in the ASEM underwent public consultation in 2024. A MoS of 100 or more is considered globally 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 of the respective ingredients in therapeutic sunscreen products (which are regulated as listed medicines). The review examined only the risk profile of the ingredients, and not the benefits that may be realised through the appropriate use of sunscreen in preventing skin cancer.

It is important to note that not all products contain maximum permitted concentrations of these actives; and that some products contain a combination of the active ingredients.

Active ingredients considered to be low risk based on the toxicological safety

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

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

The MoS for avobenzone, ethylhexyl triazone, octocrylene, octinoxate 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.

Active ingredients considered to be high risk based on the toxicological safety

In the case of homosalate and oxybenzone, the MoS using the highest estimated sunscreen exposure for application of a general sunscreen product to the body, at the maximum permitted concentration, was less than 100. Further risk estimates were modelled using the ASEM to estimate alternative lower exposures based on specific parts of the body e.g. head, face and/or hands. In these models, 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% for 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).

Limitations of this review

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, are not available for independent corroboration of the findings from these reports and literature, the veracity of this review is dependent on 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 avobenzone, homosalate, octocrylene, octinoxate and oxybenzone indicate in some studies possible endocrine modifying effects. However, the data are not adequate to derive a conclusion as to their causality in humans. Further data on whether or not these chemicals have endocrine modifying potential 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. 2) 2024* currently lists 30 sunscreen active ingredients approved for use in Australia. The safety of these ingredients has been subject to multiple assessments in the past, addressed by various means, including the assessment of toxicological data, utilisation of overseas regulatory reports, and consideration by committees such as the previously named Medicines Evaluation Committee.

The TGA has been continuously 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 measurable 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)). Of these, ensulizole, homosalate, octinoxate, octisalate, octocrylene, oxybenzone, avobenzone are currently used in Australian products.

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 risk assessment

Given the greater use and therapeutic importance of sunscreens in Australia together with the current interest by the US FDA in the ongoing safety of sunscreen active ingredients, the TGA conducted a risk assessment 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 was undertaken for 7 ingredients: avobenzone, EHT, homosalate, octocrylene, octinoxate, oxybenzone and PBSA. This document reviews whether these ingredients can be considered as low-risk at current concentrations, and therefore appropriate for use in therapeutic sunscreens.

A literature review was conducted for the scientific information available for the 7 active ingredients avobenzone, ethylhexyl triazone (EHT), homosalate, octinoxate, octocrylene, oxybenzone and phenylbenzimidazole sulfonic acid (PBSA) for use in sunscreens. These ingredients have been widely used in sunscreen products in Australia. The risk assessment is intended to provide an overview of the publicly available safety information for these ingredients, calculate the MoS as per the 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 deemed completely safe, without risk, 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.

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

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.

The TGA toxicology risk assessment 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.

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 is 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 risk assessment was based on current sun protection practices and recommendations in Australia, the TGA developed an Australian Sunscreen Exposure Model (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.

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

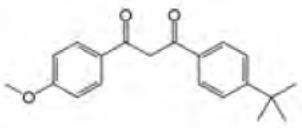
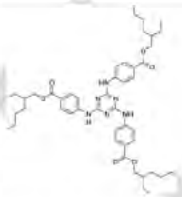
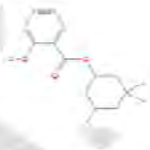
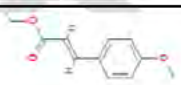
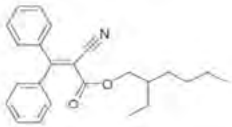
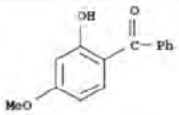
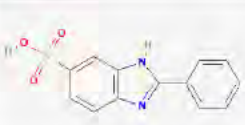
Active ingredient (*absorption spectrum*)	CAS no.	Chemical name	Molecular formula	Physical properties				Other names
				Water solubility	MW g/mol	Density	Log P_{ow}	
Avobenzone (BMDM or BMDBM) *UVA* λ_{max} *355 nm*	70356-09-1	1,3-Propanedione, 1-[4-(1,1-dimethylethyl)phenyl]-3-(4-methoxyphenyl)-	$C_{20}H_{22}O_3$	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 (EHT) *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)
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"
Octinoxate (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)

Active ingredient (*absorption spectrum*)	CAS no.	Chemical name	Molecular formula	Physical properties				Other names
				Water solubility	MW g/mol	Density	Log P_{ow}	
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 (PBSA) *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/cm³	-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
Avobenzone	
Ethylhexyl triazone	
Homosalate	
Octinoxate	
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]
Avobenzone	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)
Octinoxate	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[Δ]	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 ɣ	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; ɣ EU: cosmetics directive in annex VII, part 1 list of permitted UV filters under entry 6;
Δ 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.
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]

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/cm²)	$\frac{SSA\ x\ AF\ x\ Duration}{BWt\ x\ AT}$ = 336 cm²/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

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

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

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

[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.

ASEM	ASEM Method 1 – highest estimated sunscreen exposure (673 mg/kg bw/day)
Appl Rate	Application rate of product (2 mg/cm²) (A/NZ Standard)
SSA	Skin Surface Area that had sunscreen applied to (cm²)
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 cm²/kg bw/day)
Appl Rate	Application rate of product (2 mg/cm²) (A/NZ Standard)
SSA	Skin Surface Area that had sunscreen applied to (cm²)
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/cm²
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 the Attachment 1 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

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

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.

Avobenzone

The molecular weight of avobenzone 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 range -1 to +4). Avobenzone has a low water solubility. Based on these physico-chemical data, only low dermal penetration is expected.

The toxicokinetic data for avobenzone 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 rabbits 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 (avobenzone) 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 avobenzone 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 (avobenzone) 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 (avobenzone) 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 avobenzone after single or repeated applications of sunscreens (Montenegro *et al.* 2018). However, recent randomised clinical trials indicate that avobenzone was systemically absorbed in humans (see Clinical Trials).

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

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

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/cm² and 2 mg/cm²), 23.2 ± 4.1 mg/cm² and 18.3 ± 2.5 µg/cm² of oxybenzone and ethylhexyl triazone, respectively were found in the stratum corneum, whereas 1.5 ± 0.3 mg/cm² 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/cm² of ethylhexyl triazone (i.e., ~1.08% of the amount 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/cm² 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 cm² 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 ingested orally 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 (4×10^{-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).

[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.

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

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. (adapted from Bury *et al* 2019)*

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/cm² 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. 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/cm²) 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/cm² 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/cm² (~ 0.15% of the applied dose) consistent with previous findings. The **dermal absorption of 0.97 µg/cm²** (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).

Octinoxate

Octinoxate absorption studies (oral and dermal) in rats and mice indicate octinoxate can be absorbed dermally and orally (Fennell *et al.* 2018). Octinoxate was rapidly cleared from rat hepatocytes (half-life ≤3.16 min) compared to human hepatocytes (half-life ≤48 min). [^{14}C]-octinoxate 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 octinoxate (200 mg/kg bw and 1000 mg/kg bw) (Huang *et al.* 2019). The major metabolites of octinoxate were 4-methoxycinnamic acid (4-MCA) and 4′-methoxyacetophenone (4′-MAP). The concentration of two metabolites was found to be much higher than octinoxate, highlighting that measuring octinoxate alone could not comprehensively evaluate the human exposure to octinoxate.

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). Octinoxate 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, octinoxate penetration was not observed following the administration of octinoxate as entrapped into solid lipid microspheres (SLM) (Yener *et al.* 2003).

Studies with porcine skin showed that about 9% of the applied dose of octinoxate penetrates the skin with a flux of 27 µg/cm²·h (Touitou and Godin 2008). An accumulation of ~9% of octinoxate in epidermis and ~2-3% in dermis were observed following application of 2 mg/cm² and 0.5 mg/cm² of octinoxate, respectively for 6 h exposure (Schneider *et al.* 2005). Octinoxate 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 octinoxate or EHMC (10%) on full-thickness pig-ear skin, mimicking human in-use conditions revealed the skin distribution of octinoxate from the sunscreen dose of 0.5 mg/cm² after 6-h exposure to the epidermis of frozen-stored skin was 4.8± 0.7 µg/cm², dermis 1.2 ± 0.1 µg/cm² and undetectable in receptor fluid, whereas 3.4 ± 0.6 µg/cm² , 2.1 ± 0.4 µg/cm² and 0.9 ± 0.1 µg/cm² of octinoxate 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% octinoxate 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/cm²) (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 octinoxate 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 octinoxate in humans was demonstrated by Janjua *et al* (2008). Maximum plasma concentration of octinoxate 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% octinoxate. Octinoxate 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% octinoxate suggested that an insignificant amount of octinoxate 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 octinoxate 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 octinoxate. 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 PBSA were examined in pregnant rats (SCCP 2006b). [^{14}C]-PBSA 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 PBSA was not established, cumulative penetration of 0.159% (range 0.107-0.259%) of the applied dose (8% formulation of PBSA), 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 PBSA 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/cm²) determined** in the *in vivo* study in humans following application of an 8% formulation of PBSA was used by the SCCP to determine the margin of safety for PBSA (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/cm² on 75% of body surface area. The sunscreen products were spray 1 (3% avobenzone/ 6% oxybenzone/2.35 % octocrylene/ 0% ecamsule[8]), spray 2 (3% avobenzone/5% oxybenzone/ 10% octocrylene/ 0% ecamsule), lotion (3% avobenzone/ 4% oxybenzone/ 6% octocrylene/ 0% ecamsule); and cream (2% avobenzone/ 0% oxybenzone/ 10% octocrylene/ 2% ecamsule). The overall maximum plasma concentrations (C_{max}) of avobenzone, 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 avobenzone 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.

Similar findings were observed in a follow up study with six active ingredients (avobenzone, oxybenzone, octocrylene, homosalate, octisalate[9], and octinoxate) (Matta *et al.* 2020). Four groups (n=12) of healthy adults received 2 mg/cm² (75% of body surface area) on day 1 and 4

[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.
[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.

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 avobenzone (95%; *n* = 42/44), octisalate (75%; *n* = 24/32), and octinoxate (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
Avobenzone	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)
Octinoxate	NA	NA	7.9 (86.5)	5.2 (68.2)

Another study investigating systemic absorption of avobenzone and octocrylene using real-life exposure scenario demonstrated similar systemic absorption of the ingredients (Hiller *et al.* 2018). Following dermal exposure, avobenzone, 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. 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 avobenzone

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	Avobenzone	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)
$t_{½}$ 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 avobenzone, ethylhexyl triazone, homosalate, octinoxate, octocrylene, oxybenzone and PBSA 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

Avobenzone, ethylhexyl triazone, homosalate, oxybenzone, octocrylene, PBSA and octinoxate displayed low acute oral toxicity. Low acute dermal toxicity was observed for homosalate, oxybenzone, octocrylene, PBSA and octinoxate. Information for acute inhalational toxicity is only available for octinoxate (shown below).

Summary of acute toxicity studies for sunscreen ingredients

Avobenzone (ECHA (2021a; DEPA 2015)	Ethylhexyl triazone (ECHA 2021b; DEPA 2015)	Homosalate (SCCS 2021b,c; ECHA 2021c)	Octinoxate (ECHA 2021e)	Octocrylene (SCCS 2021d; ECHA 2021d)	Oxybenzone (SCCP 2006a; 2021c)	PBSA (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	Avobenzone (ECHA (2021a; DEPA 2015)	Ethylhexyl triazone (ECHA (2021b; DEPA 2015	Homosalate (SCCS 2021b,c; ECHA 2021c)	Octinoxate (ECHA 2021e)	Octocrylene (SCCS 2021d; ECHA 2021d)	Oxybenzone (SCCP 2006a; 2021c)	PBSA (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

Avobenzone (ECHA 2021a; DEPA 2015)	Ethylhexyl triazone (ECHA (2021b; DEPA 2015	Homosalate (SCCS 2021b,c; ECHA 2021c)	Octinoxate (ECHA 2021e)	Octocrylene (SCCS 2021d; ECHA 2021d)	Oxybenzone (SCCP 2006a; 2021c)	PBSA (SCCP 2006b)
Not sensitizing (at 6% and 20% in GPMT)	Not sensitizing (GPMT)	Not sensitizing (GPMT and mice) Not sensitizing (at 15%, HRIPT)	Not sensitizing (GPMT)	Not sensitizing (GPMT) Moderate sensitising in a LLNA (not properly conducted)	Not sensitizing (GPMT) Not sensitising (LLNA)	Not sensitizing (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[Δ]	Major findings
Avobenzone (ECHA 2021a; DEPA 2015)	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. 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 avobenzone 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	No treatment-related mortality No treatment-related clinical signs. Body weight gain: ↓ at HD in both subsets

Active ingredient	Study details[Δ]	Major findings
	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)	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
Octinoxate (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.

Active ingredient	Study details[Δ]	Major findings
		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
	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 ♀

Active ingredient	Study details[Δ]	Major findings
	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
PBSA (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 (SCCS 2021b,c; ECHA 2021c)	Rats, n=5/sex/dose, 0, 100, 300, 1000 mg/kg bw/day, 2 weeks (gavage)	Mortality: none Clinical signs: none treatment related 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,

Active ingredient	Study details[Δ]	Major findings
		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*.

Summary of genotoxicity studies with sunscreen ingredients

Avobenzone (ECHA (2021a; DEPA 2015)	Ethylhexyl triazone (ECHA (2021b; DEPA 2015	Homosalate (SCCS 2021b,c; ECHA 2021c)	Octinoxate (ECHA 2021e)	Octocrylene (SCCS 2021d; ECHA 2021d)	Oxybenzone (SCCP 2006a; 2021c)	PBSA (SCCP 2006b)
In vitro Negative AMES test and gene mutation study V79 Chinese hamster cells In vivo Negative Bone marrow poly-chromatic erythrocytes (mice)	*In vitro* Negative AMES test, Chinese hamster lung fibroblasts for chromosome aberration, Chinese hamster ovary (CHO) cells, in vivo chromosome aberration test	*In vitro* 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)	*In vitro* 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	*In vitro* 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)	*In vitro* 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)†	*In vitro* Negative AMES test and chromosome aberration test in human peripheral blood lymphocytes In vivo No data

Avobenzone (ECHA (2021a; DEPA 2015)	Ethylhexyl triazone (ECHA (2021b; DEPA 2015	Homosalate (SCCS 2021b,c; ECHA 2021c)	Octinoxate (ECHA 2021e)	Octocrylene (SCCS 2021d; ECHA 2021d)	Oxybenzone (SCCP 2006a; 2021c)	PBSA (SCCP 2006b)
			mutant colonies (up to 20 mg/mL)			

† 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 avobenzone, octinoxate, octocrylene, ethylhexyl triazone, homosalate or PBSA. 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.

Summary of carcinogenicity studies with sunscreen ingredients

Active ingredient	Study details	Major findings
Avobenzone	–	No data
Ethyl hexyl triazone	–	No data
Homosalate	–	No data
Octinoxate	–	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.
PBSA	–	No data

Reproductive and developmental studies

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

Summary of reproductive and developmental toxicity studies with sunscreen ingredients

Active ingredient	Study details	Major findings
Avobenzone (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.
	Rabbits, single dose of 500 mg/kg bw/day GD 7-19 (oral, daily)	No treatment-related effects or teratogenicity.
Octinoxate (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.	Octinoxate 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. Octinoxate 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

Active ingredient	Study details	Major findings
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 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)	↓ 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. 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.	

Active ingredient	Study details	Major findings
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.
	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	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)

Active ingredient	Study details	Major findings
	Treatment from GD1-GD13	
	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 (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.	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. 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
PBSA (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 octinoxate 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 octinoxate/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 octinoxate suggest that current evidence is not sufficient to support the causal relationship between the elevated systemic level of oxybenzone and

octinoxate 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 octinoxate 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 avobenzone, homosalate, octocrylene, octinoxate 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*

[10] EHT was included in these 14 ingredients
[11] Homosalate and avobenzone were included

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, Octinoxate 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."*

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

> *"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 octinoxate, octocrylene, avobenzone and homosalate among 35 other chemicals used in consumer products, for their ability to modulate estrogen receptor (ER) or androgen receptor (AR) *in vitro.* Octinoxate 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. Avobenzone 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 octinoxate level have been less extensively studied presumably. The current evidence shows that topical application of octinoxate does not have biologically significant effect on thyroid and reproductive hormone levels (Suh 2020). However, the topical application of octinoxate 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 octinoxate 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.

Avobenzone

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 avobenzone 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*

[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).

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."*

Octinoxate

Most of the available data suggest that octinoxate 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 octinoxate mechanism of action, several studies showed that the effects exerted by Estradiol (E2) and octinoxate were not always totally shared and it is possible that octinoxate could act by a mechanism different from the classic E2R (α y β). There are few data regarding the anti-androgenic activity of octinoxate, and the studies suggest that octinoxate is not able to bind to androgen receptors. Studies in rats showed that octinoxate 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 octinoxate 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 octinoxate, 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 avobenzone has been extensively reviewed in several publications (Nash and Tanner 2014). However, given the mechanistic understanding and known photo-degradation of avobenzone, the findings were inconsistent. For example, the *in vitro* skin phototoxicity of cosmetic formulations containing avobenzone, 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 avobenzone 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 avobenzone may be the result of the photoproducts formed following exposure to UV. These data suggest that photo-degradation of avobenzone 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 avobenzone whereas the most common contact allergens were octyl dimethyl para-aminobenzoic acid, oxybenzone and sandalwood (Yap 2017).

The SCCS (SCCS 2000) stated that octinoxate did not have phototoxic potential based on one study of 10 subjects exposed to patches of octinoxate 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 octinoxate was not phototoxicity (Gomes *et al.* 2015).

A human repeated insult patch test (HRIPT) was carried out at a concentration of 2% octinoxate in 53 subjects. There was no sensitisation. Similar studies using different formulations (7.5 % octinoxate in petrolatum or 10 % octinoxate 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 (octinoxate 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 octinoxate, 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 avobenzone was demonstrated *in vitro* by Shin et al. (2020) and Ahn et al. (2019). In normal human epidermal keratinocytes, avobenzone (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, avobenzone did not bind PPARγ and the avobenzone-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 avobenzone 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 avobenzone, 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 avobenzone, 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 avobenzone 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 avobenzone 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.

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 octinoxate 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 in* 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 avobenzone (butyl methoxydibenzoylmethane) 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 avobenzone.

The ECHA dossier suggested low percutaneous absorption of avobenzone. Potential systemic availability of avobenzone 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% avobenzone containing formulations), about 95 % of avobenzone 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% avobenzone 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 avobenzone could be systemically absorbed (Matta *et al.*, 2020; 2019). The systemic exposure of avobenzone 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 avobenzone 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% avobenzone) whereas the LOAEL (dermal) was 30 mg/kg/day bw (1.5% avobenzone) 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 avobenzone 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

Avobenzone – 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 avobenzone 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, avobenzone 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/cm² 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/cm² for 6 h (Hojerová *et al.* 2017). The study authors concluded, that approximately 0.54 mg/cm² 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

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

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)

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-trimethylcyclohexano 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 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

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

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.

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 Face	675	107	2	240	0.09	76
Adult 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).

Commented [S22]: Suggest to use same terminology as "Adult Head only" above or remove the "only" above. Need to update other references for consistency

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
Adult Head only	1350	107	2	365	0.27	25
Adult Hands only	1200	107	2	365	0.24	28
Adult Head + Hands	2550	107	2	365	0.51	13
Adult Face	675	107	2	365	0.13	50

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 + Hands	1875	107	2	365	0.37	18

*95th percentile for SSA body parts and total body weight (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, 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
Adult Head only	5.7	3.7
Adult Hands only	6.4	4.2
Adult Head + Hands	3.0	2.0
Adult Face	11.4	7.5
Adult Face + Hands	4.1	2.7

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

Recommendation

A MoS less than 100 was calculated using the ASEM at current maximum concentrations. 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 that the entry restrict the use of homosalate in therapeutic sunscreens, giving possible consideration to the following:

- Face-only 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.
- This risk assessment concludes that homosalate can be deemed low-risk and appropriate for use in therapeutic sunscreens for daily use when:
    - Used by adults only
    - Limited to face-only or face and hand application, not to the whole body
    - At a reduced maximum concentration (between 11.4% and 2.7% 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 and 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). Considering the information above, octocrylene was considered a skin sensitiser at 10%.

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. 27.50 ± 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/cm² 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/cm²** 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/cm²
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 octinoxate can poorly penetrate the skin. Systemic absorption of octinoxate 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.

Octinoxate 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.

Octinoxate 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 octinoxate 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/cm² following 6-h pig-ear skin exposure + 18-h free permeation after an application of oil-in-water emulsion sunscreen dose (0.5 mg/cm²) containing 10% octinoxate was used in the SED calculation using as per the SCCS opinion (Klimova *et al.* 2015).

Exposure estimate and Margin of Safety for Octinoxate

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

Parameter	Value
NOAEL	450 mg/kg bw/day
Dermal absorption (DAp)	1.77 µg/cm²
Highest concentration permitted to be used in Australian sunscreen products (C)	10 %

Estimated octinoxate 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.

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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

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, 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).

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	0.20	206

Scenario *	Skin Surface Area (cm^2)	Body weight (kg)	Reapplications (no. per day)	Annual use (days/year)	SED (mg/kg bw/d)	MoS
Adult Hands only	1200	107	2	240	0.18	233
Adult Head + Hands	2550	107	2	240	0.37	109
Adult Face	675	107	2	240	0.10	413
Adult Face + Hands	1875	107	2	240	0.27	149

*95th percentile for SSA body parts and total body weight (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
Adult Head only	1350	107	2	365	0.30	136
Adult Hands only	1200	107	2	365	0.27	153
Adult Head + Hands	2550	107	2	365	0.57	72
Adult Face	675	107	2	365	0.15	272
Adult Face + Hands	1875	107	2	365	0.42	98

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

For these oxybenzone-containing sunscreen products to reach a satisfactory MoS based on specific part of the body, the concentration of oxybenzone would need to be reduced as shown in the table below for 365 days per year use.

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

Scenario *	Concentration (%) 365 d/yr
Adult Head only	10
Adult Hands only	10
Adult Head + Hands	7.2
Adult Face	10
Adult Face + Hands	9.8

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

Recommendation

A MoS less than 100 was calculated using the ASEM at maximum concentrations. 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:

- Face-only 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.
- This risk assessment concludes that oxybenzone can be deemed low-risk and appropriate for use in therapeutic sunscreens for daily use when:
    - Used by adults only
    - Limited to face and hand application, not to the whole body
    - At a reduced maximum concentration (9.8% to 10% 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.
- 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 (PBSA) was assessed based on the publicly available safety data from scientific literature, and the SCCP opinion (SCCP, 2006b).

PBSA 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 PBSA did not cross the blood/brain barrier. PBSA 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 PBSA.

PBSA 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. PBSA 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.

PBSA 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 PBSA were available.

No treatment-related findings were noted in a pre-natal developmental toxicity study in rats treated with PBSA 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. PBSA 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 PBSA

PBSA – 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/cm²
Highest concentration permitted to be used in Australian sunscreen products (C)	4 %

Estimated PBSA 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.

Attachment

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 sensitization
- 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
- CosIng 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/

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Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	XX, TGA	XX 2024

Therapeutic Goods Administration

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Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Risk assessment of Benzophenone

Version 1.0, XXXX 2024

TABLE OF CONTENTS

INTRODUCTION

Benzophenone is concluded by International Agency for Research on Cancer (IARC) Working Group as a possibly carcinogenic to humans (Group 2B). It is a known potential degradant of sunscreens containing octocrylene. Although USP monograph for octocrylene has limits for organic impurities in the raw material, the monograph does not specify a safe limit for benzophenone as a degradant in finished products. Therefore, the TGA has been reviewing available information to establish a safe permitted daily exposure and a limit for benzophenone as a degradant in therapeutic sunscreens.

In August 2023, the TGA held a public consultation to discuss safe levels of benzophenone in listed medicines. The consultation document proposed to amend the requirements for the use of benzophenone and octocrylene in these medicines. However, the decision to introduce a regulatory limit for benzophenone was deferred pending further consultation to develop a sunscreen exposure model specific to the Australian context.

In July 2024, the TGA conducted a subsequent public consultation to establish the Australian Sunscreen Exposure Model (ASEM), which more accurately estimates regular sunscreen exposure for Australians. The ASEM calculates a highest estimated average daily sunscreen exposure amount based on the highest use scenarios in the most vulnerable population (toddlers aged 1-2 years), ensuring it is applicable for general therapeutic sunscreens meant to be used by the whole population.

This updated risk assessment uses the ASEM to assess the risk of benzophenone as a degradant in sunscreens.

WHAT IS THIS CHEMICAL

Benzophenone is an aryl ketone and it is the simplest member of the class of benzophenones (Figure 1). Substituted benzophenones such as oxybenzone and dioxybenzone are frequently used in sunscreen.

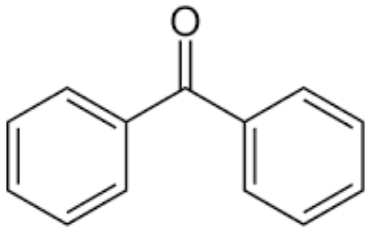

Figure 1: Benzophenone, Cas 119-61-9, synonymous: Diphenylmethanone, benzoylbenzene

Benzophenone is a naturally occurring compound used in flavouring and perfumes. It is used as fixative for heavy perfumes in soaps, detergents, and room deodorizers. It is used as a flavouring agent, ultraviolet absorber in inks and coatings, and as a polymerization inhibitor for styrene. It is used in the manufacture of antihistamines, hypnotics, and insecticides. Concentrations of benzophenone in food products range from 0.57 ppm in nonalcoholic beverages to 3.27 ppm in frozen dairy products.

The presence of benzophenone in sunscreen arises from two main sources:

(1) benzophenone contamination in the octocrylene, active ingredient in a high number of sunscreen products marketed in Australia, and

(2) accumulation of benzophenone from the degradation of octocrylene as the product ages (aminolysis and hydrolysis of octocrylene in the skin may result in the formation of benzophenone) (Figure 2).

Recently Downs and colleagues (2021) found benzophenone in 17 commercial sunscreens tested (ranging from 0 to 227.9 ppm) and after accelerated stability incubation of 6 weeks, the lowest concentration of benzophenone was 6.3 ppm and the highest was 461.4 ppm).

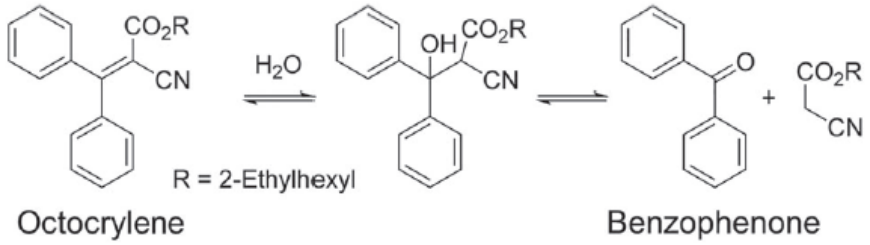

Figure 2: Degradation of Octocrylene (from Downs C.A et al. Chem. Res. Toxicol. 2021, 34, 1046-1054)

CURRENT RESTRICTIONS IN AUSTRALIA AND OVERSEAS

Australian regulations

Benzophenone is available for use in medicines, biologicals and medical devices. For listed and over the counter medicines, benzophenone is only permitted to be used in combination with other permitted ingredients as a fragrance, where the total fragrance concentration in a medicine must be no more than 1%. As of 17 September 2024, Benzophenone is currently being used as fragrance in four listed medicines, four registered medicines and two other therapeutic goods.

The Australian Industrial Chemicals Introduction Scheme (AICIS) completed a Human Health Tier II assessment for benzophenone on 1 September 2015. While showing low acute toxicity in rabbits following dermal exposure (LD_{50} of >2000 mg/kg bw), AICIS concluded that benzophenone was a potential oral carcinogen.

International regulations

Effective from November 17, 2023, benzophenone has been added to Annex II of Regulation (EC) No. 1223/2009, which lists substances prohibited in the formulation of cosmetic products within the European Union (EU). The EU has also implemented new requirements and transition periods for octocrylene and notes that 'Benzophenone as an impurity and/or degradation product of Octocrylene shall be kept at trace level', however, a numerical limit has not been specified.

In 2009, EFSA assessed benzophenone as a food contact material (EFSA, 2009). The report indicated that the margin of exposure was low and recommended that more data on the occurrence of the substance in foods should be provided as well as appropriate toxicity data corresponding to the level of exposure to enable a full risk assessment. The EFSA Panel also concluded that benzophenone was not genotoxic but caused kidney adenoma, including hyperplasia and nephropathy in rats at the lowest dose level tested of 15 mg/kg bw/day in a carcinogenicity study, and established a Tolerable Daily Intake (TDI) of 0.03 mg/kg bw/day, equating to 1.5 mg/day for a 50 kg person). The TDI is in the same order of magnitude as the chronic dietary exposure of adults and children to benzophenone in Europe (i.e. 10-20 µg/kg bw/day) for added flavouring substances. The toxicity of benzophenone was re-evaluated by EFSA in 2017 (EFSA, 2017) and the TDI established by EFSA in 2009 was re-confirmed.

In 2018, the US FDA amended its food additive regulations to no longer allow the use of benzophenone (and other substances) in food. However, the FDA stated that this removal was only a matter of law, and concluded that these substances do not pose a risk to public health under the conditions of their intended use. As of late 2020, its use in food products or food packaging was banned in the US. Under California Proposition 65, there are no legal provisions for safe levels of benzophenone in any personal care products, including sunscreens, anti-aging creams, and moisturisers.

The current USP monograph for octocrylene has general organic impurity limits, however benzophenone is not a specific impurity mentioned or considered. The impurity limits for octocrylene are based on data submitted before the monograph became official. The USP monograph can potentially be revised if new information becomes available however is subject to consideration by USP's Expert Volunteers, noting the monograph only applies to quality limits on the raw material – not safety limits when octocrylene is used in sunscreen products.

The Health Canada Natural Health Product Ingredients Database has a TDI for benzophenone of 0.03 mg/kg bw/day when the route of administration is oral for medical use, or up to 3.27 ppm for oral non-medicinal use as a flavour enhancer. In January 2021, Health Canada undertook a Screening Assessment for benzophenone to determine whether it presents a risk to the environment or to human health. Although benzophenone was found to be non-genotoxic, chronic oral exposure to benzophenone induced kidney adenoma and leukemia in male rats, liver tumours in male and possibly female mice, and histiocytic sarcomas in female mice. The assessment also indicated that dermal studies on the carcinogenicity of benzophenone performed on mice and small groups of rabbits showed no carcinogenic potential. However, the assessment could not verify the quality of the studies given the limited information provided in the published reports, and the extent of the histological examinations appears to have been limited. The Health Canada assessment concluded that benzophenone meets the human health criterion for a toxic substance and, subsequently, proposed to make an Order to add benzophenone as a toxic substance to Schedule 1 of the Canadian Environmental Protection Act (the List of Toxic Substances) in April 2022.

LITERATURE SEARCH SUMMARY

HUMAN STUDIES

No epidemiology studies related to benzophenone exposure in humans were found in the literature.

ANIMAL STUDIES

Percutaneous absorption

The percutaneous absorption of benzophenone was measured *in vivo* in monkey. [^{14}C]-benzophenone was applied to 1 cm^2 area of abdominal skin at a concentration of 4 µg/cm^2. In rhesus monkeys, percutaneous absorption of benzophenone was found to be 44% and 69% for unoccluded and occluded sites, respectively (Bronaugh et al., 1990).

A more recent study determined the in *vitro* dermal absorption of radiolabelled benzophenone in different preparation through human skin. [^{14}C]-benzophenone was added to two commercial sunscreen formulations and an acetone vehicle. Each preparation (containing 0.1 g/L benzophenone) was applied (approximately 2 µL/cm^2) to dermatomed human skin mounted in static diffusion cells, and the receptor fluid was collected up top 24 hours following application. All samples were analysed by liquid scintillation counting. The authors note that the study was compliant with Good Laboratory Practice, with OECD Test Guideline No. 428 and OECD Guidance Document No. 28. The results indicated that after 24 hours, the amount of benzophenone in the two spiked sunscreen formulation that was absorbed was (mean±SD) 9.04

± 2.61% and 10.02 ± 2.40%, respectively. The absorption of benzophenone in the acetone vehicle through human skin was documented as 5.19% of the applied dose. The [^{14}C]-benzophenone mass balances were considered low: 81.5%, 85.3% and 8.02%, respectively, with losses due to [^{14}C]-benzophenone volatility (Ejaz et al, 2024).

A dermal absorption value of the mean percent plus one standard deviation was calculated for the calculation of the maximum concentration of benzophenone in therapeutic sunscreen products. Using the highest dermal absorption value from the second spiked sunscreen preparation, a dermal absorption value of 10.02% + 2.4% = 12.42% was determined (Ejaz et al, 2024).

Acute toxicity

The median lethal (LD_{50}) doses of benzophenone given by oral, intraperitoneal, and dermal routes of administration were calculated and the result suggested that benzophenone is only slightly toxic.

The LD_{50} in an acute rat oral study was 1,900 mg/kg/day. The LD_{50} in an acute mice oral study was 2,895 mg/kg/day. The LD_{50} in an acute i.p. mice study was 727 mg/kg/day and the LD_{50} in an acute rabbit dermal was 3,535 mg/kg/day (National Toxicology Program, 2006).

Sub chronic and chronic feeding studies

There are sub-chronic and chronic feeding studies and a 2-generation reproductive gavage study of benzophenone in rodents. There are extensive mutagenicity and endocrine activity data for benzophenone. Long-term studies of toxicity and carcinogenicity were published on benzophenone.

In a sub-chronic feeding study, benzophenone was administered in the diet to both male and female Sprague-Dawley (SD) rats at 0, 20, 100 and 500 mg/kg bw/day. The low-dose group was treated for 13 weeks, while the mid- and high-dose groups were treated for 28 days (Burdock et al. 1991). Treatment-related changes, including altered haematological and clinical biochemistry endpoints, increased liver and kidney weights, and increased hepatocellular hypertrophy, occurred in both sexes of rats at mid- and high-dose levels. A No-Observed-Adverse-Effect Level (NOAEL) of 20 mg/kg bw/day was derived from this study (Burdock et al, 1991; ECHA, 2018).

In the reproductive study benzophenone caused liver hypertrophy in the rats at the lowest dose level (~6 mg/kg/day), but it was considered an adaptative response and not an adverse event (EFSA, 2017).

The one long-term study of toxicity and carcinogenicity will be analysed below (Carcinogenicity of Benzophenone)

Mutagenicity of Benzophenone

Benzophenone showed no evidence of mutagenicity *in vitro* or *in vivo*. Benzophenone (1 to 1,000 µg/plate) did not induce mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537, with or without induced rat liver metabolic activation enzymes. Intraperitoneal injections of 200 to 500 mg benzophenone/kg body weight (three injections at 24-hour intervals) did not induce micronuclei in bone marrow PCEs of male B6C3F mice.

No increases in the frequencies of micronucleated NCEs were seen in peripheral blood of male or female B6C3F1 mice administered benzophenone for 14 weeks (1,250 to 20,000 ppm) (EFSA, 2017).

Carcinogenicity of Benzophenone

In 2006 The National Toxicology Program (NTP, 2006) studied the effects of benzophenone on male and female F344/N rats and B6C3F1 mice to identify potential toxic or carcinogenic hazards to humans. Groups of 50 mice (male and female) were fed benzophenone for 2 years at 40, 80 and 160 mg/kg bw per day in males and 35, 70 and 150 mg/kg bw per day in females. The higher concentration at 160 mg/kg bw, was based on the minimum toxicity observed at this level in a previous 14-week study). The corresponding doses in rats were 15, 30 and 60 mg/kg bw per day in males and 15, 30 and 65 mg/kg bw per day in females.

The target organs of toxicity in the 2-year studies were liver, kidney, nose, and testes. Neoplastic responses occurred in the kidney, liver, and hematopoietic system. The conclusion of the panel of NTP was:

- 'Administration of benzophenone in feed resulted in increased incidences and/or severities of nonneoplastic lesions in the kidney and liver of male and female rats and in the liver, kidney, nose, and spleen of male and female mice'.
- 'There was some evidence of carcinogenic activity of benzophenone in male rats based on increased incidences of renal tubule adenoma; mononuclear cell leukemia in male rats may have been related to benzophenone exposure.'
- 'There was equivocal evidence of carcinogenic activity of benzophenone in female rats based on the marginally increased incidences of mononuclear cell leukemia and histiocytic sarcoma.'
- 'There was some evidence of carcinogenic activity of benzophenone in male B6C3F1 mice based on increased incidences of hepatocellular neoplasms, primarily adenoma.'
- 'There was some evidence of carcinogenic activity of benzophenone in female B6C3F1 mice based on increased incidences of histiocytic sarcoma; the incidences of hepatocellular adenoma in female B6C3F1 mice may have been related to benzophenone exposure.'
- The incidences of hepatocellular adenoma in the male mice showed a positive trend. No NOAEL could be identified for incidences of adenoma (the low dose of 40 mg/kg/day is the LOAEL with regard to this change).
- In rats, no NOAEL could be identified for incidence of renal tubule hyperplasia in males and females and the low dose corresponding to 15 mg/kg/day was considered a LOAEL. No NOAEL could be identified in relation to chronic progressive nephropathy for its severity in male rats and the LOAEL was the low-dose (15 mg/kg/day). In female rats the NOAEL for the severity of chronic nephropathy was the low dose.

In summary, in 2-year studies in rats and mice administered benzophenone in the feed, neoplastic responses were reported in kidney, liver and haematopoietic system. Species- and sex-specific differences in effects were observed. Effects were seen in all dose groups and no NOAEL was identified.

Table *1* below shows a summary of the 2-year carcinogenic study in rodents.

Table 1 Summary of the 2-year carcinogenesis and genetic toxicology studies of benzophenone

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Decreased incidences	None	Mammary gland: fibroadenoma (27/50, 24/50, 15/50, 7/50)	None	None
Level of evidence of carcinogenic activity	Some evidence	Equivocal evidence	Some evidence	Some evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:		Negative in strains TA98, TA100, TA1535, and TA1537 with and without S9		
Micronucleated erythrocytes				
Mouse bone marrow *in vivo:*		Negative		
Mouse peripheral blood *in vivo:*		Negative		

The potential for dermal carcinogenicity has also been studied (Stenbäck and Shubik, 1974 as reported by ECHA). Treated groups of female Swiss mice received (on 1-inch square of the dorsal skin between the flanks, which was shaved regularly) concentrations of 5, 25, and 50% benzophenone in acetone in a total volume of 0.2 ml, twice a week for a period of up to 110 weeks (the number of animals in the test groups, in the vehicle and positive control groups was 50/group, and additional untreated control group consisted of 150 animals). Although there is a lack of data on the vehicle control, and this study was conducted in 1974 (and not according to GLP/OECD guidelines), no significant difference in dermal carcinogenic effects was observed between control groups and treated groups in this study.

The potential carcinogenicity of benzophenone was also evaluated by several Regulatory Agencies and Expert Panels and the conclusions were similar to the conclusions reached by the NTP:

- The International Agency for Research on Cancer (IARC, 2012) evaluated the carcinogenic risk of several chemical present in industrial and consumer products, foods and drinking-water, including benzophenone and the conclusion was that 'benzophenone is possibly carcinogenic to humans' and it was classified in group 2B (which means that there is strong evidence that it can cause cancer in humans, but at present it is not conclusive).

- In 2009 benzophenone was evaluated as a food contact material by the European Food Safety Authority, and it was re-evaluated in 2017. The Panel concluded that benzophenone caused kidney adenoma, including hyperplasia and nephropathy in rats. Based on an NTP study (2006), the Panel established a Tolerable daily intake (TDI) of 0.03 mg/kg bw per day. The TDI is in the same order of magnitude as the chronic dietary exposure of adults and children to benzophenone in Europe (10–20 µg/kg bw per day) for added flavouring substances.

- The Joint Expert Committee of Food Additives (JECFA, 2011) noted that histiocytic sarcomas occurred only in female mice and rats and only at dose levels inducing toxicity and possibly affecting hormonal balance. A NOAEL was not identified. The sex specificity of renal pathology in rats was suggested by JECFA to be due to differences in renal clearance of metabolites and more severe ageing chronic nephropathy in males compared to females, possibly due to higher concentration of proteins, primarily α-2μ-globulin, in male rats. A conclusion from JECFA was that the increasing severity of ageing chronic nephropathy is largely responsible for the renal tubular proliferation in male rats in most strains, including F344/N, and that this mode of action is not relevant to human renal carcinogenesis.

CALCULATION OF MAXIMUM ALLOWABLE CONCENTRATION

The maximum allowable concentration of benzophenone, in general therapeutic sunscreens, was established based on the:

- Permitted Daily Exposure (PDE),
- Amount of sunscreen applied (daily), and
- Dermal absorption

As per **Equation 2**.

A PDE amount was calculated for benzophenone, using **Equation 1**, to account for risks posed to the whole population, including the most vulnerable group (toddlers aged 1-2 years).

The NOAEL obtained in different studies ranged from 20 mg/kg to 300 mg/kg. In some of the studies it was not possible to obtain a NOAEL or LOAEL. The lower NOAEL of 20 mg/kg/day was obtained in a 13-week oral study in rats (Burdock et al, 1991; ECHA, 2018), and was used to calculate the maximum allowable concentration of benzophenone.

Equation 1*: Formula to calculate the PDE

$$PDE = \frac{NOAEL \times \ body\ weight}{F1 \times F2 \times F3 \times F4 \times F5}$$

$$PDE = \frac{20\ mg/kg\ bw/day \times 50\ kg}{5 \times 10 \times 5 \times 2.5 \times 1}$$

$$PDE = 1.6\ mg/day$$

$$PDE = 0.032\ mg/kg\ bw/day$$

*Equation 1 is based on the method described in Appendix 3 of the ICH Guideline Q3C (R8) on impurities; guideline for residual solvents (EMA/CPMP/ICH/82260/2006[1]. Modifying factors of **5** (F1) for interspecies variability, **10** (F2) for variability between individuals, **5** (F3) for the short-term study (~3 months) to obtain the NOAEL of 20 mg/kg/day in rats, **2.5** (F4) for the possibility of non-genotoxic carcinogenic effects, and **1** (F5) if a no-effect level was not established, are used in the calculation. As per ICH Q3C (R8), an adult body weight of 50 kg is used in this calculation.

[1]ICH Guideline Q3C (R8) on impurities; guideline for residual solvents (EMA/CPMP/ICH/82260/2006) https://www.tga.gov.au/sites/default/files/2024-07/International-Scientific-Guideline-ICH-guideline-Q3C-R8-impurities-guideline-residual-solvents-adopted.PDF

ASEM established the highest average daily sunscreen exposure value, which was used in **Equation *2*** to calculate the maximum allowable benzophenone concentration in general therapeutic sunscreens. The value for the dermal absorption 12.42% was selected from a recently published paper (Ejaz et al, 2024).

Equation 2: Formula to calculate maximum allowable benzophenone concentration

$$Benzophenone\ conc\ = \frac{PDE\ (mg/kg\ kg/day)}{Amount\ of\ applied\ sunscreen\ (mg/kg\ bw/day) \times DA\ (\%)}$$

$$= \frac{0.032\ mg/kg\ bw/day}{673\ mg/kg\ bw/day \times 12.42\ \%}$$

$$= 0.000383$$

Converting to a percentage or ppm

$$= 0.0383\ \%$$
$$= \mathbf{383\ ppm}$$

RECOMMENDATION

To mitigate the risk from chronic exposure to benzophenone it is recommended that the Poisons Standard be amended to include a new entry for benzophenone, and:

- benzophenone is limited to a maximum concentration of 383 ppm as a potential degradant in therapeutic sunscreen containing octocrylene.
- benzophenone is not permitted to be added as a fragrance, as a precautionary approach, noting the EU has also prohibited the inclusion of benzophenone as an ingredient in cosmetic products.

When proposing risk management strategies, consideration should be given to the following:

- The risk assessment concluded that the maximum allowable benzophenone concentration in therapeutic sunscreens should not exceed 383 ppm (0.0383%).
- The 383 ppm concentration has been calculated for exposure from therapeutic sunscreen only. This value does not include benzophenone from other sources like cosmetics or fragrances in therapeutic or non-therapeutic goods. Because octocrylene is a common active ingredient used as a UV filter in therapeutic and cosmetic sunscreens and as a photo-stabiliser in other cosmetics, consumers might use multiple products, or a product could contain both octocrylene and benzophenone with the latter acting specifically as a fragrance. Consideration should be given to potential exposure different consumer products.
- Restrictions should ensure allowable limits of benzophenone as an impurity or degradation product are required to be maintained until the end of shelf life, not at release for supply of a product.
- The conditions under which octocrylene is more likely to degrade into benzophenone, such as excessive temperatures, and whether products have appropriate labelling for

storage conditions e.g. therapeutic sunscreens are required to comply with mandatory wording for storage conditions in the Therapeutic Goods Order No. 92 - Standard for labels of non-prescription medicines (TGO 92).

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Sunscreen round table discussion		Notes
Date and venue	18 December 2024, 11am -12.30pm, Canberra or Virtual	s22 contacted. Lunch to be organised by committee support
Experts	**Pending**	List of experts at Sheet 2
Agenda and invite	Pending	s22 to draft letter and agenda. Robyn to clear paper to attach to invite
C25A6:C26A6:C27AA6:C26		

Experts external	Name	Contact email	Contact phone number	Attendance	DOI in place for TGA?	
Consumer representative	Joanne Muller	s47F		yes	Yes- DOI at D24-4901319	
Toxicologist	Professor Brian Priestly (retired)			yes	Yes- DOI at D24-4816099	
Medical oncologist, with a speciality in melanoma	1. A/Prof Melissa Eastgate			yes	Yes- DOI at D24-5135081	reminder sent
	Prof Euan Walpole			yes	Yes- D24-5135053	
	s47F			yes	Yes- DOI at D24-5135028	reminder sent
Dermatologist	s47F			yes	Yes- DOI at D24-5135009	
	Dr Liang Joo Leow			yes	Yes- DOI at D24-5116321	
GP	Dr Kerrie Aust Dr Michael Bonning					
Paediatrician	Dr Ju Lee Oei			yes	Yes- DOI at D24-4816135	
	s47F				n/a	
Clinical pharmacologist	Amanda Gwee					reminder sent
Mothersafe	Dr Debra Kennedy			yes	yes	ye
Internal representatives						
Prof Robyn Langham	CMA	Robyn.Langham@health.gov.au				
Nick Henderson	MRD	Nick.Henderson@health.gov.au				
Avinash Clarke s22	COMB	s22 @health.gov.au>				
s22	COMB	s22 @health.gov.au>				
	SEB	s22 @health.gov.au				
	CHCCD	s22 @health.gov.au>				
	Scheduling	s22 @health.gov.au				

Therapeutic Goods Administration (TGA) risk assessment of sunscreen ingredients

1 Purpose of submission

1.1 To seek expert input on potential clinical matters for consideration in relation to TGA's risk assessment of sunscreen ingredients, which utilises the Australian Sunscreen Exposure Model, to support consumer and healthcare practitioner engagement and communication.

See table 1.

2 Background

Regulation of sunscreens in Australia

2.1 Australia has the highest rate of skin cancer in the world with two in three Australians will be diagnosed with skin cancer before the age of 70[1]. A range of public health preventative measures are encouraged in Australia, including the regular use of sunscreen.

2.2 In Australia, 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. All sunscreens must comply with the Australian/New Zealand Sunscreen Standard, including requirements for SPF testing and broad-spectrum performance.

2.3 All therapeutic sunscreens are included in the Australian Register of Therapeutic Goods (ARTG) via the low-risk 'listed' pathway. Listed sunscreens do not undergo pre-market evaluation. However, they must comply with Therapeutic goods legislation and may only contain TGA pre-approved ingredients included in the Therapeutic Goods (Permissible Ingredients) Determination. Further information on the regulatory framework underpinning sunscreens is available on the TGA website, available at https://www.tga.gov.au/resources/resource/reference-material/sunscreen-regulation-australia.

2.4 The Australian Industrial Chemicals Introduction Scheme (AICIS) assesses the safety of ingredients used in sunscreens that are not therapeutic goods (i.e. moisturizers, foundations). The ingredients in non-therapeutic sunscreens are regulated under *the Industrial Chemicals Act 2019*. The Australian Competition and Consumer Commission (ACCC) oversees product issues such as safety and truth in labelling.

Safety review of sunscreen ingredients to date

2.5 Sunscreens have been used to prevent sunburn and skin cancer for decades without any major safety signals. Preclinical studies have, however, raised concerns that the chemicals used in sunscreens could be associated with endocrine, reproductive, and neurologic toxicities. To date, there are no high-quality studies demonstrating these negative effects in humans.[2] In 2020, a review by Yamada et al. noted that toxicology of sunscreens is dependent on exposure and then the activity of that substance. To date, the *in vitro* literature on approved sunscreen ingredients focuses solely on defining the pathological activity of these ingredients. Yamada et al. concluded that the *in vitro* literature applied doses greatly exceed the recommended dose, highlighting the importance of separating the *in vitro*

[1] https://www.aihw.gov.au/reports/cancer/skin-cancer-in-australia/summary
[2] Adler, B. (2024). Sunscreen Safety: 2024 Updates. *Cutis*, [online] 113(5). doi:https://doi.org/10.12788/cutis.1003.

data from clinical relevance. Further innovation in sunscreen research using effective models to test delivery and effects is needed to improve confidence in sunscreen research.[3]

2.6 In 2019 and 2020, the FDA published two trials (an initial pilot study[4] and a follow up study[5]), confirming the systemic absorption of six sunscreen active ingredients (avobenzone, oxybenzone, octocrylene, ecamsule, homosalate, octisalate, and octinoxate). In the 2020 study, several chemical sunscreens were applied at the recommended density of 2 mg/cm2 to 75% of the body surface area multiple times over 4 days (a total of 13 applications). The study reported that all six of the tested active ingredients were systemically absorbed and that the plasma concentration exceeded the predetermined FDA cutoff (0.5 ng/mL), even after one application to 75% of the body surface area on day 1. It was recognised that while both studies make a great start, additional data is needed for each of these six active sunscreen ingredients in order to fully understand their absorption into the body as well as the long-term effects of absorption. The 2020 study concluded that the findings do not indicate that individuals should not refrain from the use of sunscreens and that the findings in no way imply any associated harm. Without further testing, the FDA noted that the exact levels of absorption considered safe are unknown.

2.7 This was followed by the publication of an FDA proposed rule in 2019 elaborating the requirement for testing and labelling of sunscreens by manufacturers.[6] The rule divided the 16 active ingredients approved in USA into three categories:

a) **Category I (safe and effective - GRASE)** includes Zinc Oxide and TiO2;
b) **Category II (not GRASE)** includes trolamine salicylate and para-aminobenzoic acid (PABA) (neither of which is used in products currently marketed in Australia); and
c) **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 currently used in Australian products.**

2.8 Within 2020-21, the European Commission published opinions (preliminary and/or final) on the safety of oxybenzone[7], homosalate[8] (2021 and later updated in December 2021) and octocrylene. Based on the available information, the Scientific Committee on Consumer Safety (SCCS) (an independent scientific committee managed by the Directorate-General for Health and Consumer Protection of the European Commission) 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

[3] Yamada, M., Mohammed, Y. and Prow, T.W. (2020). Advances and controversies in studying sunscreen delivery and toxicity. *Advanced Drug Delivery Reviews*, 153, pp.72–86. doi:https://doi.org/10.1016/j.addr.2020.02.001.
[4] Matta MK, Zusterzeel R, Pilli NR, et al. Effect of sunscreen application under maximal use conditions on plasma concentration of sunscreen active ingredients: a randomized clinical trial. *JAMA*. 2019;321(21):2082-2091
[5] Matta MK, Florian J, Zusterzeel R, et al. Effect of Sunscreen Application on Plasma Concentration of Sunscreen Active Ingredients: A Randomized Clinical Trial. *JAMA*. 2020;323(3):256–267. doi:10.1001/jama.2019.20747
[6] US Food and Drug Administration. Federal Register :: Sunscreen Drug Products for Over-the-Counter Human Use.
[7] Scientific Committee on Consumer Safety (SCCS, 2021e) Opinion on Benzophenone-3 (CAS No 131-57-7, EC No 205-031-5), preliminary version of 15 December 2020, final version of 30-31 March 2021, SCCS/1625/20. https://health.ec.europa.eu/document/download/5488f129-dd92-42fc-b7f5-21e1ac37ef3d_en
[8] https://health.ec.europa.eu/document/download/ddf0b68f-5c47-4ace-a87f-0a0e42ebd4a9_en0a0e42ebd4a9_en?filename=sccs_o_244.pdf [Accessed 31 Oct. 2024].

oxybenzone and homosalate used in the European market were not able to be labelled as completely safe based on the available data and proposed maximum concentration limits to ensure complete safety for all products available in the community, later put into effect by European Union (EU) legislation.

(a) For oxybenzone, the new EU requirements require oxybenzone concentrations to be restricted to 6% in face, hand and lip products, excluding aerosols, 2.2% in body products including aerosols, and 0.5% in other products.
(b) For homosalate, the new EU requirements require cosmetic products to contain a restricted concentration of homosalate at a maximum of 7.34% in face products and not to be permitted in propellent spray products, effective from 1 January 2025.

Importantly, in making the decision, the SCCS noted that the current available evidence for endocrine disrupting properties of homosalate as inconclusive, and at best equivocal. The SCCS noted 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 utilise in a safety assessment.

Furthermore, SCCS reported the data related to endocrine disrupting properties of oxybenzone as inconclusive, and at best equivocal. This conclusion was applied across all available data derived from in silico modelling, in vitro tests and in vivo studies.

2.9 On 1 October 2024, the Australian Industrial Chemicals Introduction Scheme (AICIS) published an evaluation statement on homosalate.[9] The statement noted that:

(a) based on limited available data, homosalate may adversely affect the kidney. This data was based on a combined repeated dose toxicity study in male rats at 60mg/kg bw/day. As there was insufficient data to suggest that the effect on kidneys was only relevant to rats, the observed kidney effects were considered relevant to humans and the lowest observed adverse effect level (LOAEL) was considered to be 60mg/kg bw/day.
(b) based on limited available data, homosalate may affect fertility and development toxicity (reduced fertility index, sperm changes, reduced corpora lutea and higher post-implantation loss). This data was based on one screening toxicity study in rats. The study was conducted in an environment where rats were exposed to constant lighting at doses ≥ 300 mg/kg bw/day, instead of a normal light/dark cycle. In addition, the low number of pregnancies per group questions the validity of the data on the development of offspring in this study.
(c) Homosalate was shown to interact with oestrogen, androgen and progesterone receptors in some in vitro assays. However, this was at potencies several magnitudes lower than endogenously produced hormones.

Following this statement, a recommendation has been made to the delegate of the Secretary by AICIS for Poisons Scheduling to list homosalate in the Poisons Standard and restrict the concentration of the chemical in cosmetic products.

3 Current status and future direction

[9] Australian Industrial Chemicals Introduction Scheme- Benzoic acid, 2-hydroxy-, 3,3,5- trimethylcyclohexyl ester (Homosalate) Evaluation statement 1 October 2024

3.1 In 2022, on the backdrop of the international signals, the TGA sought to better understand the long-term risk profile of sunscreen ingredients. It was recognised, however, that any analysis around sunscreen use in Australia needed to include a risk assessment lens that incorporated the greater level of sunscreen exposure of Australians over a lifetime as well as the far greater incidence of skin cancer.

3.2 The TGA conducted two independent reviews. The first review led to the development of the Australian Sunscreen Exposure Model (ASEM). The ASEM was proposed to provide a standardised method for calculating sunscreen exposure, reducing discrepancies in risk assessments. It was developed to align with Australian conditions (i.e. high UV light levels) and consumer practices (i.e. outdoor lifestyle), ensuring sunscreens are safe and effective when used as directed. The TGA undertook extensive targeted pre-public consultation between May-July 2024 to develop the ASEM and public consultation again between July and August 2024. There was broad in-principle support for the adoption of the ASEM for estimating therapeutic sunscreen exposure for ingredient risk assessments. **See Attachment A for further information on the ASEM.**

(a) It is crucial to recognise that the ASEM scenarios were constructed to reflect the higher end of sunscreen usage in Australia, rather than the average Australian's usage. This approach ensures that the risk assessments for sunscreen ingredients, when based on the highest usage scenarios, will also guarantee safety for lower usage cases where less of the ingredient may be applied to the skin. This approach provides estimations of sunscreen use based on Australian evidence-based recommendations and limited current data and epidemiology research.

(b) One assumption used in the ASEM is that a sunscreen application rate of 2mg/cm^2 is required to achieve the labelled SPF rating. The ASEM model acknowledges that not all Australian apply sunscreen at the thickness to achieve the labelled SPF. However, an application rate of 2mg/cm^2 is needed to cater for Australians who use sunscreen at the correct application rate to ensure the findings are applicable at the highest exposure level.

(c) It is important to note that actual comprehensive Australian sunscreen use data, combined with these recommendations, would provide a more robust model for estimating highest-use exposure in the Australian context. As gathering such extensive data that would be statistically representative of all Australians poses challenges, the ASEM scenarios and variables are derived from the best available information to date.

3.3 The TGA then completed a toxicology risk assessment of seven sunscreen active ingredients and benzophenone **See Attachment B and Attachment C.** The TGA tox risk assessment leverages off the risk assessment of the EU's SCCS, while recognising limited available data (2008-2023). The risk assessment also acknowledges that to accurately evaluate the long-term risk of exposure to these active ingredients from sunscreen, further randomized controlled trials may need to be conducted.

(a) The risk assessment is intended to provide an overview of the publicly available safety information for these ingredients, calculate the Margin of Safety (MoS) as per the ASEM using the maximum concentration of the ingredients approved in Australia, and provide information needed to assess the suitability of the seven ingredients for use in therapeutic sunscreens.

i. The highest estimated daily sunscreen exposure scenarios utilised in the risk assessment included a sum of a school aged child with frequent sun exposure and applying sunscreen up to three times a day to the majority of their exposed skin at a frequency of 240 days per year **and** a scenario of a SunSmart adult/child applying sunscreen up to three times a day to exposed skin (face, neck, hand ½ legs and feet) at a frequency of 26 days per year.

As such, it should be noted that the highest systemic exposure dose for all active ingredients in the risk assessment was calculated based on the highest estimated daily sunscreen exposure in the Australian context (**673mg/kg bw/day).**

(b) The two main issues considered in this risk assessment 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 MoS was determined for each of the ingredients using the ASEM. A MoS of 100 or more was considered to be satisfactory for minimising 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. 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.

3.4 Based on the best research available to date and applying the recently adopted Australian Sunscreen Exposure Model to qualify the risk assessment, the TGA's risk assessment has highlighted concerns related to the high use in their current concentrations of two sunscreen active ingredients (homosalate, oxybenzone) and a degradant (benzophenone). These concerns are related to their potential effects on humans pertaining to the **long-term exposure** of these chemicals as recognised in animal and *in vitro* studies.

Table 1 provides a summary of the main issues identified in the risk assessment for homosalate, oxybenzone and benzophenone and consequent matters for which advice from the ACM is being sought.

Table 1: Main issues identified in the risk assessment conducted by the TGA and request for ACM input:

Key findings	Important considerations	Matters for expert consideration
- Using the best available data available and in line with the SCCS review, the TGA's risk assessment concluded that homosalate may not be deemed to present a low risk to human health and safety for long-term use at the highest maximum permitted concentration of 15% in therapeutic sunscreens.	- The systemic exposure dose was based on the highest concentration permitted to be used in Australian sunscreen products (15%). 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+. - The No Observed Adverse Effect Level (NOAEL) was set at 10mg/kg bw/day. While this is consistent with SCCS's review, it is at least 30-fold lower that the general toxicity NOAEL that was established in combined repeated dose and reproductive/development screening study in rats based on mortality in female rats at the highest dose. A NOEAL of > 300mg/kg bw/day in makes and > 1000 mg/kg bw/day in females was established in a two-weekly 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 in uncertain. - The MoS calculated was 3-fold lower than the MoS from the SCCS review. This may be appropriate, noting the difference in how sunscreens are applied in Australia vs Europe.	– The TGA will be taking next steps to further evaluate the appropriateness of applying regulatory controls on homosalate, oxybenzone and benzophenone to reduce the risk of long-term exposure via therapeutic sunscreens. This may include controlling the levels of the chemical through the Poisons Standard and other regulatory measures. – As there is no immediate patient safety risk as well as a need for more robust long-term data, the TGA is proposing to publish the risk asessment in early 2025 with a communication strategy to reassure the public of the critical need for sunscreen and that there will be no recommendations to change current practice. – The TGA is seeking input from clinician experts regarding this approach to the risk assessment and any intended clinical consequences.
- Using the best available data available and in line with the SCCS review, the TGA's risk assessment concluded that oxybenzone is not deemed to present a low risk to human health and safety for long-term use at the highest maximum permitted concentration of 10% in therapeutic sunscreens.	- The systemic exposure dose was based on the highest concentration permitted to be used in Australian sunscreen products (10%). The No Observed Adverse Effect Level (NOAEL) of 67.9mg/kg bw/day utilised in the MoS calculation was based on reproductive and developmental toxicity studies in female rats that showed a potential endocrine disrupting effect. While this is consistent with the SCCS review, the SCCS did not apply any adjustment for bioavailability to this NOAEL value because of the evidence for	

	rapid and almost complete absorption of oxybenzone from the oral route. - There are other sources of oxybenzone releases into the environment such as from use of machine wash liquids and detergents, paints and coating, fragrances and air fresheners. Considering the widespread use of oxybenzone, exposure may also occur from sources other than sunscreens.	
- Based on the best available data, the TGA's risk assessment concludes that a maximum allowable benzophenone concentration should be set at 383 ppm (0.0383%) as a degradant in therapeutic sunscreens containing octocrylene and benzophenone should not be permitted to be added as a fragrance, as a precautionary approach.	-	

4 Attachments

Attachment 1: Australian Sunscreen Exposure Model (ASEM)
Attachment 2: TGA toxicology risk assessment of 7 active ingredients
Attachment 3: TGA toxicology risk assessment of benzophenone

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